Phase II Trial of Short-Course R-Chop Followed by $^{90}$Y-Ibritumomab Tiuxetan in Previously Untreated High-Risk Elderly Diffuse Large B-Cell Lymphoma Patients

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Abstract

**Purpose:** This study aimed to evaluate the efficacy and safety of the treatment with $^{90}$Y-ibritumomab tiuxetan following a short-course of rituximab with cyclophosphamide-adriamycin-vincristine-prednisone (R-CHOP) in high-risk elderly patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

**Experimental Design:** From December 2006 to October 2008, 55 high-risk elderly (age $\geq$ 60 years) untreated DLBCL patients were treated in seven Italian institutions with a short-course of chemotherapy consisting of four cycles of R-CHOP21 followed by $^{90}$Y-ibritumomab tiuxetan 6 to 10 weeks later.

**Results:** Of the 55 patients, 48 underwent radioimmunotherapy. The overall response rate to the entire treatment regimen was 80%, including 73% complete remissions and 7% partial remissions. Eight (50%) of the 16 patients who achieved less than a complete response with CHOP improved their remission status after $^{90}$Y-ibritumomab tiuxetan administration. With a median follow-up of 18 months, the 2-year progression-free survival was estimated to be 85%, with a 2-year overall survival of 86%. $^{90}$Y-ibritumomab tiuxetan toxicity consisted of grade 3 to 4 hematologic toxicity in 28 of 48 patients, mainly neutropenia (23 patients) and thrombocytopenia (15 patients). Red cells and/or platelets transfusions were given to three patients.

**Conclusion:** This study evaluated the feasibility, efficacy, and safety of a short-course R-CHOP21 regimen followed by $^{90}$Y-ibritumomab tiuxetan in high-risk elderly DLBCL patients. Clin Cancer Res; 16(15); 3998–4004. ©2010 AACR.
event-free survival (EFS) in high-risk patients was 41% versus 27%, again comparing R-CHOP and CHOP. In the latter study (Ricovero 60), conducted by the German High Grade Non Hodgkin's Lymphoma Study Group [Deutsche Studiengruppe Hochmaligne Non-Hodgkin-Lymphome (DSHNHL)], 1,222 patients were randomized to receive six or eight courses of CHOP14 with or without rituximab and radiotherapy to sites of initial bulky disease (2). R-CHOP14 significantly improved the 3-year EFS (66% versus 47%), progression-free survival (PFS), and OS when compared with six cycles of CHOP14 treatment.

Whether R-CHOP14 is superior or not to R-CHOP21 is still to be formally shown. Randomized clinical trials between R-CHOP21 and R-CHOP14 are ongoing by GELA and the British National Lymphoma Investigation (BNLI). The BNLI has recently reported some preliminary results on a phase III randomized trial comparing the two different schedules: 462 patients in the R-CHOP21 arm and 481 in R-CHOP14. The radiologic complete responses were 63% and 58%, respectively (5). Therefore, the choice between R-CHOP21 and R-CHOP14, both considered as standard therapy, should be based mainly on the experience of the center, on the patients' performance status, and on comorbidities, thus propending for a less aggressive treatment (R-CHOP21) in elderly and more clinically involved patients. To improve the efficacy of R-CHOP14 in elderly patients, the DSHNHL has explored a “dense” R-CHOP14 with an increased dose of rituximab. At present, the optimal dose of rituximab has not yet been established: rituximab serum levels build up slowly after infusion, and it might be possible that a dose-dense immunotherapy could improve the efficacy of the treatment. The aim of the DENSE-R-CHOP14 trial was to explore a supplemented dose intense rituximab during the first two cycles of R-CHOP14 in elderly patients, maintaining a single dose in the subsequent cycles, for a total of 12 doses of rituximab delivered in 6 courses of chemotherapy. Rituximab serum levels markedly increased, thus suggesting a higher efficacy in poor-risk patients, with a 1-year EFS of 74%, against 65% related to the standard R-CHOP14 treatment. On the other hand, an increased incidence of infection was also documented, mainly interstitial pneumonia (6). This strategy is currently under investigation in a controlled randomized study.

An innovative therapeutic option that should be investigated to increase patients' outcomes in poor-prognosis DLBCL might be the addition of radioimmunotherapy. The efficacy of the radioimmunoconjugate 90Y-ibritumomab tiuxetan has been shown in patients with relapsed or refractory aggressive DLBCL, with promising response rates and durable response (7–9). Preliminary data from phase II studies in aggressive lymphomas (DLBCL and mantle cell lymphoma) suggest that 90Y-ibritumomab tiuxetan is effective also in this disease setting, namely as consolidation treatment after chemotherapy or chemoimmunotherapy (10–12).

Moving from these data and from our previous experience on the role of 90Y-ibritumomab tiuxetan after CHOP in untreated high-risk elderly DLBCL patients (11), we designed a phase II trial aimed at increasing the global treatment efficacy including 90Y-ibritumomab tiuxetan, along with a decreased exposure to cytotoxic drugs by using a short-course R-CHOP chemotherapy. In this trial, patients were to receive R-CHOP21 for four cycles, instead of six cycles, followed by treatment with 90Y-ibritumomab tiuxetan.

**Patients and Methods**

**Patients' eligibility and demography**

Patients older than 65 years of age (or age 60 to 65, but not eligible for high-dose therapy with autologous stem cell transplantation) with biopsy-proven and bidimensionally measurable stage II (with bulky disease), stage III, or stage IV DLBCL, expressing the CD20 antigen, were eligible for this trial. Patients were to be previously untreated, with a WHO performance status ≤2 and a high-intermediate or high IPI score (13).

Fifty-five patients met the inclusion criteria and were subsequently enrolled in this trial that involved seven Italian cooperative institutions. Enrollment started in December 2006 and concluded in October 2008, when the study reached its completion and