

PHARMACOECONOMIC ANALYSIS OF TREATMENT OF NON- HODGKIN'S LYMPHOMA WITH BENDAMUSTINE

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ABSTRACT

Hodgkin's lymphoma (NHL) are malignant lymphoproliferative diseases arising from a mutant lymphoid cell. Follicular lymphoma is the most common indolent (low-grade) NHL. No cure approach (watch and wait) is recommended for low-grade lymphomas without B-symptoms. Mono-therapy with chlorambucil or cyclophosphamid is prescribed in case of disease progression. In NHL of high malignancy, especially with B-symptoms, an aggressive, multi-agent chemotherapy shall be started early. Most commonly prescribed regimens were CVP (cyclophosphamid, vincristin, prednisolon) and CHOP (cyclophosphamid, hydroxydarubicin, oncovin, prednisolon). This publication focuses on the use of bendamustine in the treatment of NHL in patients whose disease has progressed during or within 6 months after a treatment with rituximab or a rituximab-containing regimen. The analysis was conducted from the payer's perspective, based on results from clinical trials, measured by overall response rate and survival without disease progression. Bendamustine treatment was compared to the currently reimbursed regimen rituximab + ibritumumab tiuxetan. The analysis showed that the estimated cost for treatment of NHL with bendamustine in patients whose disease has progressed during or within 6 months after treatment with rituximab or a rituximab-containing regimen were 23264.64 BGN/patient, which is 5958.96 BGN/ patient less than the currently used treatment regimen rituximab + ibritumumab tiuxetan. Moreover, it should be noted that these significant savings are realized for the maximum treatment cycles - 8, while usually in clinical practice physicians do not apply more than 6 cycles, which means that the actual saving is 11774.55 BGN per patient.

In conclusion, treatment of NHL saves hospital costs and it provides better therapeutic results.

Key words: *rituximab+ibritumumab tiuxetan, bendamustine, pharmacoeconomics, reimbursement, non-Hodgkin's lymphoma*

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are heterogeneous group of lymphoproliferative malignancies which originate from a mute lymphoid cell. Prevalence rises with age and it is approx. 50% higher in men than in women. The disease occurrence shows two peaks: the first in young adulthood (age 15–35) and the second in those over 55 years old. [Surveillance] The most common indolent NHL is follicular lymphoma. Patients falling into the category of high risk according to Follicular Lymphoma International Prognostic Index (FLIPI) with an expected survival of 5 and 10 years were 52% and 36% respectively. Low risk patients survival rate was 91% and 71% respectively.[1,4,10]

The treatment program depends on the patient's age and general health, the extent of lymphoma, and the particular histological subtype. In some patients with low-grade non-Hodgkin lymphoma treatment may not be needed for years and substantial number of patients have spontaneous remissions (watchful waiting). Patients with early stage disease (IA or IIA) are effectively treated with radiation therapy alone. In aggressive lymphomas, CHOP (cyclophosphamid, hydroxydarubicin, oncovin and prednisolon) and CVP (cyclophosphamid, vincristin, prednisolon) continue to hold ground as first-line therapy when compared against other regimens. Patients with indolent B-type NHL may benefit from purine analogues (pentostatin,

leostatin etc.). Another type of immunotherapy that may be used to treat low grade NHL is interferon therapy (interferon-alpha (INF α)). Monoclonal antibodies (rituximab) are also used in treatment of NHL.

The potent alkylating agent bendamustine has demonstrated substantial efficacy in patients with non-Hodgkin lymphomas (NHLs), including chronic lymphocytic leukemia, follicular lymphoma, and mantle cell lymphoma. The current publication focuses on the use of bendamustine in the treatment of NHL in patients whose disease has progressed during or within 6 months after a treatment with rituximab or a rituximab-containing regimen.

