Malignant Lymphomas

research paper

haematologica 2002; 87:719-729
http://www.haematologica.ws/2002_07/719.htm

The cost of treating relapsed indolent non-Hodgkin's lymphoma in an international setting: retrospective analysis of resource use

MICHAEL HEROLD,* STEFANO SACCHI,° KLAUS HIEKE#
*HELIOS-Klinikum Erfurt; II Medizinische Klinik, Abt. Hämatologie/Onkologie, Erfurt, Germany; °Dip. di Scienze Mediche, Radiologiche e Oncologiche, Università di Modena, Italy; #NEOS Health Ltd, Binningen, Switzerland

Background and Objectives. Few economic data exist on the treatment of indolent non-Hodgkin's lymphoma (NHL) and there are none in the published literature concerning relapsed disease. This international analysis (Canada, Germany, Italy) was established to estimate the overall direct cost of treating patients with relapsed indolent NHL and determine the main cost components of treatment.

Design and Methods. Telephone interviews were used to identify the most commonly used treatment regimens in each country. CHOP, CVP and fludarabine were chosen for economic analysis, which was based on retrospective data from 424 patients.

Results. Overall treatment costs for a course of six cycles varied more than 5-fold, from €3,445 to 17,940 between regimens and countries. The treatment setting had a major impact on costs, with in-patient costs being up to three times greater than the equivalent out-patient values. Drug administration costs comprised 46–60% of the overall treatment costs in the in-patient setting. Adverse event management was the major cost component for out-patient CHOP and CVP therapy (52–75%), and a significant proportion (24–40%) of in-patient costs for these regimens. Drug acquisition accounted for less than half of treatment costs for most of the regimens analyzed.

Interpretation and Conclusions. This study shows that not simply drug acquisition costs, but the costs of drug administration, particularly in the in-patient setting, and adverse event management are major contributors to the overall treatment costs for relapsed indolent NHL.

Key words: relapse, non-Hodgkin's lymphoma, cost of treatment.

Correspondence: Klaus Hieke, NEOS Health Ltd., Parkstrasse 28, CH-4102 Binningen, Switzerland. Phone: international +41.61.4237030. Fax: international +41.61.4237043. E-mail: klaus.hieke@neoshealth.com

In the past 30 years there has been a steep rise in the incidence of non-Hodgkin's lymphoma (NHL) in the West, with incidences increasing by approximately 3-4% annually since the early 1970s.[1-3] Incidence rates in Germany and Italy (1997) were approximately 14 per 100,000 population.[4] Higher incidence rates of approximately 20 per 100,000 population per year have been reported in North America.[5,6]

Indolent B-cell lymphomas account for between 30–40% of these cases.[7,8] Patients with indolent disease typically show a median survival of between 6–10 years from diagnosis, with treatment characterized by serial remissions, gradually decreasing in duration regardless of the therapy employed. First-line therapy usually involves an alkylating agent-based regimen and median response durations of 12–30 months can be achieved.[9]

Once relapse occurs patients are offered additional chemotherapy; however, there is currently no single dominant treatment standard for relapsed indolent NHL. Patients characteristically undergo multiple cycles of therapy and a variety of different regimens are in common use. Some are internationally recognized, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), while others are nationally specific, such as DHAP (dexamethasone, high-dose cytarabine, cisplatin), which is used in the treatment of aggressive NHL, but also to treat relapsed indolent NHL in France.

Recently the purine analog, fludarabine, has shown comparatively good results.[10] Studies using fludarabine reported overall response rates ranging from 30–99%, and event-free survivals of up to 31 months.[11–23] Fludarabine treatment was, however, associated with adverse events, most commonly neutropenia (40–62%), infections and/or febrile episodes (15–19%) and deaths due to infection (5-12%).[14, 16, 24]

Innovative new treatment options have been scarce until the introduction of rituximab (mono-

clonal antibody-based therapy), which shows comparable efficacy to existing chemotherapy regimens in mono-and combination therapy (ORR 46-100%, progression-free survival up to 65.1+ months in combination with CHOP), but with better tolerability.[25–36]

In addition to clinical effectiveness, the patient's quality of life and economic factors are important in treatment choice. Adverse events such as anemia, neutropenia, thrombocytopenia, nausea and vomiting are commonly seen with many cytotoxic regimens. To date, limited published data are available on the extent of adverse events during treatment of relapsed indolent NHL, or their contribution to the overall cost of treatment.

Extensive literature searches by ourselves and others[37] revealed very few published economic analyses of direct or indirect costs of treating lymphoma, despite the call for more such evaluations of all aspects of oncology management.[38] A UK analysis comparing resource utilization and treatment costs of different schedules (CHOP vs. fludarabine vs. rituximab) for relapsed indolent NHL has been published.[39]

The few other existing studies have examined the costs of two comparatively new techniques – autologous bone marrow transplantation (ABMT)[40-42] and granulocyte colony-stimulating factor (G-CSF) use[43–45] in aggressive lymphoma. Only one study in the Netherlands[46] compared the cost of ABMT with CHOP chemotherapy. In an improvement to this situation, Tolley *et al.* (*British Office of Health Economics*) published an estimate of treatment costs using published data and expert opinion.[37]

To our knowledge this is the first international effort to study economic aspects of indolent NHL management. Drawbacks to this evaluation included: lack of pertinent published data, no standard treatment for relapsed disease, there being a variety of treatment regimens in current use, and limited information on treatment patterns, adverse events and resource use.

This study was designed as a *cost of illness study* to describe, rather than compare, treatment patterns and their economic consequences in selected Western countries from the *third party payer*-perspective. Indirect costs (lost productivity) were, therefore, not included in the analysis. The first objective was to identify standard treatment practices in the countries reviewed, then collect retrospective data from the patients' records. As this study was designed as a *cost of illness study* it was not appropriate to evaluate efficacy or remission duration, as data were taken from one single cycle of chemotherapy, and patients presented in different cycles (typically 28 days) of treatment.

