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Analysis of economic evaluations of pharmacological cancer treatments in Spain between 1990 and 2010

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Abstract Economic evaluation of pharmacological cancer treatment is a critical clinical problem currently under consideration worldwide. We have analysed their main characteristics in Spain between 1990 and 2010 following a systematic review of the 29 complete economic analyses published. The pathology most frequently evaluated was non-small cell lung cancer (31 %). Cost-effectiveness analyses (69 %) were the most frequent analyses. A wide range of incremental cost-effectiveness values (295–160,667 €/QALY) has been reported, and mostly are developed from the perspective of the National Health System (65.5 %). However, none of the studies estimated the indirect costs. The major conclusion is that the absence of regulations concerning the application of the efficiency criterion in decision-making on the subject of price and financing and, most importantly, the fact that these are not included in Spanish hospitals forms make it difficult to analyse the real impact of economic evaluations of cancer treatments on such decisions.

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Introduction

Cancer is one of the diseases with the biggest health impact due to its high rates of incidence, prevalence and mortality. Data on Spain from GLOBOCAN 2008, a World Health Organization project, estimated an incidence of 196,902 cases for all types of cancer (non-melanoma skin cancers excepted), with higher rates of prostate, lung and colorectal cancers in men, and of breast, colorectal and gynecological tumors in women [1]. The estimates for 2020, while maintaining the frequency order, do foresee an increase of 23 % in the total number of cases. The mortality rate is also important, with an estimate of 104,156 deaths in 2008 [1]; however, the global mortality has been progressively reduced since 2007 [2]; internationally, Spanish mortality rates are within the average range for men, while below the average for women [3].

Cancer management involves enormous health resources. In Spain, Antoñanzas et al. [4] estimated that direct costs associated with colorectal, prostate, breast and cervical cancer rose to 2,154 million € while indirect cost thereof rose to 3,824 million € (costs related to 2003). The economic evaluation of new interventions becomes even more relevant in the oncology area, because the cost of treatments has increased notably in recent years, mainly due to the appearance of new oncological drugs such as monoclonal antibodies, to the advances of pharmacogenomics or individualized therapy, and to the appearance of less invasive pharmaceutical forms (new oral treatments instead of injections), together with early diagnosis interventions and the population ageing factor. Different

publications [5–8] have analyzed the characteristics of economic evaluations published in Spain, including cancer pathologies.

The objective of this work is to review the characteristics of complete economic evaluations which assess the impact of pharmacological interventions on cancer treatment in Spain.

Methods

We performed a systematic review which describes the main features of economic evaluation studies of pharmacological treatments of cancer in Spain between 1990 and 2010. In the most relevant variables are analyzed timing differences.

Types of studies

Economic studies are considered, regardless of whether they were alongside effectiveness studies or were based upon them and that they meet the eligibility criteria of the review.

Quality assessment

The effectiveness outcomes were assessed by levels of evidence described by the Centre for Evidence Based Medicine [9]. The relevant economic studies were conducted through the checklist of Drummond [10].

Search strategy

A literature search was conducted in the main bibliographical databases: Medline, Embase, Índice Médico Español (IME), red Yriss, NHS EDD, Medicina en Español (MEDES) and Elsevier (before Doyma). The search strategies are presented in Table 1.

Inclusion and exclusion criteria

In order for the references to be selected, they had to comply with the following inclusion criteria: complete economic evaluations [10] (comparing costs and benefits of two or more alternatives) of cost-minimization type, cost-effectiveness, cost–utility or cost–benefit, including only pharmacological treatment of cancer, corresponding to studies which assessed their impact in Spain, and published in local or international magazines between 1990 and 2010. For the selection of the Spanish geographical environment, the geographical filter designed by Valderas et al. [11] was used. No restrictions by reason of language were applied. Those references associated with editorials, letters to the editor, reviews and congress communications were excluded.

