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Editorial/Editoriale

How to distort the scientific record without actually lying: truth, and the arts of science

Come alterare la documentazione scientifica senza in realtà falsificarla: la verità e le arti della scienza

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Summary

There are many ways to mislead readers and users of the scientific literature without resort to fraud or other kinds of lying. These include the artful choice of topics for study, framing the question so as to reach a predetermined conclusion, weak protocols (especially helpful when the investigator wants a negative conclusion), undisclosed omissions of data points and/or relevant information, and deliberate distortions in the processes of data reduction, analysis, and presentation. Overall, the problems seem to be common and widely tolerated – even, sometimes, presented as the way to get ahead in science. Their cumulative impact may be much greater than the effects of outright fraud such as fabrication, falsification, or plagiarism. Scientists, users of science, and the public should be aware of the potential for deliberate distortion of the scientific record, learn how to recognize it, and guard against it. Eur. J. Oncol., 11 (4), 217-224, 2006

Key words: **science, fraud, deception, lying**

Riassunto

Ci sono molti modi di fuorviare chi legge ed utilizza la letteratura scientifica senza ricorrere a frodi o ad altri tipi di inganno. Questi comprendono la scelta fatta ad arte degli argomenti da studiare, l'impostazione dei problemi in modo tale da raggiungere una conclusione prestabilita, protocolli inconsistenti (utili soprattutto quando il ricercatore vuole giungere ad una conclusione negativa), omissioni non dichiarate di dati e/o informazioni pertinenti, e distorsioni intenzionali nei processi di riproduzione, analisi e presentazione di dati. Nel complesso questi problemi sembrano comuni e largamenti tollerati, a volte addirittura presentati come il modo di fare carriera nel mondo della scienza. Il loro impatto cumulativo può essere molto maggiore degli effetti di frodi palesi come l'invenzione, la falsificazione o il plagio. Gli studiosi, chi usa i dati scientifici ed il pubblico dovrebbero essere al corrente della possibilità di alterazione deliberata di un resoconto scientifico, imparare a riconoscerla e difendersi da essa. Eur. J. Oncol., 11 (4), 217-224, 2006

Parole chiave: **scienza, frode, inganno, falsificazione**

Introduction

There are many kinds of paths to many kinds of truths – religion, intuition, and culture, among them. In this paper, I wish to discuss the relations between science and law, two of the important means of ascertaining truths in an uncertain world.

I will discuss science, perhaps the most important and productive means of ascertaining truths in an uncertain world, with some special attention to science and

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the law (in the US) because that is the focus of the paper. A scientific paper can be correct in every word, sentence, and paragraph, but be gravely misleading in the whole.

I want to make it clear first that I am not concerned here with honest error. Every scientist who ventures into the unknown will make mistakes, and some of those may take much time and effort to rectify, but such problems are a necessary and productive component of all science at the leading edge of knowledge. I will be writing, rather, about the willful creation of barriers to learning the truth.

Science is far from value-free[1]. It is sometimes presented as truth, which it is not, or as the search for truth, which is a lot closer to, well, the truth. Scientists in all disciplines spend a large part of their training and productive years in learning how to search, and the best of them spend much time and effort on keeping up with, and evaluating, changes in the methods of establishing truth in their fields. But the search for truth involves as much art as anything else, and I have a particular concern about the way the art is practised.

What I mean by art is educated judgement about the many choices an investigator must make: of topics to be investigated, how the research questions will be framed, how protocols are developed and implemented, how data are analysed, and countless other things. An artful design can be very helpful if one starts with an intent to find, or not find, some effect.

Most of the problems can be viewed as either manipulating and misinterpreting the scientific record itself or misrepresenting that record. Not all, however. Selzer[2] has published a set of thirteen views of a single important scientific review paper by Gould and Lewontin[3] and those views are simply not compatible. The scientific issue he examines can be stated briefly: is the force of natural selection over the millennia so great that every important change is a product of it, or are some changes more or less random, and biology learns how to make use of them? Selzer includes essays by persons with views that can be variously described as rhetorical, modernist, post-modernist, feminist, structural, deconstructionist, ethical, and otherwise. I believe that most working scientists would be astonished by this variety of views of a single issue in just one paper, influential though it was. The thirteen discussants were quite serious about their work, and I am sure that there was no attempt to deceive. Each author makes a strong case. Which of the authors is or are right in what degree about what Gould and Lewontin were writing? Are they all right in some sense, like the three famous blind men? I have no answer to that, but find the variation in views to be interesting and highly informative.

A catalogue of sins

Not all problems in coming to scientific truth have such innocent origins, and my primary focus here will be on deliberate distortions of either the record or the way the record is interpreted and presented. Table 1 presents a short catalogue of some of the ways that the results of scientific investigation can be distorted, whether deliberately or not. Little in this list will be new to working scientists, but I will illustrate each with at least one item that may be interesting and unfamiliar to most readers. For each, I will try to show how problems can happen – too often, how they can be *made* to happen.

The most common and important points of attack shown in Table 1 are varied and cover every aspect of science from the initial concept of a research study through the presentation and reception of results. Of course, others have also dealt with these issues. Huff, in his well-known book "How to Lie with Statistics"[4], hardly got started on the problems. Cohn and Cope[5] have presented a highly readable survey of the many problems in interpreting quantitative material for the lay public, especially where the material may be misrepresented.

Many examples could refer to governmental interference in scientific research, including examples from all three branches of the US Federal government, especially the Executive branch in the past 6 years. These include suppressing and distorting data, disregarding well-reasoned findings and recommendations of its own committees, second-guessing peer reviews by experts, exclusion from discussions of experts who are deemed to fail a "litmus test" for political acceptability, and applying religious beliefs to scientific matters. I present this list of inappropriate governmental actions simply because government is what I know best. Similar examples could be collected from industry, public interest groups, schools, and elsewhere in the US as well as such institutions in other countries.

What I wish to present in this paper is, of course, not intended to be used as a how-to-do-it manual; its purpose is rather to alert the honest, perceptive observer, scientist or lay person, to some of the tricks and to provide a few

Table 1 - Some points where things can be made to go wrong

Choice of Topic
Framing of Question(s)
Protocol Decisions
Study Performance
Data Reduction
Analysis
Findings and Conclusions
Presentation

tools to detect and counter some kinds of scientific fraud. And they are fraud, in the ordinary sense of the word if not in the legal sense, because they are meant to deceive and run counter to the norms of science that we have all endorsed, at least implicitly.

Choice of topic

Many legitimate considerations arise in the choice of problems to be studied, and few of these derive from the itch to peer into the unknown. Nearly all science, and nearly all scientists, are supported with much more practical objectives in mind, sometimes including the use of findings in the courtroom. Questions of the possible utility of some result, costs of study, availability of needed facilities and resources, newness of ideas, what is already known about the topic, and many other things are often determining factors. For example, how much research should be done to detect possible adverse effects of a food additive? Allied Chemical Corporation, the manufacturer of Red 40, a food dye approved for use in the United States, wanted to expand its market to Europe and Japan, where requirements for toxicity testing were somewhat different. A new long-term bioassay was required and performed, and the results appeared to show a previously unknown risk of carcinogenesis. As a result, the company almost lost its domestic market as well as the chance to sell abroad. Further work uncovered a probable problem in the experimental design[6], and a repeat bioassay did not confirm the finding of carcinogenicity, but the lesson was not lost on other manufacturers and industries: do not undertake toxicity studies that go beyond what is absolutely required by law and regulation, or you may find things you do not want to know about. Allied Chemical deserves credit for handling this matter in a way that advanced the public interest, but overall the public is the loser. We do not know as much as we should about the risks of Red 40 or indeed about most other consumer products.

A more perverse skewing of the choice of topic has been reported in tobacco-related research[7]. That industry has undertaken critical research in secret, and publicly funded and published entirely new studies only if the secret research has shown that a second, public, study will not be harmful to the industry. Tobacco in all of its forms – cigarettes, cigars, pipes, snuff for chewing or inhalation – is known to cause immense damage to health, worldwide. It is hard for me to imagine a more cynical approach to the development of scientific knowledge than that of the tobacco industry, or one that is more contrary to the public interest.

Another aspect of this is the strong tendency of the pharmaceutical industry to focus its research efforts on the development of drugs that will have broad use in economically advanced countries rather than address the major health problems of the world. As a result we know a lot more about the treatment of the common cold and minor depression than we do about the prevention of malaria or viral hepatitis, or inexpensive treatments for AIDS.

There are many other such questions. For example, what do we not know about stem cells, and what does that cost us?

Framing the question(s)

Research questions can be posed in such a way that the outcome is certain, or an investigation can be put in the hands of someone known to conduct studies and interpret results in certain ways. Many scientists know which of their colleagues engage in such practices, though others – including legislators, news media, public, judges, and juries – are kept in the dark. We could use better ways to expose and publicize such work.

One way to obtain a reliably negative result is to design a study with limited statistical power to demonstrate an effect. Serious questions have been raised regarding the health effects of the chemicals used in the semiconductor industry, especially cancer, and fragmentary evidence supports those concerns. After one small study reinforced concern, the industry proposed a study that would have been much too small to detect anything less than a massive increase in mortality among workers. An international group of scientists[8] pointed to this problem and predicted that the industry would then cite the predictably negative results, not as inconclusive, but as showing safety, and indeed that is precisely what happened[9]. An industry-supported study[10] failed to show a risk, but only three manufacturing facilities were included in the study, and one must wonder how and why other facilities were omitted. Does this train of events resemble the tobacco story? Other problems in the industry-supported report, that are not entirely the fault of the authors, include subdivision of the samples into many groups too small to show much effect and lack of information about the chemicals or levels of exposure (including a lack of focus on forms of cancer found in the laboratory to be related to exposure to some of the same chemicals); Clapp[11] has reported separately on mortality among workers at the same company, but he included all facilities. Clapp found numerous causes of death to be proportionately more frequent among the workers than in the general US popu-

lation. Clapp's series[11] was larger (almost 5-fold) than that of Beall *et al*[10], but his method of study was weaker, in part because the company refused to provide any information beyond what it had been required to divulge in a lawsuit. We still do not know with certainty what health hazards may be associated with work in the semiconductor industry, but the unexplained omission of most of the facilities from one study raises serious questions about its results.

It is important to understand that scientists may often differ in how they approach a problem and how they analyze and interpret results. However, unless more information is forthcoming, Clapp has the more convincing paper.

Protocol decisions

Many kinds of studies, especially surveys, can produce data that are profoundly affected by choice of wording and the context of specific items of inquiry[12]. Chief among these are "push polls", which appear to be scientific but are not in fact designed to produce real data; they are meant to have some other effect. As an example, one could consider a political poll in which an answer unfavourable to the sponsor is followed by a question "Would you change your vote if you knew that Candidate X was convicted of child molestation 7 years ago?" Asking a question is not a misstatement of fact, but its mere asking might change a vote, or even start a broad rumour.

Data reduction

An investigator will ordinarily come to the end of a research investigation with a mass of data that requires sorting, cleaning up, and preparation for analysis. One would get nowhere with an analysis that begins "Mouse 21347, a male treated with placebo, died over the weekend at the age of 87 weeks, and was too decomposed to determine the cause of death. Mouse 21348, also a male but treated at the low dose, was examined at autopsy and found to be cancer-free but to have a hypotrophic kidney on the left. Mouse 21349, …". Data reduction is essential, but requires many decisions by the scientist.

For example, some data points may be clearly wrong and should be deleted. Others may not fit a pattern ("outliers") and their management is a matter of judgement. There is no reliable, standard rule for this. It requires educated judgement, or art. Another question is: when do you start or stop an observational series? Some industrial hygiene data have covered the whole industry, not just those workers that have had a high exposure. Other problems that may be faced by the best of scientists include small, inadvertent deviations from protocol, unavoidable confounders and other sources of bias, and many other things. These matters require educated judgement.

The "art" part of science is focussed in large part on dealing with these matters in a way that is most likely to preserve fundamental truths, but the way is open for deliberate skewing of results to reach a predetermined conclusion.

Analysis

The investigator-analyst has countless options for determining what important messages may be buried in the data, even after substantial reductions, and another large part of the art of science is knowing how to analyze the data in ways that will not bias the findings and conclusions. One good step toward this goal is to specify in the original protocol how the primary analysis will be conducted. This may not always be needed; for example, there is a general pattern for the analysis of randomized drug trials, but even there it is a good thing to have a clear, detailed statement of how the primary analysis will be conducted. This does not preclude other analyses that will be presented as subsidiary or supporting, and such additional analyses are often of great interest and importance. Good research almost always leads to questions that the study was not specifically designed to answer, and that may not have even been thought of before the first look at the data, but the results of such additional analyses have a different and lesser degree of reliability that must not be obscured by presenting them as the primary object of the investigation.

It is common practice for scientists to practise their research methods, and to begin the "real" research only when they believe that the methods are under good control. This leads to some choice in when the results will be considered sufficiently reliable to be published, and that choice may be affected by the results themselves. Result: biased data. A related issue is that a series of cases studied for a possible adverse outcome of medical treatment, such as a new antibiotic or new chemotherapeutic agent, may be started just before or just after one or more instances of that outcome, depending on what the investigator wants to show, and similarly the series may be terminated just before or after such instances. Thus several cases may be added or subtracted from what is presented as an unbiased record, and that may be enough

to change conclusions. Unfortunate instances of this mode of procedure have been brought to light in the pharmaceutical industry, both in the past and in the present.

What about an investigator who asks for instruction on how to use a computer programme, then writes a paper based on the statistical test with the lowest p-value, without really understanding any of the tests. And what about the use of one-tailed tests? A critical question is what the investigator would do if the results pointed strongly *away* from the expected result. If he or she took that result as no more than confirmation of the null hypothesis, the problems would be reduced. If there were some effort to find an explanation not previously considered, the logical foundation of one-tailed tests would be destroyed and the results misleading. I recommend the strict avoidance of such tests unless they were prescribed in the original protocol.

Scientists have other opportunities to deal with "problem" data. One is to repeat tests that produce unwanted results, but not those more favourable to the hypothesis under study, and the random nature of outcomes will result in some bias. Or, data points may be just omitted as erroneous (and without comment in the report) if they seem inconsistent with the investigator's hopes or expectations. Such tactics may be almost undiscoverable by readers and users of the findings.

A recent report on health effects among workers exposed to hexavalent chromium reported no effects of consequence. However, the industry-sponsored investigators divided the cohort post-hoc into two subgroups, reducing the power of the study to identify an effect. They also classified the exposures, again post-hoc, into low- and high-exposure groups, making the excess risk in the intermediate exposure group "disappear", the exposure levels of particular interest in an ongoing federal occupational health rulemaking. Moreover, they failed to share the results with a federal agency, even after the agency asked specifically for exactly this sort of epidemiological data[13]. One must ask about the reasons for such obvious commissions and omission, and whether they are related to the fact that the industry supported the study.

Presentation

Again there is a catalogue of problems. Overstating the strength of conclusions is common; so is overstating their importance. As evidence, one needs look only at any issue of a scientific journal from, say, ten years ago. How much is still relevant and of interest? For more advanced self-education, one should look at the news stories published at the time. In my own field of cancer research we have seen successive waves of enthusiasm, later disappointed, over early results from virology, immunology, and many other approaches. Remember interferon? Remember interleukin? Remember the more recent hopes about angiostatin? And will you remember those and others the next time you read a report about some great advance in the treatment of cancer?

What results will be made public? Here, the first thing many scientists think about is publication bias – that is, the general tendency of scientific journals to prefer to publish "positive" findings. There are some good reasons for this tendency, most of which come down to the question: who needs to know what? For example, a study that shows great value of some new anti-cancer drug may be critically important to a broad range of medical practitioners and, through them, to their patients and the public at large, while negative findings may be important only to a handful of other investigators working on the same diseases or similar drugs. There are good ways to make results of very limited interest available to those who may need them: publication of a meeting abstract, inclusion of a paragraph or two in a later report on a related topic, even personal communication and word of mouth. Unfortunately, the structure of the reward system in science is built entirely on publication, and the perverse incentives to publish positive results have profound implications for the choice of topics to be investigated as well as the analysis and presentation of what is found (see above). Investigators tend to look for research topics that will result in publication, rather than topics that serve the public interest.

Willful suppression of data, even of whole studies, is both very old (think of Galileo) and very much with us today (think of global warming, attacks on evolution, the shameful distortion of the record on "Plan B" for contraception, denigration of studies that have failed to find long-term maternal effects of elective abortion, and many others).

An example that may be less familiar is the collapse of the Atlantic cod fishing industry[14]. Despite clear warning signs over a period of decades, governments, in collusion with the industry, refused to admit that there might be a problem of over-fishing until the cod literally disappeared from the nets. Their attitude was perhaps best summarized by a fisherman (in a different fishery) who said: "I prefer the possibility of bankruptcy tomorrow to the certainty of bankruptcy today"[15]. Few cod remain, and it is not clear whether they will ever recover, as other species have moved into their former territory and now eat the cod eggs and fingerlings as well as the food that larger fish would need to survive[15]. Atlantic cod, once the

staple seafood of this nation and much of the rest of the world, can no longer be found in your grocery store. Greed and pandering for political support assured that the scientific record was ignored. We are all losers, including the interests that promoted ever more intensive fishing as the cod were vanishing.

Much more generally, data on a range of environmental problems is routinely misrepresented, misinterpreted, or ignored, including such things as the environmental and human health effects (including cancer) of oil and gas exploration[16], the disappearances of endangered species, the rapid, marked reduction of biodiversity, and – as already noted – global climate change. Similar problems seem to afflict the whole range of the forensic sciences, including fingerprints, polygraph testing[17], analysis of hair and fabric samples, "bullet lead"[18] and ballistic findings, etc.

I am pleased, however, to be able to end this section on a higher note. Many research investigators have gone to the ultimate in the presentation of their work by making their raw or semi-processed data available to others as recommended by Fienberg *et al*[19]. This practice is not as common as one might hope, but it is far from rare.

Research on science in the courtroom

Magistrates and lawyers repeatedly comment that not enough is known about the problems of science *vis-à-vis* law, and especially about science in the courtroom, and a series of workshops have been organized, to this end, by the "Project on Scientific Knowledge and Public Policy". It is strange that this is so: many of those interested in this field are scientists, but we have not applied our professional tools to a matter that we think is important. Why? Is it a matter of lack of leadership? Insufficient funding? Not knowing just what the questions are, in a researchable sense? Not knowing the appropriate research methods? Something else? All of these?

We are talking about issues that are very important but we, as scientists, have not applied our own disciplines and skills to these matters. It is hard to find much evidence about any of the topics discussed at this series of workshops that is valid in any scientific sense. It is time for this to change, and to undertake far more research on science in the courtroom. I can suggest three research possibilities: 1) looking at places that do not have a powerful engine of tort litigation to see whether toxic exposures are treated differently (looking at other countries could help us see the rôle of our own tort system); 2) the rôle of cross-examination ("the greatest engine ever devised for eliciting the truth"?); and 3) comparison of early cases *versus* late cases in various kinds of suits regarding toxic exposures – what is the change over time in the nature of the complaints, evidence, and outcomes? There is a substantial literature on cross-examination, for example, but it does not seem to include much critical comparison of cross-examination with alternative systems. There are some preliminary comparisons of the US adversarial legal system with systems in other countries, as is dealt with in the works of Bron McKillop and John Jackson, and there is a small start out there on problems of discovery.

We must recognize that some important questions are not amenable to scientific study, and not all scientific research needs to be quantitative. There are multiple ways to pursue the truth.

I believe that there is a useful lesson to be learned on a different matter that we all considered important to science but have never examined in a scientific way: journal peer review. Anecdotes and opinions about the good and bad effects of peer review were rife, but no hard data were available[20,21]. Drummond Rennie saw an opportunity in this, and organized an international conference. He required that each paper include some data, and announced the conference three years ahead so that investigators would have enough time to produce some results. The first set of papers was not of good quality, largely because the questions were not yet clear, nor were the research methods adequately worked out. Rennie persisted, and that initial conference has become a series with papers of rapidly rising quality. By the third round some of the presentations were outstanding. The fifth International Congress on Peer Review and Biomedical Publication has been held in September 2006 in Chicago, Illinois.

The lesson for us here is that unfamiliar research territory can be developed, and that matters we regard as important deserve the best investigation that we, as scientists, can offer.

Peer review and science and law are not the only topics that we say are very important to us, but have not been investigated with the tools we profess; indeed it might take some courage to take on academic tenure.

Conclusions

Returning to Table 1 it can be seen that science is under attack from all sides. This is not all bad, when the attacks are well-motivated and really designed to elicit the truth about some matter of interest. Too many of the attacks, including most that I know about in the courtroom, are simply meant to be destructive.

Scientific findings are generally nuanced and tentative when they first begin to emerge. Early problems may lead to firm, fixed opinions that are hard to change as evidence accumulates on one side or the other. I believe that this is the basic problem with the argument over the proven carcinogenic effects of asbestos, and that the defensive instincts of the industry are less important. It has simply been hard for a lot of people to change their minds (and positions) despite the massive collection of data demonstrating a serious risk.