MATERIALS AND METHODS

The current pharmacoeconomic analysis was conducted from the payer's perspective, based on the results from clinical trials, measured as progression-free survival, response rate and toxicity. [2,3,5,9,13]

RESULTS AND DISCUSSION

I. Clinical trials results

A multicentre randomized phase III study started in 2003 [13] compared the efficacy and safety of bendamustine + rituximab combination with that of CHOP + rituximab, as first-line therapy for slow-growing follicular lymphoma and mantle cell lymphoma (MCL). 437 patients were studied (221 in combination bendamustine + rituximab and 212 combination CHOP + rituximab). The results showed that bendamustine + rituximab combination is as effective as the standard CHOP + rituximab treatment and it has a better tolerability profile. Final data was published in 2009 [12], when the number of patients who participated in the study increased to 549 patients. In this final analysis an improved progression-free survival rate was reported (54.8 months vs. 34.8 months for CHOP + rituximab therapy), and the combination of bendamustine + rituximab showed a better tolerability profile.

Michinori Ogura et al. [9] studied 52 patients with follicular lymphoma and 11 patients with MCL in a multicenter phase II study and found that bendamustine monotherapy is highly effective (response rates for all patients, 91%) and less toxic treatment for patients with relapsed or refractory slow-growing B-NHL and MCL which were previously treated with rituximab.

Nathan Fowler et al. [3] studied bortezomib, bendamustine and rituximab in 63 patients with relapsed or refractory follicular lymphoma. The overall response rate was 84%, complete response was achieved in 47% of patients and partial response - at 37%. The study showed that bortezomib, bendamustine and rituximab are effective in pre-treated high-risk population, with high complete response rates and generally well tolerated.

Burchardt et al. [2] compared the effectiveness and safety of the combination of bendamustine + rituximab (BR) with CHOP + rituximab (CHOP-R), as first-line therapy for follicular, slow-growing lymphoma and MCL in a prospective, randomized multicentre phase III study. 549 patients (260 patients treated with BR and 253 patients on CHOP-R therapy) were included in the study. The results showed that the collection of sufficient number of efficient peripheral blood stem cells after treatment with BR was possible and their number was comparable to the number of peripheral blood stem cells after pre-treatment with CHOP-R.

Kahl B. et al. [5], published in 2010 a study which proved that bendamustine was an effective therapy in patients with slow-growing B - cell NHL, resistant to rituximab. 100 patients at average age of 60 years (from U.S. and Canada) were included into the study.

Bendamustine demonstrated 75% overall response rate and 9.3 months progression-free survival in all patients and 64% overall response rate and 7.5 months progression-free survival in chemotherapy-resistant patients.

II. Published pharmacoeconomic studies

Markov model published by Rudakova in 2011 [11] showed that bendamustine provides significant improvement in patients with indolent NHL. The projected life expectancy for the extra years, upon administration of bendamustine in combination with rituximab as the first line indolent NHL therapy, was 0.803 – 1.343 years as compared to standard CHOP-R therapy. Bendamustine, in combination with vincristine and prednisolone (BOP), administered as first-line therapy for indolent NHL increases average life expectancy with 0.993-1.374 years, compared to treatment with cyclophosphane, vincristine and prednisolone (COP). Bendamustine is defined not only as an effective in the treatment of NHL, but also as a cost effective alternative (from the perspective of healthcare system in Russia), applied as a first-line therapy or in relapse.

III. Costs of therapy

According to the approved indications, the dose of bendamustine is 120 mg / m² body surface area on day 1 and day 2, every 3 weeks. Maximum treatment cycles are 8. [7] As described in NHS assessment report [6], a typical male 176 cm tall patient and weighing 68 kg has a skin surface of 1.82 m², which requires 218.5 mg/infusion or 437 mg /cycle. Since the vials are for single use and any amount unused shall be discarded, the calculation of therapy costs are based on an infusion requiring 2 vials of 100 mg and one vial of 25 mg. This means that four vials of 100 mg (2584.96 BGN) and two vials of 25 mg (323.12 BGN) are needed for one cycle, making a total of 2908.08 BGN / cycle. Treatment continues for up to 8 cycles, i.e. not more than 23264.64 BGN - the cost of treatment per patient for the maximum number of cycles -8, calculated on the price of wholesaler - Table 1.

