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ORIGINAL ARTICLE

Study of rituximab efficacy, cost, safety, and compliance of its package leaflet in a tertiary hospital

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KEYWORDS
Rituximab;
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Abstract
Introduction: The appearance of monoclonal antibodies, and specifically, rituximab, has provided a new approach to treating non-Hodgkin's lymphomas and rheumatoid arthritis. The purpose of this study is to analyse whether this drug is used according to its package leaflet in clinical practice, evaluate the treatment's efficacy, and determine its cost.
Methods: Ambispective, observational single-centre study of medication use set up as a prescription evaluation for the indication of rituximab in a tertiary hospital between March 2003 and December 31, 2007.
Results: Eighty-two of the 221 patients who were treated (37.1%) received the drug for a condition that does not appear in the package leaflet. Fifty-one point one percent and 27.5% of response and progression were registered for approved diagnoses and 34.9%and 47%for non-approved diagnoses; the death rate was 25.3%and 41.5%respectively. The mean cost per treatment episode was the highest for idiopathic thrombocytopaenic purpura (#euro11 683), whilst the highest treatment cost per patient was associated with follicular lymphoma (€15 940).
Discussion: We found that the main cause of the high rate of non-compliance with the package leaflet is patient lack of response to standard treatments, together with clinical practice guides that support the use of rituximab for conditions other than those for which it is indicated. Nevertheless, most of the clinical trials evaluating the efficacy of rituximab for these unauthorised diagnostic profiles have poor methodology, are in phase II, are open studies, have low patient numbers, or in some cases, are not comparative.

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PALABRAS CLAVE
Rituximab;
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Seguridad;
Coste

Estudio de adecuación a la ficha técnica, efectividad, seguridad y coste del rituximab en un hospital de tercer nivel

Resumen
Introducción: La aparición de los anticuerpos monoclonales, y en concreto de rituximab, ha supuesto una gran novedad en el tratamiento de los linfomas no hodgkinianos y la artritis reumatoide. Este estudio pretende analizar la adecuación de la práctica clínica de este fármaco a la ficha técnica, evaluar la efectividad de este tratamiento y determinar el coste que supone.
Métodos: Estudio observacional, unicéntrico y ambispectivo de utilización de medicamentos, del tipo prescripción-evaluación de la indicación con rituximab en un hospital de tercer nivel desde marzo de 2003 hasta el 31 de diciembre de 2007.
Resultados: De los 221 pacientes tratados, 82 (37,1 %) fue por una enfermedad no contemplada en la ficha técnica. Se ha documentado respuesta y progresión en el 51,1 y el 27,5 % de las ocasiones para los diagnósticos aprobados y en el 34,9 y el 46,7 %de las ocasiones para los no aprobados, con el 25,3 y el 41,5 %de fallecimientos, respectivamente. El coste medio por episodio de tratamiento fue superior para la púrpura trombocitopénica idiopática (11.683 euros), mientras que el mayor coste del tratamiento por paciente correspondió al linfoma folicular (15.940 euros).
Discusión: La causa principal del elevado porcentaje de falta de cumplimiento con la ficha técnica es la falta de respuesta a los tratamientos estándares y la existencia de guías de práctica clínica que sustentan la utilización de rituximab fuera de sus indicaciones autorizadas. Sin embargo, la mayoría de los ensayos clínicos que evalúan la eficacia de rituximab en esos diagnósticos no autorizados son de baja calidad metodológica, en fase II, abiertos, con bajo número de pacientes y no comparativos en algunos casos.

Introduction

Lymphomas are a type of cancer affecting more than one million people worldwide. Non-Hodgkin's lymphoma (NHL) is the third type of cancer with greatest growth, after melanoma and lung cancer.[1] Despite the high percentage of complete response in these patients with current treatments, approximately 40%50%of the total number of patients die due to lack of response or, more commonly, due to recurrence and progression of the disease.[2] Chemotherapy, radiotherapy, and bone marrow transplant are the traditional treatments for NHL. However, the latest innovation has been the appearance of monoclonal antibodies, in particular rituximab, a drug that acts specifically on lymphomas that present the CD20 antigen, which is expressed in 90% of the cells involved in B-cell NHL.[3]

