The use of Yttrium-90 Ibritumomab Tiuxetan (^{90}Y-IT) as a consolidation therapy in high-risk patients with diffuse large B-cell lymphoma ineligible for autologous stem-cell transplantation

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Aim of the study: To evaluate the efficacy and safety of Yttrium-90 Ibritumomab Tiuxetan (^{90}Y-IT) as a consolidation therapy in the management of DLBCL.

Material and methods: Patients with primary refractory or high-risk DLBCL (n = 18), ineligible for autologous stem-cell transplantation, were included in a retrospective study performed at three centers by the Polish Lymphoma Research Group (PLRG). All patients (mean age 61, range 35–82) either didn't achieve a complete response or didn't complete the scheduled therapy due to its complications. Response rates (CR, PR, SD, PD) according to Cheson criteria, overall survival (OS), progression-free survival (PFS) and adverse effects of radioimmunotherapy were analyzed.

Results: Consolidation radioimmunotherapy increased the CR rate from 38% (n = 7) to 82% (n = 15). One patient remained in PR, one patient remained in SD, while one patient remained in PD. During a median follow-up of five years, 11 patients (62%) were alive with no recurrence, 4 patients (22%) were alive with relapse while 3 patients (16%) died. There was no statistically significant difference in PFS between those in CR and those in PR before ^{90}Y-IT.

Conclusions: Radioimmunotherapy is an effective consolidation therapy for high risk/refractory DLBCL patients and worthy of further investigation in prospective trials.

Key words: diffuse large B-cell lymphoma, radioimmunotherapy, Yttrium-90 Ibritumomab Tiuxetan, consolidation.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the second most common type of lymphoma, accounting for 25–30% of all cases. The incidence of DLBCL varies from 5–6/100,000 per year in Europe to 8/100,000 per year in the U.S. [1, 2]. Anthracycline-based regimens like CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have been the cornerstone of therapy for several decades. Important progress has been made with the introduction of a chimeric anti-CD20 monoclonal antibody, rituximab. R-CHOP chemotherapy has significantly improved complete response (CR), progression-free survival (PFS) and overall survival (OS) rates; hence, it has become the recommended standard of front-line therapy in DLBCL [3–5]. Nevertheless, relapsing or refractory DLBCL poses a significant problem. The role of high-dose chemotherapy and autologous stem cell transplant (ASCT) as a part of first-line treatment is controversial. ASCT consolidation is a recommended standard for chemo-sensitive relapse. When compared with salvage chemotherapy without a transplant, ASCT consolidation significantly improved event-free survival (EFS) and OS (46% vs. 12% and 53% vs. 32%, respectively) [6, 7]. Unfortunately, present results of ASCT, in patients treated with rituximab, are worse than those described in the PARMA trial. Despite significant progress, patient outcomes in DLBCL remain unsatisfactory. This provides ample opportunity for new treatment strategies. New drugs such as lenalidomid, bortezomid and bevacizumab, introduced as monotherapy or in combination with chemotherapy are being evaluated [8, 9]. Our preliminary results suggest a possible role for radioimmunotherapy (Yttrium-90 Ibritumomab Tiuxetan) as a consolidation strategy in the management of DLBCL.

Material and methods

Eighteen patients (6 men and 12 women) with histologically confirmed CD20+ DLBCL, treated at three PLRG (Polish Lymphoma Research Group) centers, were analyzed. All patients (average age 61, range 35–82) either didn't achieve a complete response or didn't complete the scheduled therapy due to its complications. None of them could have been subjected to ASCT consolidation because of age, comorbidities or other limitations. Radioimmunotherapy (RIT) was used as first-line consolidation in 12 cases

Table 1. Patients' characteristics (n = 18) at diagnosis

Risk factors	Frequency
B Symptoms	13 (72%)
Bulky disease	9 (50%)
Advanced clinical stage	III – 4 (22%), IV – 12 (67%)
Bone marrow involvement	9 (50%)
IPI score 3–5	15 (83%)

Table 2. Patients' characteristics (n = 18) at qualifications to ^{90}Y-IT

Group characteristics	Frequency
Bone marrow involvement	3 (17%)
Lymph nodes enlargement > 2 cm	6 (33%)
2–4 prior chemotherapy regimens	6 (33%)
Previous treatment with rituximab	12 (67%)

Table 3. Responses after proceeding chemo(immuno)therapy and radioimmunotherapy consolidation

Response	After chemotherapy n (%)	After ^{90}Y-IT n (%)
CR	8 (44)	15 (82)
PR	10 (56)	1 (6)
SD	0	1 (6)
PD	0	1 (6)

(67%), while in 6 cases (33%), it was used after salvage therapy for relapsed/refractory DLBCL.