Design and Methods

Data collection

Data collection was a two-stage process:

1. *Identification of treatment regimens.* Exploratory telephone interviews with pre-selected lymphoma specialists in Canada, Germany and Italy were first conducted to determine the most commonly used regimens for treatment of relapsed indolent NHL. Interviews were performed by an independent market research company (ISIS Research, UK) using native language speakers and a set questionnaire. To be eligible for inclusion, specialists interviewed had to either run a hospital lymphoma clinic or be specialized in lymphoma management, treating 10 or more patients with relapsed indolent NHL per year. Eligible specialists were then asked to list their three most common protocols and the percentages of patients on each protocol. Eligible data from 91 telephone interviews (April 1997) were provided by 30 specialists each in Germany and Italy, and 31 in Canada. The mean number of patients seen by each specialist in the past year ranged from 21 (Italy) to 39 (Germany).
2. *Review of the patients' records.* A retrospective case record form (CRF) was specifically designed to obtain relevant treatment data from the patients' records. CRFs were mailed to each specialist who agreed to participate. Around 30% of specialists who participated in the first stage agreed to participate in the second stage as well, with the remainder recruited specifically for the second stage. A target of 50 patients per treatment group and country was set (Table 2). In total, CRFs were mailed to 179 specialists (91 in Canada, 37 in Germany, 51 in Italy). For inclusion, specialists had to see at least 10 patients with relapsed indolent NHL per year, and treat 8 or more patients with at least one of the selected regimens. Specialists completed the CRFs by extracting data from records of patients treated for relapsed indolent NHL since 1990, and who received one of the selected regimens. The mailing and receipt of CRFs was handled by ISIS Research to maintain confidentiality.

Four hundred and twenty-four completed CRFs were returned from 89 eligible specialists (50 in Canada, 19 in Germany, 20 in Italy, response rate 50%). The average number of CRFs completed per specialist was 8.0 (Italy), 5.6 (Germany), and 3.5

Table 1. Most frequently used protocols for relapsed low-grade NHL by country (1997).

Country	*Regimen*	*No. of specialists*	*Mean % of patients per specialist*
Germany	CHOP	14	39
	COP / CVP	14	32
	Fludarabine	11	44
	PmN/MPL/MCP	8	31
	KNOSPE	5	39
	DEXABEAM	3	30
Italy	CHOP	14	36
	Fludarabine	13	54
	COP / CVP	9	29
	Chlorambucil + prednisone	6	26
	FND	5	29
	CEOP	4	47
	Chlorambucil	4	40
	Fludarabine + prednisone	3	55
	Fludarabine + mitoxantrone	3	8
Canada	COP / CVP	22	29
	CHOP	20	30
	Fludarabine	18	35
	Transplantation	6	20

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone;
COP/CVP: cyclophosphamide, vincristine, prednisone;
PmN: prednimustine, mitoxantrone; MPL: mitoxantrone, prednisone, lomustine;
MCP: mitoxantrone, chlorambucil, prednisone;
KNOSPE: chlorambucil prednisone; DEXABEAM: dexamethasone;
FND: fludarabine, mitoxantrone, doxorubicin;
CEOP: cyclophosphamide, epirubicin, vincristine, prednisone.

(Canada). In total, information was provided for 424 patients. Questions in the CRF referred to events occurring during a single cycle of chemotherapy and included six sections: the patient's demographics; treatment regimen; chemotherapy setting (i.e. in-patient/out-patient); routine tests; treatment outcome; and adverse event management (including hospitalization and diagnostic tests). In-patients were defined as patients who had at least one overnight hospital stay for drug administration.

Adverse events and any subsequent treatments for events were recorded in five categories: nausea/vomiting; neutropenia and fever/infections; thrombocytopenia; anemia; and other. The use of prophylactic treatment, occurrence of an adverse event, any treatment, diagnostic test, out-patient visit and days of hospitalization were recorded.

Cost calculations

Overall costs for each selected regimen were calculated from the perspective of a third-party payer as recommended by Garattini *et al.*[47] Nationally, the unit costs for each treatment, test or procedure were used to calculate the cost per patient of a single cycle of chemotherapy. Unit costs were obtained from different sources, including published price lists, national and regional sources, and previously published economic studies. The unit costs for medications may be an overestimate as they are based on published price lists minus wholesaler and retail pharmacy add-ons and will not have reflected discounts which may have been negotiated between the manufacturer and individual hospitals. In counterbalance, figures used in the out-patient setting may be underestimated, particularly for Germany, because add-ons plus pharmacy charges for drug preparation have not been included. For Italy a 50% reduction on the public price for drugs was considered for in-patients. Each cycle was assumed to be representative of the cycles making up the whole course of treatment for each patient. Results were expressed as an average treatment cost per patient for a complete course (six cycles) of chemotherapy.

Table 2. Breakdown of patients by treatment regimen and country.

	Canada	*Germany*	*Italy*	*Total*
CHOP	57	48	70	175
CVP	56	51	–	107
Fludarabine	60	–	82	142
Total	173	99	152	424

The average costs per patient were presented for both in-patient and out-patient treatment. Further cost breakdowns of drug acquisition for the regimen, treatment administration, and treatment and management of adverse events allowed the main cost component for each regimen to be identified. Indirect costs (e.g. days lost from work) were not considered in this analysis because of the chosen perspective (third party payer) and concerns about the availability and reliability of this type of information in the patients' records.

Results

Identification of treatment regimens

Table 1 shows that fludarabine, CHOP and CVP (cyclophosphamide, vincristine, prednisone) were cited with comparable frequency by specialists in Canada. CHOP and CVP were cited most in Italy, and CHOP and CVP in Germany. Of particular interest was the use of fludarabine, which was not approved for use in NHL at the time of interview. Regimens were chosen for economic analysis based on the level of usage in each country: Canada (CHOP, CVP and fludarabine), Germany (CHOP and CVP), Italy (CHOP and fludarabine) (Table 2).

Table 3. Selected characteristics of the patients.