In July 2006, rituximab was approved for the treatment of rheumatoid arthritis (RA) due to its selective action on CD20 positive B lymphocytes, which means that it can interrupt a series of different events in the inflammatory process, due to the essential role and multiple actions of the B lymphocytes in this disease.[4]

Rituximab is a genetically engineered chimeric monoclonal antibody from both murine and human sources, which is similar to a glycosylated immunoglobulin and which specifically attaches to the CD20 antigen, a non-glycosylated phosphoprotein located in pre-13 and mature B lymphocytes. NHLs are ideal for the use of monoclonal antibodies due to their greater and more constant clonality and the fact that the phenotypic expression of lymphocytes is more well defined.[5]

The adverse reactions that have been described with rituximab are, mainly, those associated with perfusion (fever, chills, nausea, or headache) and those of a haematological type (thrombocytopaenia, neutropaenia, or anaemia) which are generally minor and reversible.[6]

Given the social and healthcare repercussions of cancer patients from different perspectives, including governmental,[7] a means of introducing a system to assess the care of such patients is under consideration. Aspects linked to results (efficacy of the treatments) must be linked to the best evidence possible (evidence-based practices) and economic assessment.[8]

On the other hand, many of the new cytostatic drugs which have appeared on the market have begun to be used for an indication other than that for which it was approved not long after marketing; their use is justified simply by the poor prognosis of the patient and the inability to obtain more consistent results with other therapeutic alternatives available,[9] without hardly any scientific evidence to support their use.

This study aims to analyse the use of rituximab in a tertiary hospital and for this purpose the following objectives were established: *a)* assess the compliance of clinical practice with rituximab with that established in the package leaflet, from March 2003 to December 31, 2007; *b)* assess the efficacy of the treatment in all patients who had received at least one dose of the drug during the study period; and *c)* assess the cost generated by this treatment.

Methods

To fulfil the above-mentioned objectives, an ambispective, observational and single-centre study was conducted on the use of drugs as a prescription-evaluation of the indication of rituximab in a tertiary hospital from March 2003 (date on which the Cytostatic Unit of the Pharmacy Department began operations) until December 31, 2007, with a follow-up period ending on April 30, 2008.

For each patient who began treatment with rituximab during the study period, an information sheet was completed with general information on the patient and those relating to the treatment regimen administered. This sheet was updated with information on subsequent cycles and the evolution of the disease.

The rituximab package leaflet was reviewed every month to detect possible modifications and determine the compliance of clinical practice with the established recommendations. On the other hand, the digital clinical history of all patients was accessed every 15 days to collect data on the possible responses to treatment, information on the progression of the disease or possible adverse reactions. For lymphomas, patient evolution was recorded by positron emission tomography or computerised tomography and for rheumatoid arthritis the response criteria of the American College of Rheumatology were used.[10] The digital history only provides information on deaths occurring in the hospital and therefore information regarding other deaths was obtained from the city's register office. All data collected was entered into a SPSS database.

The cost was calculated using PTR + VAT for drugs as at January 1, 2007. The total cost was calculated by totalling the cost of the chemotherapy regimens related to rituximab calculated for a generic patient with average body surface area of 1.8 m^2 and the cost of all rituximab vials necessary for each of the patents in the study, regardless of whether any of the vials were not completely used.

The following was analysed for each of the patients included in the study:

1. Consistency between the indications on the package leaflet and clinical practice: compliance in relation to the regimen, line of treatment, dosage, cycle frequency, and number of cycles.
2. Efficacy of the treatment: response rate, hypothetical benefit of the treatment, and progression-free survival. Where possible, the duration of the response, progression time, event-free survival and general survival were determined.
3. Cost of the treatment: per treatment episode, per patient, and up to disease progression.

Dichotomous qualitative variables (yes/no) were used to analyse the suitability of the indications in the packaging leaflet and continuous quantitative variables for the efficacy of the treatment and the cost.

