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ORIGINAL ARTICLE

Study into the use of cetuximab in metastatic colorectal cancer in a third level hospital

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KEYWORDS
Cetuximab;
Colorectal cancer;
Medication usage study

Abstract
Objectives: In this study we will analyse the use of cetuximab in the treatment of metastatic colorectal cancer (MCC) in a third level hospital. We will establish the usage conditions in our centre in keeping with those approved in current technical records. We will also record the treatment duration under the different usage conditions and use the information available in material that has been published to date.
Methods: An indication-prescription study of cetuximab in MCC was carried out on all patients treated with cetuximab for colorectal cancer in the period between 2004 and 2007 in our hospital. The number of prescriptions that do not fit the approved recommendations for cetuximab in MCC treatment (and why they do not fit) is determined. Descriptive statistical analysis was carried out for the different variables collected, and a Kaplan-Meier analysis was carried out for the treatment duration variable, so as to determine whether there is a difference in effectiveness for the common uses in our hospital.
Results: Data was recorded for 74 patients treated with cetuximab. The average cost per patient was €14 399 and on average, 15.3 dosages were administered per patient. The average initial dosage was 710 mg with an average dosage of 446 mg after that. The average duration of the treatments was 15.4 weeks. cetuximab was administered to 7 patients as first-line treatment and to 32 patients who had not used irinotecan previously. Irinotecan was not associated with cetuximab treatment in 9 patients, and it was used in 14 patients resulting in a negative outcome for the EFGR test. Treatment duration was longer in the case of its use as first-line treatment (27.7 weeks), if irinotecan had not been used before (23.3 weeks), if irinotecan was used (20.5 weeks) and in patients with positive EFGR results (19.6 weeks.) The median treatment duration, under the different conditions, was less than the average but with no major differences between them. 70.3% of prescriptions did not fit with the data sheet.
Conclusions: The use of cetuximab under different conditions to those approved on the technical data sheet creates an increase in the number of patients treated and a longer duration of the

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treatments which implies an increase in intake. The average and the mean treatment times for the usage conditions found did not present any significant statistical differences. There are a small number of patients who benefit from this treatment which can be seen by the large average, in comparison with the mean, without any of the conditions in which the analysis was carried out seeming to determine a higher response. The treatment duration in our study was similar to the durations recorded in relevant literature for these usage conditions.

PALABRAS CLAVE
Cetuximab;
Cáncer colorrectal;
Estudio de utilización de medicamentos

Estudio de utilización de cetuximab en cáncer colorrectal metastásico en un hospital de tercer nivel

Resumen
Objetivos: En este trabajo se analiza la utilización de cetuximab en el tratamiento de cáncer colorrectal metastásico (CCRm) en un hospital de tercer nivel, determinando las condiciones de uso en los pacientes de nuestro centro con relación a las aprobadas en ficha técnica en el momento. También, se compara la duración del tratamiento en las distintas condiciones de uso y con los datos disponibles en la bibliografía publicada hasta la fecha de realización de este trabajo.
Métodos: Se realizó un estudio de indicación-prescripción de cetuximab en CCRm para todos los pacientes tratados con cetuximab en CCR en el período 2004-2007 en nuestro hospital. Se determina el número de prescripciones que no se ajusta a la ficha técnica aprobada para cetuximab en CCRm y el motivo por el que no se adapta. Se realiza el análisis estadístico descriptivo para las distintas variables recogidas y un análisis de Kaplan-Meier para la variable duración de tratamiento para determinar si hay diferencia de efectividad para los usos habituales en nuestro hospital.
Resultados: Se recogieron los datos de 74 pacientes tratados con cetuximab. El coste medio por paciente fue de 14.399 € y un número medio de dosis administradas de 15,3 por paciente. La dosis media de inicio fue 710 mg y la de mantenimiento, de 446 mg. La duración media de los tratamientos fue 15,4 semanas. Cetuximab se administró a 7 pacientes en primera línea de tratamiento, y a 32 pacientes sin que previamente se hubiese utilizado irinotecan. En 9 pacientes no se asoció irinotecan al tratamiento con cetuximab y se empleó en 14 pacientes con resultado negativo para la prueba de EFGR. La duración de los tratamientos fue mayor en caso de utilización en primera línea de tratamiento (27,7 semanas), si no se empleó irinotecan previo (23,3 semanas), si se asociaba irinotecan al tratamiento (20,5 semanas) y en pacientes EFGR positivo (19,6 semanas). Las medianas de duración de tratamiento en las diferentes condiciones recogidas eran menores en magnitud a la media, no presentando diferencias significativas entre ellas. El 70,3 % de las prescripciones no se ajustaba a la ficha técnica.
Conclusiones: La utilización de cetuximab en condiciones distintas a las aprobadas en ficha técnica origina un aumento en el número de pacientes tratados y una mayor duración de los tratamientos, lo que implica un aumento en el consumo. La media y la mediana de tiempo de tratamiento para las condiciones de utilización encontradas no presentaron diferencia estadísticamente significativa. Hay un pequeño número de pacientes que se beneficia de este tratamiento, como puede ponerse de manifiesto por la mayor magnitud de la media respecto a la mediana, sin que ninguna de las condiciones en las que se realizó el análisis parezca ser determinante de una respuesta mayor. La duración de los tratamientos en nuestro estudio fue del orden de las encontradas en la bibliografía para esas condiciones de utilización.