	Canada			*Italy*		*Germany*	
	CHOP	CVP	FLU	CHOP	FLU	CHOP	CVP
Average age (years)	58	58	62	62	64	58	63
Number of males	35	24	35	43	55	26	34
Number of females	22	32	25	27	27	22	17
Stage of disease (% patients)							
I	5	3	5	3	0	6	2
II	12	10	20	14	7	17	12
III	23	13	29	31	38	19	53
IV	60	73	46	51	55	58	33
Presence of concomitant disease requiring treatment (% patients)	43.1	38	25	10.6	11.1	24.5	37.8
Average number of previous treatments	1.6	1.4	1.5	1.5	1.7	1.4	1.5

Patients

The patients' characteristics were similar across treatment regimens and countries. Concomitant diseases that required treatment occurred in 11-43% cases across treatment groups (Table 3). Fludarabine (Canada) and CVP (Germany) were less likely to be administered to patients in late-stage disease (stage 4).

Approximately 48% of returned reports were for patients undergoing cycles 1–3 of their treatment course compared to 50% of reports from the latter half (cycles 4+), with cycles in 6 reports being unspecified. Neutropenia was the most common adverse event reported and was evenly spread across the early and late treatment cycles (Table 4). The average of the data collected was therefore assumed to represent those of an *average* cycle. Comparative values for adverse events per treatment cycle for relapsed indolent disease were sought but could not be obtained from published accounts of randomized trials.

Table 4. Breakdown of cycles by number of patients and adverse events.

	N. of patients	*Occurrence of neutropenia (%)*
Cycle 1	72	9.8
Cycle 2	69	14.5
Cycle 3	63	11.1
Cycle 4	55	9.1
Cycle 5	36	11.2
Cycle 6	79	7.6
Cycle >6	44	11.4
Unknown	6	–
Total	424	n/a

Cost evaluations

Cost components. Unit costs were derived from a variety of sources (Table 5). Overall treatment costs were broken down into three components: cost of regimen medication (drug acquisition), cost of drug administration, and cost of monitoring and treating adverse events (Table 6).

Administration costs included both out-patient visits and hospitalizations for administration of the drug regimen, plus all routine diagnostic procedures (e.g. blood counts). Overall, administration costs for each treatment regimen were higher in the in-patient setting than for out-patient administration. The difference between the treatment settings was 14-fold in Italy and Germany, but only 2.5-fold in Canada. The proportion of patients receiving in-patient treatment also varied between countries. In Germany, approximately half of all patients were hospitalized for at least one treatment infusion, whereas in Canada, this was less than 15% (Table 7).

Table 5. Summary of unit costs in local currencies.

	Canada		*Germany*		*Italy*	
	Cost (Can$)	*Source*	*Cost (DM)*	*Source*	*Cost (Lira)*	*Source*
In-patient stay	521	1	650	5	694,900	7
Out-patient visit	189	2	31.8	5	50,000	8
Selected diagnostic tests						
Complete blood count	21.71	1	10.8	5	6200	9
U&E	12.72	3	7.2	5	2400	9
Platelets	12.72	3	3.6	5	2400	9
Blood culture	19.04	3	18	5	4000	9
Packed cell transfusion	32.7	3	280	5	50,000	9
Platelet transfusion	37.06	3	107	5	22,500	9
Drug costs	–	4	–	6	–	10

Table 6. Breakdown of the average cost of treatment per patient (in €) into administration (Admin), drug acquisition (Acq) and adverse event (AE) costs for in-patient and out-patient administration for 6 cycles.

Regimen/country	*In-patient*				*Out-patient*			
	Admin	*Acq*	*AEs*	*Total*	*Admin*	*Acq*	*AEs*	*Total*
CHOP								
Canada	5,639	2,217	5,036	12,892	2,187	2,216	5,036	9,439
Germany	5,512	1,706	2,515	9,733	444	1,706	2,515	4,664
Italy	3,781	470	2,179	6,430	335	929	2,179	3,445
CVP								
Canada	7,198	162	3,252	10,612	2,847	162	3,252	6,261
Germany	8,088	361	2,658	11,107	506	361	2,658	3,525
Fludarabine								
Canada	8,738	3,931	1,273	13,942	3,338	3,931	1,273	8542
Italy	9,166	3,861	4,908	17,940	770	7,723	4,908	1,3401

Conversion rate from local currency to € (April 1998): Canada, 0.672; Germany, 0.511; Italy, 0.000517.

For in-patient therapy, administration costs formed the major cost component for each regimen studied (Table 6). The cost of administration represented 68–73% of total costs for CVP treatment, 51–63% for fludarabine and 44–59% for CHOP (Figure 1a). In the out-patient setting, the proportion of administration costs was most influenced by country not regimen. In Canada, this represented 24–45% of the total, whereas in Italy and Germany, it ranged from 5.5% to 15% (Figure 1b).

Drug acquisition costs were greatest for fludarabine and lowest for CVP, irrespective of country of treatment (Table 6). Drug acquisition formed the main component of the cost of fludarabine treatment in the out-patient setting (46–58%; Figure 1b), and represented about one-quarter of the total cost for in-patient administration (Figure 1a). In contrast, drug acquisition represented less than 10% of the total cost of CVP treatment, and 7–17.5% of the total for CHOP therapy for in-patient administration and 24–36% in the out-patient setting (Figure 1).

The monitoring and treatment of adverse events was the major cost component (52–75%) for both CHOP and CVP treatment in the out-patient setting (Figure 1b), whereas for in-patient administration, the proportion ranged from 24–40%. For fludarabine, the proportion of costs due to adverse events was most affected by country, rather than administration setting, being 9% (in-patient) and 15% (out-patient) in Canada, and 27% (in-patient) and 37% (out-patient) in Italy.

Adverse event costs by category

Data were collected on rates of adverse events for each treatment (Table 8). Given the retrospective nature of the data, differences in patient selection criteria, and adverse event reporting and regulations between countries, interpretation of the data and cross-country comparisons should be approached cautiously.

For the majority of regimens, the management of neutropenia and fever/infection was the greatest component of adverse event cost (Table 9). The exception was fludarabine treatment in Italy; costs for management of nausea and vomiting exceeded those for neutropenia and fever/infection. The proportion of total adverse event costs associated with neutropenia and fever/infection was approximately one-third for fludarabine treatment in Italy, compared with 90% for the same regimen in Canada.

Costs of other adverse events varied: nausea and vomiting accounted for between €100–400 (less than 15% of the total adverse event costs), with the exception of fludarabine treatment in Italy

Table 7. Percentage of patients receiving chemotherapy as in-patients.

