COST-EFFECTIVENESS ANALYSIS OF BENDAMUSTINE + RITUXIMAB AS 1st LINE TREATMENT FOR PATIENTS WITH FOLLICULAR LYMPHOMA. PRELIMINARY RESULTS

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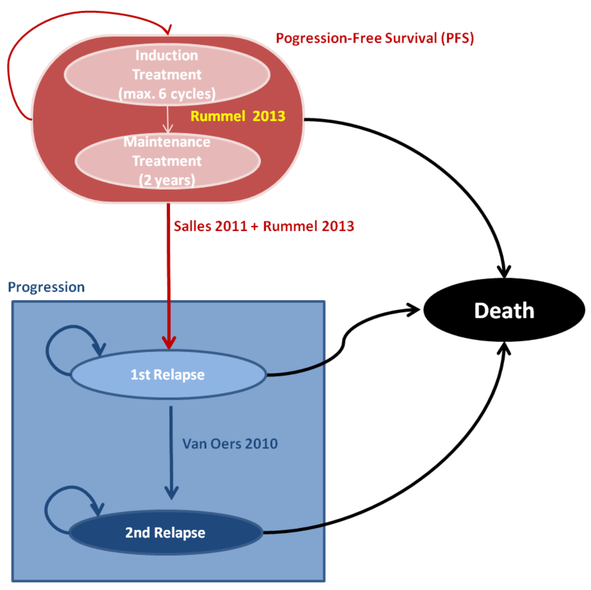
BACKGROUND & AIMS

- Follicular Lymphoma (FL) is the most common type of indolent non-Hodgkin´s Lymphoma (NHL), representing 22-40% of NHLs according to the World Health Organization (WHO) [1].
- FL is characterized by a pattern of remissions and continued relapses, and it is usually considered an incurable disease[2], although, a substantial improvement in progression-free and overall survival has been reached in the last decades since Monoclonal Antibodies therapies (MABs) were available, specifically rituximab (R).
- Patients with FL in advanced stages and high-tumour burden usually receive front-line immunochemotherapy (R + chemotherapy), during the so called induction phase, followed by maintenance therapy with R in patients who achieve at least a partial response after the induction phase, as it is recommended by several Clinical Guidelines [2-4].
- Nevertheless, it has not yet been established which polychemoterapy regimen –cyclophosphamide, vincristine and prednisone (CVP), CVP and adriamycin (CHOP) or combinations with fludarabine or bendamustine- should be prescribed along with R as induction treatment [2]
- One recent publication has shown that CHOP is the polychemotherapy with the best ristk/benefit ratio in 1st line FL treatment, to combine with R[5].
- Bendamustine is an alkylating agent indicated by the European Medicines Agency (EMA) for three different hematological malignancies: chronic lymphocytic leukemia, NHL and MM[6] and it has been applicated to the EMA for an indication extension as treatment combination with R in 1st line FL.
- A German Lymphoma Group (StiL) study, also recently published, has demonstrated that R+Bendamustine has higher efficacy and is safer than RCHOP during the induction phase[7].
- Spanish health authorities are deeply concerned about health costs to assure the sustainability of the health system. Although cost-effectiveness/utility studies are not mandatory to support either drug approvals or their price & reimbursement by the Spanish National Health System (SNHS), these studies are playing a relevant role amongst our health authorities.
- The study objective was to evaluate the cost-effectiveness of R+Bendamustine compared to RCHOP as 1st line treatment for patients with advanced FL in Spain.

METHODS

- A Markov model was developed to simulate a patient cohort of patients with FL during a time horizon of 25 years .
- Markov cycles length was 4 weeks.
- Five health states were considered : induction treatment, maintenance treatment, 1st relapse, 2nd relapse and death (Figure 1).
- Clinical data were obtained from 2 phase III randomized trials published: the StiL group trial[7], and the PRIMA trial[8].
- In the first one, where R+Bendamustine was compared to RCHOP, only the FL patients cohort has been included in the model.
- In the second trial (PRIMA), the 2 years R maintenance successful were used to run the model.
- Transition probabilities were obtained from progression-free survival (PFS) curves available in the two phase III studies used as base for this model[7-8] , and from other publication for R maintenance after 1st relapse[9].
- Mortality rates were obtained form GLOBOCAN registry[10] and from recently published epidemiological data after the "rituximab era" [11].

