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Concordance between expectations and preferences of patients and evaluation criteria of the European Medicines Agency

Concordancia entre las expectativas y preferencias de los pacientes y los criterios de evaluación de la Agencia Europea del Medicamento

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Abstract

Objective: The European Medicines Agency's marketing authorisation criteria for drugs are reflected in the *European Public Assessment Reports*. The objective is to describe the expectations and preferences of our onco-hematological outpatients with respect to their oral treatments, and to evaluate the concordance with the results of *European Public Assessment Reports*.

Method: A survey of onco-hematological patients' expectations and preferences about overall survival and quality of life was developed, with three items: expectations on treatment, preferences of benefit and willingness to receive novel treatments with non-definitive results. *European Public Assessment Reports* of the indicated drugs were reviewed. Kappa index (κ) was used to assess the agreement between patients' expectations and preferences respect to the benefit in overall survival and quality of life described in the corresponding *European Public Assessment Report*. Concordance between willingness of patients to receive novel treatments and *European Public Assessment Reports* results was evaluated by absolute agreement (Ao).

KEYWORDS
Evidence-based medicine; Hematology; Medical oncology; Quality of health care; International health regulations.

Resumen

Objetivo: Los criterios de autorización de comercialización de medicamentos de la Agencia Europea del Medicamento se reflejan en los *European Public Assessment Reports*. El objetivo es describir las expectativas y preferencias de nuestros pacientes externos oncohematológicos con respecto a sus tratamientos orales, y evaluar la concordancia con los resultados de los *European Public Assessment Reports*.

Método: Se elaboró una encuesta sobre las expectativas y preferencias de los pacientes oncohematológicos respecto a la supervivencia global y calidad de vida, con tres ítems: expectativas sobre el tratamiento, preferencias de beneficio y disposición a recibir tratamientos novedosos con resultados inmaduros. Se revisaron los *European Public Assessment Reports* de los fármacos indicados. Se utilizó el índice kappa (κ) para evaluar la concordancia entre las expectativas y preferencias de los pacientes respecto al beneficio en supervivencia global y calidad de vida descrito en el *European Public Assessment Report* correspondiente. La concordancia entre la disposición de los pacientes a recibir nuevos tratamientos y los resultados de los *European Public Assessment Reports* se evaluó mediante la concordancia absoluta (Ao).

PALABRAS CLAVE
Medicina basada en la evidencia; Hematología; Oncología médica; Calidad de la atención sanitaria; Normativa sanitaria internacional.

Results: There were 29 participants, and 19 different *European Public Assessment Reports* were consulted. Patients' expectations about their treatment: 82.1% expected improvement in overall survival and quality of life; the κ value between expectations and results of *European Public Assessment Reports* was 0.091 (confidence interval 95%: −0.025 to 0.207). Patients' preferences about benefit of their treatment: 92.6% preferred quality of life; the κ value was 0.016 (confidence interval 95%: −0.127 to 0.160). Willingness to receive novel treatments: 82.1% participants demanded benefit in overall survival or quality of life; exigences were met in Ao = 53.6% of patients.

Conclusions: Little agreement was observed between expectations and preferences of our onco-hematological patients and *European Public Assessment Reports*, according to overall survival and quality of life. Most patients preferred an improvement in quality of life, but also expected an increase in overall survival with their treatment. Almost half of patients would not meet their requirements to receive their drug when it was authorized.

Resultados: Se incluyeron 29 participantes y se consultaron 19 *European Public Assessment Reports* diferentes. Expectativas de los pacientes sobre su tratamiento: el 82,1% esperaba una mejora de la supervivencia global y calidad de vida; el valor κ entre las expectativas y los resultados de los *European Public Assessment Reports* fue de 0,091 (intervalo de confianza 95%: −0,025 a 0,207). Preferencias de los pacientes sobre el beneficio de su tratamiento: el 92,6% prefirió la calidad de vida; el valor κ fue de 0,016 (intervalo de confianza 95%: −0,127 a 0,160). Disposición a recibir tratamientos novedosos: el 82,1% de los participantes exigió un beneficio en la supervivencia global o en la calidad de vida; las exigencias se cumplieron en Ao = 53,6% de los pacientes.

