

Cost - Effectiveness Analysis by Adding Rituximab in the Treatment of Diffuse Large B - Cell Lymphoma

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ABSTRACT

Objectives: To determine cost-effectiveness of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) compared with R-CHOP (CHOP plus Rituximab) in adult patients with diffuse large B-cell lymphoma, in a Greek Academic Hospital.

Patients and methods: The control group consisted of 65 consecutive patients, observed from 1992 to 1999 and received CHOP chemotherapy. The study group consisted of 44 consecutive patients, observed from 2006 to 2011 and received R-CHOP chemotherapy. Overall survival and direct medical cost were estimated for both interventions. Clinical data from Coiffier study were used to calculate Incremental Cost-Effectiveness Ratio per life years gained (LYGs) and life years gained free from progression disease (PFYs).

Results: Overall survival rose from 50% to 72% after 5 years with the addition of Rituximab to CHOP therapy. Total cost of R-CHOP treatment was calculated at and €23,882 and at €6,909 for CHOP. Incremental cost-effectiveness ratio formatted at €3,394 for R-CHOP and €1,381 for CHOP per LYG and at €3,935 for R-CHOP and €12,470 for CHOP per PFY, with 5 and 3.6 years survival benefit in favor of R-CHOP, retrospectively.

Conclusion: Even though Rituximab increases total, direct cost of treatment, cost effectiveness analysis indicates that R-CHOP is clinically and economically effective.

Keywords: CHOP, cost-effectiveness analyses, diffuse large B-cell lymphoma, health economics, non-Hodgkin's lymphoma, rituximab.

INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of diseases that derives from lymphocytes, with increasing incidence in the developed world (Weisenberger 1992). NHL account for 4% of all newly diagnosed cancers, placing them at the fifth most common cancer diagnosis and cause of cancer death (Jemal et al. 2004).

The incidence in the general population is 15 cases / 100,000 of population per year (Cancer Mondial 2008). During 2008, 66,120 new cases of NHL (35,450 males and 30,670 females) were diagnosed in the U.S., while the National Cancer Institute estimates that incidence will rise in coming years (Surveillance Epidemiology and Ends Results 2008).

The most common type of NHL is Diffuse Large B-cell Non-Hodgkin Lymphoma (DLBCL), representing 35% - 40% of all NHL, (Coiffier 1997) while the median age at presentation is 65 years (NHL classification project 1997, International NHL Prognostic Factors Project 1993). Only one-third of patients are diagnosed in the early stages of the disease while the majority presents with advanced stage disease (Gaynor, and Fisher 2000).

DLBCL is an aggressive tumor with median survival of less than one year in untreated patients (Fisher, Miller, and O' Connor 2004). CHOP regimen, which developed at 70s, was the gold standard of treatment for decades (Fisher et al. 1993, McKelvey et al. 1976). The most important achievement in the treatment of NHL in the last 20 years was the development of monoclonal antibody Rituximab, which recognizes CD20 antigen, a significant protein expressed on the surface of almost all normal and neoplastic B-lymphocytes. The cytotoxic activity of Rituximab is mediated through different mechanisms, such as: i) complement mediated cytotoxicity (CDC), ii) antibody dependent cellular cytotoxicity (ADCC), and iii) direct activation of apoptosis (Cartron et al. 2004, Coiffier et al. 1998).

A randomized study by Coiffier et al, (2002) in patients over 60 years with DLBCL demonstrated increased complete response (CR) from 63% to 76% and overall survival (OS) from 57% to 70% after two years follow up with the addition of Rituximab to CHOP chemotherapy. Another study the MabThera International Trial (MINT), (Pfreundschuh et al. 2006) showed that the R-CHOP regimen was associated with higher rates of CR and significant increase in OS, when compared to CHOP alone, in young patients with DLBCL.

Introduction of Rituximab in current clinical protocols resulted in significant increase in the absolute financial cost of treatment. Global financial crisis resulted in an increased interest in cost effectiveness analysis of various treatments. The aim of our study was; to explore the cost-effectiveness of Rituximab, using the principles of economic theory in adult patients with DLBCL.