Selection of publications

Once the valid references were selected from the corresponding abstracts, the original articles were analyzed, their bibliography was checked and those articles meeting the selection criteria were included. In addition—also following the above described process—the tables of contents of the non-indexed publications in the previously mentioned databases were checked, as also in the case of *Pharmacoeconomics—Spanish Research Articles* and Revista Española de Economía de la Salud. Two of the authors independently checked the references found and decided by consensus on the final list of articles included in the analysis.

Studied variables

The main variables were analyzed, taking into account the recommendations included in the proposed guideline for the application of economic evaluation to health technologies [12], shown in Table 2.

Table 1 Search strategies in consulted databases

Medline	Embase	Rest
[(“antineoplastic agents” [MeSH Terms] or oncology [Title/Abstract] or neoplasms [Title/Abstract] or cancer [Title/Abstract] or “neoplasms” [MeSH Terms] or cancer [Text Word]) and (“Cost–Benefit Analysis” [Mesh] or “cost–benefit” [Title/Abstract] or “cost-effectiveness” [Title/Abstract] or “cost–utility” [Title/Abstract] or “cost minimization” [Title/Abstract]) and (“1990/01/01” [PDAT]: “2010/12/31”[PDAT])]	[(‘oncology’/exp or ‘neoplasms’/exp or ‘cancer’/exp) and (‘cost effectiveness’/exp or ‘cost utility’/exp or ‘cost benefit’/exp or ‘cost minimization’/exp or ‘cost’/exp) and (‘spain’/exp or ‘spanish’ or ‘espana’) and [embase]/lim and [1990–2010]/py)]	“coste Y cáncer”, “cost?-eficacia O cost?-efectividad O económico? O económica? O cost?-utilidad O cost?-beneficio O farmacoeconomía o farmacoeconómico? O cost?-eficiencia O cost?-rentabilidad”

Table 2 Analyzed variables in the works included in the review article

Analyzed variables	Expected values
First author affiliation	Pharmaceutical industry, National Health System, University, Consultant or other
Journal	National or international and year of publication
Pathology	Cancer type
Type of analysis	Cost-minimization, cost-effectiveness, cost–utility and cost–benefit
Perspective of the analysis	Society, National Health System, hospital, unknown
Drug	Evaluated drug and its comparators
Benefit source	Clinical trial, meta-analysis, systematic review, selection of literature, patients' database
Result variables	Objective response, LYG, QALY, progression-free time, other
Type of cost considered	Direct, indirect and intangible
Time frame	Shorter, equal or longer than a year
Discount rate	Applied (%), not applied (horizon shorter than a year), not applied
Use of models	Decision trees, Markov models, simulation of discreet events
Analysis of sensitivity	Performed—deterministic, probabilistic—or non-performed
Incremental cost-effectiveness (or utility) ratio	In monetary units for additional benefit
Financing source	Public, private, non-specified
Recommendation from the authors	If they exist, and what they are

Results

Of the initially selected articles, 29 met inclusion/exclusion criteria [13–41] (Fig. 1). These are included in Appendix 1. The most-analyzed cancer types correlated with some cancer types accounting for the highest incidence: non-small cell lung (31.0 %), breast (20.7 %) and colorectal (13.8 %) cancers. It was observed that hospitals' medical staff had an important participation as authors of the articles included: they appear as first authors in 65.5 % of the works. The results of the main analyzed variables are summarized in Table 3.

Quality of included studies

Of 24 effectiveness studies they have relied, economic analysis included in the study had an efficiency level of type 1. The remaining 5 were grouped into levels 4a and 5a, however, were not removed in order to analyze the actual situation in Spain as described in the objective. The corresponding economic studies have been discussed in detail in later sections.

Types of analysis

The cost-effectiveness analysis was the most used (69.0 %), although the second decade analyzed showed an increase of cost–utility analyses, which accounted for 45 % during this subperiod, and was frequently performed simultaneously with the cost-effectiveness analysis.

Perspective

Most studies were developed from the perspective of the National Health System (65.5 %). The perspective used was not mentioned in 10.3 % of the articles.