What are the proper rights of society to stifle, suppress, or redirect scientific research that may be generally seen as potentially harmful? There are such rights, as were exercised in the early years of genetic manipulation, when the results of new kinds of experiments could have turned out very, very badly. But such guidance must be exercised only in the open, and with adequate public participation and debate. The whole and explicit point of Plato's "Gorgias"[22] is to demonstrate the superiority of philosophy (that is, the quest for wisdom and truth) over rhetoric (that is, the art of persuasion in the quest for victory). I am with Plato on this.

There is sometimes fraud in science, in the sense of fabrication or falsification of data and procedures. Those acts are lying, and when they are detected they get broad attention followed by serious consequences for guilty scientists. But I am convinced that deliberate distortion of science without lying is far more common, and far more serious in its impact and implications for our country, our posterity, and ourselves.

It is time to get back to science and law. It is not hard to find good and honest scientists and lawyers. They deserve our thanks and support. Unfortunately, they do not always have a leading rôle in the resolution of the questions that come to our civil or criminal justice systems.

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Anaemia in patients with advanced cancer receiving palliative care

Anemia nei pazienti con tumore in fase avanzata che ricevono cure palliative

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Summary

In the last decade there has been a remarkable interest, and a growing number of publications, on anaemia and fatigue in cancer patients. The question is why there has been such an interest. Is anaemia, indeed, the most common haematological abnormality encountered by cancer patients? Do they regard fatigue as having greater negative impact on their daily lives than many other cancer- or treatment-related complications, with important emotional and mental consequences, including lack of self-motivation, sadness, frustration and mental exhaustion? Or was this remarkable interest for anaemia and fatigue in part due to the wave of enthusiasm which came about after the first production of erythropoietin? To give an answer to these questions is not easy. One thing which we can do is to find out how high the prevalence of anaemia is in the different categories of cancer patients and what rôle anaemia plays in comparison to other symptoms of advanced cancer. Available data show that anaemia with mild to moderate clinical consequences has a prevalence in 10-20% of patients and is a much less frequent symptom of advanced cancer than pain, dyspnoea and cachexia. With respect to the management of anaemia we have to differentiate between two main situations. In palliative care it is imperative that treatment is strictly individualized to meet the varying clinical, psychological, economical and ethical needs of the heterogeneous group of anaemic advanced cancer

Riassunto

Nell'ultimo decennio c'è stato un notevole interesse, con un numero crescente di pubblicazioni, sull'anemia e la *fatigue* (spossatezza ed affaticamento fisico-psichico) nei pazienti neoplastici. La domanda è sul perché c'è stato questo interesse. L'anemia è veramente la più comune alterazione ematologica osservata nei pazienti neoplastici? Essi considerano che la *fatigue* abbia un impatto negativo maggiore sulla vita quotidiana rispetto a molte altre complicanze correlate al tumore o alla terapia, con importanti conseguenze emotive e mentali, comprendenti la mancanza di motivazioni, la tristezza, la frustrazione e l'esaurimento psichico? O dietro a questo notevole interesse per l'anemia e la *fatigue* c'era il grande entusiasmo dopo la prima produzione di eritropoietina? Dare una risposta a queste domande non è facile. Una cosa che possiamo fare è trovare qual è la prevalenza dell'anemia nelle diverse categorie dei pazienti neoplastici e quale ruolo gioca l'anemia rispetto ad altri sintomi del cancro avanzato. I dati disponibili mostrano che l'anemia con conseguenze cliniche lievi o moderate ha una prevalenza nel 10-20% dei pazienti ed è un sintomo di tumore avanzato molto meno frequente del dolore, della dispnea o della cachessia. Riguardo al trattamento dell'anemia dobbiamo distinguere due situazioni principali. Nelle cure palliative è indispensabile che il trattamento sia strettamente personalizzato per venire incontro alle diverse necessità cliniche, psicologiche, economiche ed etiche del gruppo eterogeneo dei pazienti anemici con

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patients. We should keep in mind that a low haemoglobin level needs control and in some cases it needs treatment. However we should understand that we have enormous unmet needs in palliative care that have much higher priority. Certainly not all patients are appropriate candidates for erythropoiesis-stimulating proteins (ESPs) treatment. The disadvantages of ESPs include the 4-8 weeks delay before maximum benefit is achieved, possible side effects, their efficacy in only some patients, and their costs. On the other hand, an improved subjective well-being after blood transfusion is well confirmed. Careful consideration of both the advantages and disadvantages of the major choices of treatment for anaemia – transfusion and ESPs – will help avoid ineffective and costly interventions. Chemotherapy-induced anaemia needs treatment in any case. Just as a surgeon cannot leave the patient without closing the wound, the chemotherapist cannot leave the patient without control of chemotherapy-induced side effects. Neither high costs nor any other reasons could justify this. However, treatment of chemotherapy-induced anaemia does not automatically mean immediate erythropoietin administration. A short-term policy of wait and see can be useful. Moreover, the use of ESPs outside the existing guidelines should be considered only in the context of very well planned and carefully monitored clinical studies that implement strict ethical safeguards for our patients. In any case the treatment of anaemia tailored to an individual cancer patient has to be made at the bedside by an experienced medical oncologist in conjunction with the patient's preferences and values. Otherwise, we shall be treating the anaemia but not the patient. Eur. J. Oncol., 11 (4), 225-235, 2006

Key words: **anaemia, cancer, palliative care**

cancro avanzato. Dovremmo tenere presente che un basso livello di emoglobina richiede un controllo e in alcuni casi un trattamento. Dovremmo però capire che nelle cure palliative abbiamo esigenze non corrisposte da affrontare che hanno una priorità molto maggiore. Certamente non tutti i pazienti sono candidati adatti al trattamento con proteine stimolanti l'eritropoiesi (erythropoiesis-stimulating proteins = ESPs). Gli svantaggi delle ESPs comprendono il ritardo di 4-8 settimane prima che si ottenga il massimo beneficio, eventuali effetti collaterali, l'efficacia solo in alcuni pazienti ed i costi. D'altra parte è ben confermato un accentuato benessere soggettivo dopo trasfusione di sangue. Un'attenta valutazione dei vantaggi e degli svantaggi delle principali scelte terapeutiche nell'anemia – trasfusione e ESPs – aiuterà ad evitare interventi inefficaci e costosi. L'anemia indotta da chemioterapia richiede un trattamento in ogni caso. Come un chirurgo non può lasciare aperta una ferita in un paziente, così il chemioterapista non può lasciare il paziente senza un controllo degli effetti collaterali indotti dalla chemioterapia. Né gli alti costi né altre ragioni lo giustificherebbero. Però il trattamento dell'anemia indotta da chemioterapia non significa automaticamente un'immediata somministrazione di eritropoietina. Nel breve termine un atteggiamento di vigilante attesa può essere utile. Inoltre l'uso di ESPs al di fuori delle linee-guida esistenti dovrebbe essere preso in considerazione solo nell'ambito di studi clinici ben programmati e attentamente monitorati con un'accurata tutela etica per i nostri pazienti. In ogni caso il trattamento dell'anemia adattato al singolo paziente deve essere programmato al letto del paziente stesso da un oncologo medico esperto che tenga conto delle preferenze e delle convinzioni del paziente. Altrimenti ci troveremo a trattare l'anemia ma non il paziente. Eur. J. Oncol., 11 (4), 225-235, 2006

Parole chiave: **anemia, cancro, cure palliative**

Introduction

There are many data, opinions and speculations about the relation between haemoglobin level, physical strength and quality of life. The discussion on such relations includes quite different fields of our life, such as sport or medical care and concerns topics, such as doping during the last Olympic Games or the quality of life of cancer patients. In the field of doping obviously no doubt exists that higher haemoglobin levels increase physical strength. Connes *et al* [1] reported faster oxygen uptake kinetics at the onset of submaximal cycling exercise following 4 weeks of recombinant human erythropoietin (r-HuEPO) treatment, which contributed both to an acceleration of the dynamic response of pulmonary O_2 uptake to submaximal exercise and to an increase in maximal exercise capacity.

In the field of palliative care the situation is less clear. After early papers reporting that the level of haemoglobin in anaemic cancer patients correlates positively with

quality of life[2-4], Cella *et al*[5] strongly recommended "the use of erythropoietic agents in anemic cancer patients as a means of raising their haemoglobin levels and consequently improving their quality of life". Anaemia was defined as a "a multi-symptom syndrome with fatigue being the primary symptom" characterized by a "haemoglobin level of <12 g/dl". However, other researchers are much less optimistic. Already in 2002 Holzner *et al*[6] concluded that, despite significant correlations, their results indicated that haemoglobin values only partially explain subjectively experienced fatigue and worsening quality of life in cancer patients. After their excellent study, Munch *et al*[7] suggested definitively that anaemia is not one of the major contributors to fatigue in patients with cancer receiving palliative care.

The reasons for the differences between sport and palliative care are simple. In sport we can measure the physical strength and its relation with blood haemoglobin. Quality of life is not so easy to measure and, therefore, it is difficult to quantify the relation between haemoglobin and quality of life. Moreover, there are numerous confounding factors which influence the quality of life of advanced cancer patients which can create bias.

The objective of this paper is to use better the available scientific data for the actual practice of management of advanced cancer patients. The number of these patients is growing worldwide. In the industrialized world the part of the population older than 65 with high cancer risk will have doubled by 2025, and double will also be the number of patients dying from cancer in the developing countries[8-11]. This characterizes both the burden of suffering from advanced cancer and also the market for erythropoiesis stimulating proteins (ESPs). In 2001 ESPs ranked fifth in terms of total out-of-hospital expenditures on drugs by the Italian health service, accounting for 209 million Euros, and according to the IMS (Intercontinental Marketing Services) World Review they ranked seventh in global sales figures for 2003 at the figure of $10.1 billion[12]. There is no doubt that we are obliged to find a cost-effective strategy for advanced cancer care and this includes evidence-based positions regarding anaemia and the use of ESPs.

To discuss the subject adequately, the following questions have to be considered:

- what does anaemia mean in advanced cancer patients?
- how frequent is anaemia in advanced cancer patients?
- what does anaemia mean in comparison to other symptoms of advanced cancer?
- what does palliative care mean for advanced cancer patients?
- how should we treat anaemia in advanced cancer patients?

The definition of anaemia in advanced cancer patients

Traditionally, anaemia is considered as a laboratory finding (i.e. haemoglobin < 2 SD below normal for the population group being studied) for which an explanation should be sought, rather than a diagnosis. A minimal evaluation should include a review of the mean corpuscular volume, the reticulocyte count, the morphology of the peripheral smear, and the determination of the platelet count, leucocyte count and differential count. According to the WHO criteria, anaemia is defined as a haemoglobin concentration below 12 g/dl in women and 13 g/dl in man. However, most patients tolerate a haemoglobin level of 10 g/dl. Because cardiac output begins to increase as the haemoglobin drops below 10 g/dl, patients with cardiopulmonary, renal, hepatic or cerebral disease should be maintained at or above this level. In clinical routine, patients are usually considered for treatment when their haemoglobin level decreases to 8 g/dl or less[13].

However, this traditional definition needs attention with respect to the intensive research in this field during the last decade. Under the key words "anaemia in advanced cancer", between 2000 and 2005 more than 1500 Medline registered papers were published. Cancer-related anaemia has been described as a cytokine-mediated disorder resulting from complex interactions between tumour cells and the immune system. Overexpression of certain inflammatory cytokines results in shortened survival of red blood cells, suppression of erythroid progenitor cells, impaired iron utilization, and inadequate erythropoietin production[14]. However, as is well known, numerous other factors may also contribute to the development of low haemoglobin levels in cancer patients[15]. Events such as the probability of subacute bleeding should never be underestimated. Treating anaemia in cancer patients always needs to start with a careful differential diagnosis, both in routine work and in clinical studies. Unfortunately, in some clinical trials on anaemia in cancer, there is no adequate classification and grading of the anaemia reported.

Advanced cancer patients are mostly older people. Therefore a view on the situation with respect to the definition of anaemia in older patients is basic for our further consideration. In recent years, there has been an intensive discussion about anaemia in the elderly, mostly associated with the use of ESPs. In 2005 the American Society of Hematology reported, under the title "Anemia in the elderly: a public health crisis in hematology", that 11.0%

of US men and 10.2% US women were anaemic[16]. To investigate the association between haemoglobin concentration and cause-specific mortality in older persons in more detail, Izaks *et al*[17] conducted a community-based study from 1986 to 1996. Reporting on 1016 eligible community residents, they concluded that anaemia, as defined by the WHO criteria, was associated with an increased mortality risk in persons aged 85 years and older and concluded that a low haemoglobin concentration at old age signifies disease. With a very careful population-based study Nilson *et al*[18] came to a different conclusion. A representative population sample, comprising 30% of all 70-year old subjects in a Swedish city with 420,000 inhabitants, was followed at 1-5 year intervals for 18 years, as part of a longitudinal population study. Age-related changes in haemoglobin level were calculated after the exclusion of non-healthy probands and by multivariate analyses in the total study group. Mean haemoglobin level declined between the ages of 70 and 88, from 14.9 to 13.8 g/dl in men and from 13.9 to 13.5 g/dl in women. Epidemiological decision limits for anaemia declined for men from 12.8 to 11.6 g/dl and for women from 11.8 to 11.4 g/dl. Anaemia, thus defined, occurred in 3.2 to 9.7% of subjects, whereas 28.3% of the 88-year-old men had anaemia according to the WHO definition. Altogether, there was a significant age-related decline in haemoglobin levels from age 70 to 88 among healthy men and a less pronounced decline among women. The authors concluded that the study results justified the use of lower epidemiological decision limits for anaemia of about 11.5 g/dl for both men and women from the age of 80-82.

At the moment, it is still an open question whether and which haemoglobin concentration is associated with increased mortality in older persons. As Olde Rikkert[19] correctly noted, a wide-scale application of haemoglobin values for a full investigation of the causes of anaemia in clinical practice requires data on the effectiveness in terms of a net increase in quality of life at acceptable costs. At present there are no evidence-based haemoglobin limits for the elderly, because such data are lacking. As a pragmatic way out, the WHO limits can be taken for a simple and non-invasive biochemical analysis of anaemia, but individual considerations, taking into account co-morbidity, life expectation and patients' preferences, are necessary for further diagnostic investigations.

The clinical manifestations and severity of anaemia vary considerably among individual patients. Moderate anaemia can typically cause signs and symptoms such as headache, palpitations, tachycardia and shortness of breath[20]. The grading of anaemia according to the US National Cancer Institute classification[21] is certainly helpful:

- grade 0 12-16 g/dl for women and 14-18 g/dl for men without clinical symptoms,
- grade 1 > 10 g/dl with mild clinical symptoms,
- grade 2 8-10 g/dl with moderate clinical symptoms,
- grade 3 6.5-7.9 g/dl with serious-severe clinical symptoms,
- grade 4 < 6.5 g/dl with life-threatening symptoms.

If we use the word anaemia, we should in any case clearly describe what we mean. It is not correct to attribute the anaemia of cancer patients automatically to the malignancy. Patients recruited for a clinical study on anaemia should be characterized by haemoglobin count, classification of anaemia and grading. Terms like "need for transfusion" as patients' characteristics or as an endpoint for clinical studies are not sufficient, so long as no standards for the need of transfusion are defined. However, it is not easy to set up such standards.

How frequent is anaemia in advanced cancer patients?

In the last decade there has been a remarkable interest, and a growing number of publications, on anaemia and fatigue in cancer patients (Table 1). The question is why there has been such an interest. Is anaemia indeed "the most common haematological abnormality encountered by cancer patients and these regard fatigue as having greater negative impact on their daily lives than many other cancer- or treatment-related complications, with important emotional and mental consequences including lack of self-motivation, sadness, frustration and mental exhaustion?"[22] Is anaemia indeed "recognised as an independent predictor of poor prognosis in cancer patients?"[22] Is anaemia one of the main prognostic factors of loco-regional recurrence in head and neck cancer?[23] Or was this remarkable interest for anaemia and fatigue in part due to the wave of enthusiasm which came about after the first production of erythropoietin? Were there marketing or other interests behind this enthusiasm? To give an

Table 1 - Medline registered publications on anaemia in advanced cancer and related key words

Key word	Publications 1996-2001	Publications 2001-2006	Increase of papers
Anaemia and advanced cancer	167	309	+85%
Anaemia and cancer chemotherapy	1359	2127	+57%
Fatigue	8030	11364	+42%

answer to these questions is not easy, given the problems of definition, as shown above. One thing which we can do is to find out how high the prevalence of anaemia is in the different categories of cancer patients and what rôle anaemia plays in comparison to other symptoms of advanced cancer.

The European Cancer Anaemia Survey (ECAS) has provided comprehensive, prospectively collected data on the incidence and prevalence of anaemia among cancer patients. ECAS enrolled over 15,000 treated and untreated patients with various malignancies from cancer centres in 24 European countries and followed them for 6 months. The analysis of the ECAS data revealed that 39% of the total cancer patient population was anaemic (haemoglobin < 12 g/dl) at enrollment, although the rate varied according to tumour type, disease status, and cancer treatment[14]. A comparable study is available for Australia. Seshadri *et al*[24] performed a "snapshot" on anaemia in 694 patients recruited from outpatient oncology clinics in 24 hospitals in 5 Australian states. The results were similar. Prevalence of anaemia (<12 g/dl) at enrollment was 35%.

A detailed consideration of the prevalence of anaemia in advanced cancer patients has to differentiate between at least two groups of patients: those undergoing antineoplastic chemotherapy and/or radiotherapy and those receiving symptomatic treatment alone. The two groups have a different pathogenesis of anaemia, are subject to different clinical and ethical rules, and the anaemia varies with duration of treatment. Treatment-induced anaemia is a medically induced temporary event; the anaemia of end-of-life patients is a part of their end-of-life situation.

Everybody who has practised cancer chemotherapy over the last 20 years will agree with the opinion that better control of chemotherapy side effects is the most evident progress in antineoplastic drug treatment. Whether the often reported small increase of remission and survival after anticancer drug treatment is always a progress or sometimes only a business statistic is certainly a justified question. However, as we see every day, the progress in the control of nausea and vomiting, leucopoenia and anaemia reduces human suffering remarkably. For many years we believed that we could increase the antineoplastic drug dose unlimitedly and would thus have had much more and much longer remissions. However, high-dose chemotherapy is limited in its utility because dose-limiting toxicities to organs other than bone marrow may emerge.

The ECAS analysis of patients who were not anaemic at enrollment and had started cancer treatment during the survey, showed that those undergoing chemotherapy alone had an incidence of anaemia of 42%, while those receiving chemotherapy in combination with radiotherapy had an incidence of anaemia of 63%. Again, the Australian results are similar. Patients who received radiotherapy either in combination or concomitant with chemotherapy were more likely to have anaemia (73%) than those receiving chemotherapy alone (58%). Of all chemotherapy patients not anaemic at enrollment, 23% developed anaemia by the second monthly follow-up. Doubtless the probability of a chemotherapy-related anaemia depends on the regimen used. As Kosmidis and Krzakowski[25] reported, the prevalence of anaemia in platinum-treated patients was increasing from 23.5% at cycle 1 to 77.3% at cycle 6, with corresponding values for non-platinum-treated patients of 32.9% and 57.7%. In summary, there is no doubt that anaemia is a frequent chemotherapy complication. Unfortunately, even here, most available studies do not report grading and classification of the "anaemia" during chemotherapy. This would be helpful to find out patient-tailored treatment strategies.

The other group of patients are those receiving only symptomatic treatment. While data exist on the prevalence of anaemia in defined groups of cancer patients, information on palliative care patients is limited. Compared to actively treated cancer patients, for whom anaemia treatment has been demonstrated to improve the quality of life and to alleviate symptoms, studies of treatment outcomes in palliative care patients are limited. As shown in Table 2, anaemia, according to the WHO criteria, was found in about 50% of all patients. Anaemia with clinical consequences for quality of life (8-10 g/dl) has been reported in our studies and in those of other authors for about 15% of patients.

Table 2 - The haemoglobin level of advanced cancer patients

Patients		Chemotherapy/	Haemoglobin		Author
N.	Characteristics	post-chemotherapy?	<WHO (%)	<8 g/dl (%)	
105	Advanced cancer	?	77/68	-	Dunn *et al*[26]
147	Advanced cancer	?	56	15	Munch *et al*[7]
41,389	Advanced cancer	Mixed	50	15	ANT
310	Advanced cancer	No chemotherapy	-	10	ANT
15,000	All types	Mixed	39	-	ECAS
694	All types	Mixed	35	-	Seshadri *et al*[24]

Our own experience goes back to the 1980s. Between 1985 and June 2003, altogether 41,389 patients, frequently affected by anaemia, were admitted to the hospital-at-home programme of ANT Italia. Fifty percent of our patients showed haemoglobin levels of ≤12 g/dl and 15% ≤8 g/dl. In the following years the percentage of anaemic patients did not show great differences: in 2003-2004 we analysed 285 new admitted cases and observed 41 patients (14.4%) with a haemoglobin level of less than 10 g/dl[27]. The most recent analysis is available for 2005, when 1,305 new patients entered the ANT hospice-at-home programme and a total number of 2,214 patients received palliative home care: 11.3% of the patients showed a serious to moderate anaemia with haemoglobin levels of <10 g/dl.

