EUR. J. ONCOL.; Vol. 19, n. 3, pp. 144-149, 2014

Use of non-conventional medicines by cancer patients

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Summary. *Background:* The number of cancer patients undergoing anticancer treatment who concomitantly take non-conventional medicines is increasing. Among cancer patients the use of non-conventional medicines, often in the form of self-medication, is intended to counteract the side-effects of cancer treatment, alleviate symptoms or strengthen the immune system. *Aim of the work:* The present study aimed to evaluate how widespread the practice is and to identify the possible interactions between non-conventional medicines and cancer therapies. *Methods:* This research was an observational prospective study of about 10 weeks. One hundred and forty-three patients undergoing cancer treatment in our day hospital were interviewed about their use of non-conventional medicines. *Results:* 35.7% (51/143) of patients reported taking vitamin or mineral supplements, 22.4% (32/143) take medicinal herbs and 4.9% (7/143) homeopathic remedies. 75% (24/ 32) using medicinal herbs were <64 years old and 78.1% of such patients (25/32) had a higher level of education. These data are in accord with the results from a survey carried out on cancer patients (n=1498) at a hospital in Coventry, UK, where the prevalence of medicinal herb use was 19.7% (95% CI: 17.4–22.1; n= 223). *Conclusion:* A significant number of cancer patients undergoing treatment with anticancer drugs also make use of non-conventional medicines, medicinal herbs being the most commonly used. Clinicians and patients should thus be educated as to the proper use of medicinal herbs to minimise the risk of related interactions.

Key words: non-conventional medicines, drug interaction, cancer therapies

«Uso di medicinali non convenzionali da parte di pazienti con tumore»

Riassunto. *Introduzione:* Il numero di pazienti oncologici sottoposti a trattamento antitumorale che assumono medicine non convenzionali è in aumento.Tra i pazienti oncologici l'uso di medicine non convenzionali, spesso sotto forma di auto-medicazione, ha lo scopo di contrastare gli effetti collaterali del trattamento oncologico, alleviare i sintomi o rafforzare il sistema immunitario. *Scopo del lavoro:* Il presente studio mira a valutare quanto sia diffusa questa pratica e individuare le possibili interazioni tra le medicine non convenzionali e le terapie oncologiche. *Metodi:* E' stato condotto uno studio osservazionale prospettico di 10 settimane. 143 pazienti sottoposti a trattamento oncologico presso il nostro day hospital sono stati intervistati circa il loro uso di medicine non convenzionali. *Risultati:* Il 35,7% (51/143) dei pazienti ha riportato l'assunzione di integratori vitaminici o minerali, il 22,4% (32/143) di erbe medicinali e il 4,9% (7/143) di rimedi omeopatici. Il 75% dei pazienti (24/32) che ha dichiarato di assumere erbe medicinali aveva età <64 anni e il 78,1% di questi pazienti (25/32) aveva un livello di scolarizzazione elevato. Questi dati sono in linea con i risultati di un sondaggio effettuato su pazienti affetti da cancro (n = 1498) in un ospedale a Coventry, nel Regno Unito, dove la prevalenza di uso di erbe medicinali è stato del 19,7% (IC 95%: 17,4-22,1; n = 223). *Conclusione:* In conclusione, un numero significativo di pazienti oncologici sottoposti a trattamento con farmaci antitumorali utilizza medicine non convenzionali, soprattutto erbe medicinali. I clinici e i pazienti dovrebbero essere istruiti sul corretto uso di erbe medicinali per ridurre al minimo il rischio di interazioni con le terapie oncologiche.

Parole chiave: medicine non convenzionali, interazioni farmacologiche, terapie oncologiche

Background

Cancer statistics show that 7% of patients take medicinal herbs (1). Self-medication is often used to contrast the effects of cancer treatment, to relieve symptoms, to enhance the immune system and to cope with other concomitant medical conditions (2, 3). However, some medicinal herbs can cause problems not related to cancer, and can interfere with traditional cancer treatments, *e.g.* St. John's Wort speeds up the elimination time of imatinib by 44% (4). However, many people believe that 'natural' remedies are harmless (3, 5). One study of patients taking warfarin indicated that only 28% believed that other medicinal herbs could interact with the drug (6). Due to the possibility of undesirable side-effects or interactions, cancer patients undergoing treatment are generally advised to inform their oncologist if they are taking other substances (7). The majority of patients believe that non-conventional medicines are natural and not, therefore, noxious. Furthermore, both medical professionals and patients often have a limited awareness of the potential negative interactions between conventional and non-conventional treatments.