MATERIAL AND METHODS

Patients

The study group consisted of 44 consecutive patients with previous untreated DLBCL treated during a 5-year time period (2006 – 2011) in the Hematology Division of 2nd Dept of Internal Medicine, "ATTIKON" General University Hospital, Medical School, University of Athens. All patients in study group received treatment with R-CHOP.

The control group consisted of 64 consecutive patients with previous untreated DLBCL treated during years 1992 – 1997 in the same department (Tsirigotis et al. 2001). All patients in control group received treatment with CHOP. Detailed characteristics of both groups of patients are shown in Table 1.

Treatment schema

Patients (control group) treated with CHOP received Cyclophosphamide 750mg/m² iv, Adriamycin 50mg/m² iv, Vincristine 2mg (total dose) iv, and Prednisolone 50mg/m² per-os daily X five days. Patients underwent 1 cycle of treatment every 3 weeks, for a total of 8 cycles.

Patients (study group) treated with R-CHOP, received standard CHOP in the same doses as patients in control group. Rituximab was administered at a dose of 375mg/m² iv, on day 1 of each of the 8 cycles, for a total of maximum 8 doses.

Supportive care

Supportive care was similar in both groups and consisted of i) antiemetics, ii) granulocyte colony-stimulating factor (G-CSF) and iii) antibiotics. Supportive care administration was based on our institution guidelines and protocols. In more detail antiemetics (Ondansetron or similar) were administered one day before, at the day of treatment and one day after treatment for prevention of chemotherapy induced nausea and vomiting. On day +12 after each cycle of chemotherapy blood sample was taken from all patients for FBC assessment. Patients with neutropenia (ANC below 1X10³/Bl, on day +12) received G-CSF. The number of G-CSF doses was at the discretion of the treating physician. No patient in the control group (CHOP) received any kind of prophylactic antibiotics. Patients in study group (R-CHOP) received acyclovir per-os for prevention of herpes-zoster. Patients with febrile neutropenia were usually managed as outpatients by administration of broad spectrum antibiotics (usually a combination of amoxicillin/clavulanate plus ciprofloxacin) given per-os. Patients with hemodynamic instability or other signs of severe sepsis were treated as inpatients.

Definitions and assessment of treatment outcome

Overall survival- (OS) was defined as the time from the start of induction treatment until death from any cause or last follow-up. Progression free survival (PFS) was

defined as the time from the start of induction treatment until progression of lymphoma, or last follow-up. Treatment outcomes were classified according the International Workshop Criteria (Cheson et al. 1999).

Patients follow up was consisted of clinical and routine laboratory examination every 21 days and before administering the next cycle of chemotherapy. Complete restaging with total body CT-scans was performed after the end of the 3rd cycle and at the end of chemotherapy. Patients who achieved complete remission (CR) at the end of chemotherapy were then followed every 4 months for the 1st year and every 6 months for the 2nd and 3rd year from the end of treatment. Re-evaluation consisted of clinical and routine laboratory examination, as well as of total body CT-scans. Patients in study group (R-CHOP) underwent PET-CT scan at the end of chemotherapy to confirm complete remission of lymphoma. Patients with less than partial remission (PR) at the end of 3rd cycle or less than CR at the end of treatment were considered as treatment failure, first line treatment was discontinued and salvage treatment was administered.

Economic evaluation

The average absolute financial costs were estimated taking into consideration the prices of year 2006. Financial data were collected from Financial Agency

of "ATTIKON" General University Hospital, through the database of the Hospital's Information System.

Study Group (R-CHOP): Total cost of induction treatment for each of the 44 patients was estimated by taking into consideration: 1) the cost of drugs administered including chemotherapy agents, Rituximab, antiemetics, antibiotics, growth factors, etc., 2) the cost of laboratory examinations including CT-scans, hematological, biochemistry, microbiological work-out, etc., and 3) cost for day care clinic or for any hospitalization for management of a serious complication (most usually infection). The cost for PET-CT scan was excluded from the study as it didn't occur in the Hospital.