Common symptoms in advanced cancer: the rôle of anaemia

In the recent handbooks of advanced cancer care there is no special consideration of anaemia[28,29]. Other symptoms have priority. Obviously, many medical oncologists do not consider anaemia as a major problem in the daily management of advanced cancer patients. Educational events on palliative care are focussed mainly on general problems, such as pain, cachexia, dyspnoea and tumour specific symptoms such as occlusion, ulceration, and bone lesions[30]. On the other hand, experienced haematologists conclude that anaemia can be a "debilitating problem for cancer patients that negatively influences their quality of life and worsens their prognosis"[20]. The European Organisation for Research and Treatment of Cancer (EORTC) calls anaemia "a frequent finding in cancer patients which should be careful assessed".

In two observational studies we have analysed the prevalence of different symptoms in advanced cancer patients admitted to the ANT Italia hospital/hospice-at-home programme and the CANSUPPORT India home-care programme respectively. As shown in Table 3, the spectrum of symptoms is largely dependent on the socio-economical circumstances in which the patients live. Pain was on the top of the list in both groups and pain is indeed, worldwide, the great horror for advanced cancer patients. Due to the high percentage of incurable lung cancer patients admitted in any programme for palliative cancer care, dyspnoea comes second place and anorexia/cachexia is the third greatest problem. Anaemia follows far behind.

To describe the situation in still more detail, Table 4 presents an analysis of 310 advanced cancer patients admitted to the ANT Italia programme on suspicion of bone metastases. These patients are likely to have a high prevalence of anaemia due to frequently reduced bone marrow capacity. As shown, patients were suffering, first of all, from immobility and pain (73.2% and 70.6%). Other symptoms with a high prevalence were anorexia and dyspnoea. Anaemia (haemoglobin ≤ 10 g/dl) was detected in 10% of cases.

The prevalence of fatigue, which we have not listed, is given as 60-90% in several studies[29, 31]. Barnes and Bruera[32] call fatigue "the most common symptom in patients with advanced cancer". In another paper, fatigue was described as "so debilitating that 12% of patients feel their quality of life so reduced that they do not wish to continue living"[22]. This is surprising considering the fact that "fatigue" as a term was more or less unknown in advanced cancer care twenty years ago (32 publications 1980-1985). The enthusiasm for using this term now is enormous (461 publications 2000-2005). We did not use the term "fatigue" in our analysis because the definition of "fatigue" is weak. Barnes and Bruera define it as a "subjective sensation with physical, cognitive and affective modes of expression". The aetiology is often unclear and multiple potential aetiologic factors for fatigue may

Table 3 - Symptom profile of advanced cancer patients in industrialized and developing countries

Symptom	ANT Bologna 250 admitted patients (%)	CANSUPPORT New Delhi 334 admitted patients (%)
Pain	36	88
Dyspnoea	27	34
Weakness	22	82
Nausea	12	47
Anorexia	4	61

Table 4 - Anaemia in palliative care patients with high probability of bone metastases

N. of admitted patients	310
breast cancers	47%
lung cancers	33%
prostate cancers	11%
myeloma	2%
other cancers	7%
N. of patients dying within the first 2 weeks	48
N. of patients with confirmed bone metastases	219
Median age	73 years
Median duration of assistance	60 days
Symptoms at admission	
immobility	73.2%
pain	70.6%
anorexia	69.0%
dyspnoea	60.0%
anaemia (haemoglobin ≤10 g/dl)	10.0%

coexist. There are many fatigue assessment tools, but we agree with Rao and Cohen[33] who underlined that they are all subjective in nature and that none has been tested in elderly patients. As a matter of fact, potential factors contributing to "fatigue", such as the tumour itself, cachexia, pain and depression[29], can be assessed objectively much better as a separate symptom than in the mixture with others. Therefore, it seems to be justified to ask what advantage there is for suffering patients to introduce the much more subjective term "fatigue" in their management. This question could be one of the reasons for some objections of experienced clinicians with respect to the new catchword in oncology, "fatigue". Working with the bitter reality of advanced and dying cancer patients, it is necessary to make evidence-based, objective decisions. In this situation it could be a risk to introduce an only subjectively defined symptom, such as fatigue, even if it is called "the window to the brain"[34]. Whether somebody uses "fatigue" as a subjective symptom with the risk of confusing patients and opening the door for not always evidence-based interventions has to be decided by the clinicians themselves.

In numerous papers the association between anaemia and fatigue was discussed and has been seen as the key to improve patients' quality of life. Thanks to Munch's paper[7] we now know well that anaemia is not one of the major contributors to fatigue in patients receiving palliative care. Anaemia with mild to moderate clinical consequences having a prevalence in 10-20% of patients is a much less frequent symptom of advanced cancer than pain, dyspnoea and cachexia.

What does palliative care mean for advanced cancer patients?

To write on anaemia in palliative care means to understand what anaemia is. This was discussed in the first part of this paper. It also means to understand what palliative care is for advanced cancer patients. Palliative care is defined as the combination of active and compassionate therapies intended to comfort and support individuals and families who are living with or dying from a progressive life-threatening illness[35]. A good quality of life, for about 70% of advanced cancer patients, means to be treated at home and to die there. Therefore, we can offer support best by bringing palliative care to the patient and not the patient to palliative care[10].

Palliative care starts when a cure is no longer possible. This is simple to say but not always easy to do. At least three studies have shown that even maximal accuracy of prognosis will not exclude risk of errors in the large majority of patients[36-38]. Our own data show that long-term experience can improve the accuracy of the clinical estimation of life expectancy. However, the data also underline the difficulties of prognosis in advanced cancer even for doctors well-trained in end-of-life care. Two hundred and sixty-nine patients were included in our study. In only 33% of patients was the prediction of the individual life expectancy correct: 39% survived less than estimated and 28% survived longer[39].

The tightrope walk between cure and palliation can become an ethical dilemma because the decision to palliate requires a change in treatment strategy. Palliative care in cancer is concerned with people who are likely to die in the near future from an uncontrolled malignancy. It is the quality of life, rather than the length of life, that is important. Of course, one can treat advanced cancer patients with a haemoglobin level of <12 g/dl with erythropoietin, assuming that the number of eventually necessary blood transfusions will decrease. However, palliative care follows specific rules. Knowing when it is " worthwhile" to palliate a symptom means being able to estimate the possible burden of side effects and the time delay until the treatment works compared with the actual prognosis, as well as the economic consequences for the patient and the clinic. Providing patients with palliative care is a challenge for the care-giving staff, both from the professional and the psychological point of view. Functional quality of life and symptom scores are significantly worse for long-term chemotherapy users as compared to non-users. Nevertheless, analysing 793 patients with advanced cancer, assisted in the centre of Bologna, Italy, we have seen that 22.7% of the patients received cancer chemotherapy even during the last 30 days of their life (Mutri *et al*, unpublished data).

Another problem is how to carry out palliative care. In spite of many discussions and recommendations, the practice of palliative care is not always in complete accordance with the patients' needs and wishes. Sometimes, models for palliative care are developed that take into account economical, organisational and political aspects rather than the needs of patients. This should be avoided. Only the patient should be allowed to decide how he wishes to traverse, without losing his dignity, the long and difficult path leading to the end of his life, in "eubiosia" as it has been called by Pannuti[40,41].

Of course each patient has his individual feelings and needs. Sometime these are far from our expectations, organisational models and therapeutic approaches. There are differences between patients living in developed and developing countries with regard to the resources available for people dying of cancer, but also with regard to their experiences of illness. Palliative care should be

Table 5 - What incurable cancer patients fear

Separation from family and friends
Pain
Loss of personality
Loss of dignity of life
Emergency situations
Admission to the hospital

Table 6 - The top problems in palliative cancer care

Industrialized world
70% of patients want to be at home but this is realized with decreasing tendency for only 20-30%
Over-treatment with antineoplastic drugs
Patients feel unsure with respect to last minute treatment (last will)
Developing world
Insufficient pain relief for the majority of patients because morphine is not available
Insufficient medical care
Insufficient social support

strictly patient-tailored. Nevertheless, looking at the available data, we get some basic information about patients' emotions and their met and unmet needs, at least in the industrialized world. This information helps us to find out the correct strategy and the best models for palliative care. Table 5 shows what advanced cancer patients are afraid of.

Coming back to anaemia, we should keep in mind that certainly a low haemoglobin level needs control and in some cases it needs treatment. However we should understand that we have enormous unmet needs in palliative care that have much higher priority. To hope that the treatment of anaemia, with the objective of controlling "fatigue", will improve a patient's quality of life, on principle, is a concept valid only for a minority of patients. Table 6 shows what problems exist and what is the main reason for human suffering.

Treating anaemia in the palliative care of cancer patients

Rice titled her excellent review in Cancer World "Treating anemia: damned if you do, damned if you do not."[12] This title describes the situation well. After a period of great enthusiasm in which any patient with a haemoglobin value of less than 12 g/dl was treated with erythropoietin[5], there is now considerable confusion. It seemed fairly obvious that a low haemoglobin count was associated with poor outcomes in cancer patients and that increasing the haemoglobin could significantly improve quality of life. However, that was until the publication of new data that appeared to show that patients taking ESPs had worse outcomes in terms of survival. Moreover, the paper of Munch *et al*[7] showed clearly that anaemia, in contrast to numerous opposite statements, is not one of the major contributors to "fatigue" in patients receiving palliative care.

Several observations[12] have also generated the hypothesis that strategies to diminish cancer-related anaemia might not only alleviate anaemia-related symptoms but also modify tumour response and overall survival. This hypothesis is based on the assumption that tumour-associated anaemia can contribute to the development of hypoxia, which can impair the effectiveness of radiotherapy and oxygen-dependent chemotherapies[20]. On the other hand, there is some pre-clinical evidence that some cancers possess erythropoietin receptors and that these cells may proliferate in response to erythropoietin use. At the moment it remains unclear whether erythropoietin affects tumour growth and survival and this area requires further investigation.

Nevertheless, the situation seems to be less unclear than some people believe. Unchanged, there is no doubt that anaemia can be a serious problem for cancer patients. In order to manage anaemia in advanced cancer patients correctly we have to differentiate between chemo/radiotherapy-induced anaemia and anaemia in patients receiving only symptomatic treatment.

Chemotherapy induced-anaemia needs treatment in any case. Just as a surgeon cannot leave the patient without closing the wound, the chemotherapist cannot leave the patient without control of chemotherapy-induced side effects. Neither high costs nor any other reasons could justify this. An argument against the use of ESPs could be that ESPs may be tumour-inducing. Moreover, data from clinical trials suggest that erythropoietin increases the risk of thromboembolic complications. These risks should not be overestimated: even many antineoplastic agents are tumour-inducing and also pain killers, at higher doses, have side effects. I have personally seen numerous patients with bladder cancer which was induced by intensive treatment with alkylating agents for breast or ovarian cancer. What we have to investigate is how long there is a medical and professional justification to tolerate lower haemoglobin levels before starting chemotherapy. This is a medical and ethical challenge. Therefore, treatment of chemotherapy-induced anaemia does not automatically mean the immediate administration of erythropoeitin. A short-term policy of wait and see can be useful. Moreover, the use of ESPs outside the

existing guidelines should be considered only in the context of very well planned and carefully monitored clinical studies that implement strict ethical safeguards for our patients[12].

A totally different situation is that of symptomatic or end-of-life treatment. As shown above, control of anaemia is far behind other needs of the patients, and their quality of life should be improved first by giving them perfect pain relief. With respect to their anaemia an individualized treatment is advisable. Certainly Ludwig[12, 42] is correct in saying that "an old man with heart disease and mild anemia would benefit just from a small increase in haemoglobin level because he would have less angina. But a young person can tolerate a higher degree of anemia and treatment can start later".

The point is how to achieve this "small increase" quickly and without side effects. Unfortunately, there is a noticeable lack of evidence-based treatment, in the strict sense of randomised clinical trials, in the palliative care of anaemia. Certainly not all patients are appropriate candidates for ESPs treatment. The disadvantages of ESPs include the 4-8 week delay before maximum benefit is achieved, possible side effects, their efficacy in only some patients, and their costs[43]. Monti *et al*[44] studied 246 terminally ill patients admitted for end-of-life care in a palliative care unit (60% died during the same recovery, a median of 49 days after transfusion) and reported improved subjective well-being after blood transfusion in 51.4% of cases without significant relationship to pre-transfusion haemoglobin levels or performance status. The influence of blood transfusion was not related to the severity of dyspnoea or fatigue. Careful consideration of both the advantages and disadvantages of the main choices of treatment for anaemia (transfusion and ESPs) will help to avoid ineffective and costly interventions[42].

The American Society of Clinical Oncology /American Society of Hematology guidelines for the use of erythropoietin are an useful recommendation in finding a necessarily individual strategy for anaemia management in incurable cancer patients. Nevertheless, it seems that the rôle of blood transfusion as the most simple approach is still underestimated and sometimes too negatively evaluated. Transfusion is a rational and often very efficient approach. As reported already in 2004, between 1985 and June 2003 altogether 41,389 patients, frequently affected by anaemia, were admitted to the hospital-at-home programme of ANT Italia[41]. Fifty percent of our patients showed haemoglobin levels of ≤ 12 g/dl and 15% of ≤ 8 g/dl. In the case of anaemia-related symptoms, patients were treated by blood transfusion. There was no use of erythropoietin. We studied in detail, from 2000 to 2002, the effect of blood transfusion in symptom control in 112 advanced cancer patients presenting with a mean haemoglobin value of 7.1 g/dl (95% CI 7.0-7.3) and receiving a median number of 3.7 (95% CI 3.0-4.4) units of blood. All transfusions were administered at patients' homes. The mean difference between the baseline haemoglobin value and the value after the first unit of blood was + 1.75 g/dl (95% CI 1.61-1.95), and it was + 1.43 g/dl (95% CI 1.18-1.68) after the second unit. Control of symptoms was achieved for a mean duration of response of 18.5 days (95% CI 14.8-22.2) after each transfusion. The median survival of patients was 3 months (95% CI 2.43-4.93). One week after transfusion, there was excellent control of symptoms, thus improving quality of life[27].

We have concluded that transfusion does offer prompt symptom relief and improvement of well-being in anaemic patients with terminal malignant disease. In the Medline-registered literature no data exist that show that erythropoietic agents offer comparable results with respect to response rate and time to onset and duration of response. Based on 1,473 home blood transfusions performed in the city of Bologna between 25th August 1997 and 8th August 2003, we did not experience many real risks, such as infections and haemolytic reactions, which often are mentioned as reasons to avoid transfusion. There was no case of serious haemolytic reaction. Only slight immunologically mediated reactions such as flushing and itching were observed in 5.9% of patients. Concerning the risks of virus infections, we should remember that these are drastically minimized by recent technologies of blood preparation.

Conclusions

In summary, it is not too difficult to give some advice for the management of anaemia in palliative care for cancer .

1) It is imperative to start both routine treatment or scientific studies with a careful differential diagnosis of the anaemia.
2) Patients receiving chemo-radiotherapy have a right to be treated quickly and effectively if their haemoglobin is significantly decreased after antineoplastic treatment.
3) In palliative care, it is imperative that treatment is strictly individualized to meet the varying clinical, psychological, economical and ethical needs of the heterogeneous group of anaemic advanced cancer patients receiving symptomatic care.
4) Existing guidelines for the use of ESPs[12, 20] are important steps forward, but in the light of unex-

pected new results we have still to better define the strategic use of blood transfusion and of erythropoietic agents by qualified clinical studies.

5) The goal of anaemia treatment, tailored to an individual cancer patient, has to be made at the bedside by an experienced medical oncologist in conjunction with the patient's preferences and values[45]. Otherwise, we shall be treating the anaemia but not the patient.

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Steroid myopathy in cancer patients

Miopatia da steroidi nei pazienti oncologici

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Summary

Steroids have pleiotropic effects in almost all tissues in the body, and they are beneficial in relieving a broad range of cancer symptoms. However, muscle weakness and atrophy are a debilitating side effect of steroid treatment that may occur in as many as two thirds of hospitalized cancer patients. Endogenous glucocorticoids are a decisive factor for myopathy due to fasting, diabetes, acidosis, and sepsis. Their effects on protein turnover, muscle fibre excitability, and muscle fibre number are all thought to contribute to the development of muscle atrophy. Discerning a precise rôle for steroids is difficult because of the complex pathophysiology of myopathy and its occurrence in the context of serious illness. Because glucocorticoids are a mainstay for symptom relief in patients with cancer, minimizing the risk of myopathy may be preferable to not treating with these agents. This review will discuss the current understanding of the pathophysiology of steroid myopathy, the risk factors for the development of this complication in cancer patients, and the therapeutic options for patients at risk. Eur. J. Oncol., 11 (4), 237-243, 2006

Key words: **steroid myopathy, muscle atrophy, corticosteroids, dexamethasone, methylprednisolone**

Riassunto

Gli steroidi hanno molteplici effetti in quasi tutti i tessuti del corpo, e sono utili ad alleviare tutta una serie di sintomi dei tumori. Però, la debolezza e l'atrofia muscolare sono un effetto collaterale debilitante del trattamento con steroidi, che può verificarsi nei due terzi dei pazienti oncologici ospedalizzati. I glucocorticoidi endogeni sono determinanti per la miopatia conseguente a digiuno, diabete, acidosi e sepsi. Si pensa che tutti i loro effetti sul ricambio proteico, sull'eccitabilità delle fibre muscolari e sul numero di fibre muscolari contribuiscano allo sviluppo dell'atrofia muscolare. Individuare un ruolo preciso per gli steroidi è difficile a causa della complessa fisiopatologia della miopatia e della sua insorgenza nel contesto di una malattia grave. Poiché i glucocorticoidi sono un fondamento nel sollievo dei sintomi nei pazienti oncologici, ridurre al minimo il rischio di miopatia può essere preferibile a non usare questi agenti. Questo studio esamina le attuali conoscenze sulla fisiopatologia della miopatia da steroidi, i fattori di rischio per lo sviluppo di questa complicanza nei pazienti oncologici e le opzioni terapeutiche per i pazienti a rischio. Eur. J. Oncol., 11 (4), 237-243, 2006

Parole chiave: **miopatia da steroidi, atrofia muscolare, corticosteroidi, desametasone, metilprednisolone**

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Introduction

Weakness due to atrophy of skeletal muscles including respiratory muscles can result from a variety of conditions that afflict patients with cancer. Cachexia, anorexia, chemotherapy, radiation, confinement to bed, and age, in addition to direct effects of tumour growth, induce a catabolic state that may contribute to muscle loss[1, 2]. The involvement of endogenous glucocorticoids in muscle atrophy was first described in 1932 by Cushing in patients with pituitary tumours[3, 4]. Subsequently, widespread use of exogenous steroids for a variety of conditions has led to the recognition that these agents can induce muscle weakness and atrophy. Glucocorticoids are used for the management of cancer symptoms including pain, cachexia, and anorexia, as well as nausea and vomiting associated with antineoplastic treatment. Unfortunately, these conditions may predispose individuals to steroid myopathy, which adds to the symptom burden in patients with cancer.

Chronic steroid myopathy typically occurs after weeks or months of treatment with low to moderate doses (Table 1)[5]. The onset is frequently insidious and does not result in abnormal levels of serum muscle enzymes. Symmetrical loss of muscle strength begins in the proximal extremities and progresses to include the shoulder girdle and respiratory muscles. Myopathy may be accompanied by other Cushingoid symptoms including moon facies, centripetal obesity, and buffalo hump[3]. Histologic examination of biopsies may reveal variation in fibre size and centralization of the nuclei, but defining characteristics of steroid myopathy are not observed[5]. Histochemical staining reveals a selective atrophy of the type II fibres, the fibres with high glycolytic and low oxidative capacity[5].

The acute form of steroid myopathy has been described following intravenous administration of high-dose steroids in critically ill patients, particularly in the setting of polypharmacy. The incidence may be increased in patients receiving aminoglycosides[6] and in critically ill patients receiving neuromuscular blocking agents (NMBAs) to facilitate assisted breathing[5, 7, 8]. Unlike chronic steroid myopathy, the acute condition is associated with diagnostic features of rhabdomyolysis, including increased serum levels of creatinine phosphokinase and abnormal spontaneous activity on electromyography. Biopsy typically shows histology consistent with scattered myotubular necrosis[5].

