Costs of Drug Delivery for CHOP, COP/CVP, and Fludarabine: An International Assessment

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ABSTRACT

Objectives: The purpose of this analysis was to assess the real-life direct costs of drug delivery for frequently used chemotherapeutic regimens in patients with relapsed low-grade non-Hodgkin’s lymphoma (NHL).

Methods: This was a retrospective analysis of direct costs of drug delivery (acquisition plus administration) of relapsed low-grade NHL in 424 patients in Canada, Germany, and Italy. Results were expressed as an average treatment cost per patient for six cycles of chemotherapy. Exchange rates used were $1 (Canada) = € 0.672, 1 DM (Germany) = € 0.511, and 1 Lit (Italy) = € 0.000517.

Results: Direct costs of drug delivery were greater for inpatients receiving fludarabine (Canada € 12,669; Italy € 13,027) than for CHOP (Canada € 7856; Germany € 7218; Italy € 4251) or COP/CVP (Canada € 7360; Germany € 8449). Treatment administration setting was a major cost driver with inpatient treatment up to 9-fold more expensive than the same regimen given to outpatients. Drug administration costs comprised the largest proportion of the total for each regimen in the inpatient setting (69–98%). Costs of drug delivery in the outpatient setting were 10% to 65% of those in the inpatient setting. Again, fludarabine was more expensive (Italy € 8493; Canada € 7269) than CHOP (Canada € 4403; Germany € 2150; Italy € 1264) and COP/CVP (Canada € 3009; Germany € 867). Administration costs were 2.5- to 15-fold higher for inpatients compared to outpatients.

Conclusions: Costs of drug administration are a major driver for total direct treatment costs in the treatment of relapsed low-grade NHL and are at least as important as drug acquisition costs. Drug administration practices, in terms of inpatient or outpatient treatment, are a major factor in determining overall direct costs. Therapeutic strategies, which offer shortened treatment duration and/or a simple mode of administration, are likely to be economically attractive.

Keywords: CHOP, COP, cost analysis, CVP, drug delivery, fludarabine, non-Hodgkin’s lymphoma.

Introduction

Non-Hodgkin’s lymphomas (NHLs) are a heterogeneous group of malignancies arising from the uncontrolled proliferation of lymphatic cells. Over the past 30 years, the developed world has seen a substantial increase in the incidence of NHL [1]. Since the early 1970s, the incidence of NHL has increased by approximately 3% to 4% per year [2–4]. In Germany and Italy in 1997, approximately 14 per every 100,000 people of the population were diagnosed with NHL [5]. Higher incidence rates were reported in the United States, with around 53,000 new cases a year or approximately 20 cases in every 100,000 people [6]. The reasons for this increase are as yet unclear although a role for environmental factors, including pesticides, solvents, or dyes, has been postulated [3].

NHLs are most commonly of B-cell origin and can be divided into two main groups according to etiology and response to treatment: low-grade and high-grade. Low-grade B-cell lymphomas are characterized by low proliferate activity and a high proportion of resting cells. Patients have a median survival time of 3 to 8 years from the time of diagnosis during which time serial remissions often occur, gradually decreasing in duration regardless of treatment [6].

Initial management for asymptomatic patients is most commonly a period of “watch and wait” with progression usually being observed within 18 months. After progression, a single alkylating agent such as chlorambucil or an alkyl agent based combination regimen is used in first-line treatment. Response rates as high as 80% have been observed with a median duration of response of 12 to 30 months [7]. Upon subsequent relapse, patients are offered further chemotherapy, typically undergoing several cycles of relapse and therapy.
At present, there is no standard treatment for relapsed low-grade NHL and a range of therapies are available. Some of these are internationally recognized such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and cyclophosphamide, vincristine, and prednisone (CVP/COP), and others are more specific to a particular country, such as dexamethasone, high-dose cytarabine, and cisplatin (DHAP) in France. Recent studies have shown promising results with fludarabine, a purine analog and rituximab, an anti-CD20 antibody with better tolerability compared to chemotherapeutics [8–16].