Figure 1. Markov model structure



- The analysis was conducted from the perspective of the SNHS,· as recommended by local Health Economics Guidelines[12].
- Only direct healthcare costs were considered, and all of them were updated to € 2013.
- Treatment costs were obtained from the Drug Catalogue, considering Ex-Factory Prices (EFP)[13] with mandatory 7.5% rebate (RD 8/2010).
- Other healthcare costs were obtained from eSalud database[14].
- Utilities for each health state were obtained from the literature [15]:
  - PFS (induction + maintenance): 0.88
  - Disease progression: 0.62
- The final efficacy measure was Quality-Adjusted Life-Years (QALYs).
- Costs and health outcomes were discounted at a 3% annual discount rate [12].
- Treatment regimen of the drug combinations considered were obtained from Spanish Hematological treatment guides[16], StiL group trial[7] and experts opinion.
- Patients basic characteristics were the following: age = 57.8 years; body surface = 1.7m^2, and weight = 68kg.
- Maximum induction phase # cycles/patient = 6, followed by 2 years R maintenance, with bimonthly cycles [7-8].
- A probabilistic sensitivity analysis (SA), with 10,000 Monte Carlo simulations, was carried out to check the robustness of the results [12].
- During the induction phase, based on the comparative trial by the StiL study, adverse events (AE) were identified and their costs measured (Table 1) [7].
- Although in the publication, febrile neutropenia was not registered, the expert panel estimated its incidence in each treatment arm, due to its high relevance and potential impact on treatment costs.
- Other hematological AE reported in the publication, as leucopenia/lymphopenia, were considered as clinical findings without economic meaningfulness.
- Alopecia was estimated at a € 0 cost, considering the analysis perspective, although is well known its highly negative psychological impact on patients.
- When patients relapsed, different treatments were identified as 1st and 2nd FL relapse treatments, depending on the 1st line arm were patients where included. These treatment relapses alternatives where identified and quantified by the panel of experts (Tables 2-3).

Table 1. Adverse events during induction phase and associated costs

Adverse Events	R-Bendamustine arm (% patients)	RCHOP arm (% patients)	Cost/event (€ 2013)
Alopecia	0%	100%	€ 0
Anemia	3%	5%	€ 818.72
Arrhythmia	1%	2%	€ 3,328.82
Congestive heart failure	1%	3%	€ 3,970.78
Erythema	5%	1%	€ 2,289.12
Stomatitis	1%	5%	€ 886.47
Leucopenia	37%	72%	€ 0
Lymphopenia	74%	43%	€ 0,90
Neutropenia	23%	55%	€ 282.13
Febrile neutropenia*	6%	14%	€ 2,035.55
Allergic reaction	0%	3%	€ 168.35
Sepsis	3%	1%	€ 10,289.56
Thrombopenia	0.4%	3%	€ 230.65

Table 2. Treatments identified after 1st FL relapse

1st relapse treatments	R+Bendamustine arm	RCHOP arm
Rituximab	15%	15%
RCHOP	50%	0%
R-CVP	20%	15%
R-ESHAP	10%	10%
R+Bendamustine	5%	60%
2nd Rituximab maintenance	50%	50%
Autologous trasplantation	10%	10%

Table 3. Treatments identified after 2nd FL relapse

2nd relapse treatments	R+Bendamustine arm	RCHOP arm
Rituximab	15%	15%
RCHOP	5%	0%
R-CVP	10%	10%
R-ESHAP	5%	5%
R+Bendamustine	15%	15%
Bendamustine	10%	10%
R-FC	10%	15%
Chlorambucil	10%	10%
Allogenic transplantation	10%	10%
Autologous transplantation	10%	10%

RESULTS

- The StiL trial only compared R+Bendamustine vs RCHOP during the induction phase, and RCHOP PFS curve was significantly below the R+Bendamustine curve (either in all the patients or even more in the FL subgropup).
- In the PRIMA trial, most patients had been treated with RCHOP during the induction phase, with > 90% of patients who were treatment responders. Rituximab maintenance significantly improved the results compared to the observation group.
- In the PRIMA trial R+Bendamustine was not included as a treatment arm because bendamustine had not been approved by EMA when the trial had started.
- As a result of the PRIMA trial, Rituximab maintenance is broadly used (bimonthly, for 2 years) in patients who have shown either complete or parital response to the immunochemotherapy induction treatment.
- For these reasons, PFS curves of the induction phase from the StiL study had be to adjusted based on the PRIMA maintenance arm PFS curve (Figure 2), to extrapolate the health outcomes result.

Figure 2. PFS curves adjusted based on StiL and PRIMA trial results

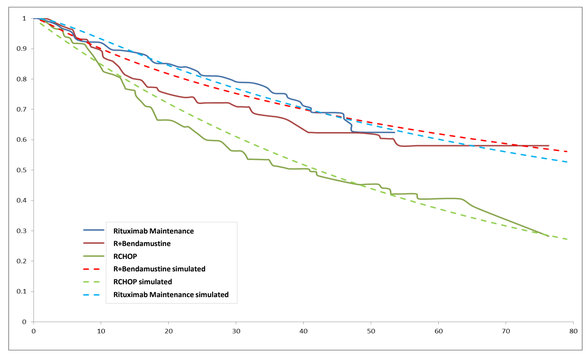
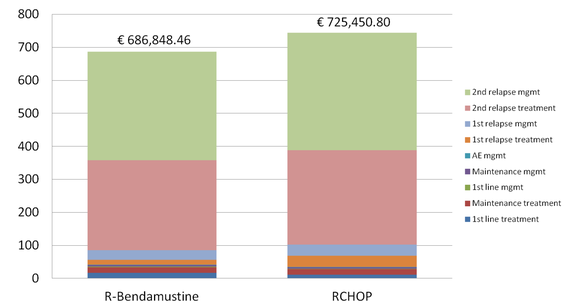