Conclusiones: Se observó poca concordancia entre las expectativas y preferencias de nuestros pacientes oncohematológicos y los *European Public Assessment Reports*, según la supervivencia global y la calidad de vida. La mayoría de los pacientes preferían una mejora de la calidad de vida, pero también esperaban un aumento de la supervivencia global con su tratamiento. Casi la mitad de los pacientes no cumpliría con sus requisitos para recibir su medicación cuando ésta fuera autorizada.

Introduction

Patient empowerment has become increasingly important in recent years. However, the lack of conceptual clarity and a specific methodology makes it difficult for patients to be included in clinical decision-making[1,2]. In the other hand, the limited resources in health systems and a growing need for health care by population make priority setting essential in clinical practice[3]. Likewise, the World Health Organization has published reports on excessive health care spending in certain clinical areas, such as oncology and hematology[4].

How can we take patients' opinions into account and set priorities? The answer to this question could be found both in studies that assess their preferences and in scientific evidence about medicines. The preferences of onco-hematological patients are clear: increased survival, quality of life (QoL), a good death and preservation of dignity[5-8]. Regarding scientific evidence about medicines, overall survival (OS) and QoL are considered the most appropriate endpoints to assess the benefit received by onco-hematological patients[9,10]. Even though progression-free survival (PFS) is a surrogated endpoint of considerable clinical relevance, this outcome must be carefully analyzed according to the clinical context, and it is not exempt from controversy in many cases[11,12].

The European Medicines Agency (EMA) is a participating institution in regulation and monitoring of drugs in the European Union (EU)[13]. This entity evaluates the benefit provided by novel drugs. Medications must be authorized before being marketed in EU. European system offers different procedures for marketing authorization. Most of drugs are not authorized in EU through a centralized procedure, but are authorized by competent national authorities of the member states. The decentralized procedure allows pharmaceutical companies to request authorization for the simultaneous marketing of a drug in several states without prior authorization in any country. The mutual recognition procedure allows companies with a drug authorized in one state to recognize the authorization in other countries.

On the other hand, centralized procedure makes it possible to market a medicine on the basis of a single European evaluation and a marketing authorization valid throughout the EU. Pharmaceutical companies present a single authorization request to EMA. The Committee for Medicinal Products for Human Use develops a scientific evaluation and makes a recommendation to the European Commission on the marketing authorization. The centralized marketing authorization of the European Commission is valid in all EU states. The use of the centralized procedure is mandatory for some drugs, such as treatments for rare diseases and antitumor therapies. The centralized marketing procedure is a legal requirement that guarantees the efficacy and safety of these drugs. Transparency is an important feature of European system of regulation of medicinal products. A European Public Assessment Report (EPAR) is published for each drug which a marketing authorisation is granted or refused following assessment of EMA.

Randomized clinical trials (RCTs) are the studies with the highest level of scientific evidence, becoming the most robust tool for analysis of health interventions[14,15]. However, evaluating agencies are often forced to position therapeutic alternatives or authorize them with minor investigations, such as retrospective descriptive studies[16]. The demand by pharmaceutical industry and patient associations for greater acceleration of drug approval processes could favour decision-making with premature data, increasing the degree of uncertainty regarding them. This could have notable consequences on effectiveness, safety and efficiency of authorized treatments, especially in onco-hematological pathologies.

Taking all of above into account, we can deduce that it is not easy to satisfy the needs of patients in the current health-economic context. Health professionals and government institutions have a common responsibility: to provide the population with the best health care available by optimizing resources. For this reason, studies that analyse the demands of patients are an enriching source of information for health systems, and could improve drug selection. There are numerous validated tools to meet the expectations of cancer patients. Trask *et al.* developed a 16-item patient-reported questionnaire to evaluate cancer patients' experiences[17]. This survey contains information about the expectations of effect of antitumor therapy on increased OS. However, this work does not provide information on whether patients expect treatment to improve QoL or patients' preferences between OS and QoL. Rose *et al.* evaluated patients' care preferences and opinions of doctors with a questionnaire[18]. In this case, the preferences of patients between OS and QoL were analyzed. On the other hand, the perspective of doctors on the OS and QoL of patients is considered. However, patients were not questioned about their expectations in the therapies received. Gleason *et al.* tested relationship between cancer patients' expectations for cure prior to interacting with their oncologist and their decisions to follow treatment recommendations[19]. This study evaluated patients' expectations about the effect of treatments on their cure –which was not exactly the increase in OS– or QoL. However, this questionnaire did not report data on patient preferences on the choice of OS or QoL.

