

A phase II trial of CHOP chemotherapy followed by yttrium 90 ibritumomab tiuxetan (Zevalin) for previously untreated elderly diffuse large B-cell lymphoma patients

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Background: A prospective, single-arm, open-label, nonrandomized phase II combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus radioimmunotherapy trial was conducted to evaluate the efficacy and safety in untreated elderly diffuse large B-cell lymphoma (DLBCL) patients.

Patients and methods: From February 2005 to April 2006, in our institute we treated 20 eligible elderly (age ≥ 60 years) patients with previously untreated DLBCL using a novel regimen consisting of six cycles of CHOP chemotherapy followed 6–10 weeks later by ⁹⁰Y ibritumomab tiuxetan.

Results: The overall response rate to the entire treatment regimen was 100%, including 95% complete remission (CR) and 5% partial remission. Four (80%) of the five patients who achieved less than a CR with CHOP improved their remission status after radioimmunotherapy. With a median follow-up of 15 months, the 2-year progression-free survival was estimated to be 75%, with a 2-year overall survival of 95%. The ⁹⁰Y ibritumomab tiuxetan toxicity included grade ≥ 3 hematologic toxicity in 12 of 20 patients; the most common grade ≥ 3 toxic effects were neutropenia (12 patients) and thrombocytopenia (7 patients). Transfusions of red blood cells and/or platelets were given to one patient.

Conclusion: This study has established the feasibility, tolerability, and efficacy of this regimen for elderly patients with DLBCL.

Key words: Chemotherapy, DLBCL, elderly patients, yttrium 90 ibritumomab tiuxetan

introduction

Curative treatment is a perfectly valid option for elderly patients with diffuse large B-cell lymphoma (DLBCL), although the prognosis worsens with increasing age. Only in cases where a careful examination of the patient and his concomitant diseases indicates that full-dose therapy may carry an unacceptable risk can a palliative treatment approach be justified. Considering the combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen as the reference therapy [1] for the treatment of DLBCL, when CHOP is used at lower doses in the elderly, the remission rate declines and survival shortens compared with results in patients aged < 60 years [2]. The standard CHOP regimen, on the other hand, achieves similar progression-free survival (PFS) to that achieved in younger patients, but carries a much higher

risk of severe toxicity or death: 15%–30% in various different retrospective series.

Recently, a combination of rituximab plus standard CHOP regimen has become the standard for treating elderly patients with DLBCL. This combination of eight cycles of chemoimmunotherapy every 3 weeks has proved superior to CHOP alone [3–5]. It increases the 'complete' response rate, decreases the relapse rate, as well as prolonging event-free survival, disease-free survival, and overall survival (OS). Improving on these results, however, poses several questions: the number of cycles (six or eight), the dose-dense regimen (CHOP-14 instead of conventional CHOP-21), and the role of radioimmunotherapy.

Pfreundschuh et al. conducted the RICOVER-60 trial in which patients were randomly assigned to receive to receive six or eight cycles of CHOP-14, with or without eight infusions of rituximab. The investigators concluded that six cycles of rituximab–CHOP-14 should be used in preference to eight cycles of rituximab–CHOP-21 in elderly patients with DLBCL [6].

Radioimmunotherapy has emerged as an important treatment option for patients with B-cell non-Hodgkin's

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lymphoma. ^{90}Y ibritumomab is a murine monoclonal immunoglobulin G1 kappa antibody to CD20, a surface antigen that is expressed on 90% of B-cell lymphomas [7] and conjugated to the metal chelator tiuxetan for retention of the beta emitter ^{90}Y for therapy. Thus, treatment with ^{90}Y ibritumomab tiuxetan targets radiation to B-cell lymphomas, which are inherently sensitive to radiation [8].