All costs were calculated individually for each patient. Total sum divided by 44 was equal to average absolute cost for 8 cycles of R-CHOP.

Control group (CHOP): was estimated as the cost of Study group minus the cost of Rituximab.

Statistical methods

To compare the clinical characteristics and prognostic factors between the 2 groups of patients (CHOP versus R-CHOP), the Fischer exact test method was used. To study and design the curve of OS and PFS, Kaplan-Meier method and Weibull distribution fitting were used. Values with $p < 0.05$ indicate statistical significance.

Table 1.

Patients characteristics: Control group consisted of 64 patients treated with CHOP. Study group consisted of 44 patients treated with R-CHOP (data from "ATTIKON" General University Hospital)

	CHOP	R-CHOP	p value
Age, mean	59	57	n.s
LDH			
Normal	37/64	25/44	n.s
above normal	27/64	19/44	
Stage			
I & II	37/64	31/44	n.s
III & IV	27/64	13/44	
Sites of Extranodal involvement			
<2	56/64	41/44	n.s
>2	8/64	3/44	
Performance Status (WHO)			
0,1	56/64	41/44	n.s
>2	8/64	3/44	
IPI			
Median, (range)	1 (0-5)	1(0-4)	n.s

IPI: International Prognostic Index

To compare the survival of different groups, the log-rank method was used. For the statistical analysis and graphics, the software: Medcalc version 11.6 and NCSS 2007 were used.

Cost – Effectiveness analysis

Cost – effectiveness analysis (CEA) compares both the financial cost and the therapeutic benefit of two alternative treatment modalities. Financial cost is presented in the form of monetary units, such as Euro (€), whereas therapeutic benefit is presented in the form of years of life gained (LYG) or life years free from disease progression (PFY) (Phillips and Thompson 2001). The results of CEA are usually expressed in the form of incremental cost-effectiveness ratio (ICER) where the denominator is the difference in the benefit (LYG, PFY) and the numerator is the difference in the costs of the two therapeutic procedures. In other words, ICER is an expression of the additional cost required for each additional unit of clinical benefit gained (Gold et al. 1996).

However, it is reasonable when try to estimate the cost of a given treatment to take into account also other subsequent treatment modalities that will be administered in patients who will fail to respond to first line treatment. Therefore, in an attempt to improve the accuracy of our results, we repeat our analysis by extrapolating absolute treatment costs collected from our hospital to data derived from LNH-98.5 trial performed by Coiffier et al. (2010).

RESULTS

1. Cost Effectiveness using data from “ATTIKON” General University Hospital

1.1 The effect of Rituximab on treatment outcome

The following prognostic variables were included in statistical analysis: i) age, ii) LDH, iii) number of extranodal sites involvement, iv) disease stage, v) performance status, and vi) IPI score. No statistically significant difference was observed between study and control group. Detailed comparison of the two groups is shown in Table 1. Thirty-four out of 44 (77%), and 48 out of 64 (75%) achieved CR after induction treatment in R-CHOP and CHOP group respectively. Response rates were not statistically different between the two groups (data not shown).