The development of a study encompassing the information of the cited tools could provide interesting information. The objective of our study is to describe the expectations and preferences of our onco-hematological outpatients treated with oral drugs, and to assess the agreement with the results described in EPARs.

Methods

Based on previous literature about preferences of onco-hematological patients[5-8], a survey was developed to collect the information of outpatients diagnosed with a neoplasm in our healthcare center. This tool was designed to record expectations and preferences of patients about their treatments, in order to compare them subsequently with results of final endpoints —OS and QoL— presented in EPARs[13]. The questionnaire presented an initial explanation to inform patients about the anonymity and voluntary participation, and it was divided into two parts. In the first part, clinical and sociodemographic variables (age, gender and clinical context of the participants) were recorded. The second part consisted of three items: (I) patients'

expectations about the benefit obtained by their treatment, (II) patients' preferences about the possible benefits that a treatment can contribute and (III) willingness to receive novel treatments with non-definitive results. The recruitment of participants was developed by two hospital pharmacists in the outpatient dispensing area between January 2020 and March 2020. The tool was given to patients, who were also reported on the possibility of requesting for pertinent explanations in case of doubts during the process. Subsequently, participants were surveyed with the necessary time and privacy. Figure 1 shows the questionnaire developed on the recruited outpatients.

Furthermore, a search was conducted of the first EPAR published about the drug received by each patient, in order to analyze results of OS and QoL in the corresponding indication. The following data were registered: date of report, study design, comparators, magnitude of effect of treatments, hazard ratio (HR), confidence intervals (CI), and statistical significance (p). The drug was assumed to provide benefit in OS respect to the comparator when statistically significant difference in OS medians was observed. Benefit in QoL of a drug was considered when a statistically significant difference was demonstrated in any of analyzed scales respect to the comparator. Non-randomized studies without control arm were excluded due to their significant biases. The main limitation of these studies is the difficulty of establishing a causal inference of effect of treatments[14,15]. The review of reports was conducted by three hospital pharmacists.

Subsequently, an analysis was developed to determine the agreement between the survey items I and II (expectations and preferences on the benefit of treatments) and the results reported in EPARs, in terms of OS and QoL. For this purpose, kappa index (κ) with its 95% confidence interval (95%CI) was used, according to the following formula: κ = [Observed agreement (Ao) – Expected agreement (Ae)] / (1 – Ae). Ao was defined as the most agreed-upon response, and Ae was the expected agreement according to the number of possible responses for each question. Landis and Koch criteria were followed to interpret the strength of agreement for κ values[20]: < 0.0 was related to non-agreement, < 0.2 insignificant agreement, 0.21-0.4 discrete agreement, 0.41-0.6 moderate agreement, 0.61-0.8 substantial agreement and 0.81-1 almost perfect agreement. The responses of patients to question III were compared with the results of EPARs to evaluate their willingness and exigencies to receive novel treatments with non-definitive results, that showed uncertain benefit in OS or QoL. The Ao value was used to determine the agreement, due to it was not possible to calculate κ. For patients who were willing to receive these novel treatments regardless of data from EPAR it was assumed that they did not have exigencies. However, patients who were not willing to receive these treatments were considered to present demands. In this group of patients, those who were treated with drugs associated with benefit in OS or QoL were considered to meet their exigencies; those users who were treated with drugs without benefit did not meet their exigencies. All calculations were performed using SPSS® v.18 statistical program and $p < 0.05$ value was considered as statistically significant.

Results

There were 29 participants in the survey, 15 (51.7%) were women and 14 (48.3%) were men. Median age of patients was 64 (28-75) years. The distribution of registered treatments was: 4 (13.8%) nilotinib, 3 (10.3%) sunitinib, 3 (10.3%) lenalidomide, 3 (10.3%) capecitabine, 2 (6.9%) abiraterone, 2 (6.9%) enzalutamide and 12 (41.4%) others. The clinical contexts of

Figure 1. *Questionnaire about expectations and preferences of onco-hematological outpatients re-garding the treatments for their pathology.*

You will be asked a series of questions about your expectations and preferences of cancer treatment you are receiving or will receive. This in an anonymous questionnaire and will be de-veloped on patients who are receiving cancer treatment and are willing to participate. Users will be attended to any questions during the survey. Please complete the following information be-fore continuing with the questionnaire:

Age: .....
Gender: .....
Treatment received: .....
Clinical context: .....

