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ORIGINAL ARTICLE

Study of use of pemetrexed in non-small cell lung cancer

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Safety

Abstract
Objective: To study the effectiveness and safety of pemetrexed in non-small cell lung cancer.
Method: Retrospective study (March 2006-May 2008) of pemetrexed use. Information was obtained from the Access database belonging to the Pharmacy and Oncology Departments, the registry of external consultations and clinical histories. Data were analysed using SPSS software version 12.0. Quantitative variables are expressed as the median (minimum-maximum).
Results: The study included 44 patients (61.7 [39-77] years old), mostly male (86%), smokers or former smokers (80%) with predominantly epidermoid/squamous disease (46%) or adenocarcinoma, in a good functional state (86%) and in stage ≥IIIl upon beginning pemetrexed treatment (93%). Prior treatment with taxanes and taxane treatment along with a prior history of neutropoenia were the criteria for changing to pemetrexed in 34.4%and 22.7%of the patients, respectively. None of the patients presented a complete or partial response: 18.2%showed disease stability and 81.8%showed disease progression. The main reasons for discontinuing pemetrexed were progression of the disease (54.5%) and worsening of symptoms (15.9%). Median survival after beginning chemotherapy was 22.2 months (ranging from 16-28.4) and 7.8 months (4.4-11.2) after beginning pemetrexed treatment. These last figures were significantly higher in women and those with an ECOG of 0 to 1. The most common adverse effects were weakness and neurotoxicity.
Conclusion: In each of the cases, pemetrexed was used as a second-line treatment or higher with a good safety profile. A complete or partial response was not reached in any of the cases, but survival after beginning pemetrexed was equal to or longer than that achieved in other studies.

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PALABRAS CLAVE
Pemetrexed;
Cáncer de pulmón no microcítico;
Estudio retrospectivo;
Estudio observacional;
Efectividad;
Seguridad

Estudio de utilización de pemetrexed en el cáncer de pulmón no microcítico

Resumen
Objetivo: Estudiar la efectividad y la seguridad del pemetrexed en el cáncer de pulmón no microcítico.
Método: Estudio retrospectivo (marzo 2006-mayo 2008) de utilización de pemetrexed. Se obtuvo la información de bases de datos Access de los Servicios de Farmacia y Oncología, del registro de visitas a consultas externas y de la historia clínica. Los datos se analizaron con SPSS v. 12.0. Las variables cuantitativas se expresaron con la mediana (mínimo máximo).
Resultados: Fueron 44 pacientes (61,7 años [39-77]) la mayoría hombres (86%), fumadores/exfumadores (80%), histología epidermoide/escamosa (46%) o adenocarcinoma (36%), con buen estado funcional (86%) y estadio III o superior al inicio del tratamiento con pemetrexed (93%). El tratamiento previo con taxanos y éste junto con la neutropenia previa fueron los criterios de cambio a pemetrexed en el 34,4 y el 22,7% de los pacientes, respectivamente. Ningún paciente presentó respuesta completa o parcial; el 18,2% mostró enfermedad estable y el 81,8% progresión de la enfermedad, siendo los principales motivos de retirada del pemetrexed la progresión de la enfermedad (54,5%) y el empeoramiento clínico (15,9%). La mediana de supervivencia desde el inicio de la quimioterapia fue de 22,2 meses (16-28,4) y desde el inicio con pemetrexed fue de 7,8 meses (4,4-11,2), siendo ésta significativamente mayor en las mujeres y de aquellos con valor 0-1 en la escala Eastern Cooperative Oncology Group. Los efectos adversos más frecuentes fueron astenia y neurotoxicidad.
Conclusión: Pemetrexed se ha utilizado en todos los casos como segunda línea o superior con buen perfil de seguridad. En ningún caso se alcanzó respuesta completa o parcial, pero la supervivencia desde el inicio de pemetrexed iguala o supera a la de otros estudios.

Introduction

Pemetrexed is an antimetabolite with antineoplastic activity that disrupts essential folate-dependent metabolic processes that are necessary for cellular replication.[1] The indications approved by the European Medicines Agency for pemetrexed use are: non-resectable malignant pleural mesothelioma, as a first line of treatment in combination with cisplatin, and advanced or metastatic non-small cell lung carcinoma (NSCLC), except for cases with a predominantly squamous histology, as a second line of treatment in monotherapy, and as a first line of treatment combined with cisplatin.[2]

NSCLC constitutes 87% of all lung cancer cases.[3] It is a heterogeneous group of histologies, with large/non-differentiated carcinoma, adenocarcinoma, and epidermoid/squamous cells being the most common. The prognosis is quite poor, and long-term survival is low.[4]