Introduction

Cetuximab is an anti-cancer drug consisting of a chimeric monoclonal IgG1 antibody that acts by blocking epidermal growth factor receptor (EGFR) and preventing it from functioning, which inhibits cell proliferation and favours apoptosis. The first indication approved for cetuximab was as follows: "indicated, in combination with irinotecan, for the treatment of patients with metastatic colorectal cancer (mCRC) expressing EGFR after the failure of a cytotoxic treatment including irinotecan." At present, cetuximab associated with radiotherapy[1] is also indicated for the treatment of head and neck cancer,[1] although in this article we will be focussing on its use in mCRC.

The use of drugs under conditions other than those approved is frequent in oncology, due to the peculiarities of

oncological pathology and the desire to incorporate new methods into the treatment of cancer patients. Different studies carried out in this field[2,3] estimate that 50% of prescriptions for the group of oncological drugs that were studied do not follow drug indications; the use of cetuximab in daily clinical practice can differ from what is stated in its data sheet. Medical literature contains references to first-line treatment for patients with mCRC[4-8] who did not express EFGR,[9-12] or use in conjunction with drugs other than irinotecan.[5,13] The use of cetuximab in these cases could be responsible for an increase in use with 2 causes:

- A higher number of patients receiving treatment including those treated on a first-line basis and the additional patients who do not express EFGR, or an increased use of the treatment due to associating the drug with medications other than irinotecan. On this subject, some authors[14] estimate the number of patients apt for receiving treatment with cetuximab at 3% of those diagnosed with CRC, or at 1.8 treatments per 100 000 inhabitants, if we adhere to what is stated in the data sheet
- A longer treatment duration in patients as a result of increased response time,[15] mean time to progression or progression-free survival

This study will analyse the use of cetuximab in mCRC at a hospital that provides oncological care to its entire area, paying special attention to how situations in which cetuximab is not used according to its indications can influence treatment time, and how this may cause increased consumption.

Methods

We performed an indication-prescription profile study for cetuximab in mCRC including data from all patients receiving treatment at our hospital, beginning when cetuximab was first marketed in 2004 up to November 2007, and who were not included in any of the active clinical trial protocols for cetuximab in that hospital. Data was collected from the information system software pertaining to oncological pharmacy and admissions, the clinical history and anatomical pathology records. The examined variables were patient age and sex, line of treatment, presence or absence of prior treatment with irinotecan, drug associated with cetuximab, cetuximab dosage, results of the EGFR expression test, treatment duration, and whether or not it continued beyond the end of the study. We also collected data regarding cetuximab consumption in the study period, as well as the number of preparations elaborated by the pharmacy division.

The qualitative variables were analysed descriptively according to frequency, and the quantitative variables were analysed using central tendency and dispersion (mean, median, standard deviation [SD]; in addition, the treatment time variable was analysed using the Kaplan-Meier method (overall and according to the line of treatment, association of irinotecan, prior treatment with irinotecan and result of the EFGR test), and the delimiting event for the above was discontinuing treatment for any reason. SPSS statistical package was used for all analyses. Treatment time according to cetuximab's data sheet can continue until the patient progresses, suffers an adverse reaction, or dies; treatment times measured in our hospital were compared with those in published clinical studies or with other available efficacy variables. Given this basis, treatment time could be a good estimator of time until treatment failure[15]; however, this variable is not considered to be a good measurement of efficacy in clinical trials, as it measures efficacy and safety at the same time, and we used progression-free time and progression-free survival as the efficacy variable.