Issues:

I. **Expectations about the benefit obtained by the treatment:**
What benefit do you think the treatment you are receiving offers you compared to other drugs?
a) Increased survival
b) Improvement of the quality of life
c) Improvement of both survival and quality of life
d) None

II. **Preferences about the possible benefits that a treatment can contribute:**
What benefit would you prefer that the treatment you receive provide you?
a) Increased survival
b) Improvement of the quality of life
c) None

III. **Willingness to receive novel treatments with non-definitive results:**
Would you be willing to receive a novel treatment with uncertain improvement in survival or qual-ity of life compared to other treatments, because of presenting non-definitive results in clinical trials?
a) Yes
b) No

participating patients were the following: 4 (13.8%) newly diagnosed clear cell renal cell carcinoma, 4 (13.8%) metastatic castration-resistant prostate cancer, 3 (10.3%) refractory multiple myeloma, 3 (10.3%) newly diagnosed chronic myeloid leukemia, 2 (6.9%) newly diagnosed breast cancer, 2 (6.9%) refractory breast cancer and 13 (37.9 %) others. Data of patients are detailed in table 1.

A total of 19 different indications were registered. There were patients who received the same treatment in the same indication. The EPARs evaluated the following drugs[21]: abemaciclib, abiraterone, capecitabine, dabrafenib associated with trametinib, enzalutamide, everolimus, ibrutinib, lenalidomide, lenvatinib, nilotinib, osimertinib, ribociclib, sorafenib, sunitinib, imatinib and vismodegib. The publication dates of reports were between 2006 and 2018. Designs of studies included in reports were: superiority RCT in 12 (63.2%) cases, non-inferiority RCT in 3 (15.8%) and 4 (21%) non-randomized studies without control arm. Placebo was the comparator in 8 (42.1%) studies. Comparative OS data were available in 15 (78.9%) indications, while comparative QoL data were available in 6 (31.6%). Individual results of EPARs consulted are shown in table 2.

Table 1. Participant data and questionnaire responses

Patient number	Age (years)	Gender	Drug	Clinical context	Response to Question I	Response to Question II	Response to Question III
1	75	Female	Abemaciclib	Metastatic breast cancer (initial therapy)	c	b	b
2	75	Male	Abiraterone	Newly diagnosed high-risk metastatic prostate cancer	c	b	a
3	82	Male	Abiraterone	Newly diagnosed high-risk metastatic prostate cancer	c	b	a
4	75	Female	Capecitabine	Refractory breast cancer after relapse to chemotherapy	c	b	b
5	68	Female	Capecitabine	Colon cancer (adjuvant therapy)	c	b	b
6	58	Female	Capecitabine	Rectal cancer	b	b	b
7	63	Female	Dabrafenib + trametinib	Metastatic melanoma with BRAF V600E mutation	c	b	a
8	68	Male	Enzalutamide	Castration-resistant metastatic prostate cancer	c	b	b
9	70	Male	Enzalutamide	Castration-resistant metastatic prostate cancer	c	b	b
10	64	Female	Everolimus	Breast cancer after endocrine therapy	b	b	b
11	82	Male	Ibrutinib	Refractory mantle cell non-Hodgkin lymphoma	c	b	b
12	58	Female	Lenalidomide	Refractory multiple myeloma	a	b	b
13	77	Female	Lenalidomide	Refractory multiple myeloma	c	a	b
14	78	Male	Lenalidomide	Refractory multiple myeloma	c	b	b
15	60	Male	Lenvatinib	Radioactive iodine-refractory papillary thyroid cancer	c	b	b
16	81	Female	Nilotinib	Refractory chronic myeloid leukemia	b	b	b
17	57	Female	Nilotinib	Newly diagnosed chronic myeloid leukemia	c	b	b
18	57	Female	Nilotinib	Newly diagnosed chronic myeloid leukemia	c	b	b
19	73	Female	Nilotinib	Newly diagnosed chronic myeloid leukemia	c	b	b
20	43	Female	Osimertinib	Refractory non-small cell lung adenocarcinoma	c	b	a
21	42	Female	Ribociclib	Metastatic breast cancer (initial therapy)	c	b	b
22	64	Male	Sorafenib	Hepatocellular carcinoma	a	b	a
23	28	Male	Sunitinib	Untreated clear cell renal cell carcinoma	c	b	b
24	63	Male	Sunitinib	Untreated clear cell renal cell carcinoma	c	a	b
25	63	Male	Sunitinib	Untreated clear cell renal cell carcinoma	c	b	b
26	65	Male	Sunitinib	Untreated clear cell renal cell carcinoma	c	b	b
27	61	Male	Imatinib	Newly diagnosed gastrointestinal stromal tumor	c	–	b
28	53	Female	Temozolomide + Capecitabine	Neuroendocrine tumor of gastrointestinal origin	c	b	a
29	63	Male	Vismodegib	Locally advanced basal cell carcinoma not candidate for surgery or radiotherapy	c	b	b