Regimen/country	*Percentage of patients receiving chemotherapy as in-patients*	*Potential savings per patient if overnight stays are avoided*
Germany/CHOP	46%	52%
Germany/CVP	51%	68%
Italy/CHOP	19%	40%
Italy/fludarabine	38%	16%
Canada/CHOP	12%	27%
Canada/CVP	14%	41%
Canada/fludarabine	7%	39%

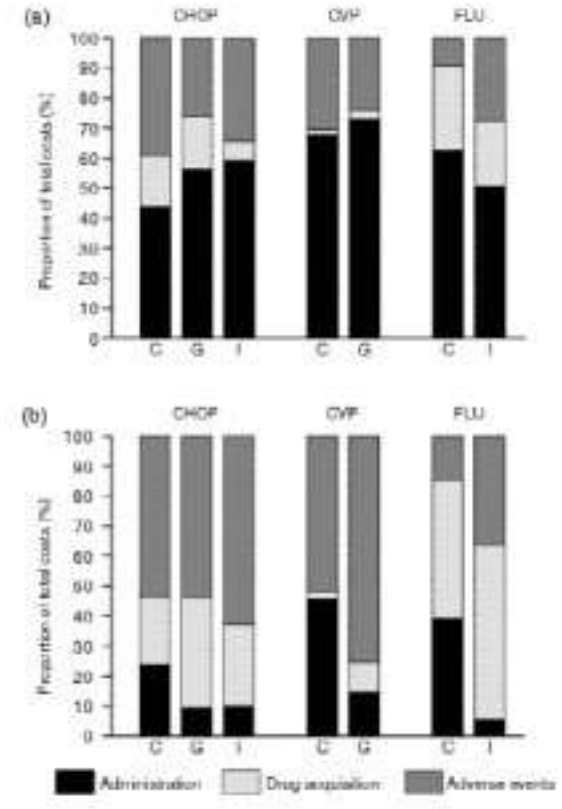

Figure 1. Costs of drug acquisition, administration and adverse event management as a proportion of total treatment costs (six cycles) for (a) in-patient and (b) out-patient administration. (C = Canada; G = Germany; I = Italy; FLU = fludarabine; conversion rates April 1998.)

where it was the most expensive adverse event, largely due to the extensive use of prophylactic 5HT3 antagonists (almost 40% of total cost) (Table 9). The costs for thrombocytopenia were less than €100 (CHOP treatment), but showed large variations for CVP and fludarabine.

Drug regimen costs between countries

No one country consistently demonstrated a significantly higher total treatment cost. CHOP therapy (in-patient and out-patient administration) was most costly in Canada, and least costly in Italy (Figure 2). Fludarabine treatment cost more in Italy than in Canada. CVP treatment cost more in Canada than in Germany (out-patient administration), but the situation was reversed for in-patient administration.

The greatest difference in costs occurred with CHOP; treatment in Canada was more than twice as costly as in Italy (Figure 2). The cost of fludarabine treatment in Canada was 79% of that in Italy (in-patient administration), and approximately two-thirds of that in the out-patient setting. Similar cost variations were seen between Canada and Germany for CVP therapy.

Total treatment costs within each country

The most marked intra-country difference in treatment costs occurred in Italy, where fludarabine treatment was 3–4 times more expensive than CHOP, depending on the administration setting (Figure 2). In Canada, CVP treatment was the least costly option for both in-patient and out-patient administration. In Germany, CHOP was more expensive than CVP (out-patient setting), but cheaper for in-patient administration. In both Canada and Germany the difference in treatment costs was less marked than in Italy.

Table 8. Incidence of grade 3 and 4 adverse events (% patients).

	CHOP		*Fludarabine*		*CVP*		
	Germany	*Italy*	*Canada*	*Italy*	*Canada*	*Germany*	*Canada*
Neutropenia	8	19	18	18	13	4	9
Fever/infections*	4	11	12	9	8	10	9
Nausea/vomiting	0	0	0	0	2	0	2
Anemia	4	7	7	10	0	12	9
Thrombocytopenia	2	7	2	15	2	2	4
Others	8	11	11	5	5	12	14
None*	17	14	12	29	17	27	11

**Requiring treatment, irrespective of grade.*

Table 9. Average cost per person (€) for the management of adverse events by category.

	CHOP			*CVP*		*Fludarabine*	
	Canada	*Germany*	*Italy*	*Canada*	*Germany*	*Canada*	*Italy*
Neutropenia	3,873	942	1,625	1,452	1,429	1,149	1655
Nausea/vomiting	142	310	191	138	404	97	1,833
Anemia	42	869	278	61	570	5	595
Thrombocytopenia	95	87	81	776	223	22	659
Other	884	307	4	825	32	0	166
Total	5,036	2,514	2,179	3,252	2,659	1,273	4,908

Conversion rate from local currency to Euros (April 1998): Canada, 0.672; Germany, 0.511; Italy, 0.000517.

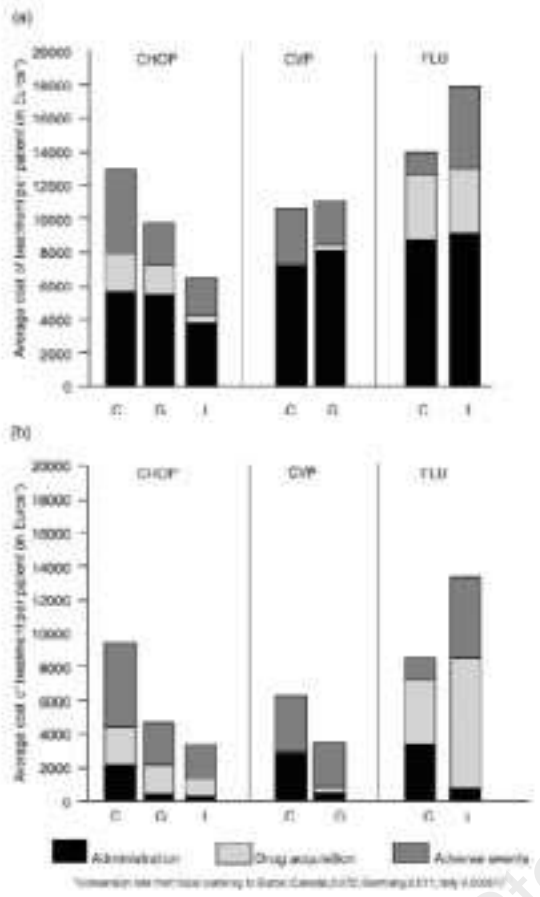

Figure 2. Average cost (in Euros) of a full course of treatment (six cycles) per patient for (a) in-patient and (b) outpatient administration. (C = Canada; G = Germany; I = Italy; FLU = fludarabine; conversion rates April 1998.)