The range of available treatments for low-grade NHL, many of which show comparable efficacy, mean that economic factors and patient quality of life are particularly important considerations when selecting the best treatment option. However, extensive literature searches have revealed very few published accounts of economic analyses of the direct or indirect costs of NHL, despite the obvious need for such information in many aspects of oncology management [17,18]. An analysis of resource utilization and treatment costs of different schedules (CHOP vs. fludarabine vs. rituximab) for relapsed low-grade NHL in the United Kingdom was published [19]. This study showed that overall treatment costs (exchange rate 1 £ = € 1.598) were higher with fludarabine (€ 15,895) than CHOP (€ 11,435) or rituximab (€ 9,642), which was associated with significantly fewer adverse events and therefore lower total cost per patient.

The purpose of this analysis was to summarize the direct costs of drug delivery for patients with relapsed low-grade NHL in Canada, Germany, and Italy. It provides the first economic data on treatment patterns and resource use for drug delivery in the treatment of relapsed low-grade NHL across different countries and identifies the main cost components for each regimen.

**Methods**

**Design**

This was a retrospective analysis of the direct costs of drug delivery of relapsed low-grade NHL in patients. Information was collected from specialists in all three countries by telephone interviews to identify the most frequently used treatment regimens. Case record forms (CRFs) were completed retrospectively to collect clinical and resource utilization data based on information from patient records.

**Data Collection**

A total of 91 telephone interviews with oncologists, hematologists, or lymphoma specialists were conducted to determine the most commonly used treatment regimens for relapsed low-grade NHL in Canada (31 specialists), Germany (30 specialists), and Italy (30 specialists). An independent market research company (ISIS Research, UK) performed interviews by using native language speakers and a set questionnaire. At the start of each interview, determining that the interviewees either specialized in lymphoma management or ran a hospital lymphoma clinic and treated 10 or more patients with relapsed low-grade NHL per year assessed eligibility. Eligible specialists were then asked which treatment regimens were most commonly used to treat the condition and the number of patients receiving each regimen.

In a second step, CRFs designed to obtain retrospective data from patient records were sent to 179 eligible specialists. Each CRF recorded information on resource utilization for drug delivery, that is, inpatient visits, outpatient visits, and routine diagnostic tests from a single cycle of chemotherapy (typically, the studied regimens comprised six cycles of chemotherapy). Patients who stayed in the hospital for at least one night for drug administration were considered to be inpatients and all others were defined as outpatients. Data were collected from patients with relapsed low-grade NHL treated after 1990 and receiving treatment with one of the selected regimens chosen on the basis of most common usage in each country. No further criteria for patient sampling were employed. Mailing and collection of CRFs was performed by an independent market research organization to maintain confidentiality. Recruitment of 50 patients per treatment group and country was targeted.

Eighty-nine of 179 specialists (Canada 50, Germany 20, and Italy 19) returned completed retrospective CRFs providing data on 424 patients in total (Canada 173, Germany 99, and Italy 152). In Canada, the number of available patients was comparable for all three treatment regimens (CHOP 57, COP/CVP 56, and fludarabine 60) (Table 1). Data from a similar number of patients for CHOP and COP/CVP were available from Germany (CHOP 48 and COP/CVP 51) and, from Italy, data were provided for 70 patients on CHOP and 82 on fludarabine.

**Cost Calculations**

Costs for each selected regimen were calculated from the perspective of a third-party payer based on
1997 costs. The cost per patient of a single cycle of chemotherapy was calculated for each country. Unit costs were estimated from several different sources in each country including previously published economic studies, published price lists and national and regional information sources [20–30]. For Italy, the mandatory 50% reduction for drugs in hospitals was considered. Each cycle was assumed to be representative of the whole course of treatment for each patient and results were expressed as an average direct cost of drug delivery per patient for a complete course of chemotherapy (six cycles). Average costs per patient were calculated in both the inpatient and outpatient settings.

Direct costs of drug delivery were calculated as the sum of the drug administration costs and the cost of drugs used in the regimen (drug acquisition). Drug administration costs included both outpatient visits and hospitalizations for administration of the drug regimen, plus all routine diagnostic procedures (e.g., blood counts).