The coincidence rate between the indication that was used and the authorised indication was established based on that approved according to the cetuximab data sheet[1] at the time when this study was carried out. Since there was the possibility of a treatment having 2 or more ways in which it did not comply with specifications in the package leaflet, we used the algorithm shown in Figure 1 to determine whether or not a treatment complied with specifications.

Results

During the study period, a total of 74 mCRC patients, 56 men and 18 women, were treated. During the same period, 694 patients were attended in the oncology division, which led to use of cetuximab in 10.6% of all colon cancer patients who were treated. Average patient age was 66 years (39-84 years). At the moment when the study started, 17 patients were already receiving treatment with cetuximab.

The average cost per patient was €14 399, giving us a total of €1 065 526 for cetuximab consumption during the entire period. Annual cetuximab consumption rose from €62 850 during 2004 to €467 467 in 2007 (January to October) (Table 1). A total of 1130 doses were administered, with a mean of 15.3 (1-68) per patient and a median of 10.

Situations in which cetuximab was used for a reason other than the approved one made up 70.3% of the total (Figure 1). According to the legislation that was applicable for the duration of this study, the use of medications for conditions other than those that are authorised should be cleared for "compassionate use" with the Spanish Agency for Medicines and Health Products, however, this study only found applications for "compassionate use" for 12 cases, which comprised 23.1% of those for which permission should have been requested.

Cetuximab was administered as a first line of treatment in 7 patients (9.5%), as a second line in 25 (33.8%), and as a third or later line of treatment in 42 (56.8%). Forty-two patients (56.7%) received treatment with irinotecan prior to taking cetuximab. Irinotecan was administered with cetuximab in 63 patients (85.1%), out of whom 5 also received fluorouracil; 7 patients (9.5%) received cetuximab monotherapy and the treatment was associated with medications other than irinotecan in 4 patients (5.4%) (Table 2). The drugs other than irinotecan that were administered in association with cetuximab were fluorouracil and oxaliplatin in 11 and 9 patients respectively. Seven patients changed treatment during therapy with cetuximab + irinotecan due to having a second treatment option in the form of cetuximab monotherapy, or cetuximab associated with oxaliplatin. Only