Table 1 - Characteristics of chronic and acute steroid myopathy

Chronic myopathy
- Low and moderate doses of steroids
- Duration of weeks or months
- No change in serum muscle enzymes
- Non-specific histopathologic changes on biopsy
Acute myopathy
- High doses of steroids
- Co-administration of aminoglycosides or muscle relaxants
- Elevated serum muscle enzymes
- Abnormal spontaneous excitability on electromyography
- Histologic evidence of necrosis

Although as many as two thirds of hospitalized patients with cancer receive corticosteroids[3], remarkably few data are available to define the impact of steroid myopathy on morbidity and mortality in this vulnerable population. The findings of one study of 15 neuro-oncology patients receiving dexamethasone suggested that steroid myopathy in patients with cancer is common and debilitating. In this study, myopathy developed within 2 to 3 weeks of treatment initiation in 9 patients (60%). Weakness was severe and led to limited activities of daily living for 6 patients, more than half of those who had become myopathic[3]. In these patients, the incidence of myopathy was associated with cumulative exposure to steroids rather than with the average daily dose or the duration of treatment *per se*[3].

Experimental evidence indicates that steroid treatment can result in diaphragmatic atrophy and weakness[3, 9]. Involvement of respiratory muscles has been reported in patients with both chronic and acute forms of steroid myopathy and is a consequence of particular concern[3,9-13]. Moreover, Batchelor *et al* [3] reported that 4 out of 9 patients with cancer who developed steroid myopathy also developed symptomatic dyspnoea. Reduced expiratory pressure was measured in 10 out of 15 steroid-treated cancer patients, including 2 individuals who did not demonstrate clinical myopathy of the skeletal muscles[3]. Another small study found respiratory involvement in 2 out of 23 myopathic patients[14]. This reduction in respiratory function can add to patient discomfort and disability.

Steroids have pleiotropic effects in almost all tissues of the body and they are beneficial in relieving a broad range of cancer symptoms. Few if any alternative treatments are currently available. Therefore, in most patients, minimizing the risk of myopathy is preferable to not treating with these agents. The present review will discuss the current understanding of the pathophysiology of steroid myopathy, the risk factors for the development of this complication in cancer patients, and the therapeutic options for patients at risk.

Pathophysiology of steroid myopathy

Elevated glucocorticoid levels have been shown to result in increased turnover of muscle protein, altered

electrical excitability of muscle fibres, and loss of muscle fibres. These steroid actions, alone or in combination, may account for the development of steroid myopathy.

Glucocorticoids elicit their effects largely through transcriptional regulation of gene expression. Once complexed to glucocorticoid receptors, these molecules can act directly as transcription factors, binding to glucocorticoid response elements (GREs) in the promoter regions of many genes. Their differential effects in specific cells and tissues may be further defined through the interaction of receptor-ligand complexes with other transcription factors including nuclear factor kappaB (NFkappaB), and numerous other types of coregulators.

In skeletal muscle, elevated levels of circulating glucocorticoids increase resistance to insulin-dependent glucose uptake, decrease protein synthesis, and increase protein degradation[15-18]. Endogenous levels of glucocorticoids are elevated in cachexia and conditions of muscle disuse and they are thought to play a rôle in myopathy in these settings.

Typically, drug-induced myopathy occurs in the context of serious illness and is likely to result from interactions of multiple factors. As a result, it is difficult to discern a specific rôle for steroids in the breakdown of skeletal muscle. Steroids appear to contribute to protein turnover in models of cachexia and are responsible for muscle atrophy in fasting[15, 19], diabetes[20], acidosis[21], and sepsis[22]. In contrast, endogenous steroids do not appear to be a decisive factor for the localized myopathy associated with muscle disuse[15].

To identify genes (termed atrogins) that are universally essential for muscle atrophy, gene expression in normal skeletal muscle was compared with gene expression in muscle atrophy due to starvation, diabetes, cancer, and renal failure. A total of 120 unique genes were identified as differentially expressed in all 4 conditions of muscle atrophy compared with normal tissue[23]. Expression of extracellular matrix proteins and those involved in adenosine triphosphate (ATP) production was down-regulated. Surprisingly, Lecker *et al* [23] did not find evidence of decreased expression of myofibrillar proteins.

In contrast, oxidative stress response genes were upregulated in this system, suggesting an important rôle of reactive oxygen species in muscle loss[23]. Generation of reactive oxygen species through increased oxidative stress occurs in myopathy and is associated with mitochondrial dysfunction[2, 24]. In cultured muscle cells, dexamethasone increased mitochondrial membrane potentials, increased the generation of reactive oxygen species, and increased apoptosis[25].

Consistent with increase in protein degradation occurring in myopathy, proteins involved in the Ub-proteasome degradation pathway were up-regulated in all 4 atrophy conditions[23]. Activation of NFkappaB typically accompanies increased activity of the Ub-proteasome degradation pathway through enhanced degradation of inhibitory protein IkappaB[15]. In turn, NFkappaB may induce atrophy by the transcriptional activation of ubiquination proteins[15]. Catabolic doses of corticosteroids have been shown to activate the ubiquitin pathway in rat skeletal muscle[26]. Paradoxically, glucocorticoid inhibition of NFkappaB activation of the Ub-proteasome pathway is thought to be responsible for some of the beneficial anti-inflammatory effects of steroids in the treatment of critical illness symptoms (fig. 1)[27, 28].

Two atrogins that were dramatically up-regulated contain glucocorticoid response elements: glutamine synthetase and metallothionein[23, 29, 30]. In catabolic states, glucocorticoid-dependent glutamine synthetase activity in muscle is increased to meet a greater demand for this aminoacid, predominantly in the liver, in lymphocytes, and in the kidney[23, 29, 31, 32]. Metallothionein, among the most strongly up-regulated genes in all four myopathic states, is known to protect DNA from reactive oxygen species through as yet unidentified mechanisms[23, 30, 33].

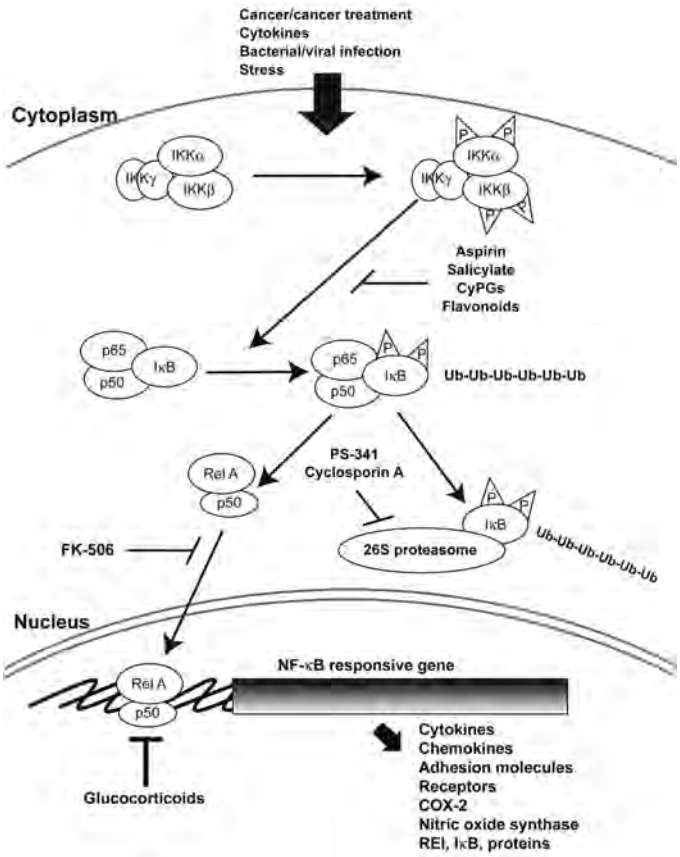

Fig. 1. Cachexia-induced NFkappaB pathway and the anti-inflammatory activity of glucocorticoids. Republished and adapted with permission from Yamamoto and Gaynor[28]

Insulin-like growth factor (IGF) binding protein, which regulates muscle response to IGF-1, also was dramatically down-regulated. However, the expression of insulin-like growth factor IGF-1 was unchanged. The IGF-1 gene is known to contain GREs, and the IGF-1 protein increases muscle protein synthesis[5, 34] and decreases protein degradation[5, 35, 36]. In addition, Kanda *et al*[5] found that IGF-1 prevented steroid-induced myopathy. This effect is thought to result from IGF-1 suppression of glutamine synthetase and skeletal muscle glutamine release.

Conversely, diaphragm muscles from rats treated with acute high-dose methylprednisolone and triamcinolone (80 mg/kg/day for 5 days) showed 44% and 69% reductions in levels of IGF-1 mRNA, respectively[37]. Levels of IGF-1 mRNA were unchanged in the diaphragms of rats that were underfed. In gastrocnemius muscle, IGF-1 mRNA was also significantly reduced with corticosteroid treatment and underfeeding. Similar patterns of gene expression were seen for IGF-2 mRNA. Dexamethasone has been shown to inhibit IGF-1 signal transduction through the phosphoinositol 3 pathway[5, 38]. Despite the strong negative correlation between IGF-1 activity and steroid myopathy, expression of genes for IGF-1 and downstream signalling molecules were not altered in skeletal muscle myopathy due to starvation, diabetes, cancer, or renal failure[23].

Other experiments have shown that the gene for myostatin, an important negative regulator of skeletal muscle mass, contains 7 putative GREs. Moreover, dexamethasone-induced myopathy is associated with dose-dependent increases in myostatin transcription[39]. Atrophy induced by dexamethasone (5 mg/kg/day for 3 days) treatment was associated with increased expression of cathepsin L in skeletal muscle, an effect that was partially prevented by co-administration of IGF-1 (3.5 mg/kg/day)[40].

Transcriptional effects of glucocorticoid on sodium channel isoforms have been postulated to explain the inexcitability of muscle fibres observed in myopathy[41]. Sodium channel fast inactivation in critical illness myopathy plays an important rôle in reduced electrical excitability, which may be exacerbated by treatment with steroids. A combination of high-dose glucocorticoids and denervation has been used to mimic critical illness myopathy in rats. In this model, denervated muscles exhibit reduced excitability in a small percentage of muscle fibres. Treatment of denervated fibres with glucocorticoids increases that percentage. Steroid-treated muscles express the embryonic $Na_v1.5$ isoform in addition to the adult skeletal muscle Na+ channel isoform. Rich and Pinter[41] have hypothesized that the increased percentage of inexcitable muscle fibres in the presence of high doses of glucocorticoids actually reflects the increased ratio of embryonic to adult sodium channels.

Myopathy in cancer

Experimental data suggest that several factors may increase the risk of developing steroid myopathy in patients with cancer. Antiproliferative treatments can impair metabolism, leading to a catabolic state even in healthy animals. In rat studies, a single peritoneal injection of cyclophosphamide (120 mg/kg), 5-fluorouracil (50 mg/kg), cisplatinum (5 mg/kg), or methotrexate (30 mg/kg) induced transient body weight loss, anorexia, and poor nitrogen balance[42]. Moreover, tumour load exacerbates the catabolic effects of chemotherapeutic agents. In these studies, drug-induced anorexia and nitrogen imbalances were more severe in tumour-bearing animals than in their healthy counterparts[42].

Cancer patients frequently experience cachexia and anorexia, independent of treatment-associated complications. Obviously, these states result in diminished nutritional status and compensatory catabolism. Also, in critically ill patients with cancer, a catabolic state produced by a combination of proinflammatory cytokines, decreased anabolic hormones (insulin and insulin-like growth factor), and increased catabolic hormones (cortisol, catecholamines, glucagon) results in critical illness myopathy[2]. This state is associated with increased protein degradation through the activation of ubiquitin-proteasomes and calpains – factors also involved in critical illness myopathy[2, 40]. Risk factors for critical illness myopathy include: multiorgan dysfunction syndrome, multiorgan failure, female gender, corticosteroid use, severe asthma, ionic abnormalities, malnutrition, and immobility.

Drug interactions

The risk of steroid myopathy has been described in critically ill patients who are treated with aminoglycosides[6] or muscle relaxants. The increased incidence of myopathy associated with NMBA was first observed in patients treated with steroids for severe asthma[7, 8]. In one study, patients who developed myopathy were found to have received significantly higher doses of vecuronium compared with patients receiving similar doses of glucocorticoids who did not develop myopathy[7, 43]. In a second retrospective study, the use of corticosteroids and an NMBA significantly increased the risk of developing myopathy regardless of whether the NMBA was a steroid or not[8]. Hanson *et al*[44] observed that patients sedated with

propofol in the absence of NMBAs developed steroid myopathy. Based on the lack of specificity of the paralyzing agent associated with myopathy, the authors suggested that muscles subjected to drug-induced paralysis become hypersensitive to corticosteroids rather than myopathy developing as a direct result of paralysis[44]. In addition, admission APACHE II score, rate of sepsis, and the total doses of steroids have been established as predisposing factors in patients treated for acute exacerbations of chronic obstructive pulmonary disease[45].

Reducing risk of steroid myopathy

Corticosteroids provide great benefit for multiple indications in cancer patients and, as a result, the choices for alternative therapy are limited. Several strategies can be used to reduce the risk of myopathy, although they are largely based on experimental rather than clinical evidence (Table 2). In patients who develop steroid myopathy, dose reduction or weaning will reverse muscle weakness. However, recovery can be prolonged, and may relate to the extent of type IIb fibre atrophy[46-48].

Fluorinated compounds (dexamethasone, triamcinolone, betamethasone) are associated with more extensive type IIb fibre atrophy than nonfluorinated compounds (prednisolone, methylprednisolone). In animal studies, triamcinolone has been shown to induce selective type IIb (fast-twitch) glycolytic-fibre atrophy, leading to deranged contractile properties of the diaphragm and atrophy of the respiratory muscles. In the same studies, although diaphragmatic contractile properties were altered by prednisolone, no histologic evidence of atrophy was apparent[9, 49]. Additionally, at equipotent anti-inflammatory doses, triamcinolone and prednisolone differentially affected the activity of enzymes involved in muscle carbohydrate utilization in rats. Body mass was reduced by 24% with triamcinolone treatment, compared with a 10% increase in body mass in those receiving prednisolone. Triamcinolone, but not methylprednisolone, induced activity of phosphofructose kinase, glycogen synthetase, and glycogen content in the tibialis anterior muscle[50]. These results suggest that nonfluorinated compounds may be preferable for treatment of patients at high risk of myopathy.

Table 2 - Reducing risks of steroid myopathy

- Avoid fluorinated glucocorticoids (dexamethasone, triamcinolone)
- Initiate therapy with low to moderate doses
- Alternate-day therapy is preferable to continuous therapy
- Avoid co-administration with muscle relaxants and aminoglycosides

However, Batchelor *et al*[3] found that in neuro-oncology patients, myopathy risk was increased by the cumulative steroid dose rather than the daily dose or duration of treatment. These findings suggest that starting patients on a low initial dose would be expected to extend the time before myopathy could become problematic.

Alternate-day therapy can be used in some settings to extend the treatment time before muscle atrophy occurs[51, 52]. This approach was tested in rats receiving methylprednisolone 1 mg/kg/day continuously, methylprednisolone 2 mg/kg every other day, or methylprednisolone 2 mg/kg/day in two 2-week bursts separated by 4 weeks of placebo[51]. Although diaphragmatic force generation was reduced in all 3 treatment groups, those receiving alternate-day treatment experienced less glycogenolytic activity than those receiving continuous therapy. The 2-week burst regimen decreased the contribution of type II fibres to total diaphragm muscle area. However, this regimen reduced creatinine kinase activity and beta-oxidation capacity in comparison to continuous treatment[51]. Alternate-day treatment with prednisolone has been shown to be effective in prolonging survival in patients with multiple myeloma[53].

Conclusion

To sum up, corticosteroids are widely used in cancer patients for multiple indications. However, development of muscle weakness is a debilitating side effect of corticosteroid use that may be more common than is generally assumed. Cancer treatments as well as direct tumour effects may predispose individuals with cancer to develop myopathy.

Myopathy is associated with substantial reductions in mobility and independence that reduce quality of life for these patients. Although the benefits of corticosteroids in patients with cancer, particularly those with advanced disease, may outweigh the disability resulting from myopathy, every precaution should be taken to reduce the risk of this disabling adverse effect. Risk reduction strategies include the avoidance of fluorinated glucocorticoids, the use of low or moderate doses whenever possible, and alternate-day dosing regimens.

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Il mesotelioma maligno in Emilia-Romagna: i dati del registro regionale

Malignant mesothelioma in the Emilia-Romagna Region of Italy: the data of the regional registry

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Riassunto

***Finalità*. I mesoteliomi maligni (MM) sono in aumento in Italia nonostante la più che decennale definitiva messa al bando dell'amianto. Il Registro Mesoteliomi (ReM) dell'Emilia-Romagna, aderente al Registro Nazionale Mesoteliomi, effettua la sorveglianza epidemiologica di questa patologia. Vengono presentati i dati raccolti nel periodo 1996-2006. *Materiali e metodi*. Vengono registrati i MM a sede pleurica ed extrapleurica (peritoneo, pericardio e vaginale del testicolo) incidenti nei residenti al momento della diagnosi. Sono acquisiti i referti diagnostici significativi e le informazioni sull'esposizione ad amianto. La rete di rilevazione comprende prevalentemente anatomo-patologi e medici del lavoro. *Risultati*. Sono stati rilevati 938 casi incidenti al 30/4/2006. I MM certi sono 764, 85 i probabili e 89 i possibili: la conferma anatomo-patologica è presente nel 90,5% dei casi. La sede pleurica prevale nell'89,8%, il peritoneo registra l'8,5% ed il pericardio e la vaginale del testicolo l'1,7%. Il rapporto di genere (M/F) totale è 2,6/1: 2,8/1 per la pleura, parità per il peritoneo (1/1). Il 67% dei casi è insorto dopo i 64 anni, il 30,1% tra i 45-64 anni ed il 2,9% sotto i 45 anni. Il tasso di incidenza standardizzato regionale per 10^5 è 2,6 nei maschi e 0,9 nelle femmine, con punte di 4,5 e 1,7 a Reggio Emilia. Esposizione ad amianto è presente nel 78,7% dei maschi e nel 45,7% delle femmine. *Conclusioni*. È confermato l'aumento di in-**

Summary

***Aims*. Cases of malignant mesothelioma (MM) are increasing in Italy, despite the fact that asbestos has been banned for more than ten years. The Emilia-Romagna Mesothelioma Registry, which works in association with the National Mesothelioma Registry, carries out the epidemiological surveillance of this pathology. Data collected in the period 1996-2006 are reported. *Materials and methods*. Cases of MM affecting the pleura and extrapleural sites (peritoneum, pericardium and tunica vaginalis of the testicle) observed among residents in Emilia-Romagna at the time of diagnosis are recorded. Significant medical reports and information about asbestos exposure are collected. The survey network is mainly composed of pathologists and occupational physicians. *Results*. At 30/4/2006, 938 cases had been detected. 764 cases were certified as sure MM, 85 as probable and 89 as possible: anatomo-pathological confirmation was present in 90.5% of the cases. Most cases affected the pleura (89.8%); other sites included the peritoneum (8.5%) and the pericardium and the tunica vaginalis of the testicle (1.7%). The overall gender ratio (M/F) was 2.6/1: 2.8/1 for pleura, parity for peritoneum (1/1). 67% of the cases were diagnosed after 64 years of age, 30.1% between 45-64 years and 2.9% under 45 years of age. The standardized regional incidence rate x 10^5 person-years was estimated to be 2.6 in males**

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cidenza del MM, la prevalente eziologia da amianto nei maschi ed il difficile reperimento dell'esposizione nelle femmine. Rilevante la quota di MM a sede extrapleurica e quella relativa alla fascia di età maggiore di 64 anni. Eur. J. Oncol., 11 (4), 245-252, 2006

Parole chiave: **mesotelioma maligno, Registro Nazionale, sorveglianza epidemiologica, asbesto**

and 0.9 in females, with peaks of 4.5 and 1.7 in Reggio Emilia. In 78.7% of males and 45.7% of females asbestos exposure was confirmed. *Conclusions*. Our study confirms the increase of MM incidence, the prevailing aetiology from asbestos in males and the difficult demonstration of asbestos exposure in females. The percentage of extrapleural MM is considerable and the number of cases observed in the age group over 64 is noteworthy. Eur. J. Oncol., 11 (4), 245-252, 2006

Key words: **malignant mesothelioma, National Registry, epidemiological surveillance, asbestos**

Introduzione

Il mesotelioma maligno (MM) è un tumore raro ma di grande interesse scientifico per la ben documentata correlazione con l'esposizione professionale e/o ambientale ad amianto e per l'aumento dell'incidenza registrato di recente in Italia e in molti altri paesi industrializzati[1-3].

Nonostante la definitiva messa al bando dell'amianto risalga, nel nostro Paese, ormai al 1994, è presumibile un incremento dell'incidenza dei casi nei prossimi 20 anni essenzialmente legata al peculiare tempo di latenza, all'allungamento della vita e al miglioramento della conoscenza di questa malattia da parte dei patologi. L'incidenza di questa temibile patologia su tutto il territorio dell'Emilia-Romagna è rilevata dall'1/1/1996 dal Registro Mesoteliomi (ReM) regionale. Il ReM, collocato presso il Dipartimento di Sanità Pubblica dell'AUSL di Reggio Emilia, registra i MM incidenti dall'1/1/1996 in cittadini residenti in Regione al momento della diagnosi.