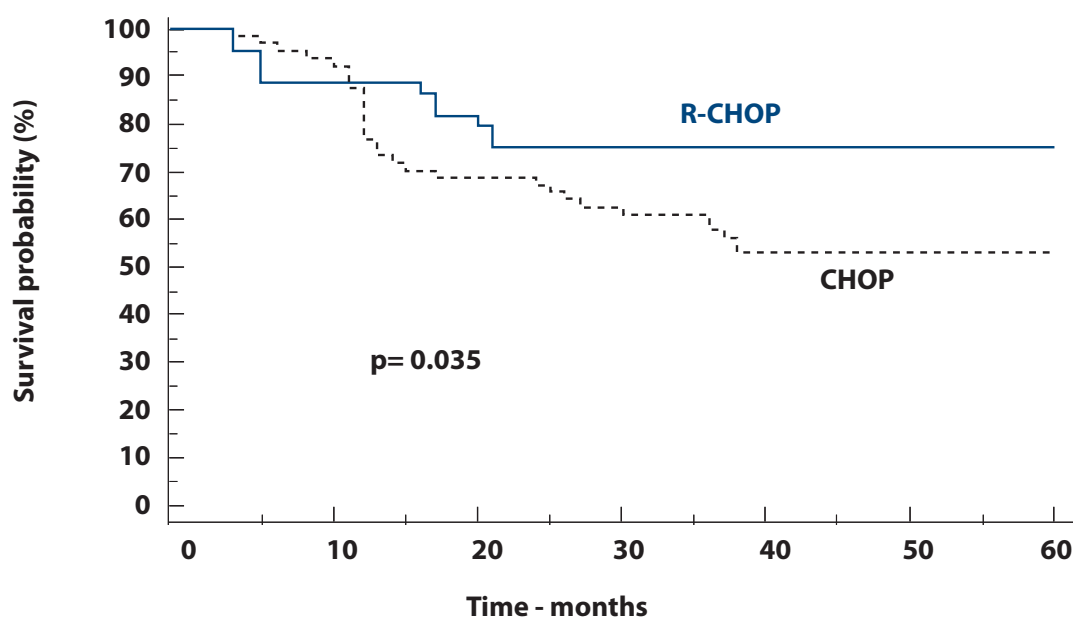
Administration of Rituximab resulted in improvement of overall survival. OS at 5 years was 72% and 50% in R-CHOP and CHOP group respectively, and this difference was statistically significant ($p=0.035$, Figure 1).

In multivariate analysis, treatment with R-CHOP was the only variable associated statistically with significantly increased probability of overall survival [OR=2.05, 95% CI (1.03 to 4.08), $p=0.04$].

1.2 Estimation of median survival

Control group: median survival was 60 months (Figure 1). Study group: median survival was not reached yet. Therefore extrapolation of survival time and estimation of Weibull survival curve was performed using the

Figure 1. Overall survival of patients with DLBCL: R-CHOP group (44 patients) and CHOP group (64 patients).



NSCC software. Estimated median survival for patients in study group was 120 months (Figure 2).

1.3 Estimation of absolute financial costs of first line treatment

The absolute average cost for 8 cycles of CHOP and R-CHOP, including chemotherapy drugs, supportive care treatment, laboratory evaluations including CT-scans was estimated at €6,909 and €23,882 respectively.

1.4 Estimation of Incremental Cost Effectiveness Ratio in Life Years Gain

DLBCL are highly aggressive tumors and median survival is measured in weeks or months in untreated patients. Cost is measured in Euro, while effectiveness in health technology assessment is usually expressed in gained years of life (LYGs).

The median number of gained years of life years (LYGs) in patients treated with CHOP was 5 years. The average cost for 8 cycles of CHOP has been estimated at €6,909. Therefore the estimated Incremental Cost-Effectiveness Ratio (ICER) for CHOP is €1,381 per LYG.

The median number of LYG in patients treated with R-CHOP was 10 years, while the average cost for 8 cycles of R-CHOP has been estimated at €23,882. The difference in the cost between CHOP and R-CHOP is €16,973 while the net benefit is 5 LYG. Therefore the estimated ICER for R-CHOP is €3,394 per LYG (Table 2).

2. Cost Effectiveness using data from "LNH-98.5" trial

2.1 Extrapolation of absolute costs at "ATTIKON" to data from "LNH-98.5" trial

In the previous we applied our financial analysis only to first line treatment of patients with DLBCL. Although it seems that the addition of Rituximab to standard CHOP adds significant therapeutic benefit at a minimal increase in cost, we consider that this analysis in fact underestimates the real ICER of R-CHOP, because we did not take into account the costs of salvage treatments administered in patients who failed to respond to induction treatment.