Discussion

Regimens studied

The telephone survey of lymphoma specialists confirmed the lack of a standardized treatment approach to relapsed indolent NHL, both within and between countries. A similar survey performed in the UK at the same time[39] supports this finding. The variety of treatment regimens reported by specialists suggests an overall dissatisfaction with available options at the time of the study (1997/98) and highlights the need for more effective treatment strategies.[48]

In this scenario, treatment-related toxicity becomes an important consideration. Although the data for CHOP chemotherapy in indolent NHL are limited, two recent studies in patients with untreated aggressive NHL reported an incidence of grade 4 neutropenia of around 30%.[50, 51] Retrospective analysis of patients' records at several centers in the UK has shown an overall incidence of neutropenia requiring intervention of 42%.[39]

Toxicity associated with fludarabine is generally greater than that associated with CHOP therapy. In an ECOG study of patients with relapsed indolent NHL, the incidence of neutropenia was 71%.[13] The incidence of thrombocytopenia can also be high, with values of 48% reported in both previously treated and untreated patients.[14] Fludarabine treatment is also often associated with problems of infection (incidences of 15% reported in the ECOG study), and there are reports of deaths due to infection in 5-12% of patients.[12, 14, 22]

Interpretation of the adverse event data needs care, as there is the possibility of pre-selection bias in retrospective reviews of patients' record. Treatment choices would have been based on factors such as age, disease stage, previous response and toxicity of previous regimens, which may have resulted in different adverse event rates to those expected from prospective, randomized trials. However, these findings can be considered more representative of the *real life* situation and therefore suitable for a *cost of illness* analysis. Adverse event rates, particularly grade 3 and 4 toxicities were similar for fludarabine and CHOP and lower for CVP, suggesting that selection of patients may compensate for the differences in toxicity profiles of regimens known from prospective, randomized trials. Although more aggressive treatment regimens generally achieve remission in a shorter time, the actual duration of the remission is not improved compared with that activated by less aggressive treatments. Theoretically, an improved remission duration would be economically attractive due to reduced costs because of a possible delay and/or a reduction in the number of subsequent treatments. More importantly, a longer remission duration would have a favorable impact on the denominator of a cost-effectiveness calculation. However, this is beyond the scope of a cost of illness study and subject of a cost-effectiveness or cost-utility analysis which requires comparative long-term data on both costs and clinical consequences of relevant treatments.

Other adverse events and concomitant diseases requiring treatment were present in 11–43% of cases (Table 8) in the different treatment groups, and contributed up to 25% of costs for adverse event management, or up to 14% of total costs (Table 9).

Some bias in cycle selection may also have occurred as the selection of consecutive cases was not specified, nor was the selection of early or late cycles predefined. However, the distribution of the cycles from the 424 records returned suggests that this was not a major factor, as there was an even distribution of patients undergoing early cycles (cycles 1–3, 48%) and late cycles (cycles 4+, 50%). Performance status was not recorded, and any assumptions made on this measure would be difficult. In theory, participating specialists could have selected patients with few adverse events and complications (e.g. to reduce documentation workload) which would have resulted in an underestimate of costs for adverse events and complications. On the other hand, one may speculate that there could have been a preference to report the most *interesting* cases, which would have been likely to result in an overestimate of costs for adverse events and complications. However, there was no indication that either of these effects played a role or specifically had an impact on data from one treatment group or country.

Collection of economic data

With the absence of available economic data on treatment for relapsed indolent NHL (clinical trial data, meta-analyses, database collections), other methods of data collection were required for this analysis. The use of specifically designed CRFs ensured collection of empirical data reflecting clinical practice, rather than relying on specialists' perceptions and memory. Data collection from patients' records provides a close reflection of the real-life situation. This is illustrated by the use of fludarabine *off label* in some countries to treat relapsed indolent NHL. A 50% response rate for the return of completed CRFs provided data on 424 patients. This is the first international economic study in low-grade NHL, and included either more patients than, or a similar number as those in other economic studies in NHL.[39, 43, 46, 52]

Cost comparisons between countries

Cross-country comparisons were interpreted with caution. Comparison of treatment costs between countries revealed no clear trends, with the exception of out-patient administration costs which were far higher in Canada than elsewhere, ranging from 3.8-fold greater for fludarabine to 5.8-fold higher for CHOP therapy in Italy. This reflects the higher unit costs of an out-patient visit in Canada (€ 127) than in Germany (€ 16) or Italy (€ 26). In contrast, the costs for each day spent as an in-patient in a non-intensive care unit were similar in all three countries (Canada, € 350; Germany, Euros 332; Italy, € 279). The difference in out-patient administration costs accounted for most of the difference in costs for CVP treatment between Canada and Germany, although for fludarabine treatment, the higher administration costs in Canada were outweighed by the higher acquisition and adverse event costs seen in Italy.

The difference in treatment strategies between countries found at the time of the study may also have an impact on treatment costs. In general, management of patients in Germany and Italy tends to be more aggressive than that in Canada, where treatment is more likely to be delayed until symptoms appear and then initiated using milder regimens.

Financial considerations could also affect the patients' management e.g. in some German hospitals reimbursement of drug costs depends on an overnight stay. This could account for the high proportion of patients (46–51%) in Germany who received treatment as in-patients.

Cross-country comparison of adverse event treatment costs showed costs of treating anemia were substantially (5–10-fold) lower in Canada than in Germany and Italy. Costs of managing nausea and vomiting were also lower in Canada than in Germany and Italy. There was no clear national trend for other categories of adverse events.

