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Autologous stem cell transplantation after conditioning with Yttrium-90 ibritumomab tiuxetan plus beam in refractory non-Hodgkin diffuse large B-cell lymphoma: results of a prospective, multicenter, phase II clinical trial

Running Heads: Yttrium-90 ibritumomab plus BEAM for refractory DLBCL

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ABSTRACT

In the rituximab era, lymphoma patients with persistent disease receiving autologous transplantation have a very poor outcome. The addition of radioimmunotherapy to the conditioning regimen may improve outcome for these patients. We have evaluated, in a prospective phase 2 study, the safety and efficacy of the addition of $^{90}$Y-Ibritumomab tiuxetan to the conditioning chemotherapy in refractory diffuse large B cell lymphoma patients. Thirty patients with induction failure (primary refractory; n=18) or refractory to salvage immunochemotherapy at relapse (n=12) were included in the study. Patients with a median age of 53 years (range, 25-67) received $^{90}$Y-Ibritumomab tiuxetan at a fixed dose of 0.4mCi/kg (maximum dose 32mCi) 14 days prior to the preparative chemotherapy regimen. Histology included de novo diffuse large B cell lymphoma (22) and transformed diffuse large B cell lymphoma (8). All patients had persistent disease at the time of transplantation, with 25 patients considered to be chemorefractory. Median time to neutrophil recovery (>500/μl) was 11 days (9-21), and to platelet recovery (>20,000/μl) was 13 days (11-35). Overall response at day +100 was 70% (95% CI, 53.6-86.4) with 60% (95% CI, 42.5-77.5) complete responses. After a median follow-up of 31 months for alive patients (range, 16-54), estimated 3-year overall and progression-free survival is 63% (95% CI, 48-82) and 61% (95% CI, 45-80), respectively. We conclude that autologous transplantation with conditioning including $^{90}$Y-Ibritumomab tiuxetan is safe, and results in a very high response rate with promising survival in this very poor prognosis group of refractory diffuse large B cell lymphoma patients. Study registered at European Union Drug Regulating Authorities Clinical Trials (EudraCT) No. 2007-003198-22.
INTRODUCTION

Despite that rituximab in combination with an anthracycline-containing chemotherapy as front-line treatment has significantly improved survival in patients with diffuse large B-cell lymphoma (DBCL), a significant proportion of patients (20-50%) either fail to achieve a complete response (CR) or relapse\(^1\)\(^-\)\(^3\). For these refractory/relapsing patients, salvage chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation (ASCT) continues to be the standard of care\(^4\). However, a number of studies have shown that chemosensitivity is the main factor that derives benefit from ASCT\(^5\)\(^,\)\(^6\). Thus, patients with chemorefractory disease (either upfront or at relapse) have a very poor outcome, with little benefit from ASCT. This particular group of patients has focused the attention to develop more effective strategies. None of the different chemotherapy-based preparative regimens for ASCT has proven to be superior and, since DLBCL is radiosensitive, total body irradiation (TBI) has been incorporated to the conditioning regimens for ASCT. In the last years, to maximize the antitumor effect and reduce toxicities, TBI has been replaced with radioimmunotherapy (RIT) in the conditioning regimen for ASCT\(^7\).

\(^{90}\)Y-Ibritumomab tiuxetan is a radiolabeled anti-CD20 monoclonal antibody with significant activity against both, indolent and aggressive B-cell non-Hodgkin lymphomas\(^8\). In recent years, RIT has been incorporated to preparative regimens for ASCT in patients with relapsed DLBCL with the intention to enhance the antitumor effect and to improve outcomes of these poor-prognosis patients\(^9\)\(^-\)\(^\)\(^1\)\(^1\). However, these studies have focused mainly on chemosensitive-relapsed DLBCL patients, while little is known about the efficacy of this treatment for patients with chemorefractory disease. Here, we present the data from a prospective, multicenter, clinical trial on the safety and efficacy of a standard dose of \(^{90}\)Y-Ibritumomab tiuxetan combined with high-dose BEAM chemotherapy followed by ASCT in patients with DLBCL refractory to a rituximab-containing chemotherapy.