In order to analyze CEA of R-CHOP more accurately we constructed a Markov state-transition model with 4 health states [continued complete remission (CCR),

Table 2
Incremental Cost Effectiveness Ratio in gained Life Years.
CHOP vs. R-CHOP ("ATTIKON" General University Hospital)

Intervention	Cost	Marginal cost	Effectiveness effectiveness	Marginal	CE ratio
No Treatment	0	-----	0 years	-----	-----
CHOP	€6.909	€6.909	5 years	5 years	€1.381/LYG
R-CHOP	€23.882	€16.973	10 years	5 years	€3.394/LYG
Incremental cost effectiveness ratio (ICER)= cost A minus cost B/benefit A minus benefit B: $22.349€ - €6.909 = €16.973 / 10 - 5 \text{ LYGs} = €3.394 \text{ per LYG-year saved life}$					

Table 3.
Number of events observed in the CHOP and R-CHOP arms
after a 10-year median follow-up period. LNH-98.5 trial

Type of event	CHOP	R-CHOP
PD during treatment	44 [22.3%]	19 [9.4%]
New unplanned treatment	9 [4.6%]	11 [5.4%]
Progression after stable disease	1 [0.5%]	1 [0.5%]
PD after partial response	5 [2.5%]	6 [3.0%]
Relapse for CR patients	71 [36.0%]	49 [24.3%]
Death without PD during Treatment	12 [6.1%]	12 [5.9%]
Death without PD after treatment	16 [8.1%]	33 [16.3%]
No event	39 [19.8%]	71 [35.1%]

CHOP indicates cyclophosphamide, doxorubicin, vincristine and prednisone, CR: complete response, R-CHOP: Rituximab-CHOP, PD: progressive disease

progressive disease (PD), relapse (REL) and death]. The model was designed for extrapolation of average costs from ATTIKON to data derived from LNH-98.5 trial [Coiffier et al. 2010]. The model is shown in Figure 3.

2.2 Treatment outcome- LNH-98.5 trial data

The events according to clinical outcome in both CHOP and R-CHOP groups from LNH-98.5 trial [Coiffier et al. 2010] are shown in Table 3. In more detail, the percentage of patients in the CHOP and R-CHOP arm who required secondary treatment after a median follow-up of 10 years was 65.9% and 42.6% respectively (Table 3).

The median PFS was 1.2 and 4.8 years for patients in CHOP and R-CHOP arms respectively ($p < 0.001$). Similarly the median OS was 3.5 and 8.4 years in CHOP and R-CHOP arms respectively ($p < 0.001$).

2.3 Estimation of absolute financial costs

In order to estimate the absolute financial costs (including the cost of salvage treatment in patients who failed to respond to induction), we hypothesize that 100 patients above 60 years with DLBCL will receive treatment with CHOP. Sixty-six out of 100 patients will receive salvage treatment (Table 3, Figure 3). The absolute average cost for salvage treatment containing direct cost for medication, supportive therapy and days