Drivers of treatment costs

For most of the regimens studied, drug acquisition costs made up less than half of the overall cost of treatment. The major influence on the total treatment cost, irrespective of country or regimen used, was administration setting. In-patient administration increased the cost of treatment as much as 3-fold over the equivalent out-patient regimen. Administration costs comprised the largest proportion of total costs for each regimen in the in-patient setting (44–73%), but only between 6–46% of total costs in the out-patient setting. Potential savings due to a reduction of overnight stays in hospital for administration of chemotherapy are considerable, particularly in Germany and Italy (Table 7). In Canada, the vast majority of NHL therapies are administered on an out-patient basis.

Treatment and monitoring of adverse events formed the main cost component of CHOP and CVP therapy in the out-patient setting, accounting for between 50–75% of total cost. This was also a significant proportion of costs for in-patient administration (CHOP, 26–39%; CVP, 24–31%). Drug

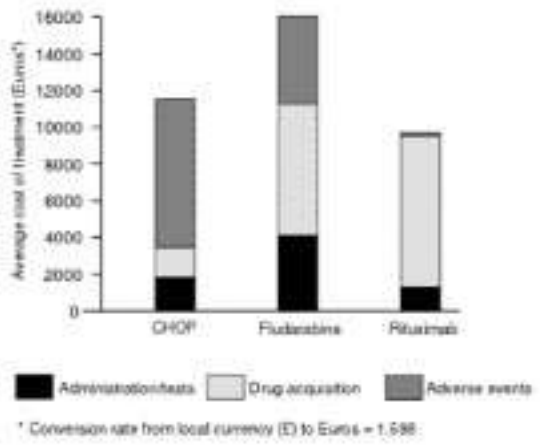

Figure 3. Average costs per patient (in Euros) of one course (six cycles) of therapy in a UK study;[25] conversion rate April 1998.

acquisition costs were the major component for treatment cost only for fludarabine administered in the out-patient setting (46–60%). In contrast, they accounted for less than 10% of the overall treatment costs for CVP therapy.

Only one other analysis of costs of treating relapsed indolent NHL has been published.[42] This UK study was also a retrospective analysis of records of patients treated with CHOP or fludarabine in several cancer centers, and compared these costs with those of patients treated in a phase II trial of the novel anti-CD20 monoclonal antibody, rituximab. Although not a direct comparison, the results were interesting, showing that the overall costs of rituximab treatment were comparable to those of CHOP and lower than fludarabine, despite higher acquisition costs (Figure 3). This disparity may be due to the good tolerability of the antibody treatment, as adverse events costs accounted for less than 2% of the total overall cost of rituximab treatment, compared with 70% for CHOP. Such a saving would more than offset the higher costs of acquisition. An easy-to-administer and well-tolerated regimen could produce overall cost benefits for health authorities as well as for patients and more attention should be paid to this in the development of new agents. Focusing on total costs of treatment rather than on drug acquisition costs alone allows the influence of factors such as tolerability and ease of administration to be more seen clearly.

An earlier study by Uyl-de Groot *et al.*[46] examining costs of CHOP chemotherapy in aggressive NHL reported an average cost of one course (five cycles) of out-patient therapy of US$3118 (€ 3057). This is similar to the cost of CHOP therapy in Italy in this study (€ 3189 for six cycles), although the drug acquisition (US$1290 [€ 1265]) and out-patient administration (US$766 [€ 751]) costs were higher in the Dutch study. Tolley *et al.* also reported estimated treatment costs for indolent NHL and aggressive NHL.[37] Costs per case for patients not receiving ABMT ranged from £3700–8800 (€ 5913–14,062) depending on the type of NHL and age of the patient. However, since these estimates represent the lifetime costs of treatment per patient, including first-line therapy, comparisons with results reported here are difficult.

Conclusions

To our knowledge, this is the first time a cross-nation economic analysis has been performed for lymphoma treatment practices, and the results provide the first economic data on treatment patterns and resource use in relapsed indolent NHL in the selected countries. Analysis of the overall costs of providing a single cycle of chemotherapy show that drug acquisition costs generally account for less than half of the total costs of treatment. The cost of adverse event management and, particularly in the in-patient setting, costs of drug administration are important cost-drivers. Thus, any formal economic evaluation of the therapeutic options for relapsed indolent NHL would need to consider the costs of administering chemotherapy and managing adverse events in addition to those of drug acquisition to obtain an accurate picture of the costs.

Contributions and Acknowledgments

MH and SS were responsible for the medical/clinical part of the paper and for checking and reviewing the economic findings from a medical perspective. Both substantially contributed to the interpretation of data and revised and approved the manuscript. KH designed the study and was responsible for its execution, analysis and the economic part of the paper. There is no additional specific meaning in the order of authorship. We thank the specialists who provided the data.

Disclosures

Conflict of interest: K Hieke is a former employee of Hoffmann-La Roche.

Redundant publications: no substantial overlapping with previous papers.

Funding

This study was supported by Hoffmann La Roche.