The SPSS 15.0 program for Windows was used for the statistical analysis of the data and a descriptive analysis of the study subjects was performed by calculating averages and standard deviations or means and percentiles for the quantitative variables according to whether these were normal or not, respectively. Frequencies and percentages were also calculated for the qualitative variables. This analysis was conducted globally and segmented for the dichotomous diagnostic variable. After describing the sample, a Kaplan-Meier survival analysis was performed and the log-rank test was applied to study the possible differences, according to the type of diagnosis and the age category, in the progression time elapsed, recurrence, change of treatment or death.

The statistically significant value was $P<.05$.

Results

The indications approved for rituximab in the package leaflet during the study period are those included in Table 1.

Of the 221 patients treated, 82 (37.1%) received the treatment for a disease that was not indicated on the packaging leaflet, and therefore more than one third had to request compassionate use.

Patients with follicular lymphoma received a total of 54 treatment regimens with rituximab, and of these, 27.8% of the regimens/lines used complied with what was indicated (13 rituximab in monotherapy for second line or subsequent and 2 CVP-R for first line). The remaining regimens used are presented in Figures 1 and 2. The analysis of the frequency of administration and the number of cycles showed that

Table 1 Summary of the indications of rituximab during the study period

		Diagnosis		
		FL	LBCL	From 7-6-2006 RA
Line	First	Second and subsequent	First and subsequent	Second and subsequent
Monotherapy	—	X	—	—
Association	CVP	—	CHOP	MTX
Mandatory tests			CD20 +	
Frequency between cycles	21 days	7 days	21 days	
No. of cycles	8	4	8	1 (2 infusions)

FL indicates follicular lymphoma; LBCL, large B-cell lymphoma; MTX, methotrexate.

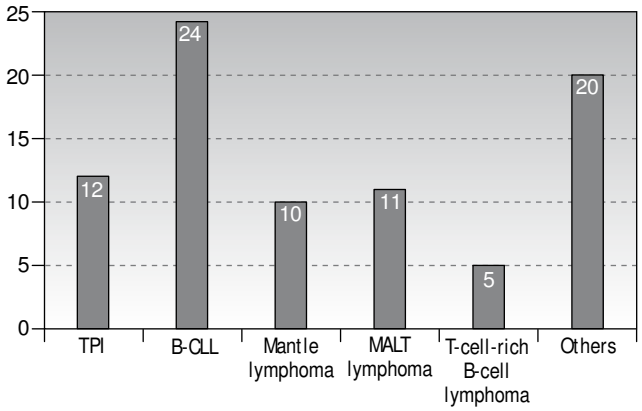

Figure 1 Distribution of non-approved diagnoses for which rituximab was used. B-CLL indicates B-cell chronic lymphocytic leukaemia; ITP, Idiopathic thrombocytopaenic purpura; others, Burkitt's lymphoma (2), Hodgkin's lymphoma (3), graft-versus-host disease (3), Wegener's disease (2), Waldestrom's disease (1), lymphoplasmacytic non-Hodgkin's lymphoma (1), conjunctival B-cell lymphoma (1), cutaneous B-cell lymphoma (1), prolymphocytic leukaemia (1), thrombocytopaenia (2), mixed connective tissue disease (1), sclerosis (1), autoimmune haemolytic anaemia (1).

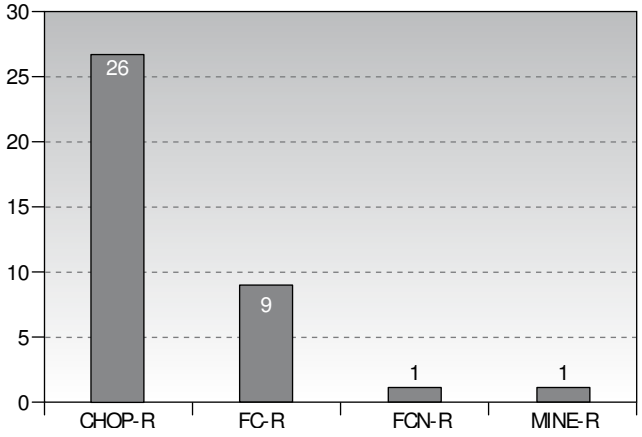

Figure 2 Regimens used in the treatment of follicular lymphoma and the number of times each of these were used.

41.7% of the above comply with what is indicated in the packaging leaflet; the dose used in all cases was the dose indicated in the leaflet (375 mg/m^2).