The three drugs that have been approved by the Food and Drug Administration and the European Medicines Agency as the second line of treatment in advanced or metastatic NSCLC refractory to the first line of treatment or with disease progression (DP) are: docetaxel, pemetrexed, and erlotinib. These agents were approved following four phase III clinical trials, in which they were compared with other antineoplastics and medical support treatments,[5-8] and in which their benefits were demonstrated in terms of survival and safety. Pemetrexed presented no advantage with respect to docetaxel as far as response and survival, but it was less toxic and caused a significantly lower rate of cases of neutropoenia and its complications.[8]

More recently, pemetrexed has also been approved as the first line of treatment in combination with cisplatin in locally advanced or metastatic NSCLC in previously untreated patients.[9]

The main objective of this study is to analyze the effectiveness and safety of the use of pemetrexed in NSCLC, as well as to analyze the factors that could influence in patient survival. The secondary objectives are to analyze effectiveness and safety stratifying the patients by age groups.

Material and methods

We performed a retrospective study on the use of pemetrexed in NSCLC patients from March 2006 to May 2008 in a general hospital with 592 beds.

Our data came from a database in Microsoft Access 2003® from the Pharmacy Department where the dispensations of antineoplastic medications were registered; a Microsoft Access 2003® (Pigeo®) database from the Oncology Department in which the treatments administered and the number of hospital appointments in the Oncology Outpatient Department were recorded, along with a review of patient clinical histories.

We analyzed variables for characterizing the patients, the disease, and the treatment received, as well as variables for measuring the effectiveness and safety of treatment.

For classifying the tumours found in the patients, we used the International System for Staging Lung Cancer created by the American Joint Committee on Cancer.[10]

The functional state of the patient was measured before pemetrexed treatment according to the Eastern Cooperative Oncology Group (ECOG) scale.[11]

The effectiveness of the treatment was measured by patient response, the causes for stopping treatment, and patient survival from the commencement of chemotherapy and from the start of pemetrexed treatment. We used the Response Evaluation Criteria In Solid Tumours[12] (unidimensional assessment of tumour by radiological tests) for evaluating patient response to treatment, expressed as a complete response (CR), partial response (PR), stable disease (SD), and DP.

Safety was evaluated by identifying the number and type of adverse effects (AE) produced by pemetrexed. We used the World Health Organization criteria for this classification.[13] Furthermore, we quantified the number of patients that had neutropoenia before pemetrexed treatment.

The data were compiled in a spreadsheet using Microsoft Office Excel® 2003 and then analyzed using SPSS® statistical software, version 12.0 (2003® SPSS Inc). Quantitative variables were summarised as median values (minimum-maximum) and the qualitative variables as frequencies and proportions. In order to compare medians, we used the non-parametric Mann-Whitney U-test, and the Fisher's exact test for comparing proportions. The probability of survival was estimated using the Kaplan-Meier method, and the Mantel-Haenszel test was used to calculate the statistical significance of the different groups.

We received the approval of the clinical research ethics committee of the hospital, and they did not consider that an informed consent was required from the patients, given that this was a retrospective study concerning evaluation of the use of a medication in clinical practice.

Results

Patients, disease, and treatment characteristics

Forty-five patients were treated with pemetrexed between March 2006 and May 2008. One patient received a single cycle and was then transferred to a reference hospital, and so follow-up was made impossible and the patient was excluded from the study.

The quantitative and qualitative variables, both global and stratified by age group, of the 44 patients included in the study are shown in Tables 1 and 2. The median age was high: 61.7 years (39-77), although only 9 patients were 70 years or older. The majority of patients were males (86%) and smokers or ex-smokers (80%). Eight patients had previously been diagnosed with and treated for other neoplasms (Table 3). In 93% of cases, the disease was diagnosed in advanced stages (IIIA, IIIB, and IV) and the predominant histology was epidermoid/squamous (46%), followed by adenocarcinoma (36%).

At the start of the pemetrexed treatment, 86% of NSCLC patients were in stage IV of the disease, and 86% also fell between 0 and 1 on the ECOG scale. No patients were scored over 2 on the ECOG scale.

In 88.7% of the NSCLC patients, the first line of treatment was a double therapy, including a platinum-type compound, principally platinum/taxanes (40.9%) and platinum/vinorelbine (36.4%) (Table 4). The median number of chemotherapy lines that were given before pemetrexed treatment was 1 (1-5). It was used as a second line of treatment in 59% of patients after producing a response of CR or PR in 34.6% of patients, DP in 53.8%, and SD in 11.5% in the first line of treatment.