Patients included in the analysis fulfilled classical eligibility criteria for radioimmunotherapy: WHO performance status from 0 to 2, bone marrow infiltration of less than 15%, lymph node diameter measuring less than 5 cm, absolute neutrophil count (ANC) of at least 1.5 × 10^9/l and platelet count of at least 100 × 10^9/l. Patient characteristics at diagnosis and prior to radioimmunotherapy are presented in Tables 1 and 2.

Radioimmunotherapy was performed on an outpatient basis and consisted of two subsequent visits. On day 7, the rituximab infusion (250 mg/m2) was administered.

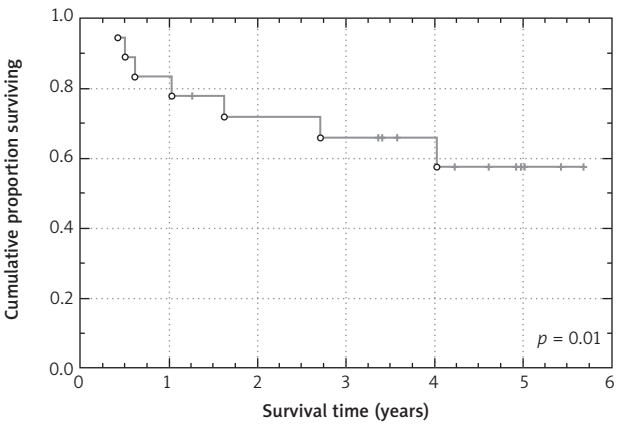

Fig. 1. Progression-free survival (PFS) for all patients (n = 18)

Seven days later, a second dose of rituximab and ^{90}Y-IT was injected intravenously for over 10 minutes. The 90Y dose (0.4 mCi per kg/14.8 MBq per kg) was conjugated with ibritumomab tiuxetan at the Nuclear Medicine laboratory immediately before infusion.

Overall response rate (ORR) was assessed according to Cheson criteria (CR, PR, SD, PD). The mean follow-up duration after ^{90}Y-IT was three and a half years. Progression-free survival (PFS) was defined as time from radioimmunotherapy initiation to lymphoma progression or death. Overall survival (OS) was defined as time from radioimmunotherapy initiation to death. Radioimmunotherapy side effects and exact causes of death were also noted and evaluated.

Statistical analysis

A statistical analysis was performed using the Statistica software suite (ver. 8.0, released in 2007). In order to compare the response before and after radioimmunotherapy, a chi-square test with Fisher's amendment was used. PFS and OS were analyzed by the Kaplan-Meier method, using Gehan's Wilcoxon test for comparison.

Results

Response to therapy

Radioimmunotherapy was administered as a consolidation strategy in patients with a partial response to preceeding chemotherapy or high-risk cases with a complete response. Out of 12 patients consolidated after the end of first-line therapy, 4 patients (2 CR and 2 PR) had an abbreviated chemotherapy restricted to four R-CHOP cycles due to treatment intolerance (two cases of myocardial infarction and two cases of severe left ventricular failure), 5 patients didn't achieve CR after completion of the first-line treatment (4 PR after six cycles, 1 SD after ten cycles), and 3 patients were regarded high-risk despite CR after eight cycles. All six relapsed/refractory cases (consolidated after 2nd–4th line of therapy) were considered high-risk, although two cases achieved CR. After radioimmunotherapy, seven cases (38%) remained in CR, a further eight cases (44%) were converted from PR to CR, one case (6%) relapsed, one case (6%) remained in SD and one case (6%) remained in PR. Consolidation radioimmunotherapy increased the CR rate from 38% (n = 7) to 82% (n = 15) (Table III). RIT consolidation significantly improved the response rates, compared to preceding chemotherapy (p = 0.01).

Survival analysis

At a median follow-up of five years, 11 patients (62%) were alive with no recurrence, 4 patients (22%) were alive with relapsed/refractory DLBCL and 3 patients (16%) died. Two deaths were due to subsequent lymphoma relapse/resistance (28 and 42 months after diagnosis), while one death resulted from transformation to acute myeloid leukemia.