Results

Treatment Regimens
Fifteen different therapies were identified as being used to treat relapsed low-grade NHL in Canada, Germany, and Italy. Specialists in Canada most commonly cited COP/CVP followed by CHOP (20 of 31) and fludarabine (18 of 31). In Germany, CHOP and COP/CVP were used most often (both 14 of 30 specialists). The most commonly used treatment regimens by specialists in Italy were CHOP (14 of 30) and fludarabine (13 of 30).

Based largely on the highest levels of usage in each country, CHOP, fludarabine, and COP/CVP were selected for economic analysis in Canada, CHOP and COP/CVP in Germany, and CHOP and fludarabine in Italy.

Patient Characteristics
The sex and average age of patients in the study was comparable across treatment regimens and countries (Table 1). The average number of previous treatments was also comparable between the treatment regimens and countries. Overall, there were very few notable differences between treatment regimens and stage of disease. However, patients treated with fludarabine in Canada or COP/CVP in Germany were less likely to be in Stage IV of their disease than patients in their respective countries treated with other regimens.

Most of the patient treatment cycles reported by the specialists occurred both early (first or second) and late (fifth or sixth+) in a treatment course, such that the data collected may be considered to be a reasonable representation of the “average” cycle. The estimated direct costs of drug delivery were therefore assumed to represent those of an average treatment cycle.

Direct Costs of Drug Delivery of Different Regimens
Unit costs were comparable between countries with the exception of costs for outpatient visits, which were highest in Canada (Table 2). They were used to calculate total direct costs of drug delivery for relapsed low-grade NHL in inpatients and outpatients in Canada, Germany, and Italy (Fig. 1). In the inpatient setting, overall costs of CHOP and COP/CVP treatment regimens were comparable within Canada and Germany. Due to the higher number of administrations per cycle, fludarabine treatment was substantially more expensive than CHOP treatment. In the outpatient setting, costs of drug delivery were 10% to 65% of those in the inpatient setting. Due to high drug acquisition costs and a higher number of administration visits per cycle, fludarabine was more expensive than CHOP and COP/CVP.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Stage of disease (%)</th>
<th>Canada</th>
<th>Germany</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>III</td>
<td>23</td>
<td>19</td>
<td>31</td>
</tr>
<tr>
<td>IV</td>
<td>60</td>
<td>58</td>
<td>51</td>
</tr>
</tbody>
</table>

Abbreviation: FLU, fludarabine.
When total costs of drug delivery for each regimen were compared between countries, no one country demonstrated consistently higher costs for disease treatment.

CHOP therapy was most costly in Canada and least expensive in Italy regardless of inpatient or outpatient administration. Indeed, the greatest difference in costs between countries occurred with CHOP.

For both COP/CVP and fludarabine therapy, the differences were less marked. COP/CVP treatment was slightly more expensive in Germany than in Canada for inpatient administration, but the situation was reversed and significantly different for outpatients. The costs of fludarabine treatment in Canada and Italy were comparable for inpatient and outpatient administration.

Cost Drivers
When therapy was given in the inpatient setting, administration costs formed the major cost component for each regimen studied (Table 3). The cost of administration represented 72% to 89% of the total costs of drug delivery for CHOP, 96% to 98% for COP/CVP treatment, and approximately 70% of those for fludarabine. In contrast, the proportion of drug delivery cost for outpatients taken up by administration appeared to be influenced more by country than regimen. In Canada, the administration costs for outpatients was consistently the highest (factor of 4–7) predominantly due to the high unit costs per outpatient visit.

Fludarabine treatment was the most expensive across the three treatment regimens (Table 3). Drug acquisition costs contributed 54% to 91% to the cost of fludarabine treatment in the outpatient setting and contributed approximately 30% of the total cost for inpatient administration. In contrast, drug acquisition represented only 2% to 28% of the total for CHOP and COP/CVP therapy for inpatients.

As expected, total costs for the treatment of inpatients were greater in all situations than for outpatients due to the increased costs of administration. The difference in cost of administration between inpatient and outpatient treatment settings was 10- to 15-fold in Italy and Germany and approximately slightly higher than 2-fold in Canada.