I compiti del registro sono stati recentemente normati dal DPCM 308/02 che, con la formalizzazione del Registro Nazionale Mesoteliomi (ReNaM) e dei Centri Operativi Regionali (COR), ha dato definitiva attuazione all'art. 36, D.Lgs. 277/91, legittimando nel nostro Paese una peculiare esperienza di sorveglianza epidemiologica per una patologia non diffusiva[4-7]. In effetti, l'attività del ReNaM è anche riconosciuta dall'art. 94, D.Lgs. 165/03 che, recando norme per la protezione dei dati personali, a volte costituisce un serio ostacolo alla rilevazione epidemiologica di dati sensibili.

In questo lavoro è riportata l'esperienza del Registro Mesoteliomi dell'Emilia-Romagna ed un'analisi dei dati raccolti al 30/4/2006. L'incidenza può considerarsi pressoché completa per gli anni 1996-2004, mentre per il periodo successivo è in corso la ricerca attiva dei casi per il completamento della rilevazione. La Regione Emilia-Romagna si estende su una superficie di 22.124 km^2; il territorio è diviso in nove province e la popolazione residente nel 2004 era 4.151.335 (2.133.556 donne e 2.017.779 uomini).

Materiali e metodi

Vengono rilevati tutti i casi di mesotelioma maligno, a sede pleurica, pericardica, peritoneale e della tunica vaginale del testicolo; vengono archiviati, ma esclusi dal calcolo dell'incidenza, anche i mesoteliomi sospetti, i benigni e quelli risultati non residenti in regione. Per ogni caso registrato si provvede all'acquisizione, oltre che dei referti delle indagini anatomo-patologiche eseguite, delle cartelle cliniche dei ricoveri significativi, effettuati presso aziende sanitarie pubbliche e private, regionali od extra-regionali. L'esame di detta documentazione sanitaria, ad opera del personale ReM, determina la classificazione diagnostica del caso e la rilevazione di gran parte delle informazioni registrate.

La classificazione dell'esposizione adottata è quella proposta dal ReNaM[8]. Le informazioni anamnestiche personali e professionali e quelle sull'ambiente di vita sono raccolte mediante un questionario analitico, proposto dal ReNaM, somministrato al paziente o ai suoi familiari più prossimi, a cura dei referenti medici del lavoro dei Dipartimenti di Sanità Pubblica, componenti la Rete Regionale di Rilevazione.

Il coinvolgimento dei medici dei Servizi Territoriali di prevenzione tende a valorizzare il patrimonio storico di conoscenze della realtà produttiva del territorio di competenza dei Servizi Prevenzione e Sicurezza Ambienti di Lavoro. Ciò è tanto più significativo, se si considera che la rete di tali Servizi in Emilia-Romagna è capillare ed operante, in genere, fin dagli anni '70.

La Rete Informativa Regionale comprende tutti gli Istituti ed i Servizi di Anatomia Patologica, pubblici e privati, operanti sul territorio regionale, i vari reparti ospedalieri ove elettivamente confluiscono i pazienti affetti da mesotelioma e tutti i Dipartimenti di Sanità Pubblica territoriali. La rilevazione dei casi avviene in parte in forma attiva, attraverso la richiesta periodica di informazioni, ed in parte attraverso segnalazioni preordinate da parte dei referenti della Rete Regionale di Rilevazione. La rete di rilevazione tende ad acquisire in tempo reale le segnalazioni dei nuovi casi appena diagnosticati, per raccogliere le informazioni necessarie direttamente dal paziente.

Per la verifica di completezza della rilevazione dei casi incidenti, sono previsti incroci con i dati acquisiti periodicamente dagli archivi regionali informatizzati (mortalità e schede di dimissione ospedaliera = SDO) e dai Registri Tumori di popolazione regionali ed extra-regionali.

Risultati

Al 30 Aprile 2006, risultano archiviati 1216 casi. Di questi, sono stati esclusi 112 incidenti in epoca anteriore all'1/1/1996, prevalentemente nella provincia di Reggio Emilia, 76 casi sospetti, risultati alle successive indagini non mesoteliomi e 90 casi diagnosticati in persone non residenti nella nostra Regione.

L'analisi dei dati, pertanto, è stata condotta sui 938 casi di MM. Per quanto attiene alla definizione diagnostica, 764 casi sono stati classificati come casi *certi (*583 confermati da esame istologico con accertamenti immunoistochimici e quadro clinico/radiologico caratteristico, 180 da istologico privo di immunoistochimica e quadro clinico/radiologico caratteristico, 1 da solo esame istologico), 85 casi come *probabili* (36 con esame istologico dubbio e conferma clinica/radiologica, 49 con conferma citologica e clinica/radiologica di cui 28 con esame TAC) e 89 come casi *possibili* (86 casi hanno conferma clinica/radiologica di cui 71 TAC, e 3 casi sono confermati unicamente dal certificato di morte (*death certificate only* = DCO) (Tabella 1).

La distribuzione per anno di incidenza, sede, genere e fascia di età è riportata nelle Tabelle 2 e 3.

L'incidenza pare attestarsi mediamente su 90 casi/anno e risulta presumibilmente completa per il periodo 1996-2004, mentre per gli anni successivi devono essere effettuati i *linkage* di completezza.

La sede colpita prevalentemente è quella pleurica (89,8%), ma non sono pochi i casi a carico del peritoneo (8,5%), nè eccezionali quelli a sede pericardica e testicolare (1,7%).

Il rapporto di genere, per la totalità dei casi, è 2,6/1 a

Tabella 1 - Distribuzione dei casi per definizione diagnostica[a]

	N. casi	Definizione
MM certo	764	Istologia presente, quadro morfologico caratteristico, immuno-istochimica caratteristica/ suggestiva/assente ± conferma diagnostica per immagini o diagnosi clinica di dimissione
MM probabile	85	Istologia presente, quadro morfologico dubbio o citologia con quadro caratteristico + conferma diagnostica per immagini o diagnosi clinica di dimissione
MM possibile	89	Istologia/citologia assente, dati clinici e radiologici indicativi + diagnosi di dimissione CC di MM oppure DCO[b] con dizione "mesotelioma"
MM da definire	0	"Contenitore provvisorio" per casi che non rientrano in nessuno dei livelli precedenti
Non mesotelioma	76	Casi deceduti da almeno due mesi che non hanno i requisiti per poter essere inclusi nei primi tre livelli
Totale	1014	

[a] Aggiornata al 30/4/2006
[b] *Death certificate only* = solo certificato di morte

Tabella 2 - Distribuzione dei casi per sede e anno di diagnosi[a]

Sede	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Totale
Pleura	62	70	77	67	75	87	97	96	103	92	16	842
Peritoneo	8	7	4	6	9	6	15	7	9	9	-	80
Pericardio	-	3	1	-	-	-	-	1	1	-	-	6
Vaginale del testicolo	2	-	1	-	1	2	1	1	-	2	-	10
Totale	72	80	83	73	85	95	113	105	113	103	16	938

[a] Aggiornata al 30/4/2006

favore dei maschi. Questo dato si ripete sostanzialmente per la sede pleurica (2,8/1) e tende alla parità per quella peritoneale (1/1).

Il 67% dei casi è stato diagnosticato dopo i 64 anni, il 2,9% prima dei 45 anni e il restante 30,1% nella fascia d'età 45-64 anni (Tabella 3).

I Servizi ed Istituti che hanno contribuito maggiormente alla segnalazione dei casi in questi anni sono: l'Anatomia Patologica (56,3%), i Servizi territoriali di Prevenzione e Sicurezza Ambienti di Lavoro (15,3%), l'Igiene Pubblica (9,0%) e i reparti di Pneumologia (2,8%); le altre strutture informative coinvolte (altri reparti ospedalieri, Registri Tumori, altri COR) costituiscono il 5,7%, mentre il *linkage* con gli archivi regionali informatizzati di mortalità e SDO ha permesso l'acquisizione del 10,9% dei casi.

Il tasso di incidenza regionale (Tabella 4), calcolato per il periodo 1996-2004 e standardizzato per la popolazione italiana in base al censimento del 1991, è pari a 2,6 nei maschi e 0,9 nelle femmine. Il tasso più alto, sia nei maschi che nelle femmine, è stato registrato a Reggio Emilia: 4,5 per i maschi e 1,7 per le femmine; anche il tasso per i maschi a Piacenza è rilevante (3,2). La provincia di Modena registra il tasso più basso per i maschi (1,5) mentre la provincia di Rimini registra il tasso più basso per le femmine (0,5).

La distribuzione di tutta la casistica per provincia di residenza è riportata nella Tabella 5. Nella stessa sono riportate, per ciascuna provincia, le informazioni espositive aggiornate al 30/4/2006.

Per valutare l'esposizione ad amianto, sono state finora raccolte informazioni su 666 casi: 28 sono risultati *non classificabili* per rifiuto od impossibilità a contattare paziente o familiari, mentre per i rimanenti 638 sono state acquisite le informazioni anamnestiche di rito, di cui 267 direttamente dal paziente (41,8%).

Questo dato è giudicato particolarmente significativo e suscettibile di miglioramento, in quanto la rete di rilevazione, fondata sulla diffusa e capillare presenza dei Servizi Prevenzione e Sicurezza negli Ambienti di Lavoro (SPSAL), è stata concepita proprio per raccogliere informazioni anamnestiche dalla viva voce del paziente al fine di ricostruire la storia lavorativa con elevata accura-

Tabella 3 - Distribuzione dei casi per sede ed età alla diagnosi[a]

Età (anni)	Pleura		Peritoneo		Pericardio		Vaginale del testicolo	Totale
	Maschi	Femmine	Maschi	Femmine	Maschi	Femmine		
< 35	-	-	2	2	-	-	2	6
35-39	4	2	1	1	-	-	-	8
40-44	7	3	1	-	-	-	2	13
45-49	18	6	-	1	-	-	1	26
50-54	33	12	2	3	-	-	1	51
55-59	55	19	4	4	-	2	-	84
60-64	86	20	7	7	-	-	1	121
65-69	104	34	6	2	1	-	1	148
70-74	107	42	5	7	2	1	-	164
75+	209	81	11	14	-	-	2	317
Totale	623	219	39	41	3	3	10	938

[a] Aggiornata al 30/4/2006

Tabella 4 - Tasso di incidenza x 10^5, standardizzato su popolazione Italia '91, per residenza, negli anni 1996-2004

Residenza	Maschi			Femmine		
	N. casi	Tasso	IC 95%	N. casi	Tasso	IC 95%
Piacenza	53	3,25	2,27-4,22	19	1,06	0,48-1,65
Parma	51	2,15	1,49-2,82	29	1,17	0,69-1,66
Reggio Emilia	87	4,51	3,53-5,48	32	1,72	1,10-2,35
Modena	52	1,54	1,07-2,00	24	0,66	0,33-1,00
Bologna	153	2,75	2,25-3,25	46	0,77	0,50-1,04
Ferrara	68	3,12	2,27-3,96	25	1,05	0,54-1,57
Ravenna	58	2,55	1,79-3,32	21	0,97	0,50-1,43
Forlì	42	2,57	1,77-3,37	21	1,22	0,66-1,77
Rimini	30	2,14	1,30-2,97	8	0,54	0,12-0,97
Emilia-Romagna	594	2,56	2,32-2,79	225	0,92	0,78-1,06

Tabella 5 - Distribuzione di MM per provincia di residenza[a]

Residenza	Maschi (N.)	Femmine (N.)	Totale (N.)	Informazioni acquisite
Piacenza	59	26	85	65
Parma	65	40	105	85
Reggio Emilia	100	40	140	101
Modena	59	25	84	43
Bologna	170	51	221	172
Ferrara	78	26	104	58
Ravenna	62	25	87	82
Forlì/Cesena	50	21	71	33
Rimini	32	9	41	27
Totale	675	263	938	666
Altre Regioni	71	19	90	-

[a] Aggiornata al 30/4/2006

Tabella 6 - Distribuzione dei MM per tipo di esposizione[a]

Tipo di esposizione	Maschi		Femmine		Totale	
	N. casi	%	N. casi	%	N. casi	%
Professionale certa	237	50,0	17	10,4	254	39,8
Professionale probabile	58	12,2	10	6,1	68	10,7
Professionale possibile	55	11,6	13	7,9	68	10,7
Familiare	4	0,8	28	17,1	32	5,0
Ambientale	12	2,5	6	3,7	18	2,8
Extra-lavorativa	7	1,5	1	0,6	8	1,3
Improbabile	40	8,4	54	32,9	94	14,7
Ignota	61	12,9	35	21,3	96	15,0
Totale casi definiti	474	100,0	164	100,0	638	100,0
Da definire	181	26,8	91	34,6	272	29,0
Non classificabile	20	3,0	8	3,0	28	3,0
Totale incidenti	675		263		938	

[a] Aggiornata al 30/4/2006

tezza. Attualmente la rilevazione di queste informazioni è piuttosto diversificata nelle varie province.

In 390 casi, l'esposizione è stata classificata come *professionale* (254 certa, 68 probabile e 68 possibile), in 58 casi *non professionale* (32 familiare, 18 ambientale e 8 legata ad attività extra-lavorative) e in 190 casi l'esposizione è risultata *improbabile-ignota* (Tabella 6).

I 58 soggetti con esposizione non professionale sono rappresentati da 35 femmine e 23 maschi. Per le femmine, l'esposizione è stata di natura familiare in 28 casi, in quanto congiunte di persone professionalmente esposte, ambientale in 6 casi, per avere abitato in vicinanza di aziende con utilizzo di quantità rilevanti di amianto ed extra-lavorativa in un caso. Nei maschi, 4 soggetti hanno subito un'esposizione familiare, 12 ambientale e 7 per attività comportanti la manipolazione di materiali contenenti amianto in attività non professionali.

Un'esposizione ad amianto è, dunque, presente in 448 casi su 638 (70,2%); nei maschi la quota sale al 78,7%, mentre nelle donne è stata rilevata nel 45,7%. Nella Tabella 7 è riportata la distribuzione dell'esposizione professionale per settore produttivo e sesso. Costruzione/riparazione di materiale rotabile ferroviario è risultato il settore maggiormente coinvolto (60 casi), seguito da costruzioni edili (47 casi) e da zuccherifici/altre industrie alimentari (44 casi). Rilevante è anche la produzione di manufatti in cemento-amianto (35 casi), e quella della produzione di vetro, gomma e ceramica (23 casi) e della fabbricazione di macchine ed apparecchi meccanici (34 casi), mentre gli altri 147 casi hanno interessato numerosi altri settori di attività economica, a riprova del fatto che l'amianto è stata una sostanza diffusa pressoché ubiquitariamente per le sue caratteristiche di materiale coibente.

Tabella 7 - Distribuzione esposizione professionale ad amianto per settori di attività economica[a]

Comparto produttivo	Maschi		Femmine		Totale	
	N. casi	%	N. casi	%	N. casi	%
Costruzione/riparazione rotabili ferroviari	58	16,6	2	5,0	60	15,4
Costruzioni edili	47	13,4	0	0,0	47	12,1
Zuccherifici/altre industrie alimentari	36	10,3	8	20,0	44	11,3
Produzione manufatti cemento-amianto	27	7,7	8	20,0	35	9,0
Fabbricazione vetro/ceramica/gomma	23	6,6	0	0,0	23	5,9
Fabbricazione macchine/app. meccanici	30	8,6	4	10,0	34	8,7
Produzione fertilizzanti/materie plastiche	21	6,0	1	2,5	22	5,6
Fabbricazione/lavorazione prodotti metallici	17	4,9	1	2,5	18	4,6
Lavori completamento edifici	16	4,6	0	0,0	16	4,1
Distribuzione gas/acqua/elettricità	11	3,1	0	0,0	11	2,8
Costruzioni/riparazione navi	8	2,3	0	0,0	8	2,1
Fusione metalli	7	2,0	0	0,0	7	1,8
Trasporti	7	2,0	0	0,0	7	1,8
Riparazione veicoli	6	1,7	1	2,5	7	1,8
Difesa nazionale	6	1,7	0	0,0	6	1,5
Altro	30	8,6	15	37,5	45	11,5
Totale	350	100,0	40	100,0	390	100,0

[a] Aggiornata al 30/4/06

Conclusioni

Il MM è un tumore raro quasi sempre associato ad esposizioni, anche modeste, ad amianto. Ogni nuovo caso, pertanto, deve essere considerato "evento sentinella" di pregresse esposizioni e valutato attentamente[9,10]. In base a queste considerazioni, obiettivo prioritario del ReM è certamente la completezza dei dati e l'accuratezza delle informazioni raccolte.

Questa finalità sembra raggiunta grazie alla capillare rete di rapporti organizzata a livello regionale, che ha permesso di garantire una copertura reale di tutto il territorio. I rapporti consolidati con centri extra-regionali e con gli altri COR nazionali hanno permesso di recuperare anche la quota di casi, invero modesta, che vengono trattati fuori regione. Anche l'accuratezza delle informazioni può essere considerata di buon livello: il 90,5% dei casi è corredato di conferma cito-istologica; i casi sprovvisti di conferma anatomo-patologica sono inseriti solo se provvisti di significativa documentazione clinico-strumentale.

Un aspetto rilevante dei MM registrati in Emilia-Romagna è l'elevata quota di casi a sede extra pleurica: il rapporto pleura/extrapleura registrato dal ReM è risultato pari a 8,8:1, superiore rispetto al 16,3:1 ed al 10,6:1 registrato dalla totalità dei COR in Italia[4,5,11] e ad alcuni *report* internazionali[12-17], in parte datati, che verosimilmente sovrastimano il dato dei MM a sede pleurica. Certamente l'articolazione della rete di rilevazione ReM favorisce l'esaustività della raccolta informazioni sia dai reparti clinici, pneumologia e chirurgia toracica principalmente, ove elettivamente affluiscono i MM a sede pleurica, che da quelli ove vengono trattati i casi a sede extrapleurica: chirurgia generale, ginecologia, cardiochirurgia, urologia e andrologia. D'altra parte, una recente ricerca svolta in ambito ISPESL/ReNaM ha mostrato come molti COR non siano ancora attrezzati per rilevare in modo sistematico i MM a sede extrapleurica e ha individuato le possibili modalità per implementare detta rilevazione[18].

Per quanto concerne l'età alla diagnosi, la media è risultata di 68,9±11,6 anni; è degno di nota che il 67% dei soggetti in Emilia-Romagna presenta un'età ≥ 65 anni al momento della diagnosi, rispetto al 52% registrato in Italia[4]. Il dato potrebbe essere correlabile ad una maggiore tendenza, nella nostra regione, ad eseguire prelievi bioptici anche in soggetti più anziani, grazie alla buona diffusione della pratica video-toracoscopica rispetto a metodiche tradizionali più invasive.

I tassi annuali di incidenza standardizzati per 10^5 mostrano un *trend* in costante aumento per il sesso maschile: si passa dal 2,2 del 1996 al 3,4 del 2004, a conferma dei dati di letteratura che prevedevano un aumento dell'incidenza nei paesi industrializzati ex utilizzatori di amianto (fig. 1).