A Kaplan-Meier survival analysis determined the PFS and OS at 5 years to be 56% and 82%, respectively (Figs. 1, 2); the median PFS and OS had not yet been reached. Radioimmunotherapy was more effective if administered early as a consolidation of first-line therapy. The differences in

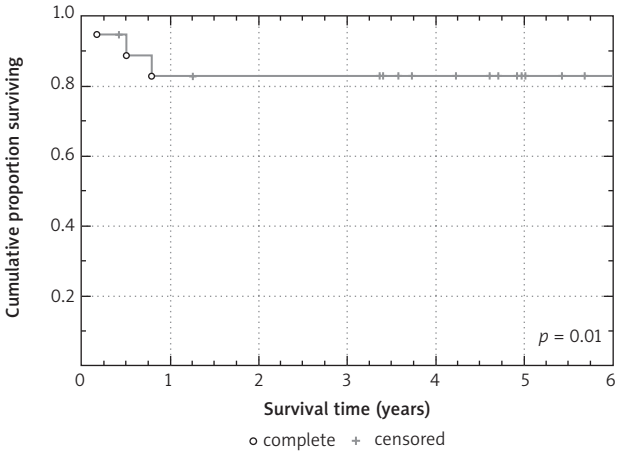

Fig. 2. Overall survival (OS) for all patients (n = 18)

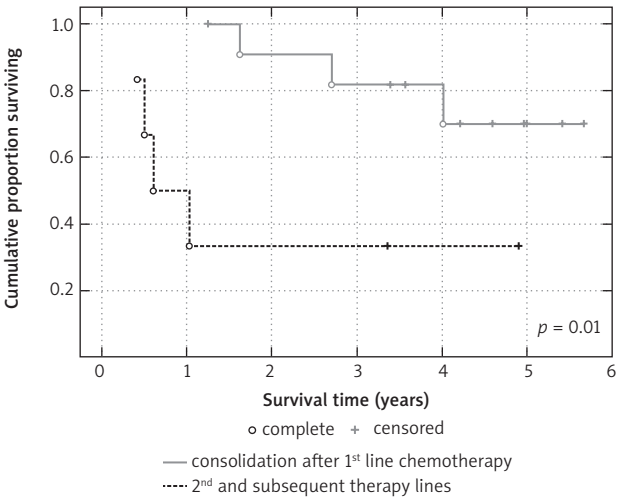

Fig. 3. Comparison of progression-free survival of DLBCL patients consolidated by radioimmunotherapy in first and subsequent therapy lines

PFS were statistically significant even in such a small group (Fig. 3, p = 0.01 in Gehan's Wilcoxon test). There was no statistically significant difference in PFS between patients previously consolidated in CR and in PR; however, only cases with adequate nodal response (lymph node diameter < 5 cm) qualified. Similarly, bone marrow involvement had no impact on PFS and OS; however, only patients with lymphoma infiltration of less than 15% were included. The use of rituximab with previous chemotherapy regimens seems to have no impact on PFS; however, it is difficult to draw reliable conclusions from such a small group.

Hematologic toxicity

Hematologic toxicity was the main adverse event. Incidences of grade 3–4 thrombocytopenia (n = 10, 56% cases), neutropenia (n = 7, 39% cases) and anemia (n = 7, 39% cases) were observed. Five patients (27%) received granulocyte colony-stimulating factors, eight patients (44%) received platelet transfusions and six patients (33%) received red blood cell transfusions.

Although recovery of platelet count, neutrophil count and hemoglobin concentration to normal levels took relatively long (57.5 days, 70.5 days and 83.5 days, respectively), there were no cases of hemorrhagic diathesis and the incidence of severe infection (grade 3–4) was low. Only three patients developed infections requiring hospital admissions: neutropenic fever of unknown origin, oral mucosa candidiasis and sepsis due to Streptococcus. None of them were fatal.

Discussion

Radioimmunotherapy (RIT) has recently become a valuable treatment option for B-cell lymphomas. The combination of an anti-CD 20 monoclonal antibody (MoAb) with a radioisotope (Ibritumomab Tiuxetan with ^{90}Y or Tositumomab with ^{131}I) may damage B-cell lymphoma cells more effectively than monotherapy with rituximab alone. A single particle of MoAb conjugated with radionuclides may be effective against several neoplastic cells as a result of the crossfire effect [10], while several hundred naked MoAb are necessary to eliminate a single neoplastic cell. The effectiveness of ibritumomab tiuxetan radiolabelled with ^{90}Y (Zevalin), as a consolidation therapy in follicular lymphoma (FL) has been proven in numerous clinical studies,evidenced by increased response rates and prolonged PFS [11–13]. Zevalin was registered for the treatment of recurrent or refractory follicular lymphoma. It should be emphasized that it is currently the only drug registered in Europe for rituximab refractory cases. Encouraging results of RIT in low grade lymphomas led to its investigation as a possible therapy in aggressive non-Hodgkin's lymphoma (NHL). Although high-dose chemotherapy followed by peripheral stem cell transplantation is a recommended standard in cases with a partial response or relapsing high grade NHL, many patients don't qualify for this procedure due to advanced age or comorbidities. RIT may be an interesting alternative in this group of patients.