Sensitivity Analysis
A multivariate sensitivity analysis including all relevant variables was conducted to test the robustness of results and conclusions. The numbers of visits (either inpatient or outpatient) and drug acquisition costs were considered to be relatively stable because of defined numbers of administrations in the respective treatment regimes or price lists. These two items were varied between 75 and 125% of the observed values. All other parameters (number and costs of diagnostic tests, costs for outpatient and inpatient visits) were varied between 50 and 200%.

Although absolute costs increased or decreased according to changed assumptions, no major changes in relative costs leading to different conclusions occurred between regimens, treatment settings, or countries when all parameters were set to either minimum or maximum levels (Figs. 2 and 3).

To induce relevant changes the following manipulations were necessary: 1) outpatient treatment for
all regimen became more expensive than inpatient treatment in Canada when costs for outpatient visits were increased to >139% and costs for overnight stays were lowered to 50% compared to baseline; and 2) inpatient treatments with COP/CVP and CHOP in Canada were similar. Therefore, relatively small changes in drug costs or number and costs of visits let one or the other regimen become the cheaper one (reducing drug costs or increasing costs of visits favors CHOP).

No combination of variations of parameters changed the conclusions for Italy and Germany. Excluding costs for drugs and tests for inpatient treatment in Germany (to better reflect the third-party payer perspective) had only a minor impact on the figures and did not notably affect the results.

Discussion

This is the first international analysis of direct costs of drug delivery associated with conventional chemotherapeutic treatment of relapsed low-grade NHL. The results indicate that, irrespective of the country or the regimen used, drug acquisition costs made up less than half of the overall direct costs of drug delivery in the inpatient setting. Administration setting had a major influence on the total cost of treatment. Inpatient administration increased the cost of drug delivery up to ninefold over the same treatment in an outpatient setting. Administration costs comprised the largest proportion of the total for each regimen in the inpatient setting (69–98%). This suggests that potential savings due to a reduction of overnight stays in hospital for administration of chemotherapy would be substantial.

Comparison of direct costs of drug delivery between countries revealed no obvious trends, with the exception of outpatient administration costs. These were much higher in Canada than in the other two countries. This reflects the higher unit costs of an outpatient visit in Canada (€127) than in Germany (€16) or Italy (€26). In contrast, the costs for an inpatient stay in a nonintensive care unit were similar in all three countries (Canada €350; Germany €332; Italy €359). In Germany, a proportion of patients received COP/CVP as a “5-day-COP/CVP” regimen which required five (instead of one) drug administrations per cycle-regimen. This caused the relatively high costs.

![Figure 2](image1.png) Sensitivity analysis of inpatient costs.

![Figure 3](image2.png) Sensitivity analysis of outpatient costs.

Table 3  Breakdown of the average cost per patient into administration (Admin) and drug acquisition (Acq) costs for inpatients and outpatients

<table>
<thead>
<tr>
<th>Regimen/country</th>
<th>Inpatient (€)*</th>
<th>Outpatient (€)*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Admin</td>
<td>Acq</td>
</tr>
<tr>
<td>CHOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>5639</td>
<td>2217</td>
</tr>
<tr>
<td>Germany</td>
<td>5512</td>
<td>1706</td>
</tr>
<tr>
<td>Italy</td>
<td>3781</td>
<td>470</td>
</tr>
<tr>
<td>COP/CVP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>7198</td>
<td>162</td>
</tr>
<tr>
<td>Germany</td>
<td>8088</td>
<td>361</td>
</tr>
<tr>
<td>Italy</td>
<td>3781</td>
<td>470</td>
</tr>
<tr>
<td>Fludarabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>8738</td>
<td>3931</td>
</tr>
<tr>
<td>Germany</td>
<td>9166</td>
<td>3861</td>
</tr>
</tbody>
</table>

*Exchange rates: $1 (Canada) = €0.672; 1 DM (Germany) = €0.511; 1 L italiane (Italy) = €0.000517.
Financial considerations could also affect the management of patients. For example, in some hospitals in Germany reimbursement depends on the patient having an overnight stay; therefore, inpatient administration may be influenced by financial rather than medical reasons. This could account for the relatively high proportion of patients (46–51%) in Germany who received treatment as inpatients (Table 4).

