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A cross-sectional observational study to establish the association between ECOG performance status and age and administration of doublet or triplet chemotherapy containing Xeloda® (capecitabine) in advanced gastric cancer patients

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Summary. *Background:* Selection of treatment for advanced gastric cancer (AGC) correlates with age and ECOG PS. This study was carried out to analyze whether previously mentioned variables are relevant for the choice of doublet or triplet regimens with capecitabine (Xeloda®) and determining prognosis. *Methods:* Multicenter, cross-sectional, observational study in patients with AGC who received at least 2 cycles of capecitabine-based doublet or triplet chemotherapy, with or without measurable disease. *Results:* A total of 175 patients were evaluated. Median age 65.5 (56-72) years, male: 68% ECOG 0/1/2: 32.7%/55.6%/11.1%; 33% underwent doublet and 67% triplet chemotherapy. Tumor histology: adenocarcinoma (27.4%), signet ring cell carcinoma (28%) and others (41.7%). Most common sites of metastases: lymph node (46.2%), peritoneum (39.4%) and liver (36.6%). Multivariate analysis demonstrated that age ≤64 (OR 0.447; p=0.016) and ECOG 0 (vs 2) (OR 0.253; p=0.016) were risk factors for the choice of triplet chemotherapy, and failed to show an association between ECOG 1 and regimen. With regard to the secondary endpoints, age was statistically related with treatment selection when considered numerical (p<0.01) or categorical (p<0.05) and ECOG PS also showed this relationship (p<0.01). Main grade 1/2 capecitabine-related toxicities: diarrhea (11.4%), mucositis (7%), hand-foot syndrome (4.6%) and emesis (4%). Most frequent grade 3 were diarrhea in 4.6% and emesis, asthenia and febrile neutropenia in 2.3%. No toxicity grade 4 occurred. *Conclusions:* Age ≤64 years and ECOG 0 are related factors of choice of capecitabine-based triplet chemotherapy in AGC.

Key words: ECOG, age, triplet or doublet chemotherapy regimen, capecitabine

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«Studio osservazionale trasversale per definire l'associazione tra ECOG performance status, età e somministrazione di doppio o triplo regime chemioterapico contenente Xeloda® (capecitabina) in pazienti con tumore gastrico avanzato»

Riassunto. *Background:* La scelta del trattamento per il Cancro Gastrico Avanzato (AGC) è correlata all'età e alla scala ECOG. Questo studio è stato condotto per valutare se le variabili precedentemente menzionate sono rilevanti nella scelta del doppio o triplo regime chemioterapico con capecitabina (Xeloda®) e dunque determinare la prognosi. *Metodi:* Studio osservazionale trasversale, multicentrico, in pazienti con AGC che hanno ricevuto almeno 2 cicli di capecitabina a doppio o triplo regime chemioterapico, con o senza malattia misurabile. **Risultati:** Sono stati analizzati un totale di 175 pazienti di sesso maschile con un'età media di 65,5 (56-72) anni: il 68% con "performance status ECOG 0/1/2", rispettivamente il 32,7%/55,6%/11,1%. Il 33% è stato sottoposto a doppio regime chemioterapico mentre il 67% a triplo. Valutazione istologica: adenocarcinoma (27,4%), carcinoma a cellule ad anello con castone (28%) e altri (41,7%). I siti più comuni di localizzazione metastatica sono stati: linfonodi (46,2%), peritoneo (39,4%) e fegato (36,6%). L'analisi multivariata dei dati ha dimostrato che l'età ≤64 (OR 0,447, p=0,016) e l'indice ECOG 0 (vs 2) (OR 0,253, p=0,016) erano fattori determinanti nella scelta del triplo regime chemioterapico, nessuna relazione tra "performance status ECOG 1" e trattamento è stata dimostrata. Per quanto riguarda gli endpoint secondari, l'età è stata statisticamente correlata con la scelta del trattamento considerando la variabile numerica (p<0,01) o categoriale (p<0,05) e anche l'ECOG ha mostrato questa correlazione (p<0,01). I principali effetti tossici di grado 1/2 relazionati alla capecitabina sono stati: diarrea (11,4%), mucosite (7%), malattia mano-piede bocca (4,6%) e vomito (4%). Gli effetti tossici di grado 3 più frequenti sono stati: diarrea nel 4,6% e vomito, astenia e neutropenia febbrile nel 2,3%. Non si è verificato nessun effetto tossico di grado 4. *Conclusioni:* L'età ≤64 anni e il performance status ECOG 0 sono variabili determinanti nella scelta del triplo regime chemioterapico a base di capecitabina nell'AGC.