Comparator used in the analysis

In most cases (75.9 %), the comparator was the alternative usually used in clinical practice. The medications that were most frequently taken as reference for economic studies were cisplatin and docetaxel (both in 5 studies) and the combination 5-fluorouracil/folinic acid (5-FU/FA) (in 3 studies).

Benefit source

Excluding the cost-minimization analyses, the efficacy data were mainly obtained from randomized clinical trial results (37.9 %). In other analyses, those data were pooled from other study types (17.2 %) or from meta-analyses (6.9 %).

Result variable

In the first decade analyzed, the economic results of cost-effectiveness analyses were expressed by means of clinical

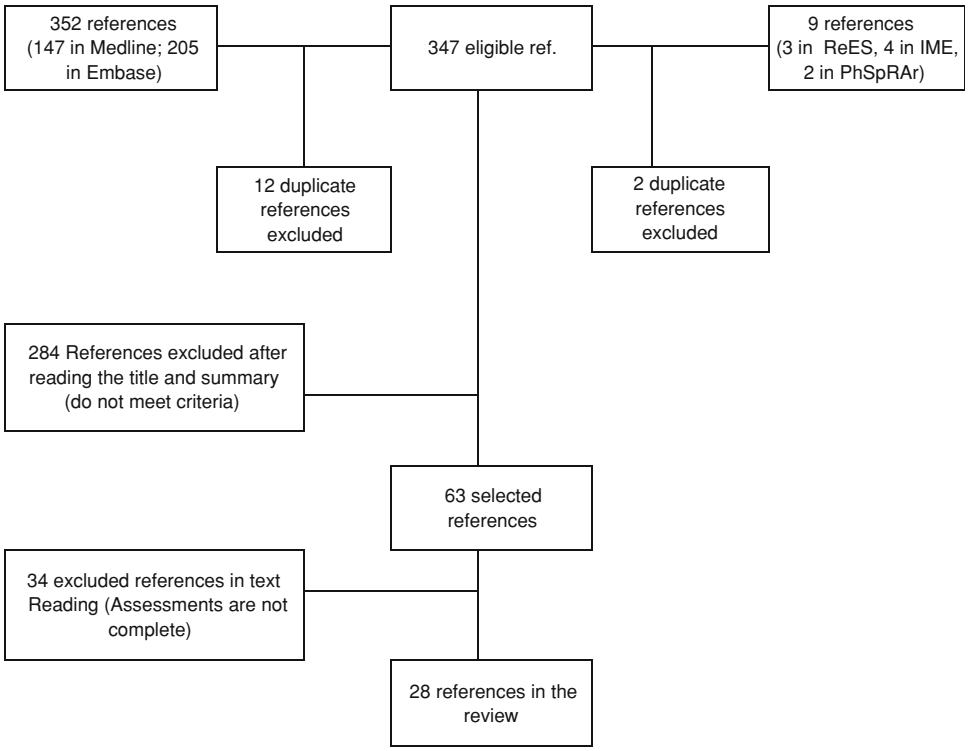

Fig. 1 Flow chart

variables such as the objective response (defined as the sum of the complete response—disappearance of the tumor-plus partial response—reduction of at least 50 % in mean tumor size, measured as the sum of the products of the largest perpendicular diameters of the tumor, without evidence of new lesions), or the survival measures, mainly total survival (as life-years gained, or progression-free time).

The quality-adjusted survival measures, such as the quality-adjusted life years (QALY), were used in the cost–utility analyses performed exclusively during the last decade studied. The exact procedure to obtain utilities was specified in 55.5 % of the cost–utility analyses, EQ-5D being the usually used instrument. In some other cases, the bibliographic reference was cited, whereas the methodology used was not.

Types of costs considered

Even if all the studies incorporated direct costs associated with the evaluated treatment (medication procurement and administration costs), 20.7 % of those studies did not incorporate other relevant direct costs, such as those derived from the management of observed adverse effects. None of the assessed studies considered indirect costs.