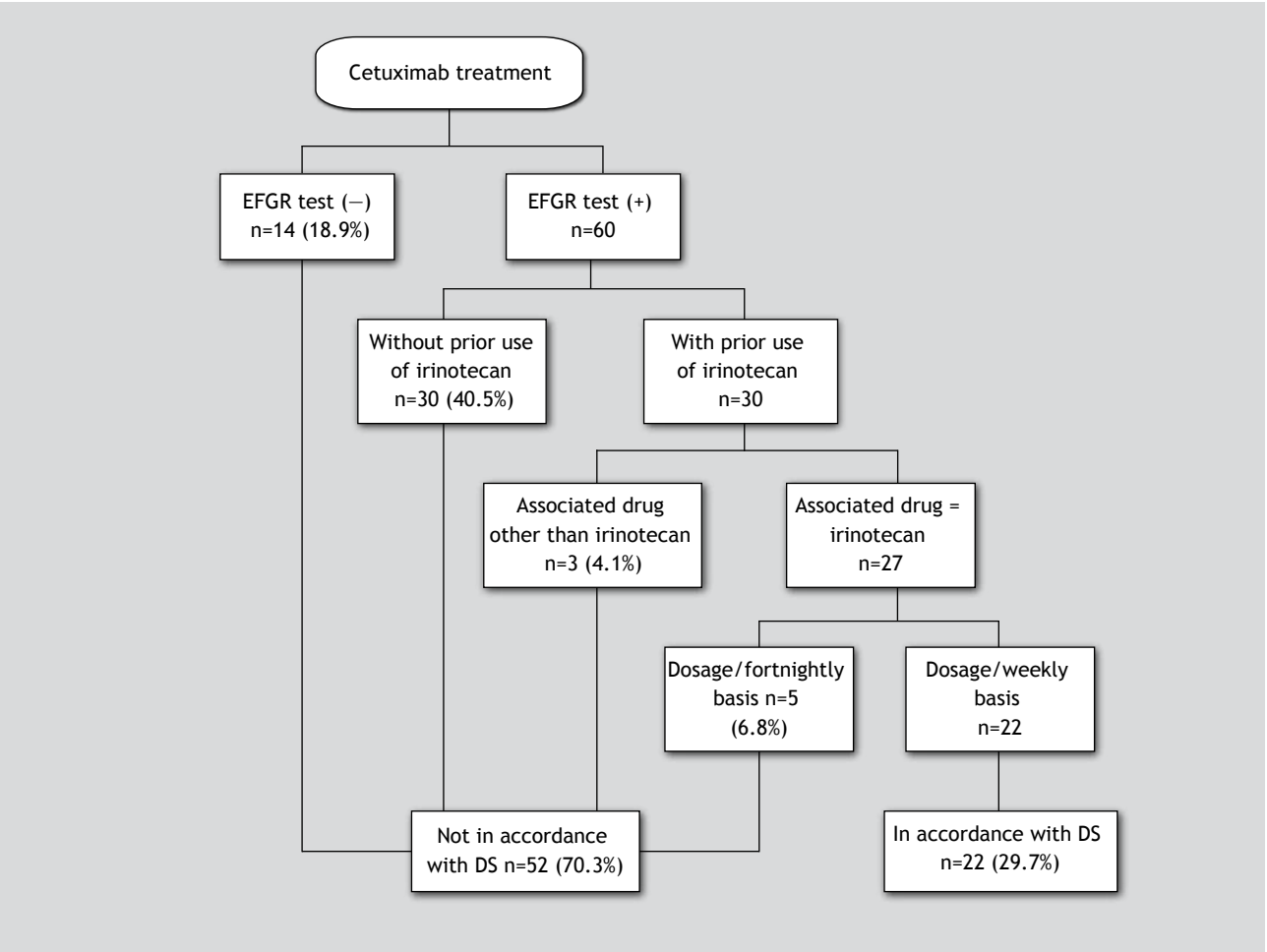

Figure 1 Number of treatments in keeping with the data sheet (DS).

Table 1 Number of patients and cetuximab consumption

	2004	2005	2006	2007[a]	Totals
Number of patients	5	28	28	40	Total:74 M: 56 F: 18
Median age (min-max)					Total: 66 (39-84) M: 66 (39-84) F: 66 (51-79)
Number of preparations	54	277	341	458	1130
Use, €	62 850	235 905	299 287	467 484	1 065 526

F indicates females; M, males.
[a]Data from January to October 2007.

34 patients underwent the EFGR test, which was positive in 20 (58.9%) and negative in 14 (41.1%).

The mean dose that was given to begin treatment was 710 mg (SD=101), and the maintenance dose was 446 mg (SD=53.4). Thirteen patients had their doses lowered during treatment; the mean decrease was 30%, and 8 received cetuximab on a fortnightly basis (500 mg/m^2).

The mean duration of cetuximab treatments (Table 2) for all patients in the study was 15.4 weeks (SD=16.1). If we take the line of treatment into account, the mean duration was 27.7 weeks for first line, 24.4 weeks for second line, and 16 for third line or later. In patients who had undergone previous treatment with irinotecan, the mean treatment duration was 17.4 weeks; for the rest, it was 23.3 weeks.

Table 2 Treatment duration according to conditions of use

		Treatment duration, weeks			
		No.	Mean (95% CI)	Median (95% CI)	
Patient total		74	15.4	9.9	
Line	First	7	27.7 (0-56.4)	8.9 (0.4-17.3)	Log-rank sig = 0.339
	Second	25	24.4 (15-33.7)	21.0 (14.5-27.5)	
	Third or later	42	16 (11-21)	10.4 (7.2-13.7)	
Previous irinotecan use	No	32	23.3 (13.8-32.9)	13.4 (2.1-24.8)	Log-rank sig = 0.47
	Yes	42	17.4 (11.9-22.9)	11.9 (6.8-16.9)	
Associated drug	Irinotecan	58	20.5 (14.8-26.2)	12.3 (0.6-24)	Log-rank sig = 0.5187
	Irinotecan + fluorouracil	5			
	Cetuximab monotherapy	7	15.1 (3.1-27.1)	10.4 (0-23.7)	
	Others	9			
EFGR test	Non-existent	40	23.1 (14.6-31.5)	21.0 (14.3-27.7)	Log-rank sig = 0.1300
	Existing	34	16.1 (9.8-22.3)	9.9 (8.3-11.4)	
	+	20	19.6 (9.5-29.8)	10.3 (9.1-11.5)	Log-rank sig = 0.1865
	—	14	11.4 (6.7-16)	8.7 (5.9-11.5)	

