R-CHOP VS. CHOP: A COST-EFFECTIVENESS ANALYSIS on Aggressive Non-Hodgkin's Lymphoma (NHL)

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Introduction

The most common type of non-Hodgkin's lymphoma (NHL) is diffuse large B-cell lymphoma (DLCL) which accounts for almost 40% of new cases of lymphoma. More than half of patients with DLCL are over 60 years of age and chemotherapy in this age group can be challenging due to toxicity and comorbid medical issues. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) is the standard treatment for younger and elderly patients with diffuse large-B-cell lymphoma, but it induces complete responses in only 40 to 50 percent of elderly patients, with three-year event-free and overall survival rates of 30 percent and 35 to 40 percent, respectively. Attempts to increase the efficacy of CHOP by adding other cytotoxic drugs have not succeeded, probably because these additional drugs cannot be administered unless the doses of cyclophosphamide and doxorubicin are reduced below those given in the CHOP regimen. Intensified chemotherapy regimens may improve the outcome in young patients with a poor prognosis, but they are not well tolerated by elderly patients. Indeed, CHOP itself may be too toxic for elderly patients.

The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) is the standard treatment for younger and elderly patients with diffuse large-B-cell lymphoma, but it induces complete responses in only 40 to 50 percent of elderly patients. The benefit of adding Rituximab (R) – a chimeric anti-CD20 IgG1 monoclonal antibody, to CHOP was observed among patients with relatively low risk disease or high risk disease. In comparative studies of CHOP and R-CHOP, the rate of complete response was significantly higher in the group that received R-CHOP than in the group that received CHOP alone. In several EU countries there are cost-effectiveness studies regarding the treatment of aggressive NHL with CHOP vs. R-CHOP, but in Romania there is no such a study done.

The authors used a cost-effectiveness model where they compared the costs of both type of treatments and the benefits expressed in gained years of life, in order to have the Romanian perspective for the economic evaluation of treatment of aggressive NHL with CHOP vs. R-CHOP. The Romanian cost-effectiveness analysis is based on a model developed by Best et al. which calculates the cost-effectiveness ratio of R-CHOP vs. CHOP over time horizon of 10 years for patients with diffuse large B-cell lymphoma DLCL. The analysis was done based on local Romanian costs and the clinical benefits from the GELA study.

Rituximab administered together with CHOP gives patients an increased chance of cure, a significantly superior survival and represents a cost-effective therapy compared to standard treatment with CHOP. When costs and survival benefits are considered over 10 years, the additional cost per patient on R-CHOP is 12,929 Euro. Over a 10 years time frame, the estimated survival benefit of R-CHOP compared to standard CHOP treatment alone in this group of patients is on average 0.60 extra years of life gained per patient. The estimated additional cost per extra year of life gained for the combination therapy is 21,549 Euro.

Using the same cost-effectiveness model we observed that using R-CHOP vs. CHOP we obtained in Romania the lowest cost per additional year of life gained compared with France or United Kingdom.

Keywords: cost-effectiveness analysis, cost per life year gained, NHL non-Hodgkin lymphoma

More easily tolerated regimens have been designed for elderly patients, but although they cause fewer side effects, they are less effective and no more beneficial than CHOP. Rituximab (R), a chimeric anti-CD20 IgG1 monoclonal antibody, is effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and has activity in relapsed or refractory diffuse large-B-cell lymphoma.

CD20 is a cell-surface protein that occurs almost exclusively on mature B cells. The chimeric antibody is a human IgG1 in which the CD20-binding region was derived by genetic engineering from a mouse monoclonal antibody. On the basis of phase 2 studies in which Rituximab in combination with CHOP had a good safety profile and induced...
responses in over 90 percent of patients with indolent or aggressive lymphoma, the Groupe d’Etude des Lymphomes de l’Adulte (GELA) undertook a study to compare CHOP plus Rituximab with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

The benefit of adding Rituximab to CHOP was observed among patients with relatively low risk disease or high risk disease according to the International Prognostic Index (IPI). Treatment with R-CHOP was well tolerated – the incidence of severe or serious adverse events was no different from that in the CHOP group. In comparative studies of CHOP and R-CHOP, the rate of complete response (CR + CRu) was significantly higher in the group that received R-CHOP (76%) than in the group that received CHOP alone (63%) (p=0.005). With a median follow-up of 2 years, event-free survival and overall survival times were statistically significantly higher in the R-CHOP group.