Patients' expectations about the drug (question I), results of preferences about the benefit obtained by a treatment (question II) and willingness to receive a novel treatment with uncertain improvement in survival or QoL (question III) can be consulted in table 3. One patient did not answer the question II. One patient was treated with a combination of drugs –capecitabine associated with temozolomide– without an indication authorized by EMA, therefore the responses to questions I, II and III could not be included in the analysis in this case. Individual responses of each patient to the questionnaire can be found in table 1.

According to willingness of patients to receive a novel treatment with uncertain benefit in survival or QoL (question III), results of EPARs met the requirements of 10 (43.5%) participants with exigencies, while not in 13 (56.5%) of these patients. If the total number of patients is considered (N = 28), 13 (46.4%) patients did not meet their requirements to access a novel treatment without confirmatory data for improvement in OS or QoL. Table 3A describes overall results of participants' responses and EPARs respect to questions and answers of the survey.

According to estimated κ values, insignificant concordance was observed between results of EPAR and patients' responses about their expectations on the drugs (question I) and preferences of the benefit obtained by a treatment (question II). Ao = 53.6% was calculated between patients' responses and results of EPAR for patients' willingness to receive a novel

Table 2. Individual results of consulted European Public Assessment Reports (EPARs)

Drug†	Indication or clinical context	Report date	Study design	Comparator	Comparative OS‡ data	Difference in medians of OS‡ between intervention and control [months (95% CI)]	HR of OS [%CI]‡	Statistical significance of OS‡	Comparative QoL§ data	Median QoL§ difference between intervention and control (months)	HR of QoL§¶	Statistical significance of QoL§¶
Abemaciclib	Metastatic breast cancer (initial therapy)	26/07/2018	Randomized, double-blind clinical trial, superiority	Placebo	Yes	Medians not reached	1.1 [95% CI: 0.68-1.60]	P = 0.80	No	–	–	–
Abiraterone with prednisone (low dose)	Newly diagnosed, high-risk metastatic prostate cancer	12/10/2017	Randomized, double-blind clinical trial, superiority	Placebo	Yes	NR (NR, NR) – 34.73 (33.05, NR)ŝ	0.621 [95% CI: 0.509-0.726]	P < 0.0001	Yes	BPI-SF: no global data; FACT-P: 4.6 months; BFI: medians not reached; EQ-5D-5L: no data	BPI-SF: no global scale data; FACT-P: 0.853 [95% CI: 0.736-0.989]; BFI: 0.652 [95% CI: 0.527-0.805]: EQ-5D-5L: no data	BPI-SF: significant differences; FACT-P: p = 0.0322; BFI: p = 0.0001; EQ-5D5L: no significant differences
Capecitabine	Refractory breast cancer after relapse to chemotherapy	02/04/2008	Randomized, open clinical trial, non-inferiority	5-fluorouracil	Yes	1¥	0.97 [97.5% CI: 0.84-1.14]	No difference	No	–	–	–
Capecitabine	Colon cancer (adjuvant therapy)	02/04/2008	Randomized, open clinical trial, non-inferiority	5-fluorouracil	Yes	1¥	0.97 [97.5% CI: 0.84-1.14]	No difference	No	–	–	–
Capecitabine	Rectal cancer	02/04/2008	Randomized, open clinical trial, non-inferiority	5-fluorouracil	Yes	1¥	0.97 [97.5% CI: 0.84-1.14]	No difference	No	–	–	–
Dabrafenib + trametinib	Metastatic melanoma with BRAF V600E mutation	02/09/2015	Randomized, double-blind clinical trial, superiority	Dabrafenib	Yes	6.4	0.71 [95% CI: 0.55-0.92]	P = 0.011	Yes	EORTC QLQC30: 3.7-5.8 points in weeks 8, 16 and 24. EQ-5D: no data	–	EORTC QLQC30: p < 0.05 in weeks 8, 16 and 24. EQ-5D: no data
Enzalutamide	Castration-resistant metastatic prostate cancer	23/10/2014	Randomized, double-blind clinical trial, superiority	Placebo	Yes	NR (31.7, NR) – 31.0 (28.9, NR)ŝ	0.73 [95% CI: 0.626-0.852]	P< 0.0001	Yes	FACT-P: 11 months; EQ-5D: no data; BPI: 0.3 score	FACT-P: 0.625 [95% CI: 0.542-0.720); EQ-5D: no data; BPI: no data	FACT-P: p < 0.0001; EQ-5D: no significant differences; BPI: p = 0.082
Everolimus	Breast cancer after endocrine therapy	21/06/2012	Randomized, double-blind clinical trial, superiority	Placebo	Yes	NR (20.7, NR) – NR (NR, NR)ŝ	0.77 [95% CI: 0.57-1.04]	P < 0.046	Yes	EORTC QLQ-C30: –5 +2 between weeks 0 and 54	EORTC QLQ-C30: no data	EORTC QLQ-C30: no significant differences in favour of intervention