CI indicates confidence interval; EGFR, epidermal growth factor receptor.

After reviewing clinical histories and searching the anatomical pathology database, we only found results from EFGR testing in 34 of the 74 patients in the study. In patients with a positive result, the average duration of the treatments was 19.6 weeks; for patients testing negative, it was 11.4 weeks (Table 2). The mean treatment duration in patients who did not undergo this test was 23.1 weeks. Values for the median treatment duration for the entire population and each stratum (line of treatment, prior administration of irinotecan, association with irinotecan and EFGR test) are also shown in Table 2 and Figure 2; for all cases, the median treatment duration was shorter than the mean.

Discussion

As shown in Table 1, there has been a gradual increase in both cetuximab treatment and in the number of mCRC patients treated with that drug. The increase in consumption (56%) is greater than the increase in patient numbers (42%), which is why we believe that it is due to a high degree of use under conditions other than those approved according to the data sheet; these comprise 70.3% of all cases. It shows situations such as cetuximab use in first lines of treatment, or in cases where irinotecan is not previously administered; these situations create a longer treatment time and an increase in cetuximab use which is proportionally greater than that of the number of patients.

Table 3 shows a summary of the data obtained through this study and from the published trials for the same clinical condition. As a reference, we also show the data from Cunningham's pivotal study[16] and the article by Tournigand et al[17] that compares 2 treatment sequences with the FOLFIRI and FOLFOX regimens.

We can observe that the mean treatment time is longer if cetuximab is used as a first line of treatment for mCRC (27.7 weeks), instead of as a second-line (24.4 weeks) or third-line (16 weeks) treatment. The mean treatment times with cetuximab as a first line of treatment is similar to the treatment times recorded by Folprecht et al[4] and Tabernero et al.[5] Analysis of the patients in our study using the Kaplan-Meier method showed a median treatment duration of 8.9 weeks as a first line of treatment; for second line, it was 21.0, and in third line, it was 10.4, with no statistically significant differences. In our population, we can observe how the median treatment duration for the first line of treatment is noticeably less than those shown in the studies by Folprecht et al[4] and Tabernero et al,[5] even if they are compared with our population's mean. This could be due to the low number of patients in our study who were undergoing a first line of treatment (7 patients).

If we consider patients previously treated with irinotecan, the mean treatment duration was 17.4 weeks (23.3 weeks without previous treatment), and this value is similar to that obtained by Cunningham.[16]

When cetuximab was used with irinotecan, the mean treatment time was 20.5 weeks compared to 15.1 weeks without irinotecan, although in this last group, cetuximab could be associated with other drugs, such as oxaliplatin and/or fluorouracil. Once again, the median for these groups is lower than the mean: 12.3 and 10.4 weeks, with and without irinotecan, respectively.

Different treatment guides for mCRC refer to the EFGR test's lack of value as a predictor, and do not recommend that test as a determining criterion for treatment with cetuximab.[18] In our population, 54% of patients had no result (whether positive or negative) for this test, with a