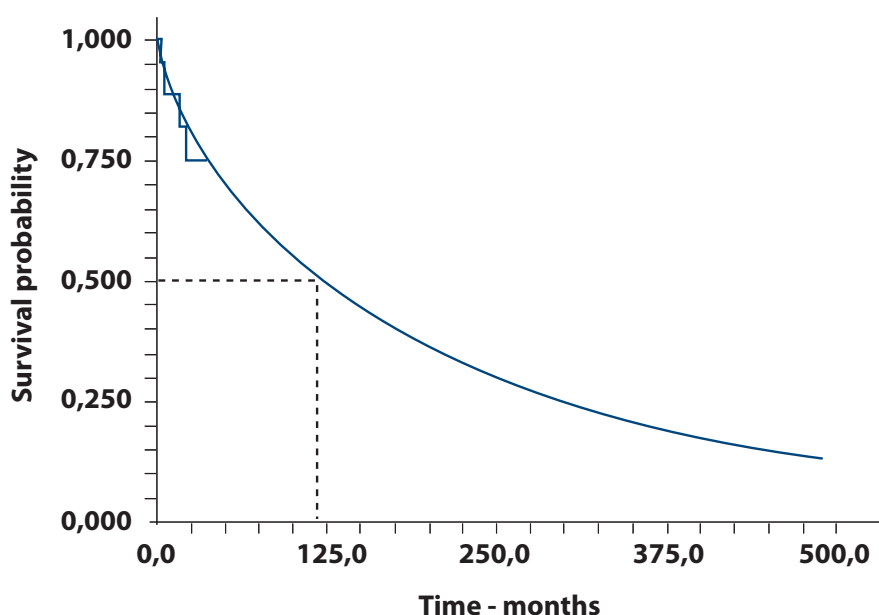
of hospitalization was estimated at €12,205. Therefore an additional cost of €805,530 will be required for administration of second line treatment. The total cost of CHOP for 100 patients is estimated at €1,496,430, meaning that the average absolute cost for a patient treated with CHOP is €14,964.

Similarly we hypothesize that 100 patients above 60 years with DLBCL will receive treatment with R-CHOP. Forty-three out of 100 patients will receive salvage treatment (Table 3, Figure 3). Therefore an additional cost of €524,815 will be required for administration of second line treatment. The total cost of R-CHOP for 100 patients is estimated at €2,913,015, meaning that the average absolute cost for a patient treated with CHOP is €29,130.

2.4 Estimation of Incremental Cost Effectiveness Ratio in Progression Free Life Years Gain

The median number of PFYs gained in patients treated with CHOP was 1.2 years. The average absolute cost was estimated at €14,964. Therefore the estimated Incremental Cost-Effectiveness Ratio (ICER) for CHOP is €12,470 per PFY. The median number of PFY gained in patients treated with R-CHOP was 4.8 years, while the average absolute cost was €29,130. The net difference in the cost between CHOP and R-CHOP was €14,166, while the net therapeutic benefit was 3.6 PFYs gained.

Figure 2.
Weibull survival curve: Patients treated with R-CHOP.
Data from "ATTIKON" General University Hospital..



Therefore the estimated Incremental Cost-Effectiveness Ratio (ICER) for R-CHOP is €3,935 per PFY (Table 4).

2.5 Estimation of Incremental Cost Effectiveness Ratio in Life Years Gain

The median number of LYGs in patients treated with CHOP was 3.5 years, while the median number of LYGs for patients treated with R-CHOP was 8.4 years. Similarly to the previous analysis the ICER for R-CHOP has been estimated at €2,891 and for CHOP at €4,275 (Table 5).

DISCUSSION

A number of concrete studies have been published in bibliography, calculating the cost for treatment and Incremental Cost-Effectiveness Ratio of R-CHOP versus CHOP for DLBCL patients. Best et al. (2005) concluded that total direct medical costs were €13,170 higher with R-CHOP, with an ICER of €12,259 per QALY (quality-adjusted life year) gained, for a time horizon of 15 years. Like in our study for the clinical data authors used data from previously-published trials, including long-term mortality rates based on the Scottish Newcastle Lymphoma Group (SNLG) data (Proctor 2002).

In another study Hornberger et al. (2005) examined cost-effectiveness of R-CHOP compared to CHOP, in elderly patients with DLBCL, for a time horizon of 5 years. Mean cost for CHOP was \$3,358, while for R-CHOP \$17,225, resulting in an increased difference in

cost in favor of R-CHOP: \$13,867. The estimated cost-utility ratio for R-CHOP was at \$19,297 per year of life gained compared with CHOP when adjusted for quality of life. Source for clinical data came from previously-published studies, such as the Group d'Etude des Lymphome d'Adulte (GELA) Trial (2008).