A multinational European survey found that medicinal herb products are by far the most commonly used group of treatments, with 5.3% of healthy individuals using them and 13.9% (5) of subjects using them after a diagnosis of cancer. Many cancer patients take natural substances because they are convinced that these have a therapeutic effect on the tumour and are safe and devoid of side-effects. The increasing use of non-conventional medicines by those with cancer is well documented (6). However, the risk of potentially harmful drug interactions remains (7). There would seem to be a culture of silence and professional disinterest in relation to the use of non-conventional medicines, *i.e.* patients may be reluctant to discuss their use of these substances in the presence of health workers or clinicians, and medical professionals may underestimate the potential relevance of such a practice (8).

Aim of the study

This study explored the use of non-conventional medicines (medicinal herbs, vitamin or mineral supplements, homeopathic remedies) by adult patients undergoing treatment at the Day Hospital (DH) of the IRST IRCCS Cancer Centre (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori) in Meldola, Italy; it also evaluated the possible interactions between non-conventional medicines and the cancer therapies.

Method

Our study analysed data obtained from a questionnaire completed by interview with cancer patients undergoing chemotherapy at the Day Hospital of IRST IRCCS.

2.1. Patient enrolment

One hundred and forty-five eligible patients (> 18 years old, diagnosis of invasive cancer at least three months previously, subjected to adjuvant, neoadjuvant or palliative antineoplastic chemotherapies [including experimental ones]) were selected from the electronic medical records database of the institute. Two patients refused to respond to the questionnaire, and a total of 143 patients were interviewed after being fully informed about the aim of the study.

2.2. Survey

The questionnaire was created after a comprehensive review of the scientific literature on the use of non-conventional medicines by cancer patients. The closed questions included in the questionnaire explored socio-demographic characteristics (age, gender, employment), characteristics related to the disease (tumor type, anticancer drugs taken) and the use of medicinal herbs, vitamin or mineral supplements and homeopathic remedies. The questionnaire included a list of the most widely used non-conventional medicines and respondents were asked to indicate which one(s) they took, adding the names of any products when these were not reported in the list.

Potential pharmacokinetic interactions and/or pharmacodynamics between the anti-cancer treatments and the non-conventional medicines taken by patients were evaluated.

The χ^2 test and Fisher's exact test were used to identify the association between demographic characteristics and the use of medicinal herbs, vitamin or mineral supplements and homeopathic remedies. A value of $p < 0.05$ was considered statistically significant.

Results

Out of 145 patients contacted, 143 (98.6%) agreed to complete the questionnaire. The socio-demographic characteristics, use of non-conventional medicines and tumour types of patients are reported in Table 1. 59.4% (85/143) were women and 40.6% (58/143) men, the median age being 64. 55.2% (79/143) were < 65 years old; 48.3% (69/143) of respondents had a primary level of education (elementary, junior high), while 51.7% (74/143) had a secondary level (senior high, graduate, post-graduate). Patients with gastrointestinal cancer (oesophagus, colon, pancreas, rectum, stomach and biliary tract) constituted the largest group by number, amounting to almost a third of the patients surveyed, 31.5% (45/143), followed by patients with breast cancer 21.7% (31/143). Patients with less frequent forms of cancer (7.7%, 11/143) were placed in the "other" group.

35.7% of patients (51/143) took vitamin or mineral supplements and 7.9% (41/143) took homeopathic remedies. 22.4% (32/143) stated that they used medicinal herbs habitually; of these 71.9% (23/32) were female and 75% (24/32) were under 64. 78.1% (25/32) of patients that were taking medicinal herbs had a higher level of education (senior high, graduate, post-graduate).