References

1. Cartwright RA, McNally RJQ, Staines A. The increasing incidence of non-Hodgkin's lymphoma (NHL): the possible role of sunlight. Leuk Lymphoma 1994; 14:387-94.
2. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res 1992; 52 Suppl 2:5432-40.
3. Morgan G, Vornanen M, Puitinen J, Naukkarinen A, Brincker H, Olsen J, et al. Changing trends in the incidence of non-Hodgkin's lymphoma in Europe. Biomed Study Group. Ann Oncol1997; 8 Suppl 2:49-54.
4. Parkin D, Whelan S, Ferlay J, Raymond L, Young J, editors. In: Cancer Incidence in Five Continents. Volume VII. Lyon: IARC Scientific Publications, Number 143; 1997.
5. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997; 33:1075-107.
6. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997; 89: 3909-18.
7. Armitage JO. Treatment of non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1023-30.
8. Aisenberg AC. Coherent view of non-Hodgkin's lymphoma. J Clin Oncol 1995; 13:2656-75.
9. Hiddemann W, Unterhalt M. Stand und Perspektiven in der Therapie follikulärer Keimzentrumslymphome. Dtsch Ärzteblatt 1998; 95:Heft 50.
10. McLaughlin P, Robertson LE, Keating MJ. Fludarabine phosphate in lymphoma: an important new therapeutic agent. Cancer Treat Res 1996; 85:3-14.
11. Hochster HS, Kim KM, Green MD, Mann RB, Neiman RS, Oken MM, et al. Activity of fludarabine in previously treated non-Hodgkin's low-grade lymphoma: results of an Eastern Cooperative Oncology Group study. J Clin Oncol 1992; 10:28-32.
12. Whelan JS, Davis CL, Rule S, Ranson M, Smith OP, Mehta AB, et al. Fludarabine phosphate for the treatment of low grade lymphoid malignancy. Br J Cancer 1991; 64:120-3.
13. Falkson CI. Fludarabine: a phase II clinical trial in patients with previously low-grade lymphoma. Am J Clin Oncol 1996; 19:268-70.
14. Pigaditou A, Rohatiner AZ, Whelan JS, Johnson PW, Ganjoo RK, Rossi A, et al. Fludarabine in low-grade lymphoma. Semin Oncol 1993; 20 Suppl 7:24-7.
15. Tsimberidou AM, McLaughlin P, Younes A. Randomized comparison of fludarabine/novantrone/dexamethasone versus CHOP-BLEO/ESHAP/NOPP (alternating triple therapy) in patients with stage IV indolent lymphoma. Blood 2000; 96 Suppl 1:508a[abstract].
16. Foussard C, Deconninck E, Desablens B. Improved response after fludarabine, mitoxantrone in first-line treatment of patients with advanced low-grade non-Hodgkin's lymphoma as compared to prednisone, doxorubicin, vindesine, cyclophosphamide: a randomized trial by the Goelams Group. Proc Am Soc Clin Oncol 2001; 20: 280a[abstract].
17. rawley CR, Foran JM, Gupta RK, Rohatiner AZ, Summers K, Matthews J, et al. A phase II study to evaluate the combination of fludarabine, mitoxantrone and dexamethasone (FMD) in patients with follicular lymphoma. Ann Oncol 2000; 11:861-5.
18. Santini G, Nati S, Spriano M, Gallamini A, Pierluigi D, Congiu AM, et al. Fludarabine in combination with cyclophosphamide or with cyclophosphamide plus mitoxantrone for relapsed or refractory low-grade non-Hodgkin's lymphoma. Haematologica 2001; 86:282-6.
19. Pott C, Unterhalt M, Sandford D. Fludarabine in combination with mitoxantrone and dexamethasone in relapsed and refractory low-grade non-Hodgkin's lymphoma. Onkologie 1994; 17 Suppl 2:114.
20. McLaughlin P, Hagemeister FB, Romaguera JE, Sarris AH, Pate O, Younes A, et al. Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. J Clin Oncol 1996; 14:1262-8.
21. Zinzani PL, Bendandi M, Tura S. FMP regimen (fludarabine mitoxantrone, prednisone) as therapy in recurrent low grade lymphoma. Eur J Haematol 1995; 55:262-6.
22. Tedeschi A, Montillo M, Capelli D. Phase I study of the combination of fludarabine, idarubicin and dexamethasone in low grade lymphoma [abstract]. Blood 1996; 88 Suppl 1: 195b.
23. Zinzani PL, Bendandi M, Gherlinzoni F, Merla E, Gozzetti A, Tura S. FLU-ID (fludarabine and idarubicin) regimen as salvage therapy in pretreated low-grade non-Hodgkin's lymphoma. Haematologica 1996; 81:168-71.
24. Zinzani PL, Lauria F, Rondelli D, Benfenati D, Raspadori D, Bocchia M, et al. Fludarabine: an active agent in the treatment of previously-treated and untreated low-grade non-Hodgkin's lymphoma. Ann Oncol 1993; 4:575-8.
25. Davis TA, Grillo-Lopez AJ, White CA, McLaughlin P, Czuczman MS, Link BK, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. J Clin Oncol 2000; 18:3135-43.
26. Davis TA, White CA, Grillo-Lopez AJ, Velasquez WS, Link B, Maloney DG, et al. Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. J Clin Oncol 1999; 17:1851-7.
27. McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16:2825-33.
28. Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997; 90:2188-95.
29. Foran JM, Gupta RK, Cunningham D, Popescu RA, Goldstone AH, Sweetenham JW, et al. A UK multicentre phase II study of rituximab (chimaeric anti-CD20 monoclonal antibody) in patients with follicular lymphoma, with PCR monitoring of molecular response. Br J Haematol 2000; 109:81-8.
30. Ogura M, Igarashi T, Morishima Y. Factors affecting toxicity, response and time to progression in relapsed patients with indolent B-NHL and mantle cell lymphoma treated with rituximab [abstract]. Proc Am Soc Clin Oncol 2000; 19:25a.
31. Ghielmini M, Schmitz SF, Burki K, Pichert G, Betticher DC, Stupp R, et al. The effect of rituximab on patients with follicular and mantle-cell lymphoma. Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol 2000; 11 Suppl 1:123-6.
32. Hainsworth JD. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma: interim follow-up of a multicenter phase II trial. Semin Oncol 2002; 29 Suppl 2:25-9.
33. Colombat P, Salles G, Brousse N, Eftekhari P, Soubeyran P, Delwail V, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 2001; 97:101-6.
34. Sacchi S, Federico M, Vitolo U, Boccomini C, Vallisa D, Baldini L, et al. Clinical activity and safety of combination immunotherapy with IFN-α2a and rituximab in patients with relapsed low grade non-Hodgkin's lymphoma. Haematologica 2001; 86:951-8.
35. Kimby E, Geisler C, Hagberg H, et al. Rituximab (MabThera®) as single agent and in combination with interferon-α-2a as treatment of untreated and first relapse follicular or other low-grade lymphomas. A randomized phase II study M 39035 [abstract]. Blood 2000; 96 Suppl 1:577a.
36. Czuczman M, Grillo-Lopez AJ, White CA, Saleh M, Gordon