METHODS

Eligibility

This study included patients with histologically-confirmed DLBCL, either de novo or transformed from a previous indolent CD20+ B-cell lymphoma. Patients were eligible if they failed to achieve at least partial response (PR) after front-line immunochemotherapy (induction failure), and were further unresponsive (i.e. fail to attain a PR) to salvage immunochemotherapy. Patients with a relapse that failed to
achieve a PR to salvage immunochemotherapy were also eligible. Other eligibility criteria included age 18 to 70 years old, a performance status of 0-1, and standard transplantation criteria (i.e. adequate cardiac, renal, and respiratory function). All patients had measurable disease by fluorine-18-fluorodeoxyglucose positron emission tomography combined with computerized tomography (PET-CT). Patients were excluded if they had CNS lymphoma at the time of enrolling, a history of HIV infection, or had previously received an ASCT.

Study design and treatment

This is a phase II study conducted at 17 centers within Spain, approved by the Ethics Committee of each center, and conducted in accordance with the Declaration of Helsinki. Patients were recruited from January 2008 to February 2010. Signed informed consent was obtained from all patients prior to any study-related procedure. The study was registered under European Union Drug Regulating Authorities Clinical Trials (EudraCT) No. 2007-003198-22.

On day -21, patients were given rituximab 250 mg/m²; on day -14, patients received 250 mg/m² rituximab followed by ⁹⁰Y-ibritumomab tiuxetan at a fixed dose of 0.4 mCi/kg (with a maximum total dose of 32 mCi) in an outpatient setting, with no dose adjustments for neutropenia or thrombocytopenia. One week later, patients were given high-dose BEAM chemotherapy (carmustine 300 mg/m² on day -6, etoposide 200 mg/m² on days -5 to -2, cytarabine 200 mg/m² twice a day on days -5 to -2, and melphalan 140 mg/m² on day -1). Autologous stem cells were reinfused on day 0. G-CSF 5μg/k/d was started on day +7 after ASCT until neutrophil recovery. Acyclovir and trimethoprim sulfamethoxazole were used as prophylaxis 1 and 3 months after ASCT, respectively. Adverse events were assessed and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

Response evaluation and follow-up

All patients were required to have a complete baseline evaluation before the treatment, including physical examination, blood count and serum biochemistry determinations, bone marrow biopsy and a whole body evaluation with PET-CT. Response was evaluated 3 months after ASCT, according to 2007 Cheson criteria¹². Follow-up procedures were done every 3 months for the first year post-transplant, and every 6 months thereafter for 2 years.
Statistical analysis

The primary end point of this study was response rate after transplantation. Secondary end points included progression-free survival (PFS), overall survival (OS), and toxicity. The study is reported on an intent-to treat basis. Probabilities of PFS and OS were estimated using the Kaplan-Meier method. Differences between the curves were assessed using the log-rank test. All calculations were analyzed using the SPSS statistical 19.0 package (SPSS Inc, Chicago, IL).

RESULTS

Patient’s characteristics

Thirty-one patients were consented to this study between January 2008 to February 2010. One patient was not evaluable since experienced explosive progression of disease between consent and the start of the therapy and did not receive any therapy. Analysis was done on an intention-to treat basis in the remaining 30 patients. Clinical characteristics are noted in Table 1. Median age at transplantation was 53 years (range, 25-67). Histology included de novo DLBCL (n=22) and transformed indolent lymphoma in 8 cases. At the time of inclusion, 15 patients had a stage III/IV disease, 13 had an IPI 2-4, and 10 patients had bulky disease (maximum diameter ≥ 10 cm). Patients received a median of 3 rituximab-containing regimens (range, 2-6). Induction therapy consisted of conventional-dose R-CHOP (6 cycles, every 21 days) in 28 cases or high-dose R-CHOP (cyclophosphamide 1500 mg/m²/day 1 with mesna 150% of total cyclophosphamide dose; doxorubicin 65 mg/m²/day 1, vincristine 2 mg day 1, prednisone 60 mg/m² days 1-5; at least 3 cycles every 21 days) in 2 cases; radiotherapy to bulky sites was given to 6 patients. Eighteen patients failed induction therapy and 12 patients had a relapse that was refractory to salvage therapy. Patients with induction failure received salvage therapy as follows: R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin; 2 cycles) followed by R-IFE (rituximab, ifosfamide, etoposide; 2 cycles)(n=3), R-IFE (3 cycles)(n=3), R-ICE (rituximab, ifosfamide, carboplatin, etoposide, 3 cycles)(n=4), R-ESHAP (rituximab, etoposide, prednisone, cytarabine, cisplatin; 2-3 cycles)(n=3), R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin; 2-3 cycles)(n=1), R-DHAP (2 cycles) followed by R-ESHAP (2 cycles)(n=1), R-GemOx (rituximab, dexamethasone, gemcitabine, oxaliplatin every 14 days, 6 cycles)(n=1), R-ESHAP (2 cycles) followed by R-GemOx (4 cycles)(n=1), and R-IFE (2 cycles) followed by R-DHAP (2 cycles)(n=1).
For relapsed patients, salvage chemotherapy was R-MINE (rituximab, ifosfamide, etoposide and mitoxantrone; 3 cycles) (n=1), R-ESHAP (2-3 cycles) (n=6), R-ESHAP (2 cycles) followed by R-GemOx (n=1), R-ICE (3 cycles) (n=1), R-ICE (2 cycles) followed by R-GemOx (4 cycles) (n=1), R-IFE (3 cycles) (n=1), and 1 patient received R-DHAP (2 cycles) followed by R-IFE (1 cycle) and R-GemOx (3 cycles).