Parole chiave: ECOG, età, doppio o triplo regime chemioterapico, capecitabina

Introduction

Although the incidence of gastric cancer is decreasing, 96,000 new cases in Europe, and approximately 71,000 deaths have been shown, representing the fifth highest incidence and fourth highest cause of cancer related death in the European Union (EU) (1).

Historically, data from randomized trials support the use of systemic chemotherapy as palliative treatment in patients with advanced or metastatic gastroesophageal cancer (mGC). Several studies investigating combination therapies have reported remission rates of 40%-60% and median survival times from 4-6 to 8-11 months (2-4). However, when this study was designed no universally accepted standard regimen for the first-line treatment of advanced gastric cancer was used, and this will depend on the patient profile. Nowadays, treatment decision considering Her2 status is the goal standard.

5-fluorouracil (5-FU) is not only the most extensively studied single agent in this disease, but it is part of most combination chemotherapy regimens as well. Doublet and triplet regimens comprising a fluoropyrimidine and a platinum compound, with or without an anthracycline or taxane are widely used for advanced gastric cancer (5). A metanalysis reported a survival advantage of the three-drug combination but with less manageable safety profile (6). One of the main disadvantages of an infusional 5-FU chemotherapy combination is the need to implant a central venous catheter. This procedure increases the costs of treatment administration, the incidence of subsequent complications, and the level of treatment-associated discomfort for the patient. In this context, capecitabine (Xeloda, Hoffman-La Roche, Ltd, Basel, Switzerland) is an oral fluoropyrimidine carbamate designed to deliver 5-FU selectively to tumor cells via metabolism by thymidine phosphorylase, an enzyme found in higher concentrations in tumors than in normal tissues. Phase I (7-9) and II (10-13) clinical trials have demonstrated that capecitabine is both safe and active in advanced gastric cancer both

as monotherapy and within a variety of combination chemotherapy regimens. Capecitabine use as a part of a doublet or triplet regimen was demonstrated to be noninferior to 5-FU in ML17032 (14) (used with cisplatin) and REAL-2 (15) (used with epirubicin and oxaliplatin or cisplatin) phase III clinical trials, respectively.

The characteristics of the patients typically enrolled in clinical trials are generally not fully representative of patients populations encountered in routine clinical practice. Patients enrolled in trials are usually relatively young, with a good performance status (PS) and no or few comorbidities, elements that are not typical of patients affected by advanced gastric carcinoma (16). Cancer occurs predominantly in older patients (17) who also have a poor PS. In this population, chemotherapy is generally associated with an increase in toxicity, mainly hematological (18). Thereby, factors such as age or PS should play a role in choosing the most appropriate therapy.

In conclusion, despite the number of studies that have been carried out in this setting, the most effective regimen for treatment of advanced disease is not clearly established, as well as in what cases three-drug combinations are more convenient than two-drug combinations. Thus, the election of a doublet or triplet in the routine clinical practice should be conditioned by the evaluation of the age and performance status by the clinician.

On this basis, the purpose of the present study is to establish the influence of age and Eastern Cooperative Oncology Group (ECOG) performance status on the use of doublet or triplet combinations in routine clinical practice.

Patients and methods

This multicenter, observational study was carried out in accordance with the Declaration of Helsinki of the World Medical Association and all its amendments, and national and local regulations. The study was performed in 37 hospitals of Spain. The study was approved by an Independent Ethics Committee and all patients provided their written informed consent prior to study enrolment.