Ferrara et Ravasio (2008) examined the cost-effectiveness of CHOP and R-CHOP in patients aged 18 to 60 years with previously untreated DLBCL. Data for clinical effectiveness came from The Mabthera International Trial (Pfreundschuh et al 2006). The study resulted that higher costs related to the addition of Rituximab were outweighed by lower rescue therapy costs and precisely €22,113 for R-CHOP regimen and €22,831 for CHOP regimen. Because of a propitious ICER per LYG; €16,816 for complete response at 5 months and €11,967 for relapse-free survival at 3 years, R-CHOP was set as the dominant treatment.

Furthermore, two other studies by Knight et al. (2004) and Groot et al. (2005) indicated that R-CHOP was cost-effective even to patients under the age of 60 years with ICERs of £7,533 and €13,983, respectively. The calculated results of all previous studies followed the perspective that, if a therapeutic intervention is below €50,000, is cost effective giving a great lead to the addition of Rituximab to CHOP regimen for first-line treatment of DLBCL (Eichler et al. 2004, Bell et al. 2006).

Table 4:
Incremental Cost Effectiveness Ratio in gained Years of life Free from Progression (PFYs).

Intervention	Cost	Marginal cost	Effectiveness	Marginal effectiveness	CE ratio
No Treatment	0	-----	0 years	-----	-----
CHOP	€14,964	€14,964	1.2 years	1.2 years	€12,470/PFY
R-CHOP	€29,130	€14,166	4.8 years	3.6 years	€3,935/PFY
Incremental cost effectiveness ratio (ICER)= cost A minus cost B/benefit A minus benefit B: €29,130-€14,964=€14,166/4.8 - 1.2 PFYs= €3,935 per PFY or life year saved free from progression disease					

Table 5:
Incremental Cost Effectiveness Ratio in gained in gained Life Years (LYGs).

Intervention	Cost	Marginal cost	Effectiveness	Marginal effectiveness	CE ratio
No Treatment	0	-----	0 years	-----	-----
CHOP	€14,964	€14,964	3.5 years	3.5 years	€4,275/LYG
R-CHOP	€29,130	€14,166	8.4 years	4.9 years	€2,891/ LYG
Incremental cost effectiveness ratio (ICER)= cost A minus cost B/benefit A minus benefit B: €29,130-€14,964=€14,166/8.4 - 3.5 LYGs=€2,891per LYG or life year saved					

Similarly, an economic study of Lee et al. (2008) comparing the costs of R-CHOP and CHOP in patients with previously untreated DLBCL from a Canadian cancer care perspective, concluded that medication cost for first line treatment contributed more in overall cost, followed by hospitalization cost. As in this study, they resulted that the cost for R-CHOP therapy was higher as initial treatment (R-CHOP: C\$33,088 - CHOP: C\$12,240), however CHOP patients end up costing nearly three times as much as R-CHOP patients (R-CHOP: C\$3,215 - CHOP: C\$8,929). The reason for the increase of the cost was due to higher incidences of disease progression, which led to higher requirements for salvage treatment, higher medication costs and finally higher hospitalization cost of CHOP patients.

The introduction of Rituximab into the clinical practice resulted in significant improvement in the treatment outcome of B-cell Non-Hodgkin lymphomas (NHL). Rituximab in combination with CHOP chemotherapy increased the response rate, the PFS, and the OS of patients with DLBCL. In our study, we retrospectively compared the outcome between two different cohorts of consecutive DLBCL patients treated with CHOP or R-CHOP in the same institution. Similarly to previous studies, a statistically significant improvement in OS was observed in the cohort of patients treated with R-

CHOP. In multivariate analysis, treatment with R-CHOP was the most significant factor associated with increased OS (Coiffier et al. 2002, Sehn et al. 2005, Sonneveld et al. 2006, Feugier et al. 2005).