By stratifying the patients by age group, we found no statistically significant differences, but the percentage of smokers/ex-smokers (85.7% versus 55.6%), patients in stage IV of the disease upon diagnosis (44.4% versus 31.4%), and mortality (68.6% versus 55.6%) were somewhat higher in patients under 70 years. The time from the diagnosis until start of pemetrexed treatment was higher in patients 70 years and older (19.5 months versus 10 months; P=.062).

According to the NSCLC hospital treatment protocol, the criteria under which the oncologist decided to initiate pemetrexed as a second line of treatment were the appearance of neutropoenia with some previous type of treatment, previous treatment with taxanes, or an age of 70 years or older. In patients under 70 years of age, the main reasons for starting pemetrexed treatment were a previous treatment with taxanes (45.7%), previous episodes of neutropoenia (11.4%), or both (28.6%). Neither of these two criteria was registered in the clinical histories of 5 patients, but all had previously been treated with platinum treatments, two of which had produced severe gastrointestinal toxicity, and one of which had paresthesia in the lower limbs and anaemia that required epoetin treatment. This was the only reason for starting pemetrexed treatment in only 2 cases (22.2%) of the 9 patients that were 70 years of age or older. Three patients (33.3%) had also previously suffered neutropoenia, and another two patients had been previously treated with taxanes (22.2%) (Table 5).

At the end of the study, 29 patients had passed away and none were still on pemetrexed treatment.

Effectiveness

The response to pemetrexed treatment and the reasons for stopping it are shown in Table 5.

DP was the most common response to pemetrexed (over 80%). No patients had a positive response to pemetrexed treatment (CR or PR) by the end of the study or the end of chemotherapy treatment. Almost half (45.5%) of patients received less than 3 pemetrexed cycles, and the median number of cycles received was 3 (1-20).

In the 36 patients with a response of DP, this was the main reason for stopping pemetrexed treatment (66.7%), followed by clinical worsening (11.1%) and death (11.1%). In the 8 patients who responded with SD, treatment was stopped due to clinical worsening in 3 cases, voluntary decision by the patient in 2 cases, minimal clinical benefit in 2 cases, and toxicity/intolerance in 1 case.

The percentage of patients with SD was somewhat higher in patients 70 years of age or older (33.3% versus 14.3%), although no statistically significant differences were observed between the two groups in the response to treatment or the causes for stopping pemetrexed treatment. The main cause for stopping treatment in both groups was DP.

The median patient survival from the start of the first chemotherapy (SSCT) was 22.2 months (95% CI: 16-28.4), and the median survival from the start of pemetrexed treatment (SSP) was 7.8 months (95% CI: 4.4-11.2) (Table 6). There appears to be a tendency, although not significant,

Table 1 Characteristics of the patients included in the study

	Total n=44, n (%)	Age		
		<70 years, n (%)	≥70 years, n (%)	*P*
Sex				
Men	38 (86)	30 (85.7)	8 (88.9)	1
Women	6 (14)	5 (14.3)	1 (11.1)	
Age				
<70 years	35 (80)	–	–	–
≥70 years	9 (20)	–	–	–
Tobacco use				
Current or former smoker	35 (80)	30 (85.7)	5 (55.6)	.068
Non-smoker	9 (20)	5 (14.3)	4 (44.4)	
Diagnostic stage				
NSCLC I	2 (5)	1 (2.9)	1 (11.1)	.393
NSCLC II	1 (2)	1 (2.9)	0 (0)	
NSCLC IIIA	4 (9)	4 (11.3)	0 (0)	
NSCLC IIIB	12 (27)	8 (22.9)	4 (44.4)	
CPNV IV	25 (57)	21 (60.0)	4 (44.4)	
Histology				
Epidermoid/squamous	20 (46)	16 (45.7)	4 (44.4)	0.381
Adenocarcinoma	16 (36)	14 (40.0)	2 (22.2)	
Undifferentiated	8 (18)	5 (14.3)	3 (33.3)	
Stage at the beginning of pemetrexed treatment				
NSCLC IIIB	6 (14)	5 (14.3)	1 (11.1)	1
NSCLC IV	38 (86)	30 (85.7)	8 (88.9)	
Score on the ECOG Scale upon starting pemetrexed treatment				
0	18 (41)	14 (40.0)	4 (44.4)	1
1	20 (45)	16 (45.7)	4 (44.4)	
2	6 (14)	5 (14.3)	1 (11.1)	
Pemetrexed line				
2nd line	26 (59)	21 (60.0)	5 (55.6)	1
>3rd line	18 (41)	14 (40.0)	4 (44.4)	
Surgery before chemo				
Yes	8 (18)	6 (17.1)	2 (22.2)	.659
No	36 (82)	29 (82.29)	7 (77.8)	
Surgery during chemo				
Yes	7 (16)	6 (17.1)	1 (11.1)	1
No	37 (84)	29 (82.9)	8 (88.9)	
Ad/Aa RT				
Yes	21 (48)	17 (48.6)	4 (44.4)	1
No	23 (52)	18 (51.4)	5 (55.6)	
Mortality				
Live	15 (34)	11 (31.4)	(44.4)	.464
Dead	29 (66)	24 (68.6)	(55.6)	

