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Upfront Consolidation Combining Yttrium-90 Ibritumomab Tiuxetan and High-Dose Therapy with Stem Cell Transplantation in Poor-Risk Patients with Diffuse Large B Cell Lymphoma

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A B S T R A C T

We evaluated the safety and efficacy of standard-dose yttrium-90 (Y^{90}) ibritumomab tiuxetan combined with high-dose BEAM (carmustine, etoposide, cytarabine, and melphalan) after first-line induction treatment in young patients with poor prognoses diffuse large B cell lymphoma (DLBCL) (clinicaltrials.gov: NCT00689169). Seventy-five high-risk (≥2 International Prognostic Index [IPI] factors) consecutive DLBCL patients (≤65 years old) in complete remission (CR) or partial remission (PR) after rituximab chemotherapy were treated with Y^{90} ibritumomab tiuxetan and BEAM regimen followed by autologous stem cell transplantation (ASCT). The median follow-up was 34 months. Of the 75 patients, 71 underwent ASCT and were eligible for analysis. Median time to reach a neutrophil count of >500/μL and platelet count of >20,000/μL was 11 days. Mucositis ≥3 (51%) occurred in most patients. Other adverse events were similar to those seen with BEAM alone. The overall response rate was 86%; 59 patients (83%) achieved a CR or unconfirmed CR. The 2-year event-free survival (EFS), overall survival (OS), and disease-free survival were 79%, 83%, and 91%, respectively. Disease status (CR/PR) and positron emission tomography (PET) findings before transplantation did not predict treatment failure. The IPI (2 versus >2) and maximum tumor diameter of ≥10 cm at diagnosis appeared to be prognosis factors for OS but not for EFS. Adding Y^{90} ibritumomab tiuxetan to BEAM is safe and does not increase transplantation-related toxicity. First-line consolidation with Y^{90} ibritumomab tiuxetan and high-dose chemotherapy induced high rates of EFS and OS in poor-prognosis patients with DLBCL, regardless of PET status after induction treatment and warrants a randomized study.

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma, accounting for 31% of newly diagnosed non-Hodgkin lymphoma. Outcomes of

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DLBCL have improved with the addition of rituximab [1], but further progress is needed for poor-prognosis patients because the results are far from satisfactory. The 3-year event-free survival (EFS) ranges from approximately 70% in patients with 2 adverse prognostic factors to 50% in patients with 3 to 5 factors [2,3], according the International Prognostic Index (IPI) [4]. Results from the Collaborative Trial in Relapses Aggressive Lymphoma showed that only 21% of patients previously treated with rituximab achieved durable remission after salvage therapies [5], demonstrating that improvement in first-line treatment in high-risk (IPI $\geq$2) patients with DLBCL is a crucial issue.

Data for young patients with at least 2 adverse prognostic factors treated with R-ACVBP (rituximab, doxorubicine, cyclophosphamide, vinblastine, bleomycine, and prednisone) and upfront consolidation with high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) showed a 4-year progression-free survival (PFS) rate of 76% [6]. Despite controversy, recent randomized studies have confirmed these encouraging results and suggested that high-dose BEAM (carmustine, etoposide, cytarabine, and melphalan) followed by ASCT resulted in a significantly higher PFS than standard dose–dense chemotherapy, especially in patients with more than 2 IPI factors responding to first-line therapy containing rituximab [7,8]. Compared with immunotherapy alone, radioimmunotherapy (RIT) provides the added advantages of radioisotope emission, which acts over a multicellular range and, thereby, distributes the radiation more uniformly throughout the malignant tissue. Yttrium-90 (Y^{90}) ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals; Irvine, CA) is a radiolabeled monoclonal antibody approved for treatment of rituximab-relapsed/refractory CD20 follicular B cell lymphoma [9]. Several studies have shown that Zevalin (Spectrum) is also effective in aggressive lymphomas [10,11]. At the recommended dose of .4 mCi/kg, Y^{90} ibritumomab tiuxetan therapy is well tolerated, with myelosuppression as the only dose-limiting factor. Its good tolerability allows for its use in combination with high-dose myeloablative regimens. The first studies in heavily pretreated patients demonstrated that the addition of Y^{90} ibritumomab tiuxetan does not increase toxicities over those in patients treated with standard BEAM [12-14]. Y^{90} ibritumomab tiuxetan–based conditioning has shown a relapse incidence similar to that of total body irradiation but with lower toxicity and better survival [15].

As a component of pretransplantation conditioning regimens, Y^{90} ibritumomab tiuxetan is an effective option for enhancing clinical outcomes when combined with HDT followed by ASCT, and it can potentially spare patients from radiotherapy or total body irradiation. We conducted a prospective phase 2 trial that was designed to allow for an increased number of patients to be studied for toxicities and to evaluate the efficacy in poor-prognosis DLBCL patients with a high risk of relapse occurring mostly in the first 2 years after transplantation.