Time frame

In just over half of the cases (55.1 %), the study comprised a time span longer than a year, the time until the patients' death being the temporal horizon in 17.2 % of the analyses. Such horizon was not specified in 13.8 % of the analyses.

Discount rate

No discount was applied in studies with temporal horizon shorter than a year, as was to be expected. Nevertheless, in an additional 24.1 % of cases, no discount was applied, although it would have been necessary because the study was performed in a temporal horizon longer than a year; the temporal horizon was not described in the other cases. In cases where it was applied, the initial discount rate was 6 %, 3.5 % between 2001 and 2008 and 3 % thereafter, applied both to costs and benefits.

Use of models

In the first half of the analyzed period, there is only one study which uses the Markov model. However, 60 % of the studies performed in the second decade used such methodology. With respect to health condition, the structure of the model used is quite similar in all cases with inclusion of a progression-free state, another one of disease progression, and one of death; in some cases, the model is designed in a more complex way, incorporating some additional states which describe associated complications, such as thromboembolism, myocardial infarction, acute cerebrovascular stroke, etc.

Table 3 Main characteristics of analyzed economic evaluations

Variable	Number	% over the total EE (29)
Type of analysis		
Cost minimization	7	24.1
Cost-effectiveness	20	69.0
Cost–utility	9	31.0
Cost–benefit	0	0.0
Perspective		
Society	0	0
National Health System	19	65.5
Hospital	7	24.1
Unknown	3	10.3
Benefit source		
Clinical trial	17	58.6
Meta-analysis	2	6.9
Systemic revision	4	13.8
Selection of literature	5	17.2
Patients' database	1	3.4
Result variable		
Objective response	6	20.7
Life years gained	13	44.8
Progression-free time	5	17.2
Quality-adjusted life years	9	31.0
Type of costs		
Direct	29	100.0
Direct and indirect	0	0.0
Use of models		
Decision trees	0	0.0
Markov models	12	41.4
Simulation of discreet events	0	0.0
Analysis of sensitivity		
Yes	25	86.2
No	4	13.8
Recommendations by authors		
Yes	28	96.6
No	1	3.4

Sensitivity analysis

The economic evaluations analyzed the robustness of the results obtained through sensitivity analysis in most of the cases (86.2 %). Since 2008, probabilistic sensitivity analyses are usually used, together with deterministic ones.

Incremental cost-effectiveness (or utility) ratio

The efficiency-result indicators used in the cost-effectiveness analyses were estimated as cost per unit of additional effectiveness (range 4,090–197,926 €/progression-free month) and cost per life-year gained (range 190–1,601,312 €/life-year gained). In the case of cost–utility analyses, the result indicator was expressed as Euros/additional QALY (range 295–160,667).

When the results were discussed, the existing limitations, according to the authors, were described in 86.2 % of the studies. During the first decade, the most frequently mentioned limitation was the small sample size of the studies. In the second decade, more emphasis is put on the absence of indirect costs and the presentation of results without taking into consideration health-related quality of life. Likewise, the uncertainty resulting from following indications from expert panels to determine the use of health resources as well as the use of decision models is pointed out as a consequence of the absence of direct comparative studies and/or the extrapolation of results towards temporal horizons greater than those determined in the corresponding clinical trials.

Finally, the authors recommended the treatment evaluated in 75.9 % of the studies based on its comparison to other health technologies accepted in the national health system; in an additional 17.2 % of the studies, the recommendation was based on efficiency thresholds accepted in usual practice.

Discussion

Economic evaluations analyzing the impact of oncology pharmacological treatments and published in the last 20 years (1990–2010) were reviewed. Even if a great number of studies were not detected initially, this number increases progressively as time goes by, as an indication of the greater interest in these analyses in our country—as is currently happening internationally [42–48]—although their utility in the decision-making process in our country seems limited so far.