In the initial phase I–II trial of ^{90}Y ibritumomab tiuxetan, responses were seen in 43% of the 14 patients with DLBCL, including complete remissions (CRs) in 29% [9]. Gordon et al. [10] provided additional data supporting the safety and activeness of ^{90}Y ibritumomab tiuxetan in patients with DLBCL. In the 12 patients in this phase I–II trial who had a median of two prior regimens, the response rate was 58%, including 33% CRs. A multicenter phase II study in Europe has assessed the role of ^{90}Y ibritumomab tiuxetan in 104 patients with relapsed or refractory elderly patients with DLBCL who were not eligible for high-dose treatment, mainly because of advanced age [11]. The overall response rate was 44% and was noted to be higher in patients who had not had prior therapy with rituximab compared with those who had been previously treated with rituximab and chemotherapy as their primary treatment; prior rituximab exposure was one among other possible explanations for the lower response after radioimmunotherapy since this subset of patient with prior rituximab also was the one with the highest proportion of primary refractory disease and poor prognostic features.

In view of these findings, we decided to investigate the efficacy and safety of a novel approach combining induction chemotherapy with CHOP followed by consolidation with ^{90}Y ibritumomab tiuxetan, in a phase II trial for elderly patients with previously untreated DLBCL.

patients and methods

patient eligibility

Patients older than 60 years of age with biopsy-proven, untreated bidimensionally measurable stage II, stage III, or stage IV DLBCL expressing the CD20 antigen were eligible for this trial if they had a World Health Organization (WHO) performance status of zero to two. All patients were notified of the investigational nature of this study and signed a written informed consent approved in accordance with institutional guidelines, including the Declaration of Helsinki. The study was approved by the institutional review board.

All diagnostic biopsies were reviewed by an expert pathologist (SP) from our institute to check the diagnosis of DLBCL according to the WHO classification [12].

baseline studies

All patients entered in this trial were required to undergo a full history, physical examination, complete blood cell count with differential leukocyte count, platelet count, computed tomography (CT) scan of the neck, chest, abdomen, and pelvis, positron emission tomography (PET) scan and bone marrow aspiration, and biopsy. As per good medical practice, patients were also tested for blood chemistry (including creatinine clearance, liver function tests, uric acid, and lactate dehydrogenase) and underwent urinalysis and electrocardiography. Patients with a history of impaired cardiac status were assessed by echocardiograph and were only eligible if the cardiac ejection fraction was normal.

treatment plan

Patients were treated by standard CHOP chemotherapy every 21 days for six cycles. Dosages of 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 1.4 mg/m² (maximum 2.0 mg) vincristine were administered i.v. on day 1, and 100 mg prednisone was given orally daily for 5 days each cycle. Allopurinol (300 mg orally) was recommended as an adjunctive therapy for patients with bulky disease. If there were <1500/μl granulocytes or <100 000/μl platelets by the time the next cycle was due, treatment was delayed for 1 week and counts were repeated. If counts had not recovered after 2 weeks, the patient was treated at 75% of the last dose of cyclophosphamide and doxorubicin received. Reescalation was at the discretion of the treating physician. Growth-stimulating factors were not administered in order to prevent neutropenia, but patients who experienced grade 3 or 4 neutropenia or developed neutropenic fever between cycles of chemotherapy were allowed to receive growth factors for subsequent cycles of therapy at the discretion of the treating physician.

restaging

Patients were restaged 4–6 weeks after completion of the sixth cycle of CHOP chemotherapy with physical examination, blood testing, CT scan, PET scan and bone marrow aspiration, and biopsy. Patients achieving at least a partial response after six cycles of CHOP were eligible for consolidation with ^{90}Y ibritumomab tiuxetan provided the granulocyte count was >1500/μl granulocytes, the platelet count exceeded 100 000/μl, and the bone marrow examination on completion of CHOP chemotherapy showed no more than a 25% involvement with lymphoma.