Table 1. Bendamustine: approved price

INN/pharmaceutical form	Manufacturer's price in BGN (VAT incl.)	Wholesaling price in BGN (VAT incl.)
Bendamustine 2.5 mg/ml, 25 mgx5 vials	806.52	824.52
Bendamustine 2.5 mg/ml, 25 mgx20 vials	3213.20	3231.20
Bendamustine 2.5 mg/ml, 100mgx5 vials	3213.20	3231.20

IV. Comparison with alternative treatment regimens

No standard treatment for relapsed indolent NHL, resistant to treatment with rituximab or a rituximab-containing regimen exists as the treatment depends on response to previous treatment, the patient's age, comorbidities, as well as therapeutic purposes. The initial treatment of patients with follicular lymphoma stage III and IV, according to the recommendation of NICE includes rituximab, in combination with cyclophosphamide, vincristine prednisolone (R-CVP). [8] There is a positive experience with the use of rituximab, in combination with cyclophosphamide, doxorubicin, vincristine prednisolone (R-CHOP), and in combination with fludarabine, cyclophosphamide and mitoxantrone (R-FCM). [14] To maintain patients in remission and relapsed patients who are not tolerant of chemotherapy, monotherapy with rituximab is applied. As a result of these most commonly applied schemes, most patients with advanced follicular lymphoma appear to be at some point in their treatment receiving rituximab. If these patients do not respond well to treatment with rituximab or relapse, it is necessary to follow treatment protocols, with different chemotherapy regimens with or without rituximab or radioimmunotherapy with ibritumomab. Some patients are suitable for treatment with autologous bone marrow transplantation, but this alternative was not examined in this analysis because of its limited application in Bulgaria.

No accurate retrospective data on what proportion of patients with NHL will develop resistance to rituximab exists. Many patients with NHL will not live long enough to become eligible for treatment with bendamustine (i.e. resistant to rituximab), but according to data from clinical trials, the disease progresses in 12% of patients receiving rituximab-containing combination therapy.

The alternative therapeutic regimen includes ibritumomab (Zevalin), a kit for the preparation of yttrium-90 ibritumumab tiuxetan, which is fully reimbursed in Bulgaria (the final product contains 2,08 mg ibritumumab tiuxetan [90Y] in a total volume of 10 ml).

The treatment regimen consists of two intravenous administrations of rituximab and a single administration of a solution of [90Y]-radiolabelled Zevalin in the following sequence: Day 1 (intravenous infusion of 250 mg/m² rituximab (425 mg per day at the skin surface 1,7 m²)), Day 7 or 8 or 9: (intravenous infusion of 250 mg/m² rituximab shortly before (within 4 hours) before the solution of [90Y]-radiolabelled Zevalin and 10-minute intravenous infusion of [90Y]-radiolabelled Zevalin).

In other words, while bendamustine can be administered as monotherapy in patients with NHL, whose disease has progressed during or within 6 months after treatment with rituximab or a rituximab-containing regimen, ibritumumab tiuxetan must be used in combination with rituximab, authorized for use in Bulgaria as MabThera, whose price is given in Table 2. The costs for alternative regimen are given in Table 3.

Table 2. Ibritumomab/rituximab prices

INN/pharmaceutical form	Manufacturer's price in BGN (VAT incl.)	Wholesaling price in BGN (VAT incl.)
Ibritumomab/kit of radiopharmaceutical preparation for infusion 1,6 mg/ml - 2 ml x 1	23315,66	23333,66
Rituximab/concentrate for solution for infusion 100 mg/10 ml x 2 vials	1177,30	1195,30
Rituximab/concentrate for solution for infusion 500 mg/50 ml x 1 vial	2926,70	2944,70

Table 3. Costs for alternative therapeutic regimen

Day	Dosage	Costs in BGN
Day 1	425 mg rituximab	2944.70
Day 7 or 8 or 9	425 mg rituximab 1 kit ibritumumab tiuxetan	2944.70 23333.66
Total		29223.03

The use of bendamustine instead of ibritumumab tiuxetan + rituximab will result in savings of 5958.96 BGN/ patient. Moreover, it should be noted that these significant savings are realized for the maximum treatment cycles - 8, while usually in clinical practice physicians do not apply more than 6 cycles, which means that the actual saving is 11774.55 BGN / patient.

CONCLUSIONS

The treatment of NHL with bendamustine saves hospital costs and it provides better therapeutic results.

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