I tassi di incidenza regionale, calcolati per il periodo 1996-2004, mostrano dati non facilmente interpretabili per Piacenza e Modena, mentre per Reggio Emilia sono principalmente correlabili alla significativa diffusione in passato di aziende dedite alla produzione di manufatti in cemento-amianto e alla costruzione/riparazione di rotabili ferroviari. In particolare, il valore più elevato della Re-

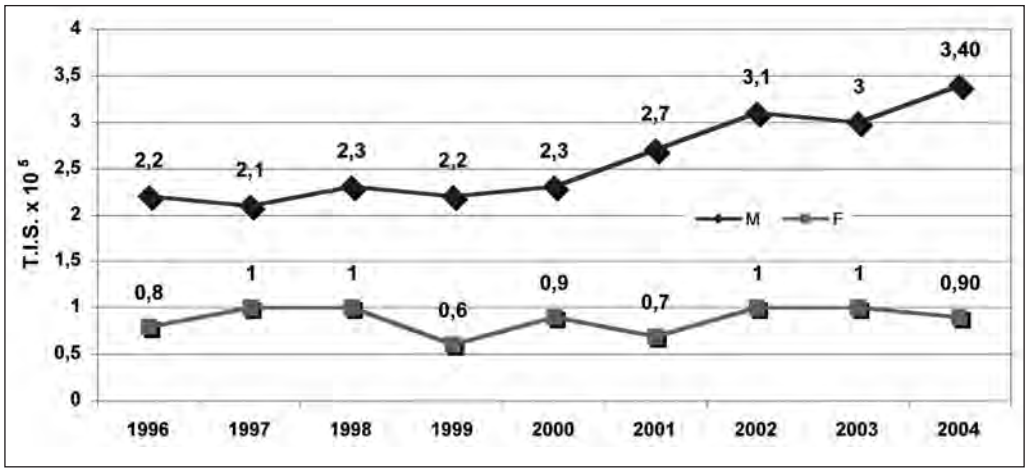

Fig. 1. Tassi annuali di incidenza standardizzati per 10^5 nella Regione Emilia-Romagna (1996-2004)

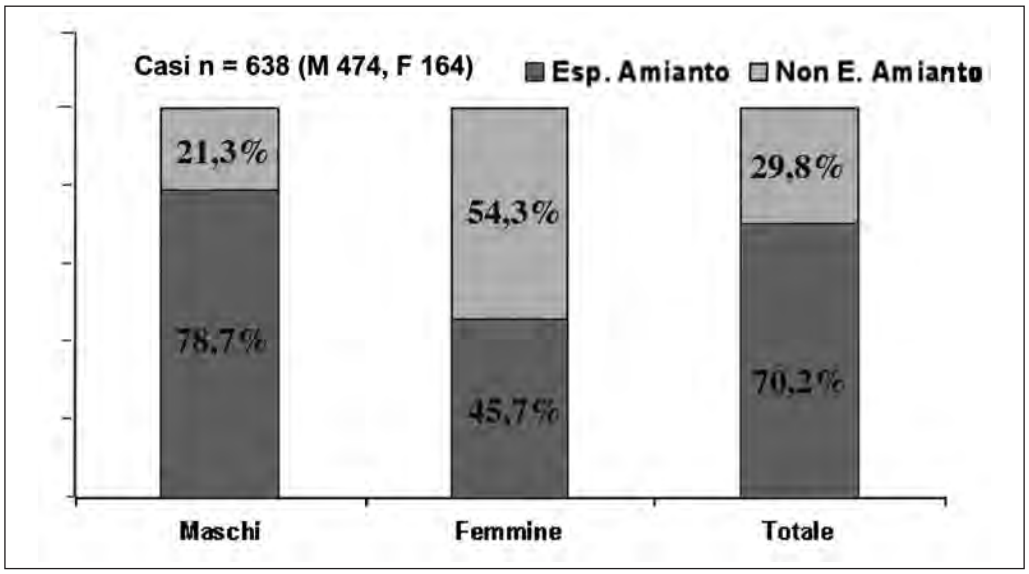

Fig. 2. Esposizione ad amianto per genere (aggiornata al 30/4/06)

gione per le donne è certamente da collegare all'impiego, peculiare in questa provincia, di mano d'opera femminile nella produzione manuale di "pezzi speciali" in cemento-amianto.

Un'esposizione ad amianto è stata documentata nel 78,7% dei maschi e nel 45,7% delle femmine (fig. 2): se consideriamo solo l'esposizione per motivi professionali, la percentuale si modifica poco nei maschi (73,8%), ma si riduce notevolmente nelle femmine (24,4%). La differenza di esposizione rilevata fra i due sessi potrebbe essere legata ad una maggiore difficoltà nella ricostruzione dell'anamnesi espositiva per il genere femminile[9]. I casi per cui non è stata registrata un'esposizione ad amianto, 21,3% nei maschi e 54,3% nelle femmine, potrebbero indurre a formulare diverse ipotesi eziologiche[19, 20] solo quando l'esaustività delle informazioni reperite consenta di escludere con ragionevole certezza il rischio amianto: indagini mirate in comparti industriali con inopinati *cluster* di casi hanno fatto emergere esposizioni ad amianto finora misconosciute[21, 22].

I settori produttivi maggiormente coinvolti sono risultati: costruzione/riparazione di rotabili ferroviari (casi in gran parte residenti nelle province di Bologna e Reggio Emilia); costruzioni edili (soggetti distribuiti in maniera uniforme in tutta la regione); produzione manufatti in cemento-amianto (27 dei 35 casi residenti a Reggio Emilia); industrie alimentari (25 dei 44 casi, addetti in zuccherifici a Bologna, Ferrara, Ravenna, Parma e Forlì/Cesena); produzione di vetro, ceramica e gomma (23 casi nelle province di Parma, Reggio Emilia, Modena, Bologna e Ravenna), fabbricazione di macchine ed apparati meccanici (34 casi uniformemente distribuiti in tutta la regione); produzione di fertilizzanti e materie plastiche/fibre artificiali (22 casi nelle industrie chimiche di Ravenna, Ferrara e Forlì/Cesena).

Ringraziamenti

La raccolta, l'archiviazione e la definizione dei casi di MM maligno incidenti su tutto il territorio regionale è stata possibile, con

un accettabile rapporto costi/benefici, solo attraverso la fattiva collaborazione dei Referenti della rete di rilevazione: 20 specialisti anatomo-patologi ed altrettanti igienisti e medici del lavoro dei Dipartimenti di Sanità Pubblica. Numerosi altri specialisti, pneumologi, chirurghi generali, ginecologi, urologi, oncologi, ma anche internisti e cardiologi, hanno dato un contributo fondamentale per l'acquisizione tempestiva dei nuovi casi. Rilevante il contributo del personale regionale del Servizio Sistema Informativo Sanità e Politiche Sociali e degli operatori dei Registri Tumori di popolazione per la realizzazione dei *linkage* di completezza della casistica, indispensabile garanzia di qualità del lavoro quando si interviene su patologie rare. A tutti va un ringraziamento non formale per i risultati raggiunti, certi che la buona collaborazione instaurata possa garantire una migliore conoscenza di questa temibile patologia.

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Determinazione dello stato di HER-2 in pazienti con carcinoma della mammella con metodica immunoistochimica e FISH: un contributo originale

Assessment of HER-2 status in patients with breast cancer by immunohistochemistry and FISH: an original contribution

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Riassunto

La determinazione dello stato del recettore per il fattore di crescita epidermico umano 2 (*human epidermal growth factor receptor 2* = HER-2) è molto importante nella selezione delle pazienti con carcinoma della mammella che devono essere trattate con trastuzumab, sia come adiuvante che in caso di recidive metastatiche. Per la determinazione di HER-2 possono essere usate sia l'immunoistochimica (IHC) che l'ibridizzazione fluorescente *in situ* (FISH). La FISH è considerata il metodo di elezione. Gli Autori riportano i risultati del loro studio riguardante 489 casi di carcinomi mammari invasivi in cui la determinazione dello stato di HER-2 è stato eseguito con la metodica FISH; la determinazione IHC era disponibile solo per 371 dei 489 casi. L'implementazione di accurati sistemi di Qualità Analitica, sia nella fase preanalitica che analitica, può garantire un'alta concordanza tra i 2 test consentendo così di inviare a FISH i casi IHC 2+ e/o IHC 1+, mentre l'IHC può dare valori accurati nei casi IHC 3+ e IHC 0. Eur. J. Oncol., 11 (4), 253-258, 2006

Parole chiave: **carcinoma della mammella, HER-2, immunoistochimica, FISH, trastuzumab**

Summary

The assessment of the human epidermal growth factor receptor-2 (HER-2) status is very important in the selection of breast cancer patients to be treated with trastuzumab, both in the adjuvant setting and in metastatic disease. Immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH) can be used for the evaluation of HER-2. FISH is considered the procedure of choice. The authors report the results of their study concerning 489 cases of invasive breast carcinoma tested by FISH; IHC was also performed in 371 cases. Setting up effective Quality Assessment programmes, involving both preanalytical and analytical stages, can guarantee a high concordance rate between these two techniques, making it possible to send all IHC 2+ and/or IHC 1+ cases on to FISH, while IHC alone can be considered accurate enough in the case of IHC 3+ and IHC 0 results. Eur. J. Oncol., 11 (4), 253-258, 2006

Key words: **breast cancer, HER-2, immunohistochemistry, FISH, trastuzumab**

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Introduzione

Il cancro della mammella è la neoplasia più frequente nel sesso femminile.

Negli Stati Uniti rappresenta circa un terzo di tutti i tumori diagnosticati nelle donne, con circa 216.000 nuovi casi e 40.000 decessi nell'anno 2004[1].

Anche in Italia il carcinoma della mammella è la neoplasia a maggiore incidenza e la principale causa di morte per tumore nelle donne, nella fascia di età compresa tra i 35 ed i 64 anni, costituendo il 28% di tutte le morti per cancro[2].

Il carcinoma mammario è una malattia eterogenea con diversi importanti sottotipi, ciascuno a diversa storia naturale ed a diverso trattamento farmacologico[3].

L'iperespressione del recettore per il fattore di crescita epidermico umano 2 (*human epidermal growth factor receptor 2* = HER-2), caratterizza uno di questi sottotipi.

Il gene HER-2 è un proto-oncogene collocato sul cromosoma 17q, che codifica per il recettore di membrana, appartenente alla famiglia dei recettori EGF (fattore di crescita epidermico = *epidermal growth factor*), che regola la fisiologia, la crescita e la differenziazione cellulare, tramite il dominio interno[4].

Il dominio extracellulare funziona da corecettore per la traduzione del segnale, interagendo con gli altri membri della famiglia EGFR[5].

L'amplificazione del gene HER-2 provoca un aumento (fino a 100 volte il valore normale) della espressione di HER-2 sulla superficie delle cellule neoplastiche, conferendo loro comportamento aggressivo[6].

I tumori della mammella HER-2 positivi hanno tratti molecolari peculiari, che li distinguono da altri tipi di cancro mammario, nonché comportamento clinico diverso[7].

Infatti, le pazienti HER-2 positive hanno tumori scarsamente differenziati, ad alto indice proliferativo, interessamento linfonodale ascellare, ridotta espressione dei recettori ormonali estroprogestinici, caratteristiche associate ad una prognosi peggiore ed a scarsa risposta a vari tipi di chemioterapici[8,9].

La scoperta, in un tumore murino chimicamente indotto, di un gene che sembrava avere una sequenza simile ad un normale gene cellulare e l'iperespressione dello stesso in tumori della mammella umani, ha portato alla sintesi di un anticorpo monoclonale ad alta affinità per il dominio extracellulare di HER-2[10].

La versione umanizzata di questo anticorpo è il trastuzumab, primo esempio di *target therapy*.

Il trastuzumab si è dimostrato efficace nel trattamento delle pazienti HER-2 positive, sia in fase adiuvante che metastatica[9,11-13].

La valutazione dello stato di HER-2 ha, pertanto, assunto grande importanza per la selezione delle pazienti candidate al trattamento immunoterapico.

L'American Society of Clinical Oncology (ASCO), già dal 2000, consiglia la determinazione di HER-2 in tutti i carcinomi della mammella, sia al momento della diagnosi che alla recidiva[14].

L'immunoistochimica (IHC) e l'ibridizzazione fluorescente *in situ* (FISH) offrono chiari vantaggi rispetto ad altre tecniche, come *Southern, Northern and Western blot* e *polymerase chain reaction*, usate inizialmente e non utilizzabili nella pratica clinica routinaria[8,15,16].

Entrambe consentono, infatti, l'identificazione specifica della alterazione in singole cellule, pur nel contesto dell'architettura tissutale.

L'IHC valuta l'espressione della proteina HER-2 ed offre i vantaggi del basso costo, della rilevanza biologica e della disponibilità tecnica in tutti i laboratori di anatomia patologica, ma presenta problemi intrinseci legati alla colorazione, alle differenze tra gli anticorpi usati, ai metodi di recupero dell'antigene, alla fissazione del tessuto, alla preparazione del vetrino ed all'interpretazione dei risultati[17,18].

Come conseguenza della soggettività nella valutazione dei dati IHC, in letteratura vengono segnalate una grande variabilità tra laboratori ed una bassa concordanza tra patologi[19].

La FISH misura l'amplificazione del gene HER-2 con grande accuratezza, eccellente sensibilità e specificità ed ha una soglia standardizzata di positività, ma presenta difficoltà tecniche e costi maggiori rispetto alla IHC e, spesso, non è disponibile in tutti i laboratori di anatomia patologica[20-22]; pertanto è importante che venga eseguita in Centri di Riferimento che garantiscono una maggiore accuratezza diagnostica.

Materiali e metodi

Dal settembre 2003 al dicembre 2005 sono stati esaminati 489 casi di carcinoma mammario invasivo per la determinazione dello stato di HER-2 con la metodica FISH.

Lo studio comprende un'analisi dei risultati della FISH per la valutazione dell'amplificazione del gene HER-2 effettuata presso il Laboratorio Analisi dell'Ospedale di Bentivoglio.

I dati ottenuti sono stati sottoposti ad una valutazione comparativa di concordanza con il test IHC per la determinazione dell'iperespressione di HER-2.

Il materiale da sottoporre a FISH proveniva dai Servizi di Anatomia Patologica di diverse istituzioni; tra questi, solo uno prevedeva la validazione di un protocollo di qualità reciproco.

I preparati giungevano alla valutazione FISH, da tale Servizio di Anatomia Patologica, allestiti su fette bianche preselezionate, sotto la guida di una sezione seriata colorata con ematossilina-eosina.

In particolare venivano predisposte tre sezioni seriate particolarmente sottili (2-3 μm), una delle quali colorata con la colorazione morfologica routinaria ematossilina-eosina.

L'area o le aree precedentemente identificate dal patologo, utilizzando le colorazioni morfologiche ed immunoistochimiche effettuate a scopo diagnostico-prognostico, sono state selezionate per la tecnica FISH, eliminando tutto il tessuto paraffinato ritenuto non significativo.

Determinazione immunoistochimica

Sezioni seriate del tessuto neoplastico, relative a ciascun caso, sono state immunocolorate, utilizzando anticorpi diretti contro il dominio interno ed esterno del recettore HER-2.

La scelta degli anticorpi è stata effettuata sulla base della letteratura disponibile. Si è pertanto utilizzato l'anticorpo clone CB11 (Biogenex Laboratories, San Ramon, USA) per il dominio interno; mentre per la determinazione del dominio esterno sono stati scelti due anticorpi monoclonali (clone Tab 250 - Zymed Laboratories, USA e clone CBE1 - Novocastra Laboratories, Gran Bretagna), la cui capacità di evidenziare la proteina specifica si è rilevata non sovrapponibile ed il cui uso continuativo per oltre 15 anni, nel laboratorio di riferimento, si è rilevato sensibile e riproducibile.

Tali anticorpi sono stati ottimizzati per l'uso combinato (*"cocktail"*), consentendo di effettuare la determinazione su un'unica sezione.

La determinazione IHC di HER-2, nei casi che non seguivano il protocollo dichiarato, era effettuata con anticorpi CB11 e/o HercepTest (Dako, Carpinteria, CA, USA).

La colorazione immunoistochimica, nel laboratorio di riferimento, è stata valutata seguendo le stesse linee guida proposte per il kit HercepTest Dako. La valutazione ha preso in esame l' intera sezione istologica, comprendendo la componente neoplastica infiltrante ed escludendo quella *in situ*.

Lo *score* applicato è stato il seguente (per una maggior sensibità del metodo rispetto allo *score* suggerito dalla casa produttrice):

Score 0 = assenza totale di colorazione; colorazione citoplasmatica o presenza di rime di membrana plasmatica incomplete o positività di rima completa, ma inferiore al 20% della popolazione neoplastica;

Score 1+ = presenza di colorazione di membrana completa in più del 20%, ma ad intensità debole;

Score 2+ = presenza di immunocolorazione netta in più del 20% della popolazione neoplastica;

Score 3+ = presenza di forte colorazione di membrana in più del 20% della popolazione neoplastica valutata.

La lettura è stata effettuata su entrambe le sezioni immunocolorate, utilizzando anticorpi diretti contro il dominio interno ed esterno. I risultati sono stati registrati separatamente ed integrati, successivamente, in uno *score* finale condizionato dal valore più alto registrato.

Determinazione FISH

L'ibridizzazione *in situ* è una tecnica che permette la visualizzazione di specifiche sequenze di acido nucleico in un preparato. In particolare, la FISH prevede l'appaiamento preciso di una sonda di DNA a singola elica con sequenze bersaglio complementari, seguendo, nel nostro caso, le indicazioni del metodo Vysis Path Vision.

La sonda di DNA LSI-HER-2 (*locus specific identifier*) è una sonda specifica per il *locus* del gene HER-2, lunga 190 Kb e direttamente marcata con *spectrum orange*.

La sonda DNA-CEP 17 (*chromosome enumeration probe*) è lunga 5,4 Kb, marcata direttamente con *spectrum green*, specifica per le sequenze di DNA alfa-satellite, nella regione del centromero 17. Le sonde sono premiscelate.

L'amplificazione del gene HER-2 è fatta su campioni di tessuto neoplastico della mammella fissato in formalina ed incluso in paraffina; il dosaggio è veloce, non radioattivo ed è in grado di rilevare da 2 ad 8 copie di oncogene.

Il DNA viene denaturato in forma di singola elica e successivamente fatto ibridare.

Ad ibridazione avvenuta, la sonda non legata viene rimossa con una serie di lavaggi ed i nuclei vengono colorati di contrasto con DAPI, un colorante DNA-specifico, che emette una fluorescenza blu. Viene, quindi, utilizzato un microscopio a fluorescenza provvisto di filtri di eccitazione e di emissione appropriati, in grado di visualizzare i segnali fluorescenti di colore arancio e verde intenso.

La conta dei segnali LSI-HER-2 e CEP 17 viene eseguita all'esame microscopico del nucleo, che dà un valore del rapporto tra il gene HER-2 ed il numero di copie del cromosoma 17. I nuclei da contare non devono essere sovrapposti e devono contenere sia i segnali arancio che quelli verdi. Il rapporto tra LSI-HER-2 e CEP 17 si ottiene dividendo il numero complessivo dei segnali LSI

per il numero complessivo dei segnali CEP 17, all'interno degli stessi nuclei. La conta viene eseguita in 60 nuclei.

Se il risultato è inferiore a 2, il gene non è amplificato, mentre se è maggiore di 2, viene considerato amplificato. Un risultato compreso tra 1,8 e 2,2 viene considerato *borderline* e deve essere interpretato con prudenza.

Controlli di qualità

Sia per la IHC che per la FISH, ogni singolo *batch* di colorazione è stato accompagnato da un controllo positivo, opportunamente selezionato e riproducibile, per evidenziare eventuali variazioni nella resa di reazione e permettere di uniformare la lettura del risultato.

È stata effettuata, per ciascun caso, una valutazione della qualità del tessuto esaminato, poiché false negatività o problemi interpretativi della reazione possono essere imputati a cattive condizioni del preparato.

Per quanto riguarda la IHC, i criteri di valutazione sono stati sia di carattere morfologico con esame all'atto della diagnosi, che di carattere immunoistochimico (resa della reazione, controlli interni al tessuto, ecc.).

È stata utilizzata una classificazione basata su tre situazioni:

- la dizione idoneo alla determinazione segnala l'idoneità del tessuto ad una piena valutazione;
- la dizione parzialmente valutabile a causa delle scadenti condizioni del tessuto sta a significare come la valutazione dei parametri sia in parte falsata dalle condizioni non ottimali del tessuto, per cui è, ad esempio, possibile una sottovalutazione della quota immunopositiva;
- la dizione non valutabile segnala l'impossibilità alla valutazione, date le condizioni del tessuto esaminato.

Per quanto riguarda la FISH sono stati utilizzati vetrini di controllo Vysis ProbeCheck, in quanto devono essere soddisfatti i criteri per l'adeguatezza del vetrino ed i risultati del rapporto LSI HER-2/CEP 17 devono rientrare nei *range* stabiliti per una prestazione corretta del test. Se i vetrini di controllo non rientrano nei criteri di accettabilità, il test può non essere stato eseguito in modo corretto o i reagenti del *kit* possono non aver funzionato correttamente. Sarà, perciò, necessario ripetere l'analisi con nuovi vetrini di controllo e di tessuto dei singoli pazienti.

Risultati

Sono stati esaminati 489 casi di carcinomi mammari invasivi per la determinazione dello stato di HER-2 con la metodica FISH. Abbiamo riscontrato 93 casi amplificati (19,2%, 20,8% escludendo i non idonei), 343 non amplificati, 11 polisomici, 42 non idonei per motivi tecnici.

La determinazione IHC era invece disponibile per 371 dei 489 casi.

La correlazione dei risultati tra FISH ed IHC, nell'insieme dei casi esaminati, è riportata nella Tabella 1, mentre nella Tabella 2 viene riportata quella del sottogruppo dell'Anatomia Patologica dell'Ospedale S. Orsola-Malpighi con controlli di qualità reciproci.

Tabella 1 - Correlazione tra IHC e FISH nella determinazione dello stato di HER-2 in 371 casi

	IHC *score* = 0 (21 casi)	IHC *score* = 1+ (79 casi)	IHC *score* = 2+ (220 casi)	IHC *score* = 3+ (51 casi)
FISH negativa	20	73	193	8
FISH positiva	1	6	7	43
Percentuale di positività	5%	8%	12%	84%

Tabella 2 - Correlazione tra IHC e FISH nella determinazione dello stato di HER-2 in 325 casi del sottogruppo della anatomia patologica con controlli di qualità reciproci

	IHC *score* = 0 (18 casi)	IHC *score* = 1+ (70 casi)	IHC *score* = 2+ (196 casi)	IHC *score* = 3+ (41 casi)
FISH negativa	18	67	175	2
FISH positiva	0	3	21	39
Percentuale di positività	-	4%	11%	95%

Discussione

Nel carcinoma mammario HER-2 positivo, la proteina è presente sulla superficie delle cellule tumorali in quantità elevata.