Figure 3. Average dissagregated cost/patient (€ +000)



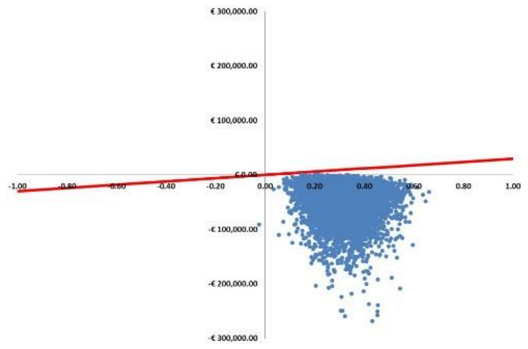
- The 6-cycles of R+Bendamustine were more expensive than RCHOP treatment (€ 16,481.63 vs € 10,793.97), during the immunochemotherapy induction phase.
- Nevertheless, the total costs recorded from both arms resulted in a higher global treatment cost of the RCHOP arma (> € 38,000), as it is shown in Figure 3.
- The main cost drivers in the model were due to the relapses management through FL evolution, where high cost interventions were considered, like bone marrow transplantations.

Table 4. Incremental Cost-Utility Ratio (ICER)

BASE CASE DETERMINISTIC ANALYSIS			
	R-Bendamustine	RCHOP	R-Bendamustine – RCHOP
Life years (LYG)	20.04	20.04	0.00
Quality Adjusted Life Years (QALY)	14.25	13.95	0.30
Costs (€ 2013)	€ 686,848.46	€ 725,450.80	€ -38,602.33
Incremental Cost Utility Ratio (ICER) = €/QALY	R-Bendamustine dominant		

- In the base case analysis, no differences in overall survival were observed between the 2 treatment options compared, expressed in "Life Years Gained" (LYG).
- However, in terms of QALYs, an advantage is shown in favour of R+Bendamustine treatment.
- Considering higher utility results and lower costs in the R+Bendamustine arm, this treatment strategy can be described as "dominant" over the RCHOP treatment.

Figure 4. Probabilistic Sensitivity Analysis (Cost-Utility plane)



- To check the robustness of the model, a probabilistic SA was carried out.
- Ten thousand Monte Carlo simulations were developed, resulting in minor result differences compared to the base case analysis.
- In 99.9% of these simulations, R+Bendamustine was dominating RCHOP, and only in 0.1% R+Bendamustine treatment resulted as more cost-effective compared to RCHOP, considering the €30,000/QALY, as the ICER threshold in Spain.
- A clearer view of the probabilistic SA results is shown in Figure 4, where points cloud are clearly concentrated in the dominant quadrant.

DISCUSSION

- Clinical data showed that R+Bendamustine had significant benefits over RCHOP in terms of efficacy and safety (Rummel, 2014), in 1st line NHL patients.
- Based on the results of this cost-utility analysis, these relevant clinical benefits were also translated into positive cost-effectiveness outcomes.
- Compared to other recent cost-utility publication in England and Wales[17], based on the same StiL trial results, the data shown are even much better.
- In this model only FL subset of patients, who were most of the total population (55%) in the StiL trial, was taken into account.
- The extrapolation of data from this trial, with the maintenance data obtained from the PRIMA trial, minimized the relevant differences observed in PFS in the StiL trail, but may be closer to real life long-term results.
- Consequently, the QALYs result in this model is lower than previous publication.
- Nevertheless, a comprehensive collection of data for AE and relapses management was made from the panel of experts, which was translated into much higher costs identified for both treatment strategies compared in this model.
- The model consider only 2 possible relapses before death to simplify the model.
- The life expectancy for general population used in this model was adapted from GLOBOCAN data, where the survival between general population and FL patients is considered as very weak by the expert panel.

CONCLUSIONS

- Despite higher initial costs of R+Bendamustine treatment during the induction phase, at the end of the 25 year period, it was less expensive than RCHOP.
- Health benefits measured as QALYs were higher in R+Bendamustine compared to RCHOP: 14.25 QALYs vs 13.95 QALYs
- Due to these cost savings and higher health benefits, R+Bendamustine can be considered as a dominant therapeutic alternative for the Spanish NHS in 1st line treatment of FL, compared to RCHOP .
- A new model with a shorter time horizon (15 years) and with different survival probabilities, obtained from recent epidemiological data after the "Rituximab era" is under development by the same group.

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