Overall, the methodology is comparable to the one observed in other countries [49]; likewise, a clear improvement is observed among the studies published during the last period analyzed. Currently, the appropriate description of the evaluation (type of intervention, alternatives to be compared and population) as well as the presentation of results using QALY gained are the almost unchanging practice, even if it would be desirable to describe explicitly and in detail the way utilities are obtained. In the same line, recent years have witnessed an increase in the use of probabilistic methods to perform sensitivity analyses. The use of models is also increasing [50]. One aspect to point out is the relatively small proportion of studies including the funding sources, in spite of the distrust (it/such practice) may generate [51, 52]. For these reasons, the quality of the current methodology of

pharmacoeconomic studies in Spain is good and can serve as reference for future studies in this field.

The mere cost estimate cannot assume the acceptance or rejection criteria of a drug. It is necessary to relate the cost incurred with the health outcome obtained to estimate the level of efficiency, which is made with respect to a threshold. In Spain, notwithstanding the absence of an officially accepted efficiency limit, it has been suggested that 30,000 € per life-year gained could be considered an acceptable figure [53]. In this review, it has been observed that many of the evaluated interventions exceed such limit, a fact that may indicate that, as in other countries, the cost-effectiveness limit implicitly accepted for cancer treatments is above that of other pathologies.

For example, the British NICE [54] has adopted, for cancer and other terminal diseases, a criterion other than the one usually used with other pathologies, and five criteria have been included to classify *life-extending, end-of-life treatment* interventions: the treatment has to be indicated for patients with a reduced life expectancy, normally of <24 months; there has to be sufficient evidence to indicate that the treatment contributes to extend life expectancy for at least three additional months with respect to the current management at the NHS; likewise, there should not be an alternative offering comparable benefits available in the NHS. Also, the treatment has to be indicated for the treatment of very low-incidence pathologies. In this way, the incremental cost-effectiveness ratio per QALY and the thresholds generally admitted by the NICE cease to be applied in cancer treatments which comply with these four conditions. NICE now has a way for recommending those interventions which benefit terminal patients for whom there are no therapies, even if the cost for QALY is very high.

Several works have analyzed interventions' cost-effectiveness in the oncology area in Spain [8, 55]. Although the number of analyses included varies because of the application of different inclusion criteria, the consistency of results stands out, especially with respect to the study-number increase over the years, which is probably derived from the fact that cost-effectiveness analysis is more frequently used in decision-making about treatment inclusion in hospital forms.

A study by Oliva et al. [6] has reviewed the economic evaluations of health interventions between 1990 and 2000; later, Catala-Lopez and Garcia-Altes [7] analyzed the 1983–2008 period, showing the relative importance of oncology studies, which represented 13.2 % of the total analyzed articles. In other countries, Earle et al. reviewed the cost–utility analyses performed worldwide in oncology between 1975 and 1997, indicating their progressive incorporation into the group of general economic evaluations [42]. Recently, Greenberg et al. [47] have extended Oliva et al. review until 2007, suggesting that the studies should be more adapted to existing recommendations. Finally, Rodriguez et al. [56] have evaluated the methodological characteristics of studies performed in Spain in which life-year gained was the effectiveness indicator.

Our study has certain limitations. First, the heterogeneity of the methodology, especially with respect to the result indicator used, limits the comparability of studies and their application in the setting of priorities. Second, the number of studies found is not large enough, which is not surprising considering that the research was circumscribed to Spain; a recent review of all oncological cost–utility analyses published worldwide between 1976 and 2007 only found 242 studies [47]. Finally, the non-existence of an officially recognized efficiency threshold in Spain makes it difficult to determine the actual practical use of these analyses.