All the patients with large B-cell lymphoma (LBCL) presented positive CD20 and of the 98 regimens used for these patients, 63 (64.3%) coincided with what was indicated on the package leaflet (CHOP-R), although only one patient also complied with the line of treatment, dose, frequency of administration and the number of cycles. The remaining regimens used for these patients is shown in Figure 3.

The 21 patients in treatment with rituximab for RA were receiving this from July 2006, date on which this drug was approved to treat this disease. In this case, compliance with the package leaflet in terms of the treatment regimen received (rituximab in monotherapy), the dose (1000 mg/ m^2) and the line of treatment (failure of at least one treatment with anti-TNF) was 100% The number of cycles was in line with that indicated in the leaflet in 18 patients (85.7%) and the time between the 2 infusions of rituximab was 14 days, as indicated in the package leaflet, in 13 patients (61.9%). A total of 8 patients (38.1%) were given a second treatment, however in all cases this was in line with the indications of the package leaflet, since the second cycle was separated from the first by a minimum of 16 weeks.

The treatment regimens used for diagnoses which were not indicated in the package leaflet are outlined in Table 2.

A total of 304 treatment episodes were recorded during the study period (182 for approved diagnoses and 122 for non-approved diagnoses). The response rate recorded was 51.1% for approved diagnoses and 34.9% for non-approved diagnoses, whereas the rate of progression was 27.5% and 46.7%, respectively. Of the 221 patients assessed, 69 (31.2%) died during the follow-up period, 35 (25.3%) in the first group, and 34 (41.5%) in the second.

The efficacy parameters determined are presented in Figure 4. There were significant differences in the time to progression (P=.005) and progression-free survival (P=.001) on comparing the approved and non-approved diagnoses.

Three patients with follicular lymphoma (FL) presented adverse reactions, 11 with LBCL, and 1 with RA; treatment had to be suspended in 8 patients.

The average cost per treatment episode was greater for idiopathic thrombocytopaenic purpura (ITP) (€11 683), followed by FL (€11 036) and MALT lymphoma (€10 283). On analysing the total cost per patient (taking into account the fact that some received more than one treatment episode),

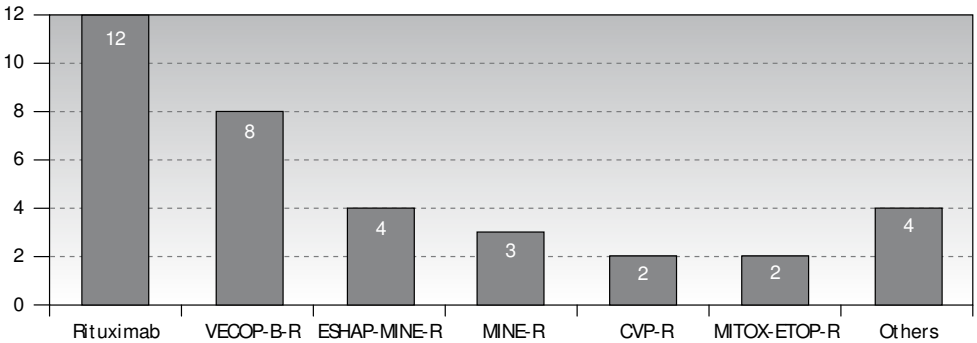

Figure 3 Distribution of regimens not indicated in the package leaflet which were used to treat patients with large B–cell lymphomas. Others indicates FC-R, etoposide-vincristine-R, methotrexate-cytarabine-R, GMZ-R.

the highest result was obtained in the case of FL (€15 940), followed by MALT lymphoma (€14 958) and B-cell chronic lymphocytic leukaemia (B-CLL) (€14 837).

The average cost to disease progression (calculated as the ratio between the total cost per patient and the disease-free months from the start of treatment) was €287 for the approved diagnoses compared with €352 for the non-approved diagnoses.