Table 2 *(cont.).* Individual results of consulted European Public Assessment Reports (EPARs)

Drug†	Indication or clinical context	Report date	Study design	Comparator	Comparative OS‡ data	Difference in medians of OS‡ between intervention and control [months (95% CI)]	HR of OS [%CI]‡	Statistical significance of OS‡	Comparative QoL§ data	Median QoL§ difference between intervention and control (months)	HR of QoL§¶	Statistical significance of QoL§¶
Ibrutinib	Refractory mantle cell non-Hodgkin lymphoma	24/07/2014	Non-randomized study without control arm	–	No	–	–	–	No	–	–	–
Lenalidomide	Refractory multiple myeloma	13/01/2012	Randomized, double-blind clinical trial, superiority	Placebo	Yes	6.5	0.833 [95% CI: 0.687-1.009]	P = 0.045	No	–	–	–
Lenvatinib	Radioactive iodine-refractory papillary thyroid cancer	26/03/2015	Randomized, double-blind clinical trial, superiority	Placebo	Yes	NR (30.9, NR) – 19.1 (14.3, NR)ϟ	0.53 [95% CI: 0.34-0.82]	P = 0.0051	No	–	–	–
Nilotinib	Refractory chronic myeloid leukemia	20/12/2010	Non-randomized study without control arm	–	No	–	–	–	No	–	–	–
Nilotinib	Newly diagnosed chronic myeloid leukemia	20/12/2010	Randomized, open clinical trial, superiority	Imatinib	Yes	–	0.7108 [95% CI: 0.30-1.66]	P = 0.4215	No	–	–	–
Osimertinib	Refractory non-small cell lung adenocarcinoma	17/12/2015	Non-randomized study without control arm	–	No	–	–	–	No	–	–	–
Ribociclib	Metastatic breast cancer (initial therapy)	22/06/2017	Randomized, double-blind clinical trial, superiority	Placebo	Yes	NR (NR, NR) – 33 (33, NR)ϟ	0.746 [95% CI: 0.517-1.078]	P = 0.059	Yes	EORTC QLQ-C30: –1.5	EORTC QLQ - C30: 0.890 [95% CI: 0.670-1.182]	EORTC QLQ - C30: no significant differences
Sorafenib	Hepatocellular carcinoma	20/09/2007	Randomized, double-blind clinical trial, superiority	Placebo	Yes	2.8	0.6931 [95% CI 0.5549-0.8658]	P = 0.000583	No	–	–	–
Sunitinib	Untreated clear cell renal cell carcinoma	13/11/2006	Randomized, open clinical trial, superiority	IFN-α	Yes	Medians not reached	–	–	Yes	FACT-G: 5.412 in cycles 1-10, EQ-5D Index: 0.006-0.047 in cycles 1-10 and EQ-VAS: 3.514-8.223 in cycles 1-10	FACT-G: no data, EQ-5D Index: no data and EQ-VAS: no data	FACT-G: $p < 0.0001$ in cycles 1-10, EQ-5D Index: significant differences up to cycle 5 and EQ-VAS: $p < 0.05$ in cycles 1-10
Imatinib	Newly diagnosed gastrointestinal stromal tumor	28/10/2015	Randomized clinical trial, superiority	Imatinib (different doses)	Yes	Medians not reached	–	–	No	–	–	–
Vismodegib	Locally advanced basal cell carcinoma not candidate for surgery or radiotherapy	25/04/2013	Non-randomized study without control arm	–	No	–	–	–	No	–	–	–