In conclusion, a progressive increase has been observed in the number of publications about complete economic evaluations which assess the impact of pharmacological interventions on cancer treatment in Spain. With regard to the applied methodology, there are three tendencies which stand out positively: (1) the increase of cost–utility studies that allow comparison of the efficiency among different treatments; (2) the increasing use of models which allow extrapolation of relatively short-duration tests results in longer periods and therefore, more relevant for the economic evaluation studies; (3) the use of probabilistic approaches that reflect in a more appropriate way than deterministic ones the uncertainty of results as a limitation for decision making. The absence of regulations for the application of the efficiency criterion about price, financing and, above all, inclusion in Spanish hospital forms makes the analysis of the actual impact of economic evaluations on such decisions difficult. Finally, the results of this review reinforce the idea that the limited use of economic evaluation studies in decision making in Spain is not caused by the lack of ability to perform quality studies, but by the lack of willingness on the part of managing organizations and by the lack of regulations intended for their application.

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Conflict of interest ASG, AH, JDL and JR have received an investigator-led research from Lilly.

Appendix 1: Articles of selected complete economic evaluations

References	Analysis	Alternatives	Pathology	Result	Recommendation
Soto [13]	MC	Interferon alpha (different presentations: 18, 10 and 25 vials)	LMC	−201,689,425 pta (18 vials presentation)	It is the cheapest option
Berger et al. [14]	CE	Paclitaxel + cisplatin vs. cyclophosphamide + cisplatin	CO	6,395 $/LYG	
Ferriols and Ferriols [15]	CE	5-Fluorouracil + folinic vs. 5-fluorouracilo	CCR	922,570 pta/LYG	The option should be considered for having RCEI similar to others. The addition of folinic assumes RCEI
Ferriols and Ferriols [16]	CE	Gemcitabine + cisplatin vs. cisplatin + iphosphamide + mesna	CPCNP	354,047 pta/objective response; 236,031 pta/1 % survival	The scheme constituted by gemcitabine plus cisplatin is an efficient option
Gallego et al. [17]	CE	All first and second line treatments	CPCNP	Stage IIIB: Cost: 3,867 € (643,403 pta) per patient; average survival: 9 months. Stage IV: 2,818 € (468,850 pta) per patient; average survival: 4.3 months	The standard patterns obtain acceptable results with reasonable costs
Annemans [18]	CE	Paclitaxel + cisplatin vs. teniposide + cisplatin	CPCNP	20,394 $ per response	It does not improve survival but improves response significantly; it may be considered as efficient intervention
Sacristan et al. [19]	CE	Gemcitabine + cisplatin vs. etoposide + cisplatin	CPCNP	−27,310 pta per response; −3,405 pta per progression-free month	A potential gemcitabine plus cisplatin efficiency is observed in advanced non-small cell lung cancer
Ferriols et al. [20]	CE	Docetaxel vs. paclitaxel	CM	6,513,075 pta per 1 % complete response with paclitaxel in 1st line poly-therapy respect to docetaxel in first line poly-therapy	Docetaxel, in first line poly chemotherapy is more cost-effective and it is presented as the reference option; in the other options, it is dominant
González et al. [21]	CE	Interferon alpha 2b vs. not giving	ML	9,015 € per LYG	It should be accepted as it presents a lower RCEI than that of other medical practices
Rubio-Terres [22]	MC	Docetaxel + cisplatin vs. paclitaxel plus cisplatin o carboplatin	CPCNP	−1,788 and −2,104 € respect to paclitaxel + cisplatin or carboplatin	Docetaxel + cisplatin produce cost saving
Lindgren et al. [23]	CE	Exemestane vs. megestrol acetate	CM	7,806 €/LYG	Exemestane is an efficient option respect to megestrol
Ojeda B et al. [24]	MC	Pegylated liposomal doxorubicin vs. topotecan	COE	−2,210 €	It is an efficient election respect to topotecan and it can be used to reduce costs
Díaz-Rubio et al. [25]	CE	Irinotecan + 5-fluorouracil and folinic vs. 5-fluorouracil and folinic	CCR	35,416 € per LYG	The combination with Irinotecan may be considered efficient in the 1st line treatment of advanced colorectal cancer
Rubio-Terres et al. [26]	MC/CU	Erlotinib vs. docetaxel, pemetrexed or supportive treatment	CPCNP	−2,554 and −9,479 € respect to docetaxel and pemetrexed; 160,667 €/QALY respect to support care	Erlotinib would provide more QALY than docetaxel and pemetrexed at a lower cost, being this treatment more effective