**Metodology**

In several EU countries there are cost-effectiveness studies regarding the treatment of aggressive NHL with CHOP vs. R-CHOP (Rituximab plus CHOP). The treatments are standardized and the data from France and United Kindom are available, but in Romania there is no such a study done.

The authors used a cost-effectiveness model where they compared the costs of both type of treatments and the benefits expressed in gained years of life, in order to have the Romanian perspective for the economic evaluation of treatment of aggressive NHL with CHOP vs. R-CHOP.

The Romanian cost-effectiveness analysis is based on a model developed by Best et al. which calculates the cost-effectiveness ratio of R-CHOP versus CHOP over time horizon of 10 years for patients with diffuse large B-cell lymphoma DLCL (Best J, et al. Cost-Effectiveness of Rituximab in Treatment of Diffuse Large B-cell lymphoma. International Society for Pharmacoeconomics and Outcomes Research 2002; Abstract, French Cost-Perspective). The analysis was done based on local Romanian costs and the clinical benefits from the GELA study, a randomized-controlled trial comparing R-CHOP with CHOP done in France, Belgium and Switzerland on 399 patients, from 1998-2000.

The two alternatives considered were:

- Patients treated with CHOP received the combination of 750 mg of cyclophosphamide per square meter of body-surface area on day 1; 50 mg of doxorubicin per square meter on day 1; 1.4 mg of vincristine per square meter, up to a maximal dose of 2 mg on day 1; and 40 mg of prednisone per square meter per day for five days. They were treated every three weeks for eight cycles of CHOP;
- Patients treated with CHOP plus rituximab also received rituximab, at a dose of 375 mg per square meter, on day 1 of each of the eight cycles of CHOP.

In the randomized-controlled trial, patients (n=399) were eligible if age 60-80 years, had stage II-IV DLCL, and had ECOG performance status of 0-2. Mean patient survival in each treatment arm and chemotherapy costs during treatment (q3 weeks x 8 cycles) were estimated from trial data.

The longest duration of follow-up was 34 months. We estimated survival and cost-effectiveness up to a time horizon of 10 years. Survival for each IPI strata was estimated using the Kaplan-Meier method; survival after the longest observed time in the trial was estimated using published mortality rates (Shipp, NEJM, 93). Monte Carlo simulation was conducted to estimate the uncertainty in survival and cost-effectiveness.

R-CHOP increased survival from 56% to 63% at the time of last follow-up (34 months). The mean duration of survival was 820 days for R-CHOP and 721 days for CHOP, resulting in a mean increase in survival of 0.27 years. Extrapolating to 10 years, R-CHOP is projected to increase mean survival by 0.6 years per patient.

The perspective is from the third-payer agency (National Health Insurance House and Ministry of Health which cover the National Program for Oncology). The results in this analysis were obtained using software which considered the following assumptions:

- The costs involve treatment costs and post-treatment costs (surveillance)
- Unit costs for drugs, cost of hospitalization days, post-treatment costs, and the number of chemotherapy cycles used, are based on Romanian values
- Treatment costs means:
  - Drug acquisition – the maximum prices from Romanian drugs list approved by the Ministry of Health in July 15, 2008, to be used within the Romanian National Health Programs, including the National Program for Oncology. The medication costs for CHOP, based on a currency exchange rate of 3.7 lei/Euro (2008) are 487 Euro, and for R-CHOP the medication costs are 13.291 Euro;
  - Hospitalization. Resource use for hospitalization costs are taken from data published by the National Health Insurance House (NHIIH) from Romania for year 2008 at Oncology Institute from Bucharest, and are calculated on a per diem of 13 Euro for <24 hours and 60 EURO for >24 hours;
Table 2. Summary of costs for CHOP vs. R-CHOP

<table>
<thead>
<tr>
<th>TIP COST</th>
<th>CHOP</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug costs</td>
<td>487</td>
<td>13,291</td>
</tr>
<tr>
<td>Hospitalization costs</td>
<td>1,062</td>
<td>930</td>
</tr>
<tr>
<td>Post-treatment surveillance</td>
<td>1,799</td>
<td>2,056</td>
</tr>
<tr>
<td>Total costs</td>
<td>3,348</td>
<td>16,277</td>
</tr>
</tbody>
</table>

Results per patient

Rituximab administered together with CHOP gives patients an increased chance of cure, a significantly superior survival and represents a cost-effective therapy compared to standard treatment with CHOP.