The χ^2 test and Fisher's exact test were used to determine the association between socio-demographic characteristics, cancer-related characteristics and the use of non-conventional medicines (Table 1). The intake of medicinal herbs was significantly correlated

Table 1. Analysis of the association between non-conventional medicines and patient/clinical characteristics *

Features	Patients	Use of medicinal herbs			Use of vitamin or mineral supplements			Use of homeopathy		
		Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
	N° cases	N° cases (%)	N° cases (%)		N° cases (%)	N° cases (%)		N° cases (%)	N° cases (%)	
Gender										
Males	58	9 (28.1)	49 (44.1)	0.1039	16 (31.4)	42 (45.7)	0.0957	2 (28.6)	56 (41.2)	0.7011
Females	85	23 (71.9)	62 (55.9)		35 (68.6)	50 (54.3)		5 (71.4)	80 (58.8)	
Age, years										
≤ 64	79	24 (75.0)	55 (49.5)	0.0107	30 (58.8)	49 (53.3)	0.5216	5 (71.4)	74 (54.4)	0.4601
> 64	64	8 (25.0)	56 (50.5)		21 (41.2)	43 (46.7)		2 (28.6)	62 (45.6)	
Education										
Primary school	69	7 (21.9)	62 (55.9)	0.0007	20 (39.2)	49 (53.3)	0.1074	1 (14.3)	68 (50.0)	0.1174
Secondary school	74	25 (78.1)	49 (44.1)		31 (60.8)	43 (46.7)		6 (85.7)	68 (50.0)	
Pathology system										
Gastrointestinal	45	8 (25.0)	37 (33.3)		18 (35.3)	27 (29.3)		0 (0.0)	45 (33.1)	
Breast	31	10 (31.3)	21 (18.9)		14 (27.5)	17 (18.5)		3 (42.9)	28 (20.6)	
Haematologic	23	7 (21.9)	16 (14.4)		4 (7.8)	19 (20.7)		4 (57.1)	19 (14.0)	
Respiratory and oral	17	2 (6.3)	15 (13.5)	0.4280	4 (7.8)	13 (14.1)	0.2788	0 (0.0)	17 (12.5)	0.0443
Female urogenital system	11	2 (6.3)	9 (8.1)		5 (9.8)	6 (6.5)		0 (0.0)	11 (8.1)	
Male urogenital system	5	0 (0.0)	5 (4.5)		1 (2.0)	4 (4.3)		0 (0.0)	5 (3.7)	
Others	11	3 (9.4)	7 (7.2)		5 (9.8)	6 (6.5)		0 (0.0)	11 (8.1)	

* information retrieved from questionnaire completed by 143 patients

with age and level of education. Patients > 64 years who used non-conventional medicines and younger users were compared (25.0% *vs.* 75.0%; $p = 0.0107$). Patients with a primary level of education (elementary, junior high) who took medicinal herbs were compared with users with a level of medium-high education (senior high, graduate, post-graduate) (21.9% *vs.* 78.1%; $p = 0.0007$). No significant relation was found between socio-demographic characteristics or cancer-related factors and the use of vitamin or mineral supplements. Conversely, statistical analysis highlighted a significant correlation between the use of homeopathic products and patients with haematological malignancies or breast cancer (N. 4, 57.1% and N. 3, 42.9%, respectively; $p = 0.0443$).

The list of medicinal herbs reported in the questionnaire comprised 19 remedies, only 10 of which were used by at least one interviewed; a further 47 remedies were indicated directly by patients. Bilberry (Vaccinium myrtillus) was the most commonly used product (16.1%, 5/32), followed by curcuma (Curcuma longa) and fennel (Foeniculum vulgare).