Ad/Aa RT, adjuvant/antalgic radiation therapy; chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung carcinoma.

Table 2 Descriptive variables of the study patients

	Total n=44. median (min-max)	Age		
		<70 years n=35, median (min-max)	≥70 years n=9, median (min-max)	*P*
Age, years	61.7 (39-77)	60.0 (39-70)	75.6 (70-77)	–
Lines before PEM	1 (1-5)	1 (1-5)	1 (1-4)	.929
Time D-PEM, months	11.1 (3-50)	10 (3-39)	19.5 (7-50)	.062
PEM dose, mg	929.9 (757.5-1107.5)	944 (757.5-1085)	894 (825-1107.5)	.664
PEM cycles	3 (1-20)	2 (1-20)	3 (1-8)	.644
Vials/patient	6 (2-40)	4 (2-40)	6 (2-16)	.644
Cost/patient, €	7,488 (2,496-49,920)	4,992 (2,496-49,920)	7,488 (2,496-19,968)	0.320

min-max indicates minimum-maximum; PEM, pemetrexed; time D-PEM, time transpired from the diagnosis until the start of pemetrexed treatment.

Table 3 Other neoplasms diagnosed in study patients before the current condition

Other cancer diagnoses	Year of diagnosis	Treatment received
Epidermoid carcinoma of the right vallecula	2000	Surgery+RT
IIB malignant fibrous histiocytoma	2007	Surgery+RT
Bladder neoplasm	1997	Surgery
Sigmoid colon adenocarcinoma	1998	Surgery+RT+chemo
Leukoplakia of the glottis	2006	Surgery
EIIA infiltrating ductal breast carcinoma	2003	Surgery+RT+chemo
Epidermoid laryngeal carcinoma	2004	Surgery+RT
Prostate adenocarcinoma	2005	Surgery+RT

Chemo indicates chemotherapy; RT, radiation therapy.

Table 4 Chemotherapy treatments as the first-fourth lines of treatment received by the patients in the study

	Treatment regimen	1st line (n=44), n (%)	2nd line (n=44), n (%)	3rd line (n=18), n (%)	4th line (n=7), n (%)
NSCLC	Carboplatin+paclitaxel	17 (38.6)	2 (4.5)	1 (5.6)	
	Cisplatin+vinorelbine	15 (34.1)	1 (2.3)		
	Cisplatin+gemcitabine	5 (11.3)	1 (2.3)		
	Cisplatin+gemcitabine+bevacizumab	2 (4.5)			
	Carboplatin+paclitaxel+bevacizumab	1 (2.3)			
	Cisplatin+docetaxel	1 (2.3)			
	Carboplatin+vinorelbine	1 (2.3)	1 (2.3)		
	Gemcitabine	1 (2.3)	2 (4.5)	1 (5.6)	1 (14.3)
	Vinorelbine	1 (2.3)	2 (4.5)	1 (5.6)	
	Docetaxel		2 (6.8)	1 (5.6)	
	Paclitaxel		3 (6.8)		1 (14.3)
	Erlotinib		2 (4.5)	2 (11.1)	1 (14.3)
	Irinotecan		1 (2.3)		
	Carboplatin+gemcitabine			1 (5.6)	
	Pemetrexed	0 (0)	26 (59.1)	11 (61.1)	4 (57.1)
	Total	*n=44*	*n=44*	*n=18*	*n=7*

NSCLC indicates non-small cell lung carcinoma.

for a greater SSCT in women, in patients 70 years of age or older, in patients with a higher ECOG scale score, in patients with epidermoid/squamous histology, when the disease was diagnosed in stages I-II, when the first line of treatment was with platinum/gemcitabine, and when pemetrexed was used as a third line of treatment or higher. SSP was significantly higher in women (*P*=.0455) (Fig. 1) and in patients with a superior functional state (*P*=.0099) (Fig. 2).