Discussion

The main cause of the high percentage of non-compliance found in this study (37.1%) was the lack of response to standard treatments. Some authors, such as Glimelius et al,[11] indicate a very clear attitude among some professionals to systematically use a new drug or a new regimen as soon as it is approved, even if the benefit of this is not clear or is very modest, compared with others who act more cautiously. Rituximab was used to treat eight types of non-approved NHLs, however some of these are recommended in the clinical practice guides.[12-14]

The low level of compliance with the package leaflet in terms of the number of cycles administered is due, in part, to the fact that patients progress and decide to change the chemotherapy regimen. On the other hand, and despite the fact that this is not indicated in the package leaflet, a high percentage of patients (36.5% with LBCL) received 6 treatment cycles, as indicated in some clinical practice guides[15] and in some clinical trials.[16,17]

During the study the association between rituximab and CVP was only indicated in the case of follicular lymphoma; however 68.4% of patients with this diagnosis received CHOP-R, the use of which is approved by a large number of clinical studies.[16-18]

Of the 34 unauthorised regimens used for LBCL, rituximab in monotherapy was the most frequently used (in 12 patients), in some cases as maintenance therapy (4 occasions) or second treatment (2 occasions) in patients who had previously received some other treatment regimen which included rituximab. There exists clinical studies which assess the efficacy of rituximab in monotherapy for patients with LBCL, however the results obtained in relation to the general response or PFS are lower than those obtained when the anti-CD20 is associated with another chemotherapy regimen.[19] Maintenance therapy only proved effective when the patients had not previously received treatment with rituximab.[20]

In terms of RA, clinical practice with rituximab shows greater compliance with the package leaflet. One of the reasons for this could be the existence of advisory commissions for the rational use of drugs in treating inflammatory rheumatic diseases within the scope of the Regional Department of Health for the Autonomous Community (Resolution S/C 2/2005 [25-01]), which aims to guarantee that these drugs are used under strict criteria for maximum efficacy, safety and efficiency, with uniform application in all centres.

In the economic section, it is to be noted that more than 98% of the cost was incurred in relation to the use of rituximab, since the chemotherapy regimens in which this drug is involved have a relatively low price. The average cost per patient is lower for RA (€6052) than for other diagnoses, since the number of infusions of rituximab received per patient varies between 2 and 4 in the majority of cases, so that although the dose per infusion received is greater (1000 compared with 375 mg/m^2), the overall cost is lower. On the other hand, with the exception of the isolated case of lymphoplasmacytic NHL, which is not representative, the higher average cost per patient was for follicular lymphoma (€15 940), due to the fact that almost 50% of patients received more than one treatment regimen with rituximab and 4 patients received second treatment and the other 9, maintenance therapy.

Reviewed clinical trials that assess the efficacy of rituximab in indications which are not authorised in the package leaflet, for which this drug was used in this study,[21-25] are on the whole of poor methodological quality, in phase II, are open studies, have a small number of patients and are not comparative in some cases. This corresponds to the fact that many drugs are approved based on results that do not provide clear benefits, are not very consistent or are obtained from non-comparative phase II clinical trials.[9] Only in 2 of the trials for the treatment of CLL were suitable means of assessing the efficacy of the treatments used, such as the mean survival, the percentage of patients alive in a certain period or the hazard ratio.[26,27]

Table 2 Number of occasions in which each of the following chemotherapy regimens was used to treat diagnoses not indicated for rituximab in the package leaflet

Diagnosis	Treatment regimen	Number
Burkitt's lymphoma	CHOP-R	1
	ESHAP-MINE-R	
	PETHEMA-R	1
Hodgkin's lymphoma	R	2
	ABVD-R	1
Graft-versus-host disease	R	3
Wegener	R	3
Waldestrom	CVP-R	1
lymphoplasmacytic NHL	CHOP-R	1
Conjunctival B-cell lymphoma	CHOP-R	1
Cutaneous B-cell lymphoma	CHOP-R	1
T-cell rich B-cell lymphoma	T CHOP-R	3
	ABVD-R	1
	ESHAP-MINE-R	1
	CVP-R	1
	FCM-R	1
Prolymphocytic leukaemia	R	2
	CHOP-R	1
Thrombocytopenia	R	2
Mixed connective tissue disease	R	1
Sclerosis	R	1
Autoimmune haemolytic anaemia	R	1