Conclusion

The data obtained on the use of medicinal herbs during chemotherapy is in line with findings reported in the literature. Interesting evidence also emerged from a search of the literature on the properties of medicinal herbs and their possible interactions with anticancer drugs. Of the 32 patients in our study who reported taking well-documented medicinal herbs during cancer therapy, 13 were identified as being at risk of an interaction and clinically significant related toxicities. Furthermore, a number of the patients were using medicinal herbs that are known to interact pharmacokinetically with cancer treatment, especially drugs metabolized by cytochrome P450 (CYP450). One patient with high-grade non-Hodgkin's lymphoma undergoing therapy with cyclophosphamide, adriamycin, vincristine, prednisone and rituximab (DLBCL protocol) reported taking the following medicinal herbs: bilberry (Vaccinium myrtillus), blackcurrant (Ribes nigrum) and elderberry (Sambucus nigra). Vincristine is metabolised by CYP3A4, an isoform of the CYP450 (9). The intake of prednisone causes a slight increase in the expression of this isoform (10), whereas maslinic acid, corosolic acid and ursolic acid contained in extracts of bilberry are known to be strong inhibitors of CYP3A4 (11, 12) thus leading to an increase in the concentration of vincristine and of its toxicity. Another patient with the same blood malignancy and receiving the same drug regimen reported taking ginseng (Panax ginseng). Like bilberry, ginseng inhibits the activity of the isoform that metabolises vincristine (13), increasing the concentration of vincristine in the bloodstream and thus its toxicity. An interaction has also been noted between cyclophosphamide and ginseng, the latter altering the kinetics of the drug through mechanisms that are still not yet fully understood (13). Another patient with extranodal low-grade non-Hodgkin's lymphoma receiving rituximab, vincristine and cyclophosphamide reported taking medicinal herbs such as chestnut (Castanea sativa), china (Cinchona officinalis), cumin (Cuminum cyminum), echinacea (Echinacea purpurea), beech (Fagus sylvatica), grindelia (Grindelia robusta), liquorice (Glycyrrhiza glabra), oregano (Origanum vulgare), primrose (primula veris), willow (Salix alba), winter savory (Santureja montana) and thyme (Thymus vulgaris, T. serpyllum). As the immunostimulant activity of echinacea is well known, its use is not recommended simultaneously with immunosuppressants such as rituximab, cyclophosphamide or vincristine (14). Liquorice (15) and echinacea (16, 17) act as inducers of the hepatic isoform, CYP3A4, potentially reducing the concentration of vincristine and its therapeutic efficacy.

It is known that some medicinal herbs interact pharmacokinetically with cancer therapy, *e.g.* the combination of ginseng and 5FU alters the kinetics of the drug, modifying its half-life and reducing its effectiveness against some forms of cancer (10). Intake of ginseng produces arterial hypertension (9) and its association with herceptin may increase the hypertensive effect of the monoclonal antibody, accentuating its cardiotoxicity. CYP3A4 is also inhibited by cat's claw (Uncaria tomentosa) (16, 18) and turmeric (19) (Curcuma longa), the latter inhibiting other isoforms of CYP450 (15, 20) and P-glycoprotein. The overall inhibitory action of isoform CYP450 could significantly increase the concentration and toxicity of vincristine.

Lapatinb is metabolized primarily by CYP3A4 and inhibitors of this isoform such as turmeric (19, 20) can induce an increase in the concentration and thus toxicity of the drug.

The pharmacological treatment of patients with cancer is associated with multiple side-effects (21). Although the cause of side-effects usually lies in the toxicity of the drugs themselves, drug interactions can reinforce or intensify adverse events and even seem to be the cause of death in 4% of cancer patients (22). Cancer patients are particularly susceptible to drug interactions as they often use several drugs as part of the cancer treatment. In addition to chemotherapy, cancer patients often use co-medication to treat cancer related pain and venous thrombosis or to reduce the side-effects of the anti-cancer drugs. In hospitalised cancer patients, the use of eight or more drugs and a hospital stay of >6 days were identified as risk factors for PDIs (23). OTC medication is popular in cancer patients, either to prevent or treat symptoms of disease or to promote health and well-being (24).

The present study indicates that a good percentage of patients undergoing cancer treatment make use of non-conventional medicines to prevent the side-effects caused by chemotherapy. The study showed that 75% of patients who use herbal medicines are women under 64 years of age with a university degree. The use of non-conventional medicines, however, can lead to clinically significant drug interactions that may affect the course of cancer treatment. For this reason, Cancer Institutes should provide patients with adequate information on the proper use of non-conventional medicines. An educational project on the good therapeutic use of drugs and non-conventional medicine was launched at IRST in January 2014.

Acknowledgements

The authors thank Ursula Elbling for editing the article.

Ethical Approval

This study was approved by the Ethics Committee of IRST IRCCS, Area Vasta Romagna, Italy.

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Received: 27.05.2014
Accepted: 09.09.2014
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