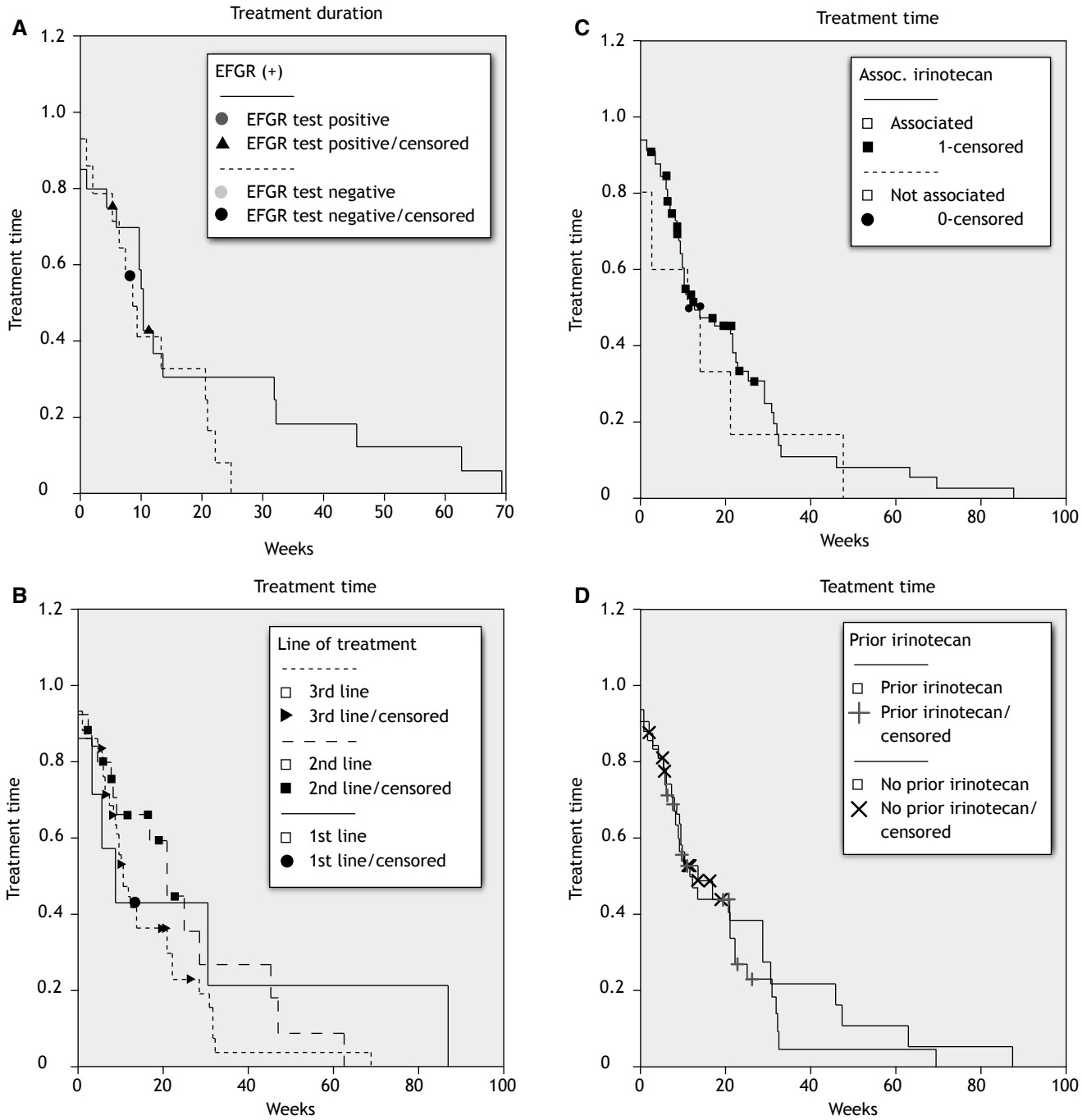

Figure 2 Survival curves for treatment time. A. According to the result of the test for epidermal growth factor receptor (EFGR). B. According to the line of treatment. C. According to whether or not irinotecan was administered, whether or not it was associated with cetuximab. D. According to whether or not irinotecan had been previously administered.

mean treatment time of 23.1 weeks, compared to 46% of patients who did have a result and whose treatment duration was 16.1 weeks. In the latter group, the mean treatment duration was longer for patients whose EFGR test showed positive (19.6 weeks) than for those with a negative result (11.4), although this difference was not significant; furthermore, there was no significant difference when the analysis was performed according to median treatment time (Table 2). Both the mean and median treatment durations for patients with a negative EFGR test were clearly lower in our study than in the studies listed in the bibliography (Table 3).