Patient population

The study population consisted of adult patients with histologically confirmed advanced gastric adenocarcinoma (AGC) who had not received any chemotherapy previous to the current treatment against AGC and had already received at least 2 cycles of capecitabine-based doublet or triplet currently regimen chemotherapy for the treatment of AGC. Patients were required to have adequate renal function, defined as CrCl >80 ml/min – measured by the Cockroft-Gault equation, and life expectancy beyond 3 months. Patients with previous history of liver/kidney transplant, previous or current clinically significant cardiovascular disease such as myocardial infarction, or uncontrolled arrhythmias within the year preceding the study were excluded from the study. Other exclusion criteria included previous history of neoplasia within the last 5 years except basal cell carcinoma and cervical cancer, major surgery within the 4 weeks prior to study treatment and fully unrecovered, evidence of central nervous system metastases and participation in a clinical trial within the previous 4 weeks to the study. Additionally, the following blood sample levels must be presented: neutrophil count $\leq 1.5 \times 10^9$/L; platelet count $<100 \times 10^9$/L, total bilirubin ≥1.5 x ULN, AST, ALT >2.5 x ULN; or >5 x ULN in patients with liver metastases, alkaline phosphatase >2.5 x ULN or 5 x ULN in patients with liver metastases or >10 x ULN in patients with bone metastases.

Between January 2009 and June 2010, 175 patients were included. Regarding the primary objective, the following variables were assessed: age, performance status and chemotherapy regimen (doublet or triplet). Demographic and anthropometric data, and those related with previous clinical history (relevant concomitant diseases and blood sample pre-treatment and last results) as well as tumoral disease (TNM status, histological type, metastasis locations, neoadjuvant and/or adjuvant therapy, radiotherapy and surgical history and adverse reaction to first-line treatment) were collected for fulfillment of secondary objectives.

Statistical considerations

For the sample size calculation, it was considered that age was examined for treatment (doublet or

triplet) selection. It was also assumed that one of the groups (doublet or triplet) had 50% of patients with advanced age, while the other group differed in at least 21%. Considering a 1:1 relationship between groups, based on a power of 80% and a type I error rate of 5%, a total population of 84 patients was required for each group. The same criterion was adopted for ECOG PS but considering one group with half of patients with an ECOG PS of less than 2.

Two groups were defined (doublet and triplet group) for the statistical analysis. A descriptive analysis of patient characteristics was performed for each group. The quantitative variables were described by central tendency and dispersion measures (i.e. mean, median, standard deviation [SD], minimum, and maximum). The qualitative variables were expressed as number of patients and relative and absolute frequency. Primary study endpoints were analyzed using a multiple logistic regression model for assessing the possible association between age and PS and treatment regimen (doublet or triplet). For the univariate analysis other tests were used (Fisher and Chi-square). A Receiver Operating Characteristic (ROC) curve was used to define the cutoff points in the continuous variable age. From this analysis two cutoff points were selected, 64 and 71 years. Based on the available evidence pointing to 65 years as a very frequently used cutoff point throughout a large portion of the epidemiological literature (19), the cutoff point of 64 years was selected for the present article. In this context, results of age considered as numerical or categorical (> 64 and ≤ 64 years) are presented. The toxicity of capecitabine-based regimens was evaluated considering the absolute frequencies of adverse events experienced during the study.

The statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

A total of 175 patients were enrolled into the study, of whom 60 and 115 received a doublet and triplet regimen, respectively. Their characteristics are summarized in Table 1 (total percentages are shown). More males than females were present in the selected population (67.4% of total patients), and the median age was 65.5 (55.8-71.8) years. Among those patients who received a doublet regimen, median age was 67.3 (60.1-75.9) years and 61.7% were males. Regarding the triplet regimen population, median age was 63.4 (55.2-69.9) years and 70.4% were males.