When costs and survival benefits are considered over 10 years, the cost of treating an elderly patient with diffuse large-B-cell lymphoma (DLCL) is:
- 3,348 Euro for patients on CHOP;
- 16,277 Euro for patients on R-CHOP.

This equates to an additional cost per patient on R-CHOP of 12,929 Euro, and the aggregated costs (in Euro) obtained for each of the two arms CHOP and R-CHOP are presented in Table 2.

Over a 10 years time frame, the estimated survival benefit of R-CHOP compared to standard CHOP treatment alone in this group of patients is on average 0.60 extra years of life gained per patient. The estimated additional cost per extra year of life gained for the combination therapy is 21,549 Euro over 10 years.

R-CHOP remained cost effective over wide ranges of variables in sensitivity analyses, and the results were identical even for a lower discount rate for costs of only 3%.

Table 1. The content and tariffs for the post-treatment surveillance in patients with DLCL treated with CHOP or R-CHOP (1 Euro =3.70 lei)

<table>
<thead>
<tr>
<th>No.</th>
<th>Services</th>
<th>Volumes/year</th>
<th>Total Euro</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HLG</td>
<td>6</td>
<td>21.2</td>
</tr>
<tr>
<td>2</td>
<td>LDH</td>
<td>6</td>
<td>11.6</td>
</tr>
<tr>
<td>3</td>
<td>Uric Acid</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>C Reactive Protein</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>5</td>
<td>CT Thorax</td>
<td>2</td>
<td>151.6</td>
</tr>
<tr>
<td>6</td>
<td>CT Abdomen</td>
<td>2</td>
<td>153.2</td>
</tr>
<tr>
<td>7</td>
<td>CT Pelvis</td>
<td>2</td>
<td>143.6</td>
</tr>
<tr>
<td>8</td>
<td>Bone marrow aspiration</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>9</td>
<td>Citodiagnostic</td>
<td>1</td>
<td>8.1</td>
</tr>
<tr>
<td>10</td>
<td>Control Visit</td>
<td>6</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>Total monitoring 1 year</td>
<td>-</td>
<td>514.2</td>
</tr>
</tbody>
</table>

⇒ The number of hospitalization days for each treatment was considered from the original study as follows18:
- Day-hospitalization: an average per patient of 16.43 for CHOP and 14.41 for R-CHOP;
- Continuous-hospitalization: an average per patient of 6.04 for CHOP and 5.14 for R-CHOP.
- The cost of post-treatment surveillance is based on an annual cost of 514 EURO and is based on the NHIH reimbursed tariffs for year 2008 (table 1);
- Cost has been discounted at a rate of 6.0% and no discount rate was used for survival years.

CHOP (Cyclophosphamide, Doxorubicin, Vincristine și Prednisone); R (Rituximab)
Using the same methodology and software, the results obtained in France and United Kingdom were as follows:

- In France: The additional cost per patient on R-CHOP was 15.270 Euro and the estimated additional cost per extra year of life gained was 28,410 Euro\(^9\).
- In United Kingdom: The additional cost per patient on R-CHOP was 12.579 Euro and the estimated additional cost per extra year of life gained was 22,437 Euro\(^20\).

**Conclusions**

R-CHOP increases chance of cure compared with CHOP and is cost-effective compared with other treatments in widespread use.

Even if in Romania the standard treatment is cheaper than in other EU countries, the cost-effectiveness ratio compares favorably with other oncology treatments in wide use.

Using the same cost-effectiveness model we observed that using R-CHOP vs. CHOP we obtained in Romania the lowest cost per additional year of life gained compared with France or United Kingdom.

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**References**