†The standard schemes associated with the novel drug and comparator were not detailed to simplify the information in table. ‡HR: hazard ratio. OS: overall survival. %CI: confidence interval percentage. §QoL: quality of life. ¶The acronyms of this column correspond to the names of different scales analyzed in studies. ϟNR: not reached. ¥Confidence interval percentage: 97.5%.

Table 3. Results of statistical analysis

A) Overall results of users' responses and European Public Assessment Reports (EPARs)

		n (%)	
		Patients	EPAR† consulted
(I) Patient expectations about the benefit of treatment received (N = 28)	OS increase‡	2/28 (7.1%)	5/28 (17.8%)
	QoL improvement§	3/28 (10.7%)	4/28 (14.3%)
	Both	23/28 (82.1%)	5/28 (17.8%)
	None	0	14/28 (50%)
(II) Patient preferences about the benefits of a treatment (N = 27)¶	OS increase‡	2/27 (7.4%)	10/27 (37.0%)
	QoL improvement§	25/27 (92.6%)	9/27 (33.3%)
	None	0	0
(III) Willingness to receive novel treatments with non-definitive results (N = 28)	Without exigencies	5/28 (17.9%)	It meets absence of exigencies 5/5(100.0%) 5/28 (17.9%)
	With exigencies	23/28 (82.1%)	It meets exigencies 10/23 (43.5%) 10/28 (35.7%); It does not meet exigencies 13/23 (56.5%) 13/28 (46.4%)

†EPAR: European Public Assessment Report. The total number of EPARs consulted was considered equal to the number of patients (N) for each question: 28 EPARs for questions I and III; 27 EPARs for question II. There are patients with the same treatment indication and therefore share the same EPAR (19 different indications). ‡OS: overall survival. §QoL: quality of life. ¶The results of EPARs were: 5 increased survival, 4 improved quality of life, 5 increased both quality of life and survival, and 13 did not increase either aspect. This is the reason about percentage sum of EPARs is not equal to 100%.

B) Agreements and concordances between patient responses and European Public Assessment Reports (EPARs)

	Ao†	κ‡ (CI 95%)	p
(I) Patient expectations about the benefit of the treatment received	7/28 (25%)	0.091 (–0.025 to 0.207)	0.079
(II) Patient preferences about the benefits of a treatment	9/27 (33.3%)	0.016 (–0.127 to 0.160)	0.757
(III) Willingness to receive novel treatments with non-definitive results	15/28 (53.6%)	–	–

†Ao = observed agreement. ‡κ = kappa value.

treatment with uncertain improvement in survival or QoL (question III). Ao values and concordances between patient responses and EPAR are represented in table 3B.

Discussion

The criteria for marketing authorization of drugs by the EMA are described through EPARs. According to our study, the results of final endpoints described in these EPARs do not fully meet expectations and preferences of our onco-hematological outpatients. The opinion of patients on their treatment should be one of the basic pillars in selection of treatments. Thus, empowerment of patients in clinical decision making would be favoured.

In this work, OS and QoL were the endpoints selected to assess the efficacy of treatments described in EPARs, according to patients' preferences[5-8]. These endpoints are the most relevant for onco-hematological patients[9,10]. PFS is also important because it could represent a good indicator of response to treatment. However, we excluded PFS to assess the efficacy of treatments because its interpretation may present a higher degree of subjectivity than the selected endpoints, since it depends on multiple factors such as research center, progression criteria, etc. Likewise, clinical contexts with a doubtful correlation between PFS and OS were described, requiring in-depth analysis. For example, this finding was observed in lung and ovarian cancer studies[12,22]. Moreover, the understanding of PFS by patients with high age or low sociocultural level could be limited when completing our survey.