Six to 10 weeks after completing the sixth cycle of CHOP chemotherapy, the eligible patients were treated with one course of ^{90}Y ibritumomab tiuxetan (Figure 1), consisting of an initial infusion of rituximab 250 mg/m² on day 1 and then on days 7, 8, or 9; a second infusion of rituximab 250 mg/m² was followed by a weight-based dose of ^{90}Y ibritumomab tiuxetan (provided by Bayer Schering Pharma, Berlin, Germany), given as a slow i.v. bolus >10 min. The dose of ^{90}Y ibritumomab tiuxetan was 11.1 MBq/kg (0.3 mCi/kg) in patients with a pretreatment platelet count of 100 000–149 000/μl and 14.8 MBq/kg (0.4 mCi/kg) in those with a count of 150 000/μl or higher. In all cases, the maximum total dose was 1184 MBq (32 mCi).

^{90}Y ibritumomab tiuxetan was routinely administered on an outpatient basis in view of the lack of gamma emissions.

Disease status was evaluated by using physical examination, bone marrow biopsy, a computer tomography scan of the neck, chest, abdomen, and pelvis, and PET scan as well as other clinically relevant information. This assessment was repeated 3 months after ^{90}Y ibritumomab tiuxetan infusion.

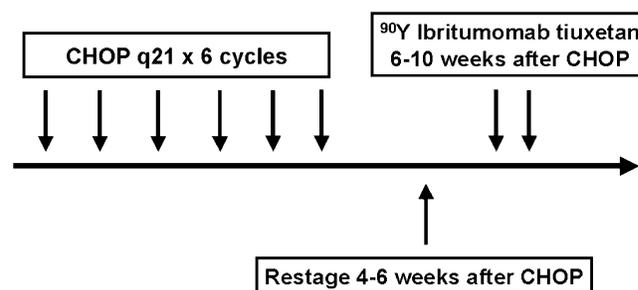


Figure 1. The combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and ^{90}Y ibritumomab tiuxetan regimen.

Safety and tolerability were assessed by monitoring the incidence, severity, and type of any adverse event. Adverse events were graded according to the Common Toxicity Criteria.

Responses were classified according to the International Workshop Response Criteria [13].

statistical analysis

The primary end point of this study was the complete response rate (including PET evaluation) associated with CHOP plus radioimmunotherapy.

Sample size estimation was carried out by Fleming's single-stage procedure [14, 15]. Previous experience shows that the response rate, adjusted for the response criteria as in par, has been 50%. Defining π_0 as the proportion of response below the treatment that does not warrant further investigations and π_a as the proportion of responses beyond a phase III trial should be carried out, we set $\pi_0 = 0.5$ and $\pi_a = 0.8$. The number of patients required, given a type I error (α) at 0.05 two-sided and a power of $1 - \beta = 80\%$, is 18 and the number of successes (responses) 13. If, at the end of the trial, at least 13 responses (successes) are observed, the treatment will be accepted for a phase III trial [16]. OS and PFS curves were plotted by the Kaplan–Meier method [17]. PFS was defined as the time from registration to the first observation of progressive disease or death as a result of any cause.

results

patient characteristics

Twenty patients were registered in this trial from February 2005 to April 2006 when the study reached completion and was closed. The patients' characteristics are listed in Table 1. The median age of patients on the trial was 68 years, with a range of 61–84 years. Twelve (60%) were male and eight (40%) were female. Six patients were stage II and 14 stage III–IV. Two patients (10%) had bulky disease. Globally, 16 patients were intermediate and high risk according to the International Prognostic Index score [18].

clinical response

All patients completed the CHOP and ^{90}Y ibritumomab tiuxetan protocol. There is no record of any patient receiving

Table 1. Patients' characteristics ($n = 20$)

Median age, years (range)	68 (61–84)
Sex, n (%)	
Male	12 (60)
Female	8 (40)
Symptoms, n (%)	
A	18 (90)
B	2 (10)
Bulky disease, n (%)	
Yes	2 (10)
No	18 (90)
LDH level, n (%)	
Elevated	16 (80)
Normal	4 (20)
Stage, n (%)	
II	6 (30)
III	5 (25)
IV	9 (45)
IPI score, n (%)	
0–1	5 (25)
≥ 2	15 (75)

LDH, lactate dehydrogenase; IPI, International Prognostic Index.

a reduced dose of ^{90}Y ibritumomab tiuxetan because of the persisting thrombocytopenia following CHOP.