The fact that the mean treatment duration shows a higher value than the median could be due to the fact that benefit from cetuximab occurs in certain patients and is not homogeneous; we did not find that the different variables analysed (line of treatment, previous administration of irinotecan, association with irinotecan and EFGR test) had

Table 3 Efficacy results in clinical trials of cetuximab

		Median RD, weeks	RD, months	ORR,% (95% CI)	Mean PFS,s months	Mean OS, months
First line						
Result of this study (n=7 patients)		8.9 (0.4-17.3)	Not collected in this study			
Tournigand et al[17] (n=220 patients)	A	—	—	56 (47-65)	8.5 (7-9.5)	21.5 (16.9-25.2) (1st + 2nd line)
	B	—	—	54 (45-63)	8 (6.2-9.4)	20.6 (17.7-24.6) (1st + 2nd line)
Folprecht et al[4] (n=27 patients)		28.1 or 24.7	—	67 (47-87)	—	33 (20-n)
Tabernero et al[5] (n=43 patients)		24 (1-78)	10.8 (7.1-13.9)	72 (56-85)	12.3 (7.7-15.8)	30 (17.8-33.8)
Rougier et al[6] (n=23 patients)		—	—	46 (25-66)	10.9 (PFT)	—
Bokenmeyr et al[7] (n=337 patients)		—	—	49 (PS=0-1)	[a]	[a]
Seufferlein et al[8] (n=49 patients)		—	—	54 (38-69)	[a]	[a]
Second line						
Result of this study (n=25 patients)		21 (14.5-27.5)	Not collected in this study			
Tournigand et al[17] (n=220 patients)	A	—	—	15 (7-23)	4.2 (3.7-5.2)	21.5 (16.9-25.2) (1st + 2nd line)
	B	—	—	4 (0-9)	2.5 (2.1-3.3)	20.6 (17.7-24.6) (1st + 2nd line)
Cunningham et al[16] (n=329 patients)	C+I	18	5.7	22.9	4.1 (PFT)	8.6
	M	7	4.2	10.8	1.5 (PFT)	6.9
Negative EGFR						
Result of this study (n=14 patients)		8.7 (5.9-11.5)	Not collected in this study			
Huertas Fernández et al[9] (n=9 patients)		28 (12-64)	—	—	7 (3-16)	10.2 (4-24)
Hebbar et al[10] (n=20 patients)		16 (10-56)	—	20	7.3	9.5
Chung et al[11] (n=16 patients)		15 (8-17)	—	25 (4-46)	—	—
Vincenzi et al[12] (n=10 patients)[b]	Decrease VEGF	—	—	60%	6.5 (3.7-10.9) (PFT)	14
	No decrease	—	—		3 (2.5-4.5) (PFT)	6.5
Other drugs						
Result of this study (n=10 patients)		10.4 (0-23.7)	Not collected in this study			
Tabernero et al[5] (n=43 patients) (FOLFOX4)		24 (1-78)	10.8 (7.1-13.9)	72 (56-85)	12.3 (7.7-15.8)	30 (17.8-33.8)
Souglakos et al[13] (n=40 patients)[c]		8		20 (9-32)	3	10.7

CI indicates confidence interval; EGFR, epidermal growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFT, progression-free time; RD, response duration; TD, treatment duration; VEGF, vascular endothelial growth factor.

[a]PFS or PFT date from the studies by Bokemeyer et al[7] and Seufferlein et al[8] were not available at the moment when this study was carried out.

[b]Response measured as a decrease in VEGF values.

[c]Patients resistant to previous treatment, refractory to oxaliplatin or with a resistant disease.

any influence on the duration of the treatment, and therefore, on its effectiveness.

Conclusions

The use of cetuximab in different clinical situations in our hospital is parallel to the publication of new studies (Table 3). The mean treatment time values are similar to median treatment durations found in the published literature for these conditions of use. The fact that few requests for compassionate use are submitted could be due to the false belief that the indications for the drug have been amplified based on the publication of new evidence. Likewise, use of this drug under new conditions is responsible for an increase in cetuximab treatment, motivated by the 2 causes indicated in our working hypothesis: increase in patient number, and longer duration for those patients. No significant differences were observed for treatment times according to the different conditions of use that we discovered in our hospital. However, one aspect that should be highlighted is that a longer duration is observed in the mean, and not the median, treatment duration; this is likely due to the fact that only certain patients benefit from this treatment. It must be determined which of the patients truly benefit from treatment with cetuximab, considering the monetary impact of introducing this treatment for mCRC.

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