Livelli elevati di HER-2 sono presenti in una forma di malattia particolarmente aggressiva, caratterizzata da una risposta molto scarsa alla chemioterapia classica ed alla ormonoterapia.

Il carcinoma mammario HER-2 positivo, che colpisce circa il 20-30% delle donne con tumore mammario[6,8], richiede un'attenzione particolare ed immediata, poiché tali tumori evolvono rapidamente.

I risultati di quattro imponenti studi (di cui 2 pubblicati), con quasi 12.000 pazienti arruolati in tutto il mondo e trattati in fase adiuvante, provano con evidenza che tra-

stuzumab riduce il rischio di recidiva di circa il 50%, offrendo, pertanto, la migliore possibilità di sopravvivenza a lungo termine alle pazienti colpite da questa aggressiva forma di carcinoma[12, 13].

Trastuzumab è un anticorpo monoclonale umanizzato creato per identificare e bloccare l'attività di HER-2, proteina prodotta da un gene specifico a potenziale cancerogeno. Oltre alla sua efficacia nel *setting* adiuvante, trastuzumab ha indotto un miglioramento della sopravvivenza nella malattia metastatica, dove la sua aggiunta alla chemioterapia ha consentito alle pazienti un aumento della sopravvivenza di circa un terzo, rispetto alla sola terapia antiblastica[9, 11].

Negli ultimi anni è stata pubblicata un'ampia documentazione scientifica su quale possa essere il test migliore (immunoistochimica *vs* ibridizzazione *in situ*) per la valutazione di HER-2 e quali possano essere i vantaggi e gli svantaggi dell'uno rispetto all'altro, con alti livelli di concordanza fra le due metodiche[16, 23].

È stata sempre documentata una generale e primaria predilezione per il metodo FISH rispetto alla IHC in funzione della sua presunta superiorità in termini di accuratezza e precisione.

In una coorte di carcinomi della mammella caratterizzati e validati da un punto di vista molecolare (DNA, RNA, E Proteina, Matrix *blotting technique*) ed usati come *gold standard*, in termini di accuratezza, la IHC, con vari anticorpi, ha mostrato una concordanza (96,6%-Ab R60; 95,7%-Ab10H8; 89,7%-AbCB11- Dako HercepTest) abbastanza sovrapponibile alla FISH (FISH 97,4% per Vysis; 95,7% per Ventana)[18].

Se la IHC e la FISH mostrano una simile ed alta accuratezza nel valutare lo stato di HER-2, è ragionevole aspettarsi un alto livello di concordanza tra le due tecniche, come ampiamente riportato in letteratura.

I risultati degli ultimi *trials* hanno reso ancora più emergente il problema di come e quando valutare HER-2 e quale algoritmo (FISH *vs* IHC) utilizzare, anche nell'ottica di una razionalizzazione delle risorse.

I dati della letteratura richiedono una concordanza fra IHC 3+ *vs* FISH del 90-95% ed una correlazione fra IHC 0 e 1+ *vs* FISH del 5-10%, con la necessità, nell'ambito di una *Quality Assurance*, di mantenere i livelli entro tali standard.

Poiché IHC e FISH possono costituire un controllo reciproco, sulla base dei dati sopra citati, l'algoritmo più accreditato in letteratura vede la conferma della concordanza FISH *vs* IHC superiore al 90%, nei casi IHC 3+ = amplificati e IHC 0 = non amplificati, con il suggerimento di sottoporre a FISH tutti i casi IHC 1+ e 2+, con l'ottenimento di una concordanza IHC 1+ / FISH superiore al 95%[24].

L'analisi critica dei nostri risultati, confrontando i livelli di concordanza nella casistica generale (Tabella 1) con quella proveniente dal laboratorio con implementati controlli di qualità reciproci (Tabella 2), mostra come tali standard di correlazione possano essere ottenuti solo con l'avvenuta pianificazione di un reciproco Standard di Qualità.

Infatti, la casistica ottenuta nel gruppo con controllo di qualità (Tabella 2), valuta attentamente ogni *step* sia nella fase preanalitica che analitica ed amplifica l'accuratezza diagnostica con l'utilizzo di anticorpi verso entrambi i domini di HER-2.

Inoltre la preselezione delle aree da esaminare con la metodica FISH, con l'eliminazione sia della componente in esubero e/o della componente *in situ* e/o della paraffina in eccesso, rende il test FISH ancora più preciso ed accurato.

Conclusioni

La nostra esperienza, su un'ampia ed eterogenea casistica di carcinomi mammari, con la contemporanea applicazione dei test FISH ed IHC, mostra come l'implementazione di accurati sistemi di Qualità Analitica, sia nella fase preanalitica che analitica, possa garantire un'alta concordanza tra i due test, in accordo con i dati della letteratura. Solo mantenendo tali livelli di qualità e concordanza si possono inviare a FISH i casi IHC 2+ e/o IHC 1+, mentre l'IHC può dare valori accurati nei casi IHC 3+ e 0.

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Doxorubicin-induced acute congestive heart failure associated with hypocalcaemia

Scompenso cardiaco acuto congestizio indotto da doxorubicina associato ad ipocalcemia

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Summary

A case of doxorubicin (adriamycin) – induced acute congestive heart failure associated with hypocalcaemia after an ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy regimen is reported. Hypocalcaemia and acute congestive heart failure were refractory to inotropic support and calcium infusion without associated phosphate or magnesium abnormality. Finally the patient died, despite every effort by the medical team, within twenty-four hours of receiving ABVD chemotherapy. The authors conclude that, in this type of recalcitrant heart failure, mechanical intervention, such as an intra-aortic balloon pump, should be planned and inserted at an early stage. Eur. J. Oncol., 11 (4), 259-261, 2006

Key words: **doxorubicin, cardiotoxicity, congestive heart failure**

Riassunto

Viene presentato un caso di scompenso cardiaco acuto congestizio indotto da doxorubicina (adriamicina), associato ad ipocalcemia, dopo un regime chemioterapico ABVD (adriamicina, bleomicina, vinblastina, dacarbazina). L'ipocalcemia e lo scompenso cardiaco acuto congestizio erano refrattari a supporto inotropico ed infusione di calcio senza associate anomalie del fosfato e del magnesio. Alla fine la paziente è deceduta, nonostante tutti i tentativi dell'*équipe* medica, entro 24 ore dal trattamento chemioterapico con ABVD. Gli Autori concludono che, in questo tipo di scompenso cardiaco refrattario, dovrebbe essere programmato ed inserito precocemente un supporto meccanico come una pompa a palloncino intraaortica. Eur. J. Oncol., 11 (4), 259-261, 2006

Parole chiave: **doxorubicina, cardiotossicità, scompenso cardiaco congestizio**

Introduction

Treatment methods used in patients with cancer may damage the heart in a variety of ways. Damage results from physical agents, such as ionizing radiation, and chemical agents, such as anthracyclines, cyclophosphamide and related substances. The combination of cardiac irradiation and anthracyclines produces additive or supra-additive toxicity[1].

The anthracycline quinone doxorubicin (adriamycin) is prescribed for the treatment of several human tumours and leukaemias and it is an integral component of most treatment regimens for Hodgkin's and non-Hodgkin's lymphoma. Despite its recognized effectiveness against

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so many neoplasias, the clinical success of doxorubicin is limited due to its dose-dependent and cumulative cardiotoxicity. Electrolyte abnormalities, especially hypokalemia, increase its acute cardiotoxicity with the onset of arrhythmias. A rare case of doxorubicin-induced acute congestive heart failure associated with hypocalcaemia is here reported.

Case report

A 30 year old woman, with a body surface area of 1.57 m^2, suffering from Hodgkin's lymphoma, stage IIa, nodular sclerosing type, presented with more than 4 sites of nodal involvement and mediastinal mass ratio > 0.35. She was treated with 6 cycles of combination chemotherapy, ABVD regimen (adriamycin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastine 6 mg/m^2 and dacarbazine 375 mg/m^2) from January 2004 to June 2004, followed by mantle field radiotherapy till September 2004. A reassessment CT scan showed good response to therapy.

The patient had a relapse in January 2005 and was sent to our hospital for salvage treatment. BEAM (carmustine 300 mg/m^2, etoposide 100 mg/m^2, cytarabine 200 mg/m^2, melphalan 140 mg/m^2) conditioning chemotherapy was given in May 2005 followed by stem cell auto-transplantation in June 2005. In September 2005, the patient again presented with breathlessness, right breast enlargement and multiple palpable lymph nodes; two more cycles of ABVD regimen were planned. A MUGA Scan was performed and showed left ventricular ejection of 48%; previously in May 2005 it was 52%.

On December 1st the patient was given ABVD regimen in day care and, shortly after the conclusion of the treatment, in the evening, she had uneasiness, shortness of breath and excessive sweating. On clinical examination her extremities were cold. She had crepitation and rhonchi in the chest, her pulse was 130/min and her blood pressure (BP) was 90/60 mmHg. Within a few minutes O_2 saturation started to fall, the pulse became feeble, the BP was unrecordable and the patient became drowsy and irritable. Oxygen was given through a facemask, but saturation was not detected by pulse oxymeter and bradycardia started. The patient was immediately given 1 mg atropine and ventilated with bag and mask: the bradycardia did not respond to atropine and the patient lost consciousness. She was intubated and connected to a ventilator, and intravenous atropine 1 mg was repeated after three minutes. After 4-5 minutes, the pulse was palpable, the BP was 80/50 mmHg and the patient started breathing irregularly with ventilator. Her chest was full of coarse crepitations and rhonchi, with an O_2 saturation of 85%. Intravenous morphine 5 mg and then again 3 mg were given. Infusion of dopamine 10 mcg/kg/min and dobutamine 10 mcg/kg/min was started and intravenous furosemide 40 mg was given and repeated after a few minutes. A central venous catheter was inserted into the right internal jugular vein and baseline central venous pressure (CVP) was 20 mmHg. In half an hour the patient regained consciousness and sense of orientation, but felt uneasiness due to the endotracheal tube; pulse was 100/min and BP was 80/60 mmHg. Infusion of morphine 1 mg/hr and midazolam 1 mg/hr was started, in order to sedate the patient. An arterial blood gas test (ABG) was performed which showed mild metabolic acidosis. On investigation, cardiac enzymes and electrolytes proved normal, except for the total calcium value, which was 6.4 mg/dl. Intravenous Ca-gluconate was given, 200 mg elemental Ca over 2 hr. After the next reading of calcium of 7.2 mg/dl, an infusion of Ca-gluconate 45 mg/hr was started. Within a few hours, the patient's chest became clear, but systolic BP never went above 80 mmHg and the calcium reading was still 7.6 mg/dl. The patient was evaluated by a cardiologist and was found to have S_3 and S_4 heart sounds. Immediate echocardiography was performed and showed a severe wall motion abnormality with ejection fraction of 20%. There was no pericardial effusion. Intra-venous inotropic drugs and calcium were given continuously through infusion.

The next day, in spite of full inotropic support and calcium infusion, her BP was still 80/50 mmHg. She was again evaluated by a cardiologist and intra-aortic balloon pump insertion was planned, but before this could be done, the BP and O_2 saturation started to fall, and inotropic support was increased to maximum level, including that of intravenous adrenaline.

At midday, the patient had cardiac arrest and was revived with bolus adrenaline and cardiac massage. She had two further cardiac arrests and finally expired, despite every effort by the medical team, within 24 hours of receiving ABVD chemotherapy.

Discussion

Anthracyclines are the best studied of the anticancer drugs with established cardiotoxicity. They cause acute, subacute and late cardiac complications.

Acute complications are observed in 0.4-41% patients[2-6]. These acute complications include non-specific ST changes, low voltage QRS complexes, sinusal tachycardia, ectopic ventricular and supraventricular beats, QT interval prolongation[2, 4, 7] and acute myocardial ischaemia[2,7,8]. These disturbances are usually asymptomatic or cause minor complaints, ceasing spontaneously several hours (arrhythmia) or weeks (changes in ST- T) after the completion of chemotherapy.

Less than 1% patients suddenly die of heart attack, probably connected with arrhythmia, some days after administration of doxorubicin[4-6, 9]. It has been observed that fatal complications occur mainly in the presence of co-existing electrolyte disorders[9]. Lacasse and Bolduc reported two cases of ventricular arrhythmias leading to sudden death associated with severe hypokalemia. These cases suggest a synergistic effect between anthracyclines and electrolyte disorders, resulting in the acute cardiotoxicity of these drugs. It is maintained that sudden deaths following heart attack are the result of the synergistic action of anthracycline antibiotics and/or their metabolites and potassium deficiency upon the conduction system[8-10]. Therefore, close monitoring of electrolyte levels is important[9].

Previously published cases have not reported death within 24 hours due to acute congestive heart failure with

calcium abnormality caused by doxorubicin toxicity. Bleomycin causes hypocalcaemia, which was given in the ABVD regimen[11]. Pegoraro and Rutecky[12] have also described doxorubicin-caused hypocalcaemia. Hypocalcaemia due to doxorubicin has also been reported by others authors, but in monkeys[13]. Low calcium values cause decreased cardiac contractility, which aggravates the underlying cardiac disease.

In this case, refractory hypotension, high CVP and low ejection fraction, suggesting acute congestive heart failure due to doxorubicin, presented as acute pulmonary oedema, which was managed initially with diuretics, inotropes and morphine, but heart failure persisted even after high doses of inotrope and diuretics. In this case, the synergistic action of doxorubicin and low calcium aggravated the acute heart failure and finally it became intractable. Even after a high loading dose of calcium and continuous infusion, hypocalcaemia remained unsolved without associated phosphate and magnesium abnormalities. Other factors that could have been responsible for this heart failure were ischaemia and myopericarditis, but a normal level of cardiac enzymes, the absence of pericardial effusion and normal ECG excluded these possibilities. Previous thoracic irradiation and repeated doses of anthracyclines were the risk factors for this acute congestive heart failure, although the dose of doxorubicin was low and the patient was young. Increased sensitivity to anthracycline-derived reactive oxygen species (ROS) is the most plausible explanation for the cardiotoxicity.

The relationship between acute and chronic cardiac toxicity is not clear. Acute toxicity is attributed to damage caused by ROS arising from 1-electron reduction of anthracyclines. It has been proposed that the chronic form results, at least in part, from the effects of anthracycline alcohols, which are generated by their 2-electron reduction by enzymes such as aldo-keto reductases and carbonyl reductases[14-16]. In addition acute cardiotoxicity is assumed to be due to an indirect effect associated with the intensive release of catecholamines and histamine[2,8,17], the release of free hydroxide radicals and a disturbed membrane transport of potassium, sodium and calcium ions[2,9].

Conclusion

Acute cardiotoxicity due to doxorubicin can develop at any time[18] and the probability is higher in patients with electrolyte imbalance. While potassium abnormalities increase arrhythmia, low calcium levels aggravate acute congestive heart failure, and intractable hypocalcaemia can even lead to death in acute congestive heart failure patients. In this type of refractory hypotension, due to acute congestive heart failure associated with hypocalcaemia, mechanical interventions, such as intra-aortic balloon pump insertion, should be performed at an early stage.

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Eur. J. Oncol., vol. 11, n. 4, pp. 263-264, 2006

Short congress report
Breve resoconto di congresso

International Meeting on Ipsilateral Breast Cancer Recurrence, London 12th, 13th October 2006
Convegno Internazionale sulle Recidive Ipsilaterali da Carcinoma Mammario, Londra, 12, 13 ottobre 2006

An important international meeting on "Ipsilateral breast cancer local recurrence" was held on the 12th and 13th of October 2006 in the elegant Cavendish Conference Centre in London.

The organizer of the meeting, Mr Guidubaldo Querci della Rovere, Consultant breast surgeon at the Royal Marsden Hospital, had prevously published with Mr John Benson, Consultant breast surgeon at Addenbrooks Hospital in Cambridge, a very interesting paper on the topic of ipsilateral breast cancer local recurrence in the presence or absence of micrometastases; in the paper the Authors discussed the Halstedian and Fisherian paradigms and proposed a randomised trial to test Bernard Fisher's hypothesis.

Opening the symposium, Mr John Benson explained that two dominant paradigms (the Halstedian and the Fisherian) of cancer pathogenesis have governed the management of breast cancer over the last Century. An intermediate paradigm is however now emerging due to the biological heterogeneity of breast cancers. According to the Halstedian paradigm, local recurrence should be interpreted as a determinant of distant metastases and therefore rapid diagnosis, radical and effective treatment should prevent dissemination of cancer cells. According to the Fisherian paradigm instead, local recurrence represents simply a marker of poor prognosis due to pre-existing micrometastases: in other words distant metastases will develop irrespective of the radicality of loco-regional treatment.

The newly emerging intermediate paradigm, encompassing elements from both Fisher and Halsted hypotheses, might be relevant; with the aid of molecular profiling of each tumour it might be possible in the future to distinguish between the two different types of behaviour and avoid under or over-treatment.

Professor Sarah Darby, on behalf of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) presented the most recent results of local therapy trials: the conclusion was that for every 4 local recurrences prevented by local treatment at five years one life is saved at twenty years.

Dr Sarah Pinder, Consultant breast pathologist at Addenbrooks Hospital in Cambridge, described modalities to try to differentiate a local cancer recurrence from a new breast primary cancer, either by traditional morphological histopathological assessment of the two lesions, or by means of more sophisticated techniques such as immunohistochemical phenotyping, DNA analysis and new molecular techniques, including examination of loss of heterozygosity, microsatellite instability and comparative genomic hybridisation, that are capable of detecting potential similarities and differences. Those investigations could give new insight into breast cancer prognosis as women with true local recurrences can have a worse outcome than those with a second primary carcinoma.

Professor Michael Baum delivered a thought-provoking lecture: "Does surgery accelerate the appearance of distant metastases?". He put forward the hypothesis that the act of surgery has a deleterious effect by stimulating angiogenesis and distant metastases. He supported his hypothesis by analysing the hazard ratios of women treated for early breast cancer and demonstrating a high peak of local recurrence at 2 years, followed by wider flatter peak extending over the 5-7 year period. The

first could be related to the surgical procedure and the second to the natural cancer progression, modulated by different cancer treatments.

Dr Hiram Cody, of the Sloan Kattering Medical Center in New York, supported the view that ipsilateral breast cancer local recurrence affects survival rate.

The opinions on the significance of ipsilateral breast cancer recurrence were presented by speakers from England, Wales, Scotland, Ireland, Spain, Greece, and Italy.

Dr Maurizio Nava, from the Istituto Nazionale Tumori in Milan, discussed the relevant rôle of oncoplastic surgery which, in selected cases, can avoid a mastectomy or achieve wider margins of excision.

Dr Gillian Ross, Consultant clinical oncologist at the Royal Marsden Hospital, discussed the possible benefits and disadvantages of partial breast irradiation.

Mrs Hazel Thornton, Honorary Visiting Fellow from the Department of Health Sciences, University of Leicester, provided the opinion of the patient. She stressed the need not only of the best possible medical treatment but also of the necessity of human sensitivity whilst communicating with patients and choosing balanced strategies to treat cancer.

Dr Stephen Johnston, Consultant medical oncologist at the Royal Marsden Hospital, acknowledged that breast cancer local recurrence is associated with a worse prognosis, but stated that at present we have no knowledge of whether systemic treatment at the time of local recurrence improves survival.

Dr Stefan Aebi, medical oncologist from Berne University Hospital, stressed the need for an international multi-centre randomized clinical trial to evaluate the benefit of systemic treatment at the time of local recurrence. Dr Aebi is the leading investigator of an international trial (ibcsg27-02-big1-02@ibcsg.or).

The following conclusions were reached at the end of the open debate: the Fisherian paradigm is correct in 75% of cases, but 25% of breast cancers behave in a Halstedian way.

It is impossible at present to distinguish how each individual cancer is going to progress.

Breast conservation surgery and radiotherapy should remain the treatment of choice in most cases.

Complacency towards local recurrence should be discouraged.

If local recurrence rates can be kept at about 1% per annum there is no need for more aggressive local treatment.

If, after breast conservation surgery and radiotherapy, the characteristics of the patient and the tumour indicate that mastectomy would decrease the risk of local recurrence at five years by >10%, this should be considered and discussed with the patient.