Only one other analysis of the costs of treating relapsed low-grade NHL has been reported to date. This was a retrospective analysis of patient records conducted in the UK and assessed costs for patients treated with CHOP, fludarabine, or rituximab at several treatment centers in a Phase II clinical trial. Interestingly, the overall direct costs of drug delivery for CHOP, COP/CVP, and fludarabine therapy were comparable in the UK study, with those reported in this study for Canada, Germany, and Italy. In addition, although the comparison of chemotherapy and rituximab from different data sources should be treated with caution, the UK study showed total direct treatment costs were comparable for rituximab and CHOP but less than fludarabine. Lower costs for drug administration in combination with the superior tolerability of rituximab offset the higher drug acquisition costs of rituximab.

The telephone survey employed in the first stage of the present study demonstrated the lack of a standardized treatment approach to relapse low-grade NHL within and between the countries studied. This observation is supported by data from the UK published by Sweetenham et al. [19]. The number and variety of regimens employed may well reflect similarities in response rates and remission times among the available therapies and emphasizes the need for new treatment strategies [31]. Indeed, the similarity of response with the regimens investigated here has been well documented [19,32–35] and, in the absence of new treatment strategies, particular emphasis will be placed on tolerability and cost-effectiveness by clinicians when deciding which treatment regimens to use. Therefore, economic studies such as this one may well provide valuable information for the future management of patients with low-grade NHL.

A possible criticism of studies, which use retrospective collection of data using patient records as opposed to data from randomized trials, is that pre-selection bias could be a factor, introduced by the selection of patients for a particular protocol (based on age, stage, response to previous regimen, etc.). However, it could be argued that data collected in retrospective analyses better reflect the real-life situation as a cross-section of patients are assessed as opposed to sequentially enrolled subjects. Indeed, in economic studies such as this, “patient selection” and a closer reflection of the real-life situation may well be more suitable. The use of data from patient records further underlines that the study data reflects the real-life situation.

Some bias in cycle or patient selection may have occurred because the selection of consecutive cases was not specified, nor was the selection of early or late cycles predefined. However, the distribution of patient cycles from the 424 records returned suggests that this was not a major factor, because there was a even distribution of patients undergoing early cycles (cycles 1–3, 48%) and late cycles (cycles 4+, 50%). Similarly, patient characteristics (Table 1) do not show any major imbalances between the groups, and no evidence for patient selection was found.

Patient selection would have been more of a potential issue if outcomes, such as efficacy parameter, had been collected. For the assessment of resource utilization for drug delivery potential patient selection is expected to have limited impact only as drug delivery for the regimens were defined by treatment schedules.

It is generally accepted that studies that draw comparisons between countries should be interpreted with a degree of caution, particularly with respect to factors that are potentially country-specific, such as patient selection criteria or regulations. However, the preparation of a single retrospective CRF for use in all three countries investigated here should, at least in part, address this concern.

**Table 4** Number (%) of patients receiving at least one infusion of the treatment regimen in the inpatient setting (overnight stay in hospital)

<table>
<thead>
<tr>
<th></th>
<th>CHOP</th>
<th>COP/CVP</th>
<th>Fludarabine</th>
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<tbody>
<tr>
<td>Canada</td>
<td>7/57 (12)</td>
<td>8/56 (14)</td>
<td>4/60 (7)</td>
</tr>
<tr>
<td>Germany</td>
<td>22/48 (46)</td>
<td>26/51 (51)</td>
<td>—</td>
</tr>
<tr>
<td>Italy</td>
<td>13/70 (19)</td>
<td>—</td>
<td>31/82 (38)</td>
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</table>

**Conclusion**

This study shows that drug administration costs are a major driver for total direct costs of drug delivery in the treatment of relapsed low-grade NHL and are at least as important as drug acquisition costs. Drug administration practices, in terms of treatment inpatient or outpatient treatment, are a major factor in determining overall direct costs.
peutic strategies, which offer shortened treatment duration and/or a simple mode of administration, are likely to be economically attractive.

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