Table 5 Criteria for the start, response, and causes for stopping pemetrexed treatment

	Total, n (%)	Age		
		<70 years, n (%)	≥70 years, n (%)	*P*
Criteria for starting pemetrexed treatment				
Previous neutropoenia	4 (9.1)			<.0001
Previous taxane treatment	16 (36.4)	16 (45.7)		
Age >70 years	2 (4.5)		2 (22.2)	
Neutropoenia and previous taxane treatment	10 (22.7)	10 (28.6)		
Previous neutropoenia and >70 years	3 (6.8)		3 (33.3)	
Previous taxane treatment and >70 years	2 (4.5)		2 (22.2)	
Neutropoenia and previous taxane treatment and >70 years	2 (4.5)		2 (22.2)	
Other criteria	5 (11.4)	4 (15.3)		
Response to pemetrexed				
CR (disappearance of lesions)	0 (0)	0 (0)	0 (0)	.329
PR (reduction in lesions/is ≥30%, no new lesions)	0 (0)	0 (0)	0 (0)	
SD (reduction in lesions/is <30%or increase <20%, without DP or new lesions)	8 (18.2)	5 (14.3)	3 (33.3)	
DP (increase in lesions/is <25%or new lesions)	36 (81.8)	30 (85.7)	6 (66.7)	
Causes for stopping pemetrexed treatment				
DP	24 (54.5)	20 (57.1)	4 (44.4)	.640
Clinical worsening	7 (15.9)	5 (14.3)	2 (22.2)	
Death	4 (9.1)	3 (8.6)	1 (11.1)	
Toxicity/poor tolerance	3 (6.8)	2 (5.7)	1 (11.1)	
Patient's choice	2 (4.5)	2 (5.7)	0 (0)	
Minimal clinical benefit in spite of SD	1 (2.3)	1 (2.9)	0 (0)	
SD	1 (2.3)	0 (0)	1 (11.1)	
Surgical procedure	1 (2.3)	1 (2.9)	0 (0)	
Chemotherapy focused on another carcinoma	1 (2.3)	1 (2.9)	0 (0)	

CR, complete response; DP, disease progression; PR, partial response; SD, stable disease.

Although not a significant result, more histology tests resulted epidermoid/squamous when the disease was diagnosed in stages I-II and when the first line of treatment was with platinum/gemcitabine. As opposed to SSCT, SSP was higher when pemetrexed was used as a second line of treatment. The higher SSCT in patients in which pemetrexed was a third line of treatment or greater is logical, given that patients that get to this stage have been diagnosed and treated for a longer period of time.

Safety

All patients received the appropriate amount of folic acid and vitamin B_{12} supplements. Of patients, 43.2%suffered neutropoenia during chemotherapy treatments before receiving pemetrexed, mainly grade (G) 3 (42.1%), with a median of 0 episodes (0-3) of neutropoenia per patient. Of the neutropoenia episodes, 21.1%were accompanied by fever. The percentage of previous neutropoenias was somewhat higher, although not statistically significantly so, in patients 70 years of age or older (55.6%versus 40%), and significant differences existed in the grade of neutropoenia, this being mainly G3 in patients under 70 years of age and G2 in patients 70 years of age or older (*P*=.041). None of the patients that were previously treated with docetaxel (n=5) had neutropoenia. There were no cases of neutropoenia associated with pemetrexed.

The median number of AE associated with pemetrexed treatment was 0.5 (0-3). Among the AE, asthenia (34.1%), neurotoxicity (paresthesia in limbs and muscle pain) (18.2%), and gastrointestinal intolerance (9.1%) stood out (Table 7). The three patients that had anaemia following administration of pemetrexed received epoetin treatment.

The number of AE was greater, although not significantly so, in patients 70 years of age or older. The most frequent AE in both age groups were asthenia and neurotoxicity.

The clinical repercussions of the AE were not relevant: treatment was suspended in 3 patients (in 2 due to gastrointestinal intolerance, neurotoxicity, and diplopia, and in one case due to a coetaneous reaction to the first treatment cycle), and in another 2 patients, the pemetrexed cycles were delayed (in one case due to a G3 thrombocytopoenia and in the other due to a worsening of the ECOG score). A dosage reduction was not necessary in any case.