Preliminary results from other studies also suggest possible benefits of ^{90}Y-IT, such as overall response rates ranging from 58% to 78.6% (associated CR of 32–40%) with an estimated 2-year PFS of 75–85% [14–17]. Our observations showed that RIT consolidation improved the quality of response, converting PR to CR in nearly 45% of cases (ranging from 38% to 83%). Median OS and PFS had not yet been reached at 5 years, while projected OS and PFS were 56% and 82%, respectively. Our patients could neither be subjected to ASCT consolidation, nor continue their last chemotherapy protocol (it was either completed or prematurely stopped due to toxicity or complications). Additionally, all patients were complete or partial responders according to Cheson criteria. In responsive patients, the tumor burden, bone marrow involvement, clinical stage of lymphoma (II vs. III and IV), and IPI (0–2 vs. 3–5) at diagnosis had no prognostic significance on a response after RIT consolidation. Similarly, we couldn't demonstrate the impact of disease status at the time of RIT, since the response (CR vs. PR), diameter of the largest lymph nodes (less than 2 cm vs. 2–5 cm) and bone marrow involvement (absent vs. present) did not significantly influence PFS. However, it should be noted that sample size was too small for any meaningful

analysis and only responsive patients with low tumor burden (maximal lymph node diameter < 5 cm and bone marrow involvement < 15%) were subjected to RIT. Our results are not fully consistent with other reports [16, 18].

In a retrospective study of 28 NHL patients subjected to RIT [16], the extent of lymphoma infiltration was evaluated on pre-therapy ^{111}In-ibritumomab scans. A higher rate of complete response after ^{90}Y-ibritumomab treatment was seen in patients with negative ^{111}In-ibritumomab findings, raising questions of its diagnostic role. A better response was observed, the sooner RIT was started. The median duration of PFS has not been reached after 5 years of observation in patients consolidated in first-line therapy compared to 8 months in those consolidated in first or subsequent relapses. Similar results have been presented by Emmanouilides et al. [19].

In 211 patients with relapsed B-cell NHL (FL, DLBCL) where RIT was used as a chemotherapy consolidation, a higher percentage of CR and a longer median PFS were obtained at first relapse compared with patients treated after two or more lines (49% vs. 28% and 12.6 months vs. 7.9 months, respectively).

In a phase II prospective study published by Morschhauser *et al.* [15], the response to Zevalin in relapsing patients depended on prior usage of rituximab: OS and PFS were significantly longer in patients relapsing after CHOP compared to R-CHOP therapy (21.4 months vs. 4.6 months and 5.9 months vs. 1.6 months, respectively). Such diminished responses in patients relapsing after initial R-CHOP are also observed after ASCT salvage therapy. We haven't seen such a difference; however, RIT was given as a consolidation to chemo-sensitive patients with a small tumor burden and not as a sole treatment in relapsing/refractory cases. RIT efficacy has been previously demonstrated in rituximab resistant cases of DLBCL (44% RR including 27% CR [20]) and FL (77% RR, 15% CR [21]); however, a small tumor burden seems to be crucial for long term efficacy. Efficacy of RIT in were further confirmed in recent publication, where RIT was used in previously untreated FL patients, in IIBX- IV-th clinical stage: ORR – 94%, median 3-year estimated PFS and OS rate 63·4% and 90%, respectively [22].

In most patients, the only significant adverse events were due to hematological toxicity manifesting as neutropenia and thrombocytopenia. Grade 3 and 4 toxicity were relatively common (39% and 56%, respectively); however, only three patients had infections that required hospitalization and there were no reported cases of bleeding diathesis. Hence, myelosuppression after RIT, although frequent, was predictable and manageable.

In conclusion, analysis of our study results confirms the efficacy of ^{90}Y-IT consolidation treatment for refractory and recurrent DLBCL. ^{90}Y-IT is well tolerated with manageable side effects. We did not find a relationship between the clinical stage of DLBCL at diagnosis and response to ^{90}Y-IT. Response to induction chemotherapy preceding ^{90}Y-IT does not have an impact on its effectiveness as a treatment option. The lesser the time between initial DLBCL diagnosis and ^{90}Y-IT usage, the more efficient the treatment. Given these results, early usage of ^{90}Y-IT as a consolidation of first-line treatment, even in patients with PR, seems to be the most beneficial.

The authors declare no conflict of interest.

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