continued

References	Analysis	Alternatives	Pathology	Result	Recommendation
Gil et al. [27]	CU	Exemestane or anastrozole vs. tamoxifene or letrozol vs. placebo	CM	Exemestane vs. tamoxifene: 50,801–62,522 €/QALY; anastrozole vs. tamoxifene: 104,272 €/QALY; letrozol vs. placebo: 91,210 €/QALY	Compared to tamoxifene, exemestane offers more efficiency than anastrozole and letrozol respect to tamoxifene
Ballester et al. [28]	CE	Letrozol or anastrozol vs. tamoxifene	CM	Letrozol and anastrozol: metastatic cancer: 197,926 and 56,525 €/progression-free month; neoadjuvant therapy: 2,548 and 969 €/objective response; 4,842 and 779 €/conservative surgery	More efficiency is observed with aromatase inhibitors, being cost effective for presenting a ratio less than 1,000 € with anastrozole per unit of extra effectiveness
Ferriols et al. [29]	CE	Taxanes (docetaxel and paclitaxel) vs. not giving taxanes	CPCNP	Taxane-free schemes dominate paclitaxel (similar effectiveness, objective response and 1 year survival) and lower cost; with 2-year survival, the ratio is 1,601,312 € per LYG. Respect to docetaxel: 96,527 € per objective response; 27,203 and 26,559 € per LYG, with 1 and 2-year survival	The taxanes are valid alternatives as they show an effectiveness which is similar or slightly superior to taxane-free schemes but with a very high cost
Casado et al. [30]	CE	IFL (Irinotecan, fluorouracil, leucovorin) + bevacizumab vs. FOLFOX4 (oxaliplatine, fluorouracil, leucovorin)	CCR	62,790 €/progression-free year; 149,126 €/LYG	Each therapeutic regime associated to monoclonal antibodies should be evaluated individually to determine if the increase of efficiency compensates for the cost associated to its use and determine the type of patient to whom the monoclonal antibody was efficient
Alberola et al. [31]	MC	Vinorelbine (po e iv), gemcitabine, Docetaxel and paclitaxel	CPCNP	Average annual cost/patient: vinorelbine iv: 2,937–3,075 €; vinorelbine po: 3,571 €; gemcitabine iv: 4,240–4,356 €; docetaxel iv: 6,494 €; paclitaxel: 7,493–11,752 €	The use of vinorelbine in the management of lung cancer is a new alternative which allows to make savings with respect to traditional treatments with taxanes and gemcitabine
Grupo de Farmacoeconomía del Linfoma Folicular [32]	CE/CU	Rituximab vs. not doing anything	LF	RCEI: 8,493 €/LYG; 9,358 €/QALY; 5,485 €/progression-free year	In comparison with the option of waiting and see, the maintenance treatment with rituximab provides more QALY at a cost per QALY of 9,358 € in patients with resistant advanced follicular lymphoma or in relapses who have responded to CHOP or R-CHOP before
Maroto et al. [33]	CE	Sorafenib + best supportive care vs. better medical treatment	CCRe	RCEI at 1 year: 153,083 €/LYG; throughout life: 21,058 €/LYG	The addition of sorafenib to a better medical treatment is cost-effective respect to the medical treatment alone
Paz-Ares et al. [34]	CE/CU	Sunitinib better supportive treatment vs. better supportive treatment	TEGI	4,090 €/progression-free month; 30,242 €/LYG; 49,090 €/QALY	Depending on the efficiency thresholds in oncology in developing countries, sunitinib is considered cost effective with respect to the best supportive care