LI, LoBuglio AF, et al. Progression free survival (PFS) after six years (median) follow-up of the first clinical trial of rituximab/CHOP chemoimmunotherapy [abstract]. Blood 2001; 98 Suppl 1: 601a.
37. Tolley K, Morgan G, Cartwright R, Williams R. Economic aspects of non-Hodgkin's lymphoma. Office of Health Economics 1998; Paper No. 123.
38. Maynard A. Economic aspects of cancer care. Eur J Cancer 1993; 29A Suppl 7:S6-9.
39. Sweetenham J, Hieke K, Kerrigan M, Howard P, Smartt PF, McIntyre AM, et al. Cost-minimization analysis of CHOP, fludarabine and rituximab for the treatment of relapsed indolent B-cell non-Hodgkin's lymphoma in the UK. Br J Haematol 1999; 106:47-54.
40. Bennett CL, Armitage JL, Armitage GO, Vose JM, Bierman PJ, Armitage JO, et al. Costs of care and outcomes for high-dose therapy and autologous transplantation for lymphoid malignancies: results from the University of Nebraska 1987 through 1991. J Clin Oncol 1995; 13:969-73.
41. Smith TJ, Hillner BE, Schmitz N, Linch DC, Dreger P, Goldstone AH, et al. Economic analysis of a randomized clinical trial to compare filgrastim-mobilized peripheral-blood progenitor-cell transplantation and autologous bone marrow transplantation in patients with Hodgkin's and non-Hodgkin's lymphoma. J Clin Oncol 1997; 15:5-10.
42. Woronoff-Lemsi MC, Arveux P, Limat S, Deconinck E, Morel P, Cahn JY. Cost comparative study of autologous peripheral blood progenitor cells (PBPC) and bone marrow (ABM) transplantations for non-Hodgkin's lymphoma patients. Bone Marrow Transplant 1997; 20:975-82.
43. Dranitsaris G, Sutcliffe SB. Economic analysis of prophylactic G-CSF after mini-BEAM salvage chemotherapy for Hodgkin's and non-Hodgkin's lymphoma. Leuk Lymphoma 1995; 17:139-45.
44. Bobey N, Woodman RC. Neutropenic complications in advanced-stage non-Hodgkin's lymphoma: implications for the use of prophylactic recombinant human granulocyte-colony stimulating factor (G-CSF). Clin Invest Med 1998; 21: 63-70.
45. Tarella C, Castellino C, Locatelli F, Caracciolo D, Corradini P, Falda M, et al. G-CSF administration following peripheral blood progenitor cell (PBPC) autograft in lymphoid malignancies: evidence for clinical benefits and reduction of treatment costs. Bone Marrow Transplant 1998; 21:401-7.
46. Uyl-de Groot CA, Hagenbeek A, Verdonck LF, Lowenberg B, Rutten FF. Cost-effectiveness of ABMT in comparison with CHOP chemotherapy in patients with intermediate- and high-grade malignant non-Hodgkin's lymphoma (NHL). Bone Marrow Transplant 1995; 16:463-70.
47. Garattini L, Grilli R, Scopelliti D, Mantovani L. A proposal for Italian guidelines in pharmacoeconomics. The Mario Negri Institute Centre for Health Economics. Pharmacoeconomics 1995; 7:1-6.
48. Vose JM. Classification and clinical course of low-grade non-Hodgkin's lymphomas with overview of therapy. Ann Oncol 1996; 7 Suppl 6:S13-9.
49. Kimby E, Bjorkholm M, Gahrton G, et al. Chlorambucil/prednisone vs. CHOP in symptomatic low-grade non-Hodgkin's lymphomas: a randomised trial from the Lymphoma Group of Central Sweden. Ann Oncol 1994; 5 Suppl 2:S67-71.
50. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002-6.
51. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998; 339:21-6.
52. Zagonel V, Babare R, Merola MC, Talamini R, Lazzarini R, Tirelli U, et al. Cost-benefit of granulocyte colony-stimulating factor administration in older patients with non-Hodgkin's lymphoma treated with combination chemotherapy. Ann Oncol 1994; Suppl 2:127-32.

Appendix
Sources for unit cost data.

1. Dranitsaris G, Altmayer C, Quirt I. Cost-benefit analysis of prophylactic granulocyte colony-stimulating factor during CHOP antineoplastic therapy for non-Hodgkin's lymphoma. Pharmacoeconomics 1997; 11:566-77.
2. Jacobs P, Bachynsky J. Working Paper Series. Institute of Pharmacoeconomics; 1997. p. 97.
3. Dranitsaris G, Phillips P, Rotstein C, Puodziunas A, Shafran S, Garber G, et al. Economic analysis of fluconazole versus amphotericin B for the treatment of candidemia in non-neutropenic patients. Pharmacoeconomics 1998; 13:509-18.
4. PPS Pharma Publications. Moncton NB: Total Pricing Systems Inc., 1998 [fludarabine]; Ontario Ministry of Health. Drug Benefit Formulary/Comparative Drug Index, No. 35. Queen's Printer for Ontario: Toronto, 1996 (27 August 1997 update) [all other products]. Wholesaler and retail pharmacy margins were deducted.
5. Kassenärztliche Vereinigung Südbaden, 1997
6. Rote Liste, wholesaler and retail pharmacy margins were deducted.
7. Aggiornamento della tariffe delle prestazioni di assistenza ospedaliera, Ministero della Sanità, Gazzetta Ufficiale dell, 8 Settembre 1997, DRG 404.
8. Servizio Sanitario Nazionale, 1997.
9. Prestazioni di assistenza specialistica ambulatoriale erogabili nell'ambito del Servizio Sanitario Nazionale e relative tariffe, 1996.
10. L'Informatore Farmaceutico, 1997 (for inpatients a 50% reduction on the public price was included according to Italian regulation).

Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Paolo G. Gobbi, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Prof. Gobbi and the Editors. Manuscript received January 26, 2000; accepted May 23, 2002.

What is already known on this topic

Very few economic studies are available in literature on the costs of treating patients with indolent lymphomas.

What this study adds

The authors found that higher costs are related to the inpatients treatment setting and to the management of adverse clinical events occurring during treatment, while drug acquisition accounts for less than half of the whole treatment costs.

Potential implications for clinical practice

The work offers interesting data for the recurrent reanalyses we are compelled to do of our treatment strategies under the point of view of the cost/benefit ratio.

Paolo G. Gobbi, Deputy Editor