All patients had active disease at the time of inclusion in the trial, as defined by PET-CT. At the time of ASCT, 25 patients were chemorefractory and 5 patients had chemosensitive disease (3 induction failure patients achieved PR to salvage treatment -2 of them after additional radiotherapy-, and 2 relapsed patients did not responded to salvage chemotherapy but did achieved a PR after radiotherapy).

PBPCs were mobilized with G-CSF alone in 8 patients and with chemotherapy + G-CSF combination in the remaining 22 patients. Chemotherapy included ESHAP in 8 patients, ICE in 4, IFE in 9, and one patient received DHAP. All patients had a successful peripheral stem cell collection prior to ASCT, with a median yield of 3.9 x 10^6/kg CD34+ cells (range, 2-18.3).

Early toxicity and engraftment

One patient had a grade 1 reaction to 90Y-ibritumomab tiuxetan infusion, and three patients developed grade 4 hematological toxicities related to 90Y-ibritumomab tiuxetan (neutopenia in two patients and thrombocytopenia in one) before ASCT. One patient had a bacterial sepsis after 90Y-ibritumomab tiuxetan infusion that fully recovered with antibiotics. Two patients died during the conditioning treatment, one with a cerebral hemorrhage and one patient due to disease progression. The remaining 28 patients proceed to ASCT. All 28 patients engrafted. The median time from ASCT to neutrophil engraftment was 11 days (range, 9-21), and median time to platelet engraftment was 13 days (range, 11-35). Fever was documented in 23 patients, with a median duration of 6 days (range, 1-16). Mucositis was presented in 25 patients, grade 3 in 6 cases and grade 4 in 6. Three patients developed grade 3 non-infectious enteritis. One patient died early after transplantation due to gram-negative bacterial sepsis (Table 2). Transplantation-related mortality at 100 days was 3.5%.

Response and survival

Response was evaluated on an intent-to treat basis. The overall response rate was 70% (95% CI, 53.6%-86.4%). Eighteen patients (60%) achieved CR with a negative PET-CT (95% CI, 42.5%-77.5%) and 3 patients had a PR. Ten patients experienced
progressive disease and 9 of them died as a result of lymphoma. Among 5 patients with PR at the time of ASCT, 4 are alive and free of lymphoma at last follow-up. Disease progression occurred within 18 months in all cases. With a median follow-up of 31 months among surviving patients (range 16-54), 11 patients have died. The estimated 3-year OS and PFS is 63% (95% CI, 48%-82%) and 61% (95% CI, 45%-80%), respectively (Figures 1-2). Patients with PR (n=5) at the time of ASCT had a 3-year OS and PFS 80% (95% CI, 65%-95%), while chemorefractory patients (n=25) had a 3-year OS and PFS 60% (95% CI 41%-79%) (p=0.48). Survival according to PET-CT status at 3 months after ASCT was different. Patients with a negative PET-CT (n=18) had a 3-year OS and PFS of 70%, (95% CI, 52%-87%) while it was 0% for those patients (n=3) with a positive PET-CT (p=0.005) (Figure 3).

Concerning patients with transformed DLBCL (n=8), 7 were chemorefractory to salvage and 1 patient achieved a PR at the time of ASCT. No differences in survival were found between patients with de novo DLBCL (OS/PFS 63%; 95% CI, 43%-82%) and those with transformed DLBCL (OS/PFS 66%; 95% CI, 48%-85%)(p=0.9).