ECOG PS at study visit was as follows: PS 0, 56 patients (32.7%); PS 1, 95 patients (55.6%); and PS 2, 19 patients (11.1%). In patients with a doublet regimen, 16 patients (27.1%) were PS 0, 31 patients (52.5%) were PS 1 and 12 were PS 2 (20.3%) while in

Table 1. Baseline characteristics of patients

Patient characteristics	Doublet (n=60)	Triplet (n=115)
Median (range) age, years	67.3 (60.1-75.9)	63.4 (55.2-69.9)
≤64 years	19 (31.7%)	59 (51.3%)
>64 years	41 (68.3%)	56 (48.7%)
Gender, n (%)		
Male	37 (61.7)	81 (70.4)
Female	23 (38,3)	32 (27.8)
Concomitant disease, n (%)	40 (66.7)	60 (52.2)
TNM status, n (%)		
T3/T4	37 (62.7)	68 (59.2)
N1/N2	24 (40.0)	50 (45.0)
M1	42 (71.2)	123 (72.4)
ECOG PS, n (%)		
0	16 (27.1)	40 (35.7)
1	31 (52.5)	64 (57.1)
2	12 (20.3)	7 (6.3)
Histologic type, n (%)		
Adenocarcinoma	13 (22.1)	35 (31.5)
Signet ring cell carcinoma	18 (30.5)	31 (27.9)
Others	28 (47.5)	45 (40.5)
Metastatic sites, n (%)		
Lymph node	20 (33.9)	61 (55.0)
Peritoneum	22 (36.7)	47 (42.3)
Liver	27 (45.0)	37 (33.3)
Lung	6 (10.0)	15 (13.0)
Bone	6 (10.0)	11 (9.9)
Nº of metastasis location, n (%)		
1	38 (64.4)	68 (61.3)
2	16 (27.1)	30 (27.0)
<2	5 (8.5)	13 (11.7)
Surgical procedure, n (%)	31 (51.7)	44 (38.3)

triplet regimen 40 patients (35.7%) were PS 0, 64 patients (57.1%) were PS 1 and 7 were PS 2 (6.3%). Of the total of patients, 97.1% presented metastatic locations. More than half of population showed only one metastatic site (60.5%), being lymph node (46.2%), peritoneum (39.4%) and liver (36.6%) the more frequent location of metastases.

Study treatment

Patients received the study treatments from commercial sources administered according to the Summary of Product Characteristics, and under clinical practice conditions. Although sample size calculation was performed considering a 1:1 doublet/triplet proportion, the recruitment was opened in order to achieve the total sample size. As a result, it was observed a higher proportion of patients treated with triplet regimen vs doublet regimen (64.7% vs 32.6%, respectively).

Overall, considering both doublet and triplet, the most frequent treatment used with capecitabine was oxaliplatin (53.1%), followed by capecitabine-cisplatin in 42.9% of the patients. Treatment characteristics are depicted in Table 2.

Capecitabine was administered in a triweekly regimen (1,000 mg/m^2/12 h twice daily for 14 days followed by a 1-week rest) in 93.2% of the doublet treated patients and in 57.7% of the triplet treated patients; while a 3.3% and a 26% treated with doublet and triplet regimen, respectively, received it in a continuous regimen (625 mg/m^2).

The multivariate regression analysis indicated that age either as a continuous or a categorical (Table 3) variable (>64 vs ≤64 years) was a prognostic factor of the use of doublet or triplet regimen OR: 0.962; CI 95%: 0.930-0.994; p=0.021 and OR: 0.447, CI 95%: 0.227-0.880; p=0.016, respectively). Regarding ECOG PS, differences between 0 and 2 were observed (OR: 0.253, CI 95%: 0.083-0.775; p=0.016).