MATERIALS AND METHODS

Eligibility

Patients from 18 to 65 years old at diagnosis with pathologically proven $CD20^+$ DLBCL (World Health Organization classification) with 2 or more IPI factors were eligible for this study. All patients were included after R-CHOP (rituximab, doxorubicine, cyclophosphamide, vincristine, and prednisone) (4 to 6 cycles) or R-ACVBP (rituximab, doxorubicine, cyclophosphamide, vinblastine, bleomycine, and prednisone) (4 cycles) if they were chemosensitive (complete remission [CR], unconfirmed CR [CRu], or partial remission [PR]), according to the 1999 International Workshop Criteria [16]. Positron emission tomography (PET) scans interpreted according to the consensus criteria of the International Harmonization Project (IHP) [17] were required before transplantation, but they were not decisional. All patients had sufficient peripheral blood stem cells harvested before study entry ($\geq 3 \times 10^6$ CD34 cells/kg). Additional requirements included a World Health Organization performance status of 0 or 1; seronegativity for human immunodeficiency virus, hepatitis B, and hepatitis C; no serious active disease or comorbid medical conditions; creatinine level of <2.5 times the upper normal limit; bilirubin level of <30 μmoL/L; transaminase levels of <2.5 times the upper normal limit; adequate pulmonary function; and a left cardiac ejection fraction of >50%. The exclusion criteria included other lymphoma diagnoses, histological transformation in diffuse large cell from a low-grade B cell lymphoma, involvement of the central nervous system, bone marrow infiltration before transplantation, or poor bone marrow reserve defined by a neutrophil count of <1.5 Giga/l or platelet count of <100 Giga/l. All patients had previously provided written informed consent approved by local ethical committees in accordance with the Declaration of Helsinki.

Study Design

This prospective phase 2 open-label multicenter study was designed to assess the safety and efficacy of a preparative regimen comprising Y^{90} ibritumomab tiuxetan (Zevalin, Spectrum) and high-dose BEAM followed by ASCT after first-line treatment containing rituximab in patients with poor-risk DLBCL. A screening examination was performed before registration and included a clinical examination, staging of the disease with computed tomography, bone marrow biopsy (if positive at diagnosis), fluorodeoxyglucose (FDG)-PET scanning, and laboratory testing. A central review of the histological diagnosis was performed for each patient enrolled in the trial. Pathological specimens of 49 of 75 patients with histological material available at diagnosis were more extensively analyzed to classify the tumor biopsy specimens into germinal center B cell–like (GCB) or non-GCB subtypes as previously published by Hans et al. [18]. The expression of additional biological markers, such as *BCL2* oncoprotein, was determined by immunohistochemistry. Immunostaining was performed on either full slides or tissue microarrays and reviewed until consensus by 2 pathologists at the Lymphoma Study Association (LYSA) Center of Pathology.

All adverse events that occurred during the study treatment or follow-up periods were graded using the Common Terminology Criteria for Adverse Events version 3.0. Patients were required to undergo formal disease assessment 3 months after ASCT by computed tomography. A PET scan was performed if positive before ASCT. After day 100, disease assessment was performed every 3 months for 2 years, then every 6 months for 3 years. The expected total study period was 5 years.

Treatment

On day -21, patients received an infusion of rituximab (250 mg/m^2), and on day -14, patients received a dose of rituximab (250 mg/m^2) followed by Y^{90} ibritumomab tiuxetan. The exact dose of Y^{90} ibritumomab tiuxetan was based on the patient's weight during the baseline evaluation and platelet count 3 days before Zevalin (Spectrum) administration. If the platelet count was $\geq$150 G/L, then .4 mCi/kg (15 MBq/kg) of Y^{90} ibritumomab tiuxetan was administered; if the platelet count was $\geq$100 Giga/l, then .3 mCi/kg (11 MBq/kg) of Y^{90} ibritumomab tiuxetan was administered. A maximum dose of 32 mCi of Y^{90} ibritumomab tiuxetan was administered to those patients whose body weight exceeded 80 kg. On days -7 to −2, high-dose BEAM was administered based on the adjusted ideal body weight (carmustine at 300 mg/m^2 on day −7, etoposide at 100 mg/m^2, cytarabine at 200 mg/m^2 twice daily on days −6 to −3, and melphalan at 140 mg/m^2 on day −2) (Z-BEAM). Peripheral blood stem cells were infused on day 0 according to institution protocol. After ASCT, hematopoietic growth factor support could be given according to local policy. Supportive treatments in the form of hydration, antiemetics, antimicrobial prophylaxis, blood component therapy, and nutritional supportive care were administered according to the standard use in each center.

Statistics

Patients' results were analyzed on an intent-to-treat (ITT) and per-protocol basis. All time-to-events endpoints were assessed both from date of inclusion and from date of transplantation. The primary endpoint was EFS and was used to assess sample size. In previous studies, 2-year EFS was estimated to 70%. We estimated the 2-year EFS of Z-BEAM to 85%. A sample size of 75 patients, recruited over 3 years and followed for a minimum of 1 year, will provide 80% power at the overall 5% (2-sided) significance level to detect a 2-year EFS above 70%. Event is defined as death of any cause, relapse in complete responders, progression during or after treatment, and therapy changes during allocated treatment. The overall response rate, CR,