Late effects

One patient died of a septic shock due to pneumonia 14 months after ASCT, while being in CR. One patient developed pneumococcal meningitis 11 months after ASCT with full recovery with antibiotics. One patient in remission of his lymphoma died 14 months after ASCT as a result of a secondary acute myeloid leukemia with a complex karyotype. One patient experienced pancytopenia 33 months after ASCT. A bone-marrow biopsy showed a myelodysplastic syndrome consisting on refractory anemia with excess of blasts-2 with cytogenetic studies showing monosomy 7; at the last follow-up, the patient was receiving 5’azacytidine treatment with no evidence of lymphoma.

DISCUSSION

In the rituximab era, high dose chemotherapy followed by ASCT remains a reasonable option for relapsed patients with DLBCL\textsuperscript{13}. Patients with chemosensitive disease have better outcomes compared to those who are chemorefractory, who have a 3-year PFS of 20%\textsuperscript{14}. Nevertheless, relapsed DLBCL patients treated with rituximab-containing chemotherapy that have persistent disease (i.e. PET positive) do very poor after ASCT\textsuperscript{15}. To improve the outcome of this group of patients, RIT has been used as part of the transplantation preparative regimen. Phase II studies have shown promising
results in relapsed DLBCL patients. Our study has preferentially focused on chemoresistant patients, since the majority (84%) did not achieve a PR to salvage chemotherapy, either after front line therapy or at relapse. Our data are in agreement with previous studies suggesting an improved outcome for DLBCL patients receiving RIT as part of the conditioning treatment before ASCT. In our study, 61% of patients were alive and free of disease at 2.5 years. These numbers are similar to those reported by Shimoni et al. in a similar group of patients. Other phase II studies with the addition of RIT (90Y-ibritumomab tiuxetan) to the conditioning regimen for ASCT have also shown promising results in relapsed DLBCL patients. In a recent comparative study in patients with relapsed/refractory DLBCL, addition of RIT (90Y-ibritumomab tiuxetan) to BEAM followed by ASCT resulted in a superior OS but not PFS. Low numbers of patients, however, precluded definitive conclusions and the therapeutic benefit of RIT in the setting of ASCT remains unproven.

Very recently, Vose et al. showed that relapsed DLBCL patients treated with RIT (131I-tositumomab) plus BEAM and ASCT had a 2-year PFS of 48%, similar to those patients receiving rituximab plus BEAM as a transplantation regimen. However, the radiolabeled antibody used in that study (131I-tositumomab) was different from the one used in our study (90Y-ibritumomab tiuxetan) and our results, with longer follow-up, seem to be better in a more chemoresistant patient population. Although both antibodies target the CD20 antigen and are beta emitters, the monoclonal antibodies are completely different, and their antitumor effect may not necessarily be identical. Besides the killing of the targeted tumor cells, an additional mechanism of tumor killing is the crossfire effect that might eliminate non-targeted tumor cells. In line with this, 90Y-ibritumomab tiuxetan emits beta radioactivity with a path length 6-fold larger than 131I-tositumomab, which could potentially contribute to a better disease control. Unfortunately, there is no comparative data available on the efficacy of those radiolabeled antibodies. Nevertheless, the fact that the addition of RIT failed to significantly improve the outcome of relapsed chemosensitive DLBCL patients raises concern about the clinical impact of addition of RIT to the preparative regimen for ASCT.

The 90Y-ibritumomab tiuxetan dose in this study was chosen based on previous phase I studies showing substantial myelosuppression at a fixed 0.4mCi/kg dose with a maximum of 32mCi, and the fact that no dosimetry was needed when using this dose, which allows to delivering the treatment in an outpatient setting. Since patients received an ASCT, myelosuppression is no longer a problem, and higher doses of RIT may be given which potentially could improve the effectiveness of this treatment. Preliminary studies have shown that 90Y-ibritumomab tiuxetan can be safely given at a
dose up to 0.95 mCi/kg followed by high-dose chemotherapy and ASCT, which represents at least twice the conventional 0.4 mCi/kg dose. Studies attempting to translate high-dose RIT followed by ASCT to patients with relapsed/refractory lymphoma have shown feasibility with no increased toxicities, but an improvement in the outcome of patients treated with this approach compared to conventional dose RIT has not been formally shown. Our study shows that, even in this very poor-risk patient population, addition of RIT to the preparative regimen before ASCT is safe, and does not seem to add to the toxicity of the BEAM conditioning regimen. All patients had an adequate hematopoietic recovery with no late engraftments and, with perhaps the exception of mucositis, the remaining adverse events were similar to those expected with BEAM alone. A transplantation-related mortality of 3.5% is in keeping with current experience with other high-dose therapies.