The overall response rate to the entire treatment regimen was 100%, including 95% CR and 5% partial remission (PR). Therapy with ^{90}Y ibritumomab tiuxetan substantially improved CR rate (Table 2). Of the five patients initially with a PR on CHOP regimen alone, addition of ^{90}Y ibritumomab tiuxetan improved the overall best response (from PR to CR) in four (80%); this evaluation was done utilizing CT and PET scans; all these four patients achieved a PET negativity after radioimmunotherapy.

With a median follow-up time of 15 months, 3 of 20 eligible patients have experienced progression or died, yielding an estimated 2-year PFS rate of 75% (Figure 2). One patient died because of lymphoma progression; the 2-year estimate of OS was 95% (Figure 2). Regarding the three patients who progressed or died, after CHOP alone two had obtained PR (one high-risk and one low-risk IPI, respectively) and one a CR (low-risk IPI); subsequently, after ^{90}Y ibritumomab tiuxetan two of them were in CR (PET negativity) and one in PR (the high-risk IPI one had achieved a PR with CHOP alone).

safety

There were no treatment-related deaths. The CHOP regimen was well tolerated by most patients. Reversible hematologic toxic effects constituted most of the adverse events, including grade 4 hematologic toxicity in 3 (15%) patients and grade 3

Table 2. Response to therapy

Response	After CHOP n (%)	After CHOP + ^{90}Y ibritumomab tiuxetan n (%)
Complete remission	15 (75)	19 (95)
Partial remission	5 (25)	1 (5)

CHOP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone.

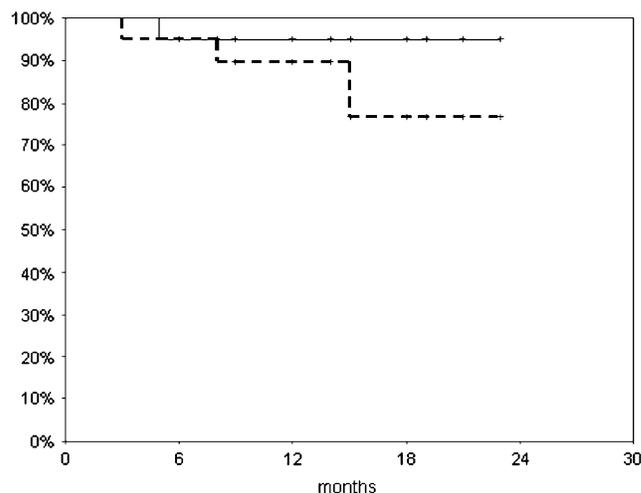


Figure 2. Overall survival (solid line) and progression-free survival (dotted line) curves of all 20 patients.

hematologic toxicity in 10 (50%) patients. It was noted that all these patients presented neutropenia. Three patients (15%) developed febrile neutropenia, and two of them were hospitalized due to febrile neutropenia. Two (10%) patients experienced grade 2 nausea and vomiting and one (5%) patient had grade 3 neuropathy.

regarding ^{90}Y ibritumomab tiuxetan, there were no infusion-related reactions

Adverse events after ^{90}Y ibritumomab tiuxetan treatment were primarily hematologic and transient; no patient discontinued treatment because of an adverse event. The duration of hematologic toxicity is listed in Table 3. Grade 3–4 thrombocytopenia and neutropenia occurred in 7 patients (37%) and 12 patients (58%), respectively. Two patients (10%) received granulocyte colony-stimulating factors; only one patient (5%) received platelet transfusions, and none received red blood cell transfusions.