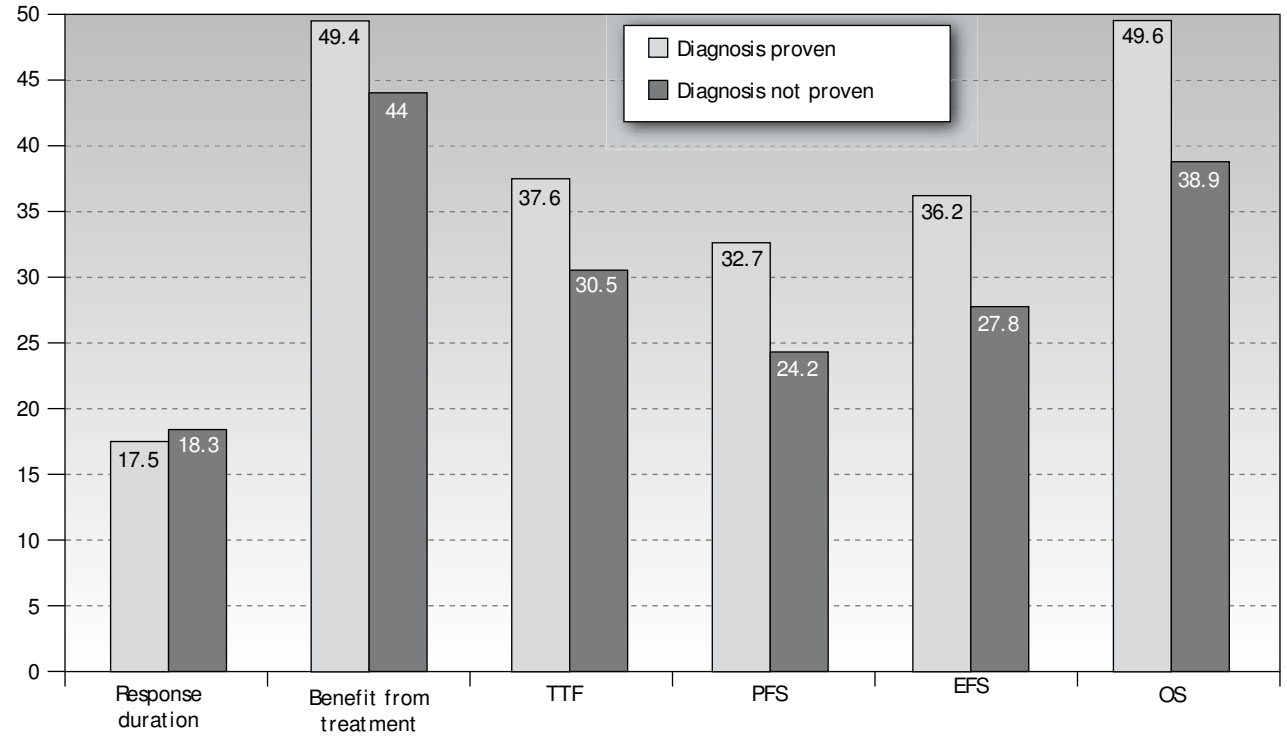

Figure 4 Comparison of the efficacy results (expressed in months) for the approved and non-approved diagnoses.