Table 6 Global survival from the start of chemotherapy and from the start of pemetrexed treatment

Characteristics	n	Median SSCT, months (95% CI)	Value *P* (log rank)	Median SSP, months (95% CI)	Value *P* (long rank)
Sex					
Men	38	22.2 (13.5-31.0)	.2504	6.1 (4.7-7.5)	.0455
Women	6	29.7* (21.9-37.4)		14.6* (11.7-17.6)	
Age					
<70 years	35	19.6 (12.1-27.2)	.2039	7.8 (3.1-12.5)	.9756
≥70 years	9	53.3 (NC)		6.7 (0.6-12.7)	
Score on the ECOG Scale upon starting pemetrexed treatment					
0	18	19.6 (18.1-21.2)	.9613	10.9 (8.9-12.9)	.0099
1	20	23.2 (20.0-26.5)		5.7 (3.4-8.0)	
2	6	6.9 (0.0-34.8)		2.3 (0.0-4.7)	
NSCLC histology					
Epidermoid/squamous	20	24.4 (22.4-26.4)	.2611	10.2 (8.0-12.4)	.2951
Adenocarcinoma	16	16.8 (11.5-22.1)		6.1 (3.8-8.5)	
Undifferentiated	8	18 (0-37.1)		4.2 (1.1-7.3)	
NSCLC stage upon diagnosis					
I-II	3	23.2 (5.2-41.3)	.6784	6.7 (NC)	.4878
III	16	23.9 (15.5-32.3)		10.9 (8.4-13.4)	
IV	25	18.0 (9.8-26.2)		6.1 (2.8-9.4)	
Response to the first line of treatment in NSCLC					
Complete/partial response	9	18.8 (16.5-21.1)	.6816	10.8 (8.6-12.9)	.8381
Stable disease	3	16.2 (15.1-17.2)		10.2 (3-17.5)	
Disease progression	14	24.4 (8.2-40.6)		6.8 (0-20)	
First line in NSCLC					
Platinum/vinorelbine	7	14.5 (4.3-24.6)	.2149	4.2 (2.7-5.6)	.0958
Platinum/taxanes	14	16.8 (11.1-22.4)		10.2 (4.7-15.8)	
Platinum/gemcitabine	5	31.3* (21.8-40.8)		19.2* (12.9-25.4)	
Pemetrexed line in NSCLC					
Second line	26	18.0 (14.0-22.0)	.2590	10.2 (7.8-12.7)	.1284
≥Third line	18	30.3 (19.4-41.3)		5.8 (2.6-8.9)	

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NC, not calculable; NSCLC, non-small cell lung carcinoma; SSCT, survival from the start of chemotherapy treatment; SSP, survival from the start of pemetrexed.
*Means.

Discussion

Pemetrexed was used above all in men, as in other studies,[5-8] which confirms that this type of neoplasm is currently more prevalent in men. Furthermore, 80% of patients diagnosed with NSCLC were or had been smokers, which confirms tobacco use as one of the most crucial risk factors for lung cancer.[3] A good functional state along with being female and having a non-squamous histology have been described as favourable factors for surviving to a second line of chemotherapy in NSCLC patients.[14] Therefore, the clinical guidelines[15,16] recommend pemetrexed as a second line of treatment for NSCLC when the patient is in a good clinical state.

Pemetrexed was not used as a first line of treatment in any of our patients, which is due to the finalization of the data collection for our study before May 2008, before the approval of using pemetrexed under this indication.[9]

First-line chemotherapy regimens, usually double therapy including platinum, are usually adjusted to the recommendations of the guidelines of the American Society of Clinical Oncology[15] and the National Comprehensive Cancer Network.[16]

The majority of our patients (81.8%) responded with DP, and none had a CR or PR. These results diverge from those observed in the clinical trial that approved pemetrexed as a second line of treatment for NSCLC,[8] in which 9.1% of patients responded (CR/PR) to treatment, and the only

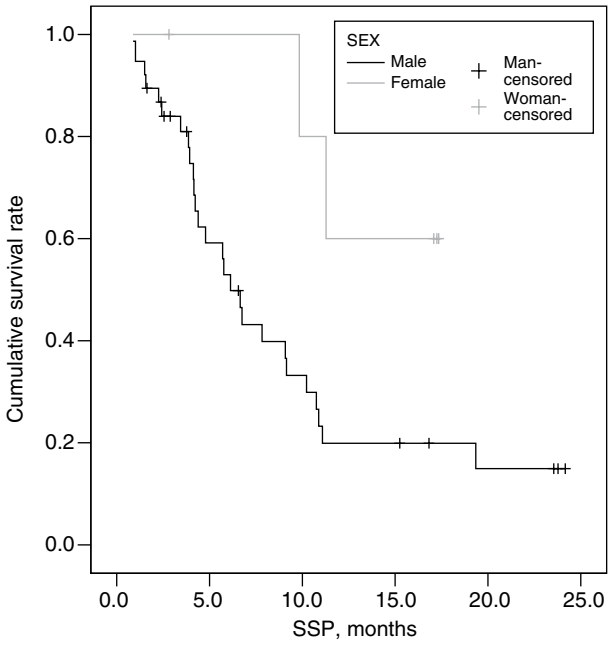

Figure 1 Survival graph from the start of pemetrexed treatment by sex. SSP indicates survival from the start of pemetrexed.