With regard to the secondary endpoints (Table 4), age was statistically related with treatment selec-

Table 3. Multivariate logistic regression analysis (n=170)

	OR	IC (95%)	p-value
Age (>64 vs ≤64)	0.447	(0.227-0.880)	0.016
ECOG (1 vs 0)	0.901	(0.431-1.881)	0.780
ECOG (2 vs 0)	0.253	(0.083-0.775)	0.016

Table 4. Univariate analysis

	Treatment scheme		p-value
	Doublet	Triplet	
ECOG PS, n(%)			
0	16 (27.1)	40 (36.0)	<0.05
1	29 (52.5)	64 (57.7)	
2	12 (20.3)	7 (6.3)	
Age, n(%)			
≤64	19 (31.7)	59 (51.3)	<0.05
>64	41 (68.3)	56 (48.7)	

Table 2. Use of doublet or triplet scheme

	N (%)	ECOG PS		Age	
		0-1	2	≤64	>64
Doublet scheme		47 (78.3)	12 (20.0)	19 (31.7)	41 (68.3)
Capecitabine+oxaliplatin*	43 (71.7)	35 (58.3)	8 (13.3)	13 (21.7)	30 (50.0)
Capecitabine+irinotecan	2 (3.3)	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Capecitabine+cisplatin†	14 (23.3)	11 (18.3)	3 (5.0)	5 (8.3)	9 (15.0)
Capecitabine+epirubicin	1 (1.7)	0 (0)	0 (0)	0 (0)	1 (1.7)
Triplet scheme‡		102 (88.7)	7 (6.1)	58 (50.4)	54 (47.0)
Capecitabine+oxaliplatin+epirubicin	49 (42.6)	41 (35.6)	6 (5.2)	26 (22.6)	23 (20.0)
Capecitabine+oxaliplatin+docetaxel	1 (0.9)	1 (0.9)	0 (0)	0 (0)	1 (0.9)
Capecitabine+cisplatin+epirubicin	29 (25.2)	29 (25.2)	0 (0)	14 (12.2)	15 (13.0)
Capecitabine+cisplatin+docetaxel+others	1 (0.9)	1 (0.9)	0 (0)	0 (0)	1 (0.9)
Capecitabine+cisplatin+docetaxel	32 (27.8)	30 (26.1)	1 (0.9)	18 (15.6)	15 (13.0)

* One patient add bevacizumab; † 1 patient add trastuzumab; ‡ 3 patients do not have valid information

tion when considered numerical (p<0.01) or categorical (p<0.05). ECOG PS also showed this relationship (p<0.01).

Safety

One hundred patients (57.1%) did not report any adverse reaction to the study treatment. Therefore, 42.6% experienced an adverse reaction of any grade. Of them, 37.9% of the patients were grade 3-4.

Nonhematologic and hematologic treatment-related adverse events are summarized in Table 5. The hematologic adverse events were infrequent and mostly mild.

No grade 3-4 adverse events were reported in patients treated with doublet regimen. Only 3 patients (2.6%) treated with a triplet regimen experienced grade 3 neutropenia and 1 patient suffered grade 3 anemia.

Gastrointestinal disorders were the most frequent nonhematologic adverse events reported. In patients treated with doublet the most common grade 1-2 adverse events reported were: asthenia (5.4%), nausea/vomiting (5.4%), diarrhea (4.8%), and neurotoxicity (4.2%). In the same group, the most common grade 3-4 toxicities were diarrhea in 2 patients and asthenia and nausea/vomiting each in 1 patient. Regarding the patients treated with a triplet regimen the most common adverse events grade 1-2 reported were asthenia (7.8%), nausea/vomiting (7.8%), diarrhea (6.0%), and mucositis (5.4%). In this group, diarrhea (1.2%), asthenia (1.2%) and nausea/vomiting (0.6%) were the most common grade 3-4 toxicities reported. Only one patient experienced a grade 3 neuropathy and grade 3 anorexia.

Hand-foot syndrome grade 1-2 was observed in 1 patient treated with a doublet regimen and in 7 patients treated with a triplet regimen. Hand-foot syndrome grade 3-4 was not reported either for the doublet or for the triplet regimen.