References

1. Wikipedia, la enciclopedia libre. Linfomas [accessed Apr 19, 2009]. Available from: http://es.wikipedia.org/wiki/Linfoma
2. Rabasa RM. Factores pronósticos en los linfomas: linfomas no Hodgkin y linfoma de Hodgkin [accessed Apr 19, 2009]. Available from: http://www.cfnavarra.es/salud/anales/textos/vol24/biblio13/bsuple13.html
3. Eficacia frente a los linfomas. Hematología. FSM/JMH. Selección de noticias, PLANNER Media [accessed Apr 19, 2009]. Available from: http://www.medicodirecto.com/~temasalud/noticias/index2.php?noticia=14
4. Rituximab: tratamiento de la artritis reumatoide en pacientes que no responden a los tratamientos biológicos actuales con anti-TNF. Offarm. 2007;26(5).
5. Gómez Codina J. Artículos de revisión: Anticuerpos monoclonales anti-CD20. [accessed Apr 19, 2009]. Available from: http://www.merck.es/servlet/PB/menu/1401810/index.html
6. Medciclopedia. Diccionario ilustrado de términos médicos. Ciencias Básicas. Farmacologia. Vademecum [accessed Apr 19, 2009]. Available from: http://www.iqb.es/cbasicas/farma/farma04/r021.htm
7. Department of Health. NHS Cancer Plan. London: Department of Health; 2000.
8. Ferguson JSJ, Summerhayers M, Masters S, Schey S, Smith IE. New treatment for advanced cancer: and approach to priorization. Br J Cancer. 2000;83:1268-73.
9. Expósito J, Hernández J, Fernández Feijóo A, Briones Pérez de la Blanca E. Evaluación de las prácticas y del coste-efectividad de los tratamientos quimioterápicos en pacientes oncológicos avanzados. Agencia de Evaluación de Tecnologías Sanitarias de Andalucía; 2002.
10. Bernal Rivera L, Guerrero Aznar MD, Monzón Moreno M, Beltrán García M, Hernández Cruz B, Colmenero MA. Eficacia y seguridad de adalimumab y etanercept en artritis reumatoide en un hospital de tercer nivel. Farm Hosp. 2006;30:223-9.
11. Glimelius B, Bergh J, Brandt L, Brorsson B, Gunnars B, Hafstrom L, et al. The Swedish Council on Technology Assessment in Health Care (SBU) systematic overview of chemotherapy effects in some major tumour types-summary and conclusions. Acta Oncol. 2001;40:135-54.
12. NCCN Clinical Practice Guidelines in Oncology. Non Hodgking's lymphomas. Vol 3; 2008.
13. Zucca E, Dreyling M and On behalf of the ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Onc. 2008;19:70-1.
14. Eichhorst B, Hallek M, Dreyling M and On behalf of the ESMO Guidelines Working Group. Chronic lymphocytic leukemia: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Onc. 2008;19:60-2.
15. Tilly H, Behalf M of the ESMO Guidelines Working Group. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Dreyling and On clinical recommendations for diagnosis, treatment and follow-up. Ann Onc. 2008;19:67-9.
16. Marinus H, van Oers J, Klasa R, Marcus RE, Wolf M, Kimby E, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without intergroup trial rituximab during induction: results of a prospective randomized phase 3. Blood. 2006;108:3295-301.
17. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106:3725-32.
18. Czuczman MS, Weaver R, Alkuzweny B, Berlfein J, Grillo-López AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with

rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol. 2004;22:4711-6.
19. Tobinai K, Igarashi T, Itoh K, Kobayashi Y, Taniwaki M, Ogura M, et al. Japanese multicenter phase II and pharmacokinetic study of rituximab in relapsed or refractory patients with aggressive B-cell lymphoma. Ann Oncol. 2004;15:821-30.
20. Habermann TH, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, et al. Rituximab-CHOP versus CHOP alone with maintenance rituximab in older patients with diffuse large B-Cell lymphoma. J Clin Oncol. 2006;24:3121-7.
21. Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopaenic purpura. Ann Intern Med. 2007;146:25-33.
22. Wierda W, O'Brien S, Faderl S, Ferrajoli A, Xuemei W, Do Kim-An H, et al. A retrospective comparison of three sequential groups of patients with recurrent/refractory chronic lymphocytic leukaemia treated with fludarabina-based regimens. Cancer. 2005;106:337-45.
23. Keating MJ, O'Brien S, Albitar M, Lerner S, Plunkett W, Giles F, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leucemia. J Clin Oncol. 2005;23 Suppl 18:4079-88.
24. Lenz G, Dreyling M, Hoster M, Wörmann B, Dührsen U, Metzner B, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol. 2005;23:1984-92.
25. Martinelli G, Laszlo D, Ferreri A, Pruneri G, Ponzoni M, Conconi A, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. J Clin Oncol. 2005;23:1979-83.
26. Buyse M, Thirio P, Carlson R, Burzykouwski T, Molenberghs G, Piedbois P, for the Meta-Analysis Group in Cancer. Relation between tumour response to first line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Lancet. 2000; 356:373-8.
27. Freedman LS, Granbard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronics disease. Stat Med. 1992;11: 167-78.