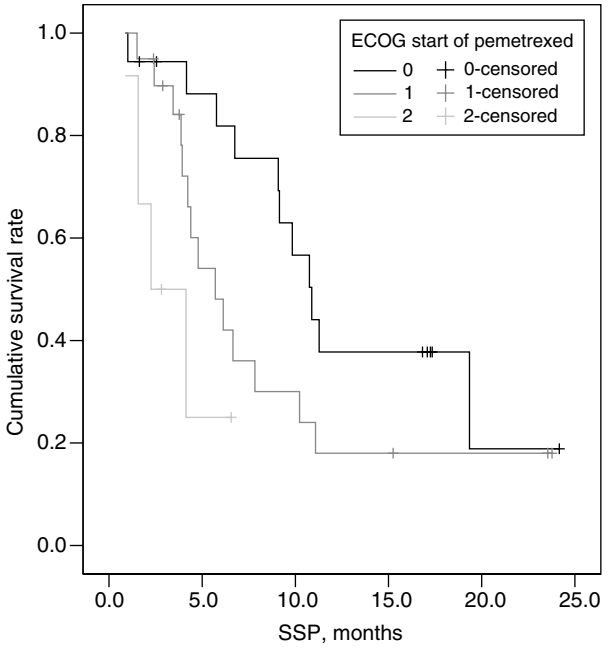

Figure 2 Survival graph from the start of pemetrexed treatment according to the eastern cooperative oncology group scale. ECOG indicates Eastern Cooperative Oncology Group; SSP, survival from the start of pemetrexed.

retrospective study published in Spain,[17] in which the response was even higher: 29.2% These differences could be due to the high percentage of patients in our study in stage IV before the start of pemetrexed treatment: 86%as opposed to the 37.5%observed in the Picaza[17] study, or the 74.9%observed in the Hanna[8] study.

In the Hanna[8] study, the survival from the inclusion in the study of patients treated with pemetrexed as a second line of treatment was 8.3 months, a similar value to the SSP in our study: 7.8 months. However, Picaza et al[17] obtained a lower value, between 4.5 and 5 months, according to the stage of the disease and the number of months since the last treatment, in spite of the high percentage of patients that responded to pemetrexed (29.2%). These results show that the response to pemetrexed is not related to survival.

A retrospective analysis[18] concluded that if the patient was a woman, was in stage III upon diagnosis of the disease, had a better functional state upon initiating the second line of treatment (0-1 on the ECOG scale), or had a better response to the first line of treatment, survival was significantly higher from the point of inclusion in the clinical trial,[8] in which the retrospective analysis was based on the NSCLC patients treated with pemetrexed as a second line of treatment. In our study, SSP would be the closest equivalent to the measure of survival in this study, and we found significant differences with greater SSP in women and patients in a better functional state. In the Weiss study,[18] the median survival in women was lower than in our study (9.4 months versus 14.6 months), but we must be cautious in our interpretation, since the patients grouped by sex are not homogeneous, with only 6 women and 38 men. The functional state before the second line of chemotherapy treatment in NSCLC is a prognostic factor of greater survival for the three agents tested.[5-8,18] In our study, the median SSP for the three ECOG scores are similar to those from the Weiss study[18] (0 on the ECOG scale: 10.9 months versus 12.7 months; 1 on the ECOG scale: 5.7 months versus 8.3 months; 2 on the ECOG scale: 2.3 months versus 2.6 months; $P=.0099$ versus $P<.0001$).

In NSCLC with squamous histology, pemetrexed has shown fewer advantage with respect to global survival than docetaxel as a second line of treatment (6.2 months versus 7.4 months),[8] and fewer advantages than gemcitabine/cisplatin as a first line of treatment (9.4 months versus 10.8 months).[9] However, in our study, the majority of patients (46%) had epidermoid/squamous histology. This situation was also produced in another retrospective study,[17] in which squamous histology was the most frequently observed in the NSCLC patients treated with pemetrexed (58.3%). We observed no significant differences in terms of survival between the different types of histology. Unlike in the Weiss study,[18] the NSCLC state upon diagnosis of the disease and the response to the first line of chemotherapy treatment were not prognostic factors for survival in our study. However, our results are very similar. Our median values of SSP for stages III and IV were 10.9 and 6.1 months versus 9.5 and 7.8 months, respectively, in the Weiss[18] study. Similarly, our median SSP values for patients with SD or DP following the first line of treatment are similar to those found in this study: 10.2 versus 10.5 months and 6.8 versus 4.6 months. However, our survival rates following CR or PR to the first line of treatment are somewhat lower: 10.8 months versus 15.8 months. Although the type of first-line chemotherapy treatment is not considered to be a prognostic factor for survival, we observed better SSP values in our study in the patients treated with platinum/gemcitabine (19.2 months) and platinum/taxanes (10.2 months), these survival rates being greater than those observed by Weiss[18]: 9.1 months and 7.4 months, respectively.