No patient developed elevated thyroid-stimulating hormone levels and any secondary malignancies.

discussion

This study has established the feasibility, tolerability, and efficacy of sequential treatment with six cycles of CHOP chemotherapy followed by ^{90}Y ibritumomab tiuxetan as front-line therapy for untreated elderly DLBCL patients. Patients up to age 84 tolerated the sequential treatment regimen well.

The clinical evaluation of immunotherapy on the basis of anti-CD20 monoclonal antibodies has markedly affected the treatment approach for elderly patients with DLBCL. Rituximab is widely employed as a treatment administered alone or in combination with chemotherapy. In parallel, radioimmunotherapy with ^{90}Y ibritumomab tiuxetan has been developed and proves to be among the most active agents in lymphoma therapy. Its toxicity is manageable and consists primarily of transient myelosuppression in addition to the typical antibody-associated infusion reactions. Clinical trials with this agent have shown significant activity in transformed B-cell non-Hodgkin's lymphoma and in DLBCL [9, 10], including disease that is resistant to chemotherapy or unlabeled rituximab [11].

The data have demonstrated that a substantial proportion of patients can have durable remissions, extending in some cases longer than 3 years. On the basis of these data, further investigations are monitoring radioimmunotherapy either as

a stand-alone initial treatment [19] or as a consolidation after initial treatment with chemotherapy (with or without rituximab) [20–22]. Initial reports from these studies have shown acceptable toxicity with promising antilymphoma activity, and randomized studies are in progress. The principal challenge when it comes to applying these radiolabeled immunotherapies is how to integrate them into the treatment approach in the most effective manner. The fact that radioimmunotherapy has demonstrated the highest response rate of any 'single-agent' approach in lymphoma therapy highlights the potential importance attaching to this therapeutic modality.

The reason why we decided to conduct this sequential treatment utilizing conventional chemotherapy followed by radioimmunotherapy (^{90}Y ibritumomab tiuxetan) was to test its degree of activeness and safety in this particular subset of elderly patients. By the end of sequential combined treatment, 19 (95%) had achieved CR and the remaining patient had PR. More importantly, among the five patients who achieved a PR with CHOP, four (80%) improved their remission status after treatment with ^{90}Y ibritumomab tiuxetan.

Toxic effects were generally mild without any aspect of cumulative toxicity. Hematologic toxicity was moderate with ^{90}Y ibritumomab tiuxetan, following six cycles of CHOP and rarely led to infection or required transfusion support. On the other hand, non-hematologic toxicity was practically absent with ^{90}Y ibritumomab tiuxetan.

Because this novel sequential treatment appears promising compared with the literature data on the combination of CHOP plus rituximab, we are currently carrying out a trial with CHOP plus rituximab followed by ^{90}Y ibritumomab tiuxetan in untreated elderly DLBCL patients, reducing the number of CHOP cycles from six to four, with a rituximab administration for each CHOP cycle. The rationale is to utilize all the therapeutic approaches—chemotherapy, immunotherapy, radioimmunotherapy—reducing conventional chemotherapy and probably its related toxicity, hematologic and non-hematologic, in elderly patients. In addition, CHOP plus rituximab followed by ^{90}Y ibritumomab tiuxetan is certainly a sequence to be tested in a proper phase III, but the comparative efficacy (with CHOP-14 plus rituximab) can only be assessed in this trial.

funding

BolognAIL.

Table 3. Hematologic toxicity post radioimmunotherapy

Variable	Baseline	Nadir (range)	Days from baseline to nadir	Median duration for patients with grade 3 or 4 nadir (days)
ANC, cells/mm ³	3300 (1600–5460)	800 (255–3000)	39 (20–60)	32 (10–66)
Platelets, cells/mm ³	217 (150–500)	42 (9–187)	35 (20–43)	22 (10–49)
Hemoglobin, g/dl	13.5 (12–14.5)	11.8 (8.7–14.2)	43 (20–60)	–

ANC, absolute neutrophil count.

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