continued

References	Analysis	Alternatives	Pathology	Result	Recommendation
Martín-Jimenez et al. [35]	CE/CU	Docetaxel + doxorubicin and cyclophosphamide vs. fluorouracil + doxorubicin and cyclophosphamide	CM	2,631 €/QALY; 2,345 €/LYG	The docetaxel scheme is cost-effective compared to that of fluorouracil and it is positioned below the threshold used in Spain
Arocho et al. [36]	MC	Panitumumab vs. cetuximab	CCR	Without reutilization of vials: −5,285 €; with reutilization: −2,864 € per patient	Biological therapy of metastatic colorectal cancer with panitumumab in third line can generate savings for the NHS hospitals compared to treatment with cetuximab
Delgado et al. [37]	MC	Oral fludarabine (alone or with cyclophosphamide) vs. fludarabine iv	LLC	Mono therapy: −1,908 €/patient; with cyclophosphamide: −1,292 €/patient	Oral Fludarabine is associated to economic saving in the treatment of B cell chronic lymphocytic leukemia
Asukai et al. [38]	CE/CU	Pemetrexed vs. docetaxel	CPCNP	23,967 €/QALY; 17,225 €/LYG	Pemetrexed is a cost effective option for docetaxel in the treatment of advanced non-small cell lung cancer with predominant non-squamous histology, being below the threshold of 30,000 €/additional QALY, accepted in Spain
Paz-Ares et al. [39]	CU	Sunitinib vs. better supportive care	CCRe	6,073 €/progression-free month; 25,199 €/LYG; 34,196 €/QALY	Sunitinib has a good profile of efficiency in metastatic renal cell cancer; the cost per additional QALY is affordable according to thresholds in developed countries (50,000 €/QALY)
Frías et al. [40]	CE/CU	Docetaxel vs. paclitaxel	CM	190 €/LYG; 295 €/QALY	Docetaxel is a cost-effective treatment compared to paclitaxel in the treatment of metastatic breast cancer previously treated with anthracycline
Gómez et al. [41]	CE/CU	Rituximab + CVP, MCP, CHOP, CHVP + I	LF	R + CVP vs. CVP: 10,158 €/LYG; 10,171 €/QALY; R + MCP vs. MCP: 6,330 €/LYG; 6,083 €/QALY; R + CHOP vs. CHOP: 8,165 €/LYG; 7,837 €/QALY; R + CHVP + 1 vs. CHVP + I: 8,453 €/LYG; 8,026 €/QALY	The addition of rituximab to any of the usual first line advanced follicular lymphoma chemotherapy treatment schemes is an efficient option

Spanish acronyms and their English equivalents: MC, minimización de costes (CM: cost minimization); CPCNP, Cáncer de pulmón de células no pequeñas (NSCLC: non-small cell lung cancer); LMC, Leucemia mieloide crónica (CML: chronic myeloid leukemia); CO, cáncer de ovario (OC: ovarian cancer); LYG, años de vida ganados (LYG: Life-years gained); RCEI, ratio coste efectividad incremental (ICER: Incremental cost-effectiveness ratio); CCR, cáncer colorrectal (CRC: Colorectal cáncer); CM, cáncer de mama (BC: Breast cancer); ML, melanoma; COE, cáncer de ovario epitelial (EOC: epithelial ovarian cancer); LF, linfoma folicular (FL: Folicular lymphoma); CCRe, cáncer de células renales (RCC: Renal cell cancer); TEGI, tumor de estroma gastrointestinal (GST: gastrointestinal stromal tumor); LLC, leucemia linfocítica crónica (CLL: chronic lymphocytic leukemia); R, rituximab; CVP, ciclofosfamida + vincristina + prednisone (CVP: cyclophosphamide + vincristine + prednisone); MCP, mitoxantrona + clorambucilo + prednisolona (MCP: mitoxantrone + chlorambucil + prednisolone); CHOP, ciclofosfamida + doxorrubicina + vincristina + prednisona (CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone); CHVP + I, ciclofosfamida + doxorrubicina + etopósido + prednisona + interferón (CHVP + I: cyclophosphamide + doxorubicin + etoposide + prednisone + interferon)

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