An important issue regarding long-term toxicities after ASCT is the occurrence of treatment-related myelodysplasia (tMDS) or acute myeloid leukemia (tAML). With the increasing use of RIT, mostly as part of the preparative regimen for ASCT, the risk of developing tMDS/AML is of concern and deserves careful attention. In our study, two patients developed tMDS/tAML between 1 and 3 years after RIT that accounts for a crude incidence of 7%. One patient, with a de novo DLBCL, received 3 previous regimens before RIT, including alkylating agents and etoposide, and developed tAML with a complex karyotype. A second patient, with a transformed DLBCL, had a tMDS with cytogenetic changes involving chromosome 7. This patient had previously been treated with a combination of fludarabine and alkylating agents for an indolent NHL, before transformation to a DLBCL. The true incidence of tMDS/tAML after RIT and ASCT is not known, since it has not been prospectively studied in a large series of patients with a long follow-up. In our study, bone marrow assessments during the follow-up were only done if additional abnormalities were detected on routine lab counts which may contribute to an underreported incidence tMDS/tAML.

In a recent randomized study assessing the use of RIT versus rituximab as part of the conditioning regimen before ASCT, the incidence of tMDS was less than 1% in each arm, although follow-up was short. In a recent retrospective survey on NHL patients treated with $^{90}$Y-ibritumomab tiuxetan as single agent, the crude incidence of tMDS/tAML was found to be 2.5%. Interestingly, an association between previous fludarabine treatment and an increased risk of tMDS/tAML was found in this study, with frequent cytogenetic changes involving chromosomes 5 and 7; this was the case for one of the patients in our study. Overall, the use of RIT seems not to be associated with an increased risk of tMDS/tAML, higher than the reported 2-10% for conventional high-dose chemo-radiotherapy and ASCT. Longer follow-up is needed to draw
definitive conclusions, and a special focus on those patients with a history of previous fludarabine treatment is warranted. Of note, a very recent study with RIT and ASCT as front-line treatment in mantle cell lymphoma reported a 20% incidence of secondary malignancies, unusually higher than expected24.

In summary, the use of RIT as part of the preparative regimen for ASCT in chemorefractory, rituximab-exposed DLBCL patients is safe, and may be associated with a high response rate. Randomized clinical trials either with conventional or high-dose RIT are necessary to definitively confirm the therapeutic benefit of this approach.

AUTHORSHIP AND DISCLOSURES

JB was the principal investigator, designed the trial, interpreted the data, and wrote the paper; SN contributed to statistical analysis; JGM, IJ, JMM and DC contributed to the final draft of the paper; JB, JGM, JFT, TB, CG, MC, AT, JMM, CP, FP, IJ, MH, EGB, DL, and DC recruited patients. All authors reviewed and approved the final version of the manuscript. The authors report no potential conflicts of interest.

REFERENCES


Table 1. Patient’s characteristics

| Total No (%)                                      | 30 (100%)  |
| Gender (male/female)                             | (14/16)    |
| Median age (years) at transplantation             | 53 (range, 25-67) |
| **Histology**                                     |            |
| Diffuse large B-cell lymphoma                     | 22 (73%)   |
| Transformed indolent lymphoma                     | 8 (27%)    |
| **Median No. of prior therapies**                 | 3 (range, 2-6) |
| **Disease status at the time of enrollment**      |            |
| Induction failure                                 | 18 (60%)   |
| Refractory relapse                                | 12 (40%)   |
| Stage III-IV                                      | 15 (50%)   |
| Bulky disease (≥ 10cm)                            | 10 (33%)   |
| IPI 0-1                                          | 17 (59%)   |
| IPI 2                                            | 7 (23%)    |
| IPI 3                                            | 5 (16%)    |
| IPI 4                                            | 1 (3%)     |
| Partial response                                  | 5 (16%)    |
| Non response                                     | 25 (84%)   |
Table 2. Nonhematological toxicities within 2 years after transplantation

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FIGURE LEGENDS

Figure 1. Overall survival for all patients (N=30)
Figure 2. Progression-free survival for all patients (N=30)
Figure 3. Overall survival according to PET-CT response at 3 months after autologous stem cell transplantation