Table 5. Common adverse events

Adverse event	Grade 1-2		Grade 3-4	
	Doublet	Triplet	Doublet	Triplet
Hematologic, n(%)				
Neutropenia	3 (1.7)	2 (1.2)	0 (0)	3 (1.7)
Anemia	1 (0.6)	1 (0.6)	0 (0)	1 (0.6)
Leukopenia	0 (0)	2 (1.2)	0 (0)	0 (0)
Thrombocytopenia	1 (0.6)	1 (0.6)	0 (0)	0 (0)
Other	1 (0.6)	1 (0.6)	0 (0)	0 (0)
Nonhematologic, n(%)				
Diarrhea	8 (4.8)	10 (6.0)	2 (1.2)	6 (3.6)
Asthenia	9 (5.4)	13 (7.8)	1 (0.6)	3 (2.3)
Nausea/Vomiting	9 (5.4)	13 (7.8)	1 (0.6)	3 (2.3)
Neurotoxicity	7 (4.2)	7 (4.2)	0 (0)	1 (0.6)
Mucositis	3 (1.7)	9 (5.4)	0 (0)	0 (0)
Anorexia	3 (1.7)	3 (1.7)	0 (0)	1 (0.6)
Hand-foot syndrome	1 (0.6)	7 (4.2)	0 (0)	0 (0)

Discussion

The age and ECOG PS are crucial factors in the treatment choice by the clinician. Elderly patients often show distinct characteristics that must be considered when planning cancer treatment (17). In this regard, performance status should be carefully assessed when identifying the optimal treatment strategy (20).

The impact of these two variables has been widely studied, but the present study is the first survey to combine both. A German study, carried out by Hofheinz *et al.* (21), reported that therapy patterns significantly varied by age and Karnofsky Performance Status (KPS), where older or KPS <80% patients were significantly less likely to receive chemotherapy triplets. Our multivariate model is consistent with this results; the combination of the selected factors, the primary endpoint in this study, demonstrated their influence on the treatment decision. Age, as a numerical or categorical variable, was assessed as a prognostic factor of treatment choice. In both cases, young patients were most likely to be treated with a triplet scheme. Regarding ECOG PS, patients with ECOG 0 were most likely to be treated with triplet than those with ECOG 2. It is noteworthy that slight differences in PS did not seem to have influence on the choice of a doublet or triplet therapy. In the univariate analysis, the results were confirmed, showing the known influence of the factors on the treatment decision.

Regarding the regimens used, a doublet or triplet regimen comprising capecitabine and a platinum compound is the accepted standard (22). Oxaliplatin

was more used in doublet schemes than cisplatin (71.67% vs 23.33%), which could be explained by its more favorable toxicity profile (22). On the contrary, cisplatin was used to a small extent and mostly administered as a part of a triplet regimen (23.3% vs 53.9%) where patients may withstand more intensive treatment, highlighting the above-mentioned idea. The most frequent therapy used together with capecitabine and a platinum compound was epirubicin (67.8%). Taxanes as the third component of the triplet scheme were used in 29.6%. This could reflect the degree of penetration of the clinical trials performed with epirubicin and docetaxel in the clinical practice. Hofheinz *et al* (21), who investigated therapy trends in Germany from 2006 to 2009, found that use of oxaliplatin and docetaxel increased while cisplatin and irinotecan slightly declined. The figures reported in 2009, the closest period to our study, showed the following proportion of use: cisplatin (49%), irinotecan (4%), docetaxel (29%) and oxaliplatin (36%), results that are concordant with those reflected in our study.

The authors acknowledge that although observational studies provide valuable information about the administration of treatments in clinical practice conditions, they are not capable of providing either strong evidence or establishing cause-effect relationships. The lack of a comparator group and the cross-sectional collection of data from patients' medical charts are also limitations to be taken into account. As mentioned above the original design included a 1:1 doublet/triplet recruitment, but finally it was opened. Despite this, sample size was totally achieved and the proportion of triplets-treated patients was higher, a finding which may point to an increment in the use of this regimen. In addition, the present study would have been reinforced by adding an efficacy assessment. Consequently, the results of the present study should be interpreted with caution based on the previously mentioned limitations.

In conclusion, the present study shows the important role of age and performance status in the treatment decision. However, more studies would be necessary to assess their impact on treatment efficacy. The incorporation of other factors like the presence of specific symptoms (20) and comorbidities could be the starting point to built a model that allows the physician to appropriately evaluate the patient's clinical status and plan the most suitable therapy accordingly.

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