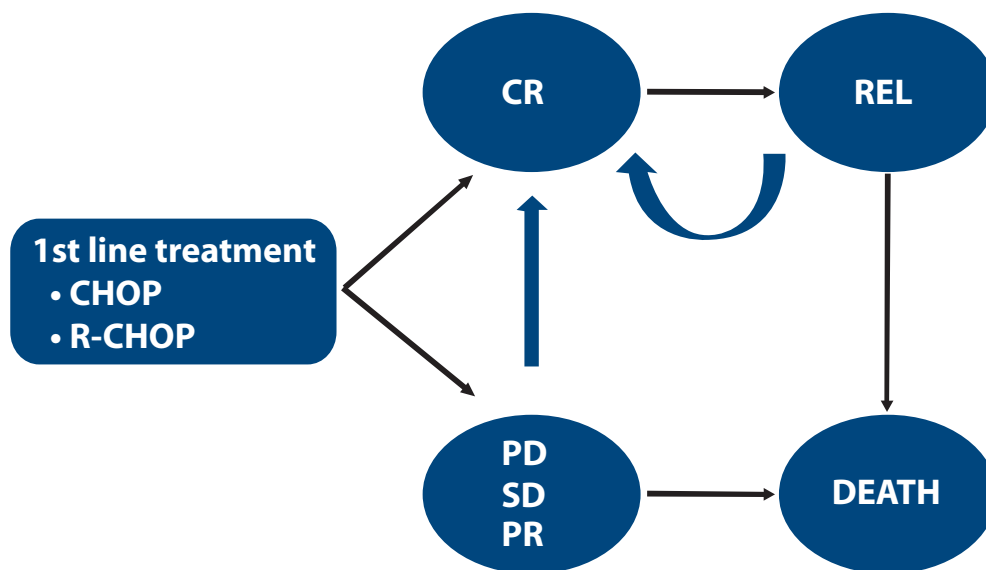
Financial analysis revealed mostly favorable ICER for the R-CHOP arm. Briefly, when analysis was restricted to absolute costs of first line treatment only, then ICER for CHOP and R-CHOP was 1.381€ per LYG and 3.394€ per LYG respectively.

Moreover, in order to analyze Cost-Effectiveness more accurately, we took into consideration not only the cost of 1st line treatment but also of subsequent treatment modalities in patients who failed to respond or relapsed after 1st line treatment. Therefore we used data from "LNH-98.5" (Coiffier et al. 2010) a prospective randomized trial with a long follow-up. Estimation of absolute average costs was based on data collected from financial agency of "ATTIKON" hospital and these costs were extrapolated on data from LNH-98.5 trial. When analysis took into consideration the costs of subsequent treatments then ICER for CHOP increased to €4,275per LYG, while ICER for R-CHOP remained (showed minimal increase) constant to €2,891per LYG.

The cost effectiveness of R-CHOP was further highlighted when ICER per PFY were estimated. Briefly, ICER for CHOP and R-CHOP was €12,470 per PFY and

Figure 3.

Markov state-transition model. Following 1st line treatment (TX) patients can achieve complete remission (CR), or in case of TX failure they may develop progressive disease (PD), stable disease (SD) or partial remission (PR). Second line TX is administered to patients who failed initial TX as well as those who relapsed after an initial CR. A new CR might be achieved after 2nd line TX. No-responders to TX have very poor prognosis and usually die in a few months.



€3,935 per PFY respectively.

Taken together our analysis support the concept that the addition of Rituximab into the treatment of patients with DLBCL improves outcome, which is the most important goal from our point of view. Moreover, and despite its absolute cost, Rituximab is financially cost effective and this efficacy is more pronounced if we take into consideration additional costs from subsequent treatments administered in patients who failed to respond to initial treatment.

In conclusion these study results demonstrate that the addition of rituximab to CHOP chemotherapy for DLBCL patients not only raises the benefits of clinical efficacy but economical efficacy as well. Especially, in a time of economic crisis like this, expensive interventions are targeted to be excluded. Economic analysis helps decision makers to arrive at the choice that will maximize the health benefits to the population. That was the goal of this study, to demonstrate that even an expensive medicine like Rituximab, can end up being cheaper and more effective.

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