Beniamino Palmieri
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University Hospital of Modena
and Reggio Emilia, Italy
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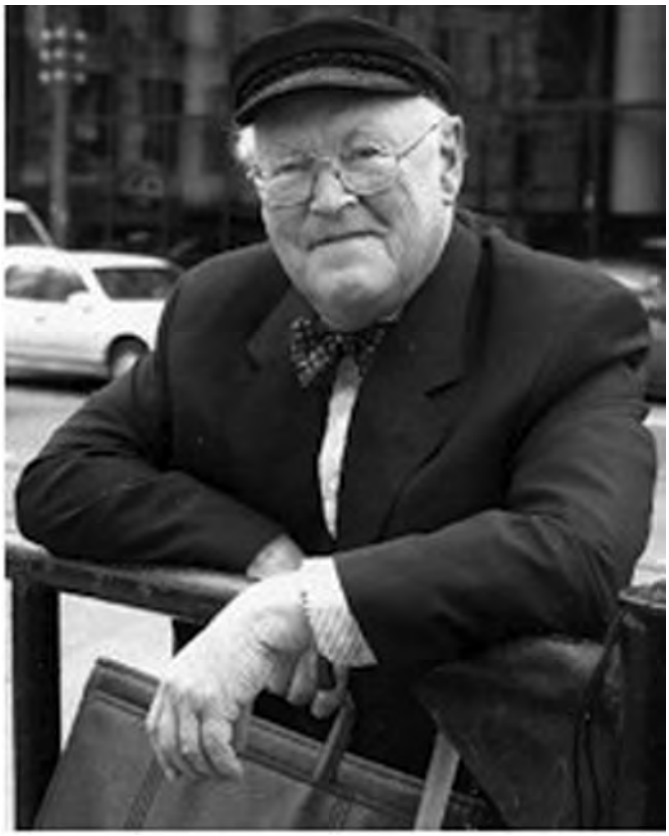
Doctor David V. Bates
(1922-2006)



David V. Bates, M.D. died peacefully at his home in Vancouver, Canada on 21st November 2006. Professor Bates was a superb Fellow of the Collegium Ramazzini. He was a skilled physician and a noted researcher who focussed his work on the diseases of the lung, and especially on the diseases caused by asbestos, silica and other toxic dusts. He was a gifted teacher. He was a man of great courage who was never afraid to speak truth to power.

Born in West Malling, Kent, on 20th May 1922, David Bates received his medical education in England and then moved to Canada. He served as Dean of the School of Medicine of the University of British Columbia from 1972 to 1977. He was inducted into the Order of Canada in 2003. He was poet, a voracious reader, a gifted academic, a scientist, a mentor, a gardener and a vintner.

I came to know Dr Bates in the 1980s when we served together on a committee at the US National Academy of Sciences investigating the human health effects of air pollution. From the beginning I was captivated by this warm, talented and courageous man who was always ready to extend the hand of friendship and never shy about expressing his views. I remember especially that David put me in touch with a long lost branch of our family, whom we had not seen for several generations after they had emigrated to Canada.

David Bates was a dear friend and a true follower of Ramazzini. We shall miss him deeply.

Philip J. Landrigan
President, Collegiun Ramazzini
Professor and Chairman
Department of Community and Preventive Medicine
Professor of Pediatrics
Mount Sinai School of Medicine
New York, NY, USA

INDICE

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European Journal of Oncology

Official Organ of the Italian Society of Tumours (SIT)
Prevention, Diagnosis, Therapy

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Bernardino Ramazzini
Biography and bibliography
Biografia e bibliografia

Pericle Di Pietro

First volume of the "Ramazzini Library" series. Dedicated to the life and work of Bernardino Ramazzini, acknowledged founder of occupational medicine, by Professor Pericle Di Pietro, authority on the Master from Carpi. English and Italian Texts.

Primo volume della collana "Ramazzini Library". Dedicata alla vita e alle opere di Bernardino Ramazzini, riconosciuto fondatore della medicina del lavoro, è opera del Professor Pericle di Pietro, illustre conoscitore del grande Maestro carpigiano. In lingua italiana e in inglese.

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Issue	1

Foreword

The European Journal of Oncology is publishing a monograph dedicated to Bernardino Ramazzini (biography and bibliography) (GEO/ EJO Library, vol. 1) by Professor Pericle Di Pietro, the well-known authority on the life, works and cultural legacy of the Maestro from Carpi. This monograph was commissioned from the eminent scholar by the Collegium Ramazzini.

The text is in Italian with a parallel English translation, and is illustrated with plates giving the original documentation in essential form.

The Scientific Editors of the journal are indebted to Professor Di Pietro for his generosity in undertaking a text, which will surely remain a landmark in the historiography of Bernardino Ramazzini.

Ramazzini's contribution stands as a milestone in the history of medicine. Not only is he the acknowledged founder of Occupational Medicine; he it is who clarified the fact that many diseases are exogenous in origin and hence preventable; he it is to whose vigour and originality we owe the notion that "Longe praestantius est praeservare quam curare, sicut satius est tempestatem praevidere ac illam effugere quam ab ipsa evadere", which is to say "it pays far more to prevent than to treat, since it is easier to anticipate and avoid the disease than to shake it off".

The lesson of Ramazzini remains acutely topical, as happens with the work of the great pioneers and anticipators of history.

There are many reasons why an oncology journal like ours should think fit, as a duty even, to publish a monograph on Bernardino Ramazzini.

Firstly, tumours are now a largely exogenous disease. The epidemiological proportions they have taken on in our times are due not only to population ageing, but to environmental pollution and a characteristic industrial era lifestyle.

In the present day scenario, moreover, many of the populations most at risk of cancer are from the categories of industrial worker.

Again, as many tumours are caused by exogenous agents, which are hence removable, they form a paradigm case of a disease in controlling which prevention is the main and most incisive course of action.

It should not, lastly, be forgotten that Ramazzini's specific contribution to oncology – in what may be seen as the first "aetiological epidemiology" research in the history of the discipline – that is, the observation of an increased risk of mammary cancers among nuns, anticipates the scientific evidence on the subject by some two and a half centuries: he makes a strict connection of these tumours with women's reproductive and hormonal patterns and, even more specifically, with the fact that the nullipara belongs to a bracket of the population at risk.

Written in the year 2000

Cesare Maltoni†
Scientific Director of the
European Ramazzini Foundation and
Secretary General of the Collegium Ramazzini

Presentazione

Il Giornale Europeo di Oncologia pubblica questa monografia dedicata a Bernardino Ramazzini (biografia e bibliografia) (GEO/EJO Library, Vol. 1), ad opera del Professor Pericle Di Pietro, illustre conoscitore della vita, delle opere e della eredità culturale del grande Maestro carpigiano. Questa monografia era stata richiesta all'illustre studioso dal Collegium Ramazzini.

Il testo esce in lingua italiana e in traduzione inglese, ed è illustrato da alcune figure che riproducono in maniera essenziale una documentazione originale.

I Direttori Scientifici della Rivista sono profondamente grati al Professor Di Pietro per l'impegno profuso a scrivere un testo, che certamente rimarrà un punto di riferimento nella storiografia di Bernardino Ramazzini.

Il contributo di Ramazzini rappresenta una grande pietra miliare nella storia della medicina. Ramazzini non solo è il riconosciuto fondatore della Medicina del Lavoro; è anche Colui che con precisione ha indicato che molte malattie sono di origine esogena e perciò prevenibili, e che ha introdotto con assoluta originalità e con forza il concetto che "Longe praestantius est praeservare quam curare, sicut satius est tempestatem praevidere ac illam effugere quam ab ipsa evadere", cioè che "è di gran lunga più conveniente prevenire che curare, poiché è più agevole prevedere la malattia ed evitarla, che liberarsi da essa".

La lezione di Ramazzini rimane oggi di grande attualità come capita per l'opera dei grandi pionieri che hanno anticipato la storia.

Le ragioni per cui una rivista di oncologia, come è la nostra, ha ritenuto opportuno, ed anzi un suo compito preciso, pubblicare la monografia "Bernardino Ramazzini" sono molteplici.

Innanzitutto i tumori sono oggi una malattia in larga misura di origine esogena: infatti la dimensione epidemiologica che essi hanno assunto nei nostri tempi è dovuta, oltre che all'invecchiamento delle popolazioni, anche all'inquinamento ambientale e agli stili di vita, caratteristici dell'era industriale.

Inoltre nell'attuale scenario molte delle popolazioni a maggiore rischio di cancro sono proprio categorie di lavoratori dell'industria.

Ancora, siccome molti tumori sono causati da agenti esogeni e quindi rimovibili, essi rappresentano un esempio emblematico di malattia per il controllo della quale la prevenzione rappresenta il maggiore e più incisivo intervento.

Non va dimenticato, infine, il contributo specifico di Ramazzini all'Oncologia, con quella che può essere considerata storicamente la prima ricerca "epidemiologica eziologica" oncologica, e cioè l'osservazione di un aumento del rischio di cancro mammario nelle monache, anticipando così di circa due secoli e mezzo l'evidenza scientifica che il rischio mammario è strettamente connesso alla storia riproduttiva e ormonale della donna e, in maniera più specifica, che le nullipare rappresentano una fascia di popolazione a maggiore rischio.

Edito nell'anno 2000

Cesare Maltoni†
Direttore Scientifico della Fondazione
Europea Ramazzini e
Segretario Generale del Collegium Ramazzini

The Precautionary Principle
Implications for research and prevention in environmental and occupational health

P. Grandjean, M. Soffritti, F. Minardi, J.V. Brazier (Editors)

Second volume of the "Ramazzini Library" series. Proceedings of the International Conference "The Precautionary Principle. Implications for Research and Prevention in Environmental and Occupational Health", held in Bologna, Italy, in October 2002. English text

Secondo volume della collana "Ramazzini Library". Raccoglie gli atti del Convegno Internazionale "Il Principio di Precauzione. Implicazioni per la Ricerca e la Prevenzione nella Medicina Ambientale e del Lavoro", svoltosi a Bologna nell'ottobre del 2002. In lingua inglese

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Preface

By his effort over the millenia, man has surely been the motor driving what is called "development", by which we mean productive growth, technological progress, innovation, welfare and availability of goods.

Human effort on this planet of ours has been the chief factor determining the quality of the environment in which man has lived. In its turn, the quality of the environment has conditioned the gamut of pathologies that have progressively set in and, as a result, the state of human health.

But whereas man in the past ages had to defend himself from nature's aggressions in order to survive on the planet, nowadays, if he is to go on living, and above all give future generations a chance of doing so, he must take steps to protect nature from himself.

Such positive action will only be possible if one bears in mind certain inescapable starting assumptions: 1) our planet is in all likelihood unique as a biological scenario; 2) it is finite and so are its raw material and environmental resources; 3) there is a legitimate escalation in human demands.

But if such assumptions cannot be gainsaid, we must ask ourselves: is the current development model compatible with finite resources and legitimate growing human demands? And if the current development model is not compatible, what other form might it take and, above all, how might this be achieved?

To answer these questions we must rise above the ambiguities and irresponsibilities upon which our present development model is based, namely:

– first, that of taking it for granted that the answers to the main problems are essentially technological, economic and political in nature;
– second, that of assuming this development model to be unique, or at least a lesser evil, and that only its internal mechanisms may be adjusted, while the overall design of it cannot be changed, not to mention replaced by alternative models;
– lastly, the failure to recognize that what we hail as progress and creative expression by modern man has brought with it an artificial expansion of production and consumerism, aptly summed up in the fad for "disposable" wares.

Under the social, economic and political impact of the problem of reconciling development, environment and health, dare we claim nowadays to possess the right cognitive tools to guide our decisions towards so-called compat-

ible development? The answer may be yes. We do today possess a lot of scientific tools which can be used to predict (rather than observing later) the effects of development strategies which are mainly (though not entirely) geared to maximizing profits and petty group interests.

One classic case is the long-term carcinogenicity trials on experimental animals to identify carcinogens. When properly planned and conducted, above all when closely reproducing human exposure scenarios, such trials can give precise indications as to agent carcinogenicity and environmental risks conditions, the time-scale being relatively short (2-3 years). The results of such studies can be extrapolated to man, in both qualitative and quantitative terms, and thus form the most effective instrument for predicting the carcinogenic hazard of such agents.

Safeguarding the environment, public health and the quality of life is a planet-wide issue, an integral part of any strategy to achieve a more physiological development model, harbouring resources whilst more fairly satisfying the legitimate claims of the whole world population.

It is quite true that many mistakes have been made, many disasters caused: our society today is justly disoriented. But all is lost? Certainly not. If man takes the situation in hand, without leaving the initiative to egoism or letting things slide, there is clearly hope.

Science can make an important contribution, bringing about a change of course.

But science must be free to identify the problems, set priorities, decide its own programmes, assess the results as they come in; above all it must establish relations with society, and society must make use of its contribution. These relations, however, must not undermine its independence: in other words, the relationship is one of interaction and interdependence, not dependency.

Is all feasible? Maybe it is, probably the time is ripe. At all events, we must strive to think the answer is yes.

In this context, the Precautionary Principle approach to governing the regaining of a just equilibrium between development, environment and health represents an adequate approach augured by many.

The Collegium Ramazzini is grateful to Professor Philippe Grandjean for promoting and organizing the Workshop on the “Precautionary Principle: implications for research and prevention in environmental and occupational health”. This has reviewed what scientific basis we possess today for properly applying the Precautionary Principle to safeguarding the environment and public health.

The Collegium Ramazzini is also grateful to the Emilia-Romagna Region, the European Environmental Agency, the Ramazzini Foundation, the World Health Organization, the National Institute of Environmental Health Sciences, the National Institute of Occupational Safety and Prevention, the Regional Agency for Health Prevention and Environmental Protection in the Emilia-Romagna Region, the Province of Bologna and the Municipality of Bentivoglio, as well as to industry. Our thanks to all of them for their generous support.

Morando Soffritti
Scientific Director of the
European Ramazzini Foundation of Oncology and
Environmental Sciences and
Secretary General of the Collegium Ramazzini

Ban on asbestos in Europe
Messa al bando dell'amianto in Europa

C. Bianchi, M. Soffritti, F. Minardi, J.V. Brazier (Editors)

Third volume of the "Ramazzini Library" series. Proceedings of the International Conference "Ban on Asbestos in Europe", held in Monfalcone, Italy, in February 2003. English text, with summaries in English and Italian

Terzo volume della collana "Ramazzini Library". Raccoglie gli atti del Convegno Internazionale "Messa al Bando dell'Amianto in Europa", svoltosi a Monfalcone nel febbraio del 2003. In lingua inglese, con riassunti in inglese e italiano

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Presentation

The Proceedings of the Conference on asbestos in Europe, held in Monfalcone in 2003, are published at a time of great relevance in European history. Starting in May 2004, the European Union will enlarge eastwards so that it will include a large part of our micro-continent. Huge problems, cultural as well as economic and political, will have to be to faced and resolved. The asbestos problem may be considered as a paradigm. Europe is affected by an epidemic of tumours induced by asbestos. Of such an epidemic it is not easy to predict the end. Asbestos consumption reached a peak in Europe in the 1970s. Since the mean latency periods of asbestos-related mesothelioma are about 50 years, a further worsening of the situation has to be expected over the next decades. Furthermore the diagnosis of mesothelioma is seldom timely and the results of treatment are still usually disappointing.

Asbestos legislation in Europe has been extremely heterogeneous. Once again the serious delays have demonstrated that scientific knowledge and political decisions run on parallel tracks. However, the most worrying factor is that the asbestos tragedy does not seem to have taught any lessons. The uncontrolled use of substances, the carcinogenic effect of which is well known continues, as does the use of substances whose long-term effects are completely unknown. Increasing risks are encountered in the sector of physical agents (e.g. electromagnetic fields), and the destruction of the environment continues.

Even in the case of asbestos, the European Union presents itself as a virtuous brother, whose example should be followed. However, there are some macroscopic exceptions. Still in the year 2000, Greece was the first among the "minor" asbestos producers, and the mineral was still used in the Iberian peninsula. Moreover, recent estimates show that, even in the virtuous European Union, great attention does not seem to be devoted to occupational cancer.

The contributions published in this book are not only a presentation and a discussion of scientific, historic, and legislative data. They are also a further call to change the course of events.

The asbestos tragedy has been the result of a series of mistakes. It is not by chance that the call comes from an area such as Monfalcone: an area, where a majority of families have a member struck by asbestos-related diseases. A large number of people exposed to asbestos over the last decades, now healthy, remain at high risk for asbestos disease. A campaign for the surveillance of this population has already been started. But the aim of the research is to identify ways of neutralizing the asbestos present in the tissues of a large number of people.

Presentazione

Gli Atti del Convegno sull'amianto in Europa, svoltosi a Monfalcone nel 2003, vengono pubblicati in un momento di grande portata storica. Dal maggio 2004 l'Unione Europea si ingrandirà verso est in modo da comprendere larga parte del nostro microcontinente. Immensi problemi culturali, economici e politici, dovranno essere affrontati e risolti. Il problema amianto può essere considerato un paradigma significativo. L'Europa è coinvolta da un'epidemia di tumori indotti dall'amianto, epidemia di cui non è facile prevedere la fine. I consumi di amianto hanno toccato il vertice in Europa negli anni '70 dello scorso secolo. Poiché i tempi medi di incubazione del mesotelioma da amianto si aggirano sui 50 anni, è da attendersi un peggioramento della situazione nei prossimi decenni. Inoltre per questo tumore la diagnosi non riesce ad essere tempestiva e la terapia rimane per lo più deludente.

La legislazione sull'amianto nel continente è stata estremamente disomogenea. Si sono verificati gravi ritardi, dimostrando ancora una volta che le conoscenze scientifiche e le decisioni politiche viaggiano su binari paralleli. Ma l'elemento più preoccupante è che la tragedia amianto sembra non aver insegnato niente. L'uso incontrollato di sostanze di cui si conosce l'effetto cancerogeno continua, come pure continua l'uso di sostanze di cui si ignorano del tutto gli effetti a lungo termine. Rischi sempre maggiori si incontrano nel campo degli agenti fisici (p.es. campi elettromagnetici) e continua lo scempio dell'ambiente.

Anche nel caso dell'amianto l'Unione Europea si presenta come un fratello virtuoso, del quale bisogna seguire l'esempio. Ma con qualche vistosa eccezione. Nel 2000 la Grecia era ancora il capofila tra i "piccoli" produttori di amianto e il minerale era ancora in uso nella penisola iberica. Inoltre anche nella virtuosa Unione Europea sembra non si presti molta attenzione ai tumori professionali, come recenti stime dimostrano.

I contributi riuniti in questo volume non sono solo un'esposizione e una discussione di dati scientifici, storici, legislativi. Sono anche un ulteriore richiamo ad invertire la rotta.

La tragedia amianto è stata il risultato di una sequenza di errori. Non è casuale che il richiamo venga da un'area come quella di Monfalcone: una zona dove la maggioranza delle famiglie ha avuto un proprio membro colpito da malattie asbesto-correlate. Un gran numero di persone esposte negli ultimi decenni e attualmente sane rimane ad alto rischio per malattie da amianto. Una campagna per la sorveglianza di tale popolazione è già stata avviata. Ma l'obiettivo della ricerca è individuare vie attraverso le quali neutralizzare l'amianto presente nei tessuti di un gran numero di persone.

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Genetic testing at work
Ethical and legal implications
Test genetici nell'ambito lavorativo
Implicazioni etiche e legali

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F. Minardi, J.V. Brazier (Editors)

Fourth volume of the "Ramazzini Library" series. Proceedings of the International Conference "Genetic Testing at Work. Ethical and Legal Implications", held in Carpi, Italy, in October 2003. English text, with summaries in English and Italian.

Quarto volume della collana "Ramazzini Library". Raccoglie gli atti del Convegno Internazionale "Test Genetici nell'ambito Lavorativo. Implicazioni etiche e legali", svoltosi a Carpi nell'ottobre del 2003. In lingua inglese, con riassunti in inglese e italiano

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Introductory remarks

The Committee on Ethics of the Collegium Ramazzini decided some time ago to organize a special workshop on ethical issues related to occupational genetic testing as part of the Collegium's Annual Ramazzini Days 2003. With the generous support of the Collegium Secretariat in Bentivoglio, the endeavour was realized as a one-day symposium on 24th October at the former Convent of San Rocco in the historical town of Carpi, birthplace of Bernardino Ramazzini.

The timeliness of the topic relates to the rapid developments of molecular genetic techniques which allow potential applications in various biomedical fields with societal impact and interest. This concerns also the workplaces, with the possibilities that employers, either current or prospective, might be interested in applying the new genetic methods to select the best, fittest and healthiest job applicants or employees on the basis of their molecular genetic profile. This presumption is based on the idea that genetic tests might predict our future health and potential need for sick leave, thus leading to lower work efficacy and less economic profits. Such presumptive thinking needs to be openly discussed and analysed within the Collegium Ramazzini to bridge the science with the social and political impact, within the objective of the Collegium to conserve life and prevent disease.

The symposium comprised excellent lectures by guest speakers and Collegium Fellows followed by lively debates among all international participants. This proceedings volume collects the keynote lectures, but unfortunately leaves the comments and discussions for the imagination of the readers. A long and complex chain of potentially "ethically risky" behaviour is identified in the papers included. The true predictivity of present tests is questionable, both scientifically and statistically; the principle of free and informed consent is often dubious; and the ethical principles of beneficence, non-maleficence and respect for autonomy are vulnerable in global commercialisation and mass marketing of genetic tests. Legal rules and ethical codes have been established and this development should be encouraged to protect the well-being of workers.

This proceedings volume calls for further ethical discussions among its readers, persons involved with occupational safety and health issues and researchers on genetic susceptibility at work.

The organisers and the General Secretariat of the Collegium Ramazzini sincerely thank all authors and participants of the Carpi symposium for their valuable contributions.

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