The criterion we established for considering the benefit in both OS and QoL was the statistically significant difference between intervention and control arms. For the development of this study, it would have been reasonable to assess the clinical relevance of treatment effect. However, we decided not to contemplate clinical relevance due to heterogeneity of analysed pathologies, controversy about establishing a limit of clinical relevance and lack of consensus in some clinical contexts. Adding the concept of clinical relevance could decrease the number of treatments with positive evaluation in terms of OS and/or QoL, showing a minor agreement between patient opinions and results of EPARs. Moreover, the use of suboptimal treatments or placebo as control arm in RCTs, instead of active treatments, could have a possible influence on the results[23,24]. The absence of head-to-head trials and indirect comparisons in EPARs was another limitation in the evaluation of benefit of new treatments against the gold standards. Furthermore, it was not assumed that non-randomized studies were able to demonstrate the benefit associated with a treatment. In studies with this design, it is difficult to discern the influence on results of disease, population baseline characteristics and other variables[14,15].

Despite not applying the criterion of clinical relevance, almost half of our onco-hematological outpatients received a treatment without benefit in OS or QoL according to EPARs from EMA. The absence of statistically significant difference in OS of novel drugs respect to their comparators is understandable in early clinical contexts or patients with insufficient follow-up[25]. However, the absence of benefit in QoL of treatments authorized by EMA is hardly justifiable considering the importance of this endpoint[26]. Almost all our patients preferred an improvement of QoL rather than increase in survival. This finding has already been observed in previous studies[6].

Notwithstanding the enormous economic impact of onco-hematological treatments[4], EMA does not evaluate the costs associated to treatments. For

this reason, it seems reasonable for EPARs to precisely delimit the benefit of novel drugs compared to therapeutic alternatives in a specific clinical context. In this regard, the design of clinical studies that evaluate drugs is of paramount importance. The accelerated access to medicines considering premature results, non-randomized studies or whose validity is not clear, could increase the uncertainty of the benefit-risk ratio. This fact has been verified in the revocation of marketing authorisation for olaratumab associated with doxorubicin in soft tissue sarcoma[27] or in the authorization of osimertinib in lung cancer, using non-randomized studies –when there were already approved alternatives with RCTs–[28].

A critical analysis of scientific evidence by different health professionals in multidisciplinary committees, also considering the individual opinions of patients, could favour optimization of the drugs selection. We have also observed that almost half of our onco-hematological outpatients would not have been willing to receive their treatment as their requirements had not been met in EMA authorization criteria. Finally, taking all this information into account during the treatment selection process could contribute to patient empowerment.

Our study has several limitations. The questionnaire used was not a validated tool. However, no questionnaires were found that would allow us to collect all the information necessary to develop our study. The selection of individual questions from different questionnaires was not accepted as a feasible option[17-19]. Therefore, it was necessary to design a new questionnaire. Another limitation of our research was the sample size. The results obtained in this work should be confirmed in investigations with a larger number of patients. Patient selection, time since diagnosis, duration of current treatment, and line of treatment are factors influencing outcomes[29]. Our study provides individual data on situation of patients (naive or refractory). However, data on the treatment line and time since diagnosis could not be recovered due to the appearance of the COVID-19 health emergency, anonymization of patients and logistical problems. This work could be a pilot study with preliminary results as support for multicenter future research with validation of tools used, larger sample sizes and better selection of patients with criteria according to disease stages, type of neoplasms, time since diagnosis and lines of treatment received.

In conclusion, this study found little agreement between expectations and preferences of our onco-hematological outpatients regarding their oncological treatment and results described in the EPARs from EMA, considering OS and QoL endpoints. Almost half of our onco-hematological participants would not meet their requirements to receive their drug when it was authorized. Other studies should be developed to contrast the results observed in this work.

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Conflict of interest

Gil-Sierra MD participated in an *advisory board* sponsored by Janssen Pharmaceutica and in several symposia on hemato-oncologic drugs hosted by Janssen Pharmaceutica and Pfizer. The remaining authors have no conflict of interest.

Contribution to the scientific literature

A little agreement was found among preferences and expectations of oncohematology patients and EMA drug evaluation criteria.

This type of study could expose the need to improve the European marketing authorization process in onco-hematology therapies.

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