Table 7 Neutropoenias before pemetrexed treatment and the adverse effects associated with pemetrexed

	Total n (%)	Age		
		<70 years, n = 35, n (%)	≥70 years, n=9, n (%)	*P*
Percentage of previous neutropoenias	19 (43.2)	14 (40.0)	5 (55.6)	.467
Percentage of previous feverish neutropoenias	4 (9.1)	3 (21.4)	1 (20.0)	1
Grade of previous neutropoenias				
G2	5 (26.3)	2 (14.3)	3 (60.0)	.041
G3	8 (42.1)	8 (57.1)	0 (0)	
G4	6 (31.6)	4 (28.6)	2 (40.0)	
Asthenia	15 (34.1)	11 (31.4)	4 (44.4)	.464
Anaemia:	3 (6.8)	1 (2.9)	2 (22.2)	.101
Thrombocytopoenia	2 (4.5)	1 (2.9)	1 (11.1)	.371
Gastrointestinal intolerance	4 (9.1)	2 (5.7)	2 (22.2)	.180
Neurotoxicity	8 (18.2)	5 (14.3)	3 (33.3)	.329
Conjunctivitis	3 (6.8)	2 (5.7)	1 (11.1)	.506
Skin reactions	2 (4.5)	2 (5.7)	0 (0)	1
Changes in taste	2 (4.5)	2 (5.7)	0 (0)	1
	Total, median (min-max)	**Age**		
		<70 years median (min-max)	≥70 years, median (min-max)	*P*
No. of previous neutropoenias	0 (0-3)	0 (0-3)	1 (0-3)	.493
No. of AE from pemetrexed	0.5 (0-3)	0 (0-3)	2 (0-3)	.110

AE, adverse effects; G, grade; min-max, minimum-maximum.

We observed no significant differences in survival when separating patients by age groups, although the SSCT was greater in patients 70 years of age or older, and the SSP was greater in patients under 70 years of age. In another study by Weiss,[19] no significant differences were detected in the response to treatment or survival from the inclusion of the patient in the study between the two age groups: 7.8 months for those younger than 70 and 9.5 months for those 70 years of age and older. However, in our study, SSP for patients 70 years of age or older was somewhat lower than for patients under 70 (6.7 months versus 7.8 months).

Pemetrexed has been demonstrated to be significantly safer than docetaxel with respect to the production of G3 and G4 neutropoenia (5.3% versus 40.2%) and feverish neutropoenia (1.9% versus 12.7%), hospitalizations caused by this condition (1.5% versus 13.4%), and infections associated with neutropoenia (0% versus 3.3%).[8] Therefore, pemetrexed is the agent recommended as the second line of treatment in NSCLC patients previously treated with first-line treatment regimens including platinum, and that had suffered neutropoenia or other toxicities, whether haematological or not.[20] Forty-three point two percent of our patients had at least one episode of neutropoenia from previous treatments, this being the reason or one of the reasons for applying the pemetrexed treatment. No patients developed neutropoenia as a result of pemetrexed treatment. Most of the AE observed were not haematological.

The main limitation of this investigation was that it was a retrospective study in which no control group existed in order to compare pemetrexed with other treatments, and so we cannot come to definitive conclusions with respect to the prognostic factors for survival. Furthermore, the reduced number of patients and heterogeneity of the groups classified by sex and age require caution when analyzing the observed results. However, some useful information is provided regarding the use of pemetrexed in normal clinical practice. Prospective studies will be necessary in order to confirm the effect of the observed prognostic factors in this and other retrospective studies, as well as comparative studies with docetaxel and erlotinib.

Conflict of interest

The authors affirm that they have no conflicts of interest.

This study was previously presented at the 52 congress of the *Sociedad Española de Farmacia Hospitalaria* (Spanish Society of Hospital Pharmacy) in Tenerife in 2007, and the evaluating committee deemed that its publication would be of interest. We have not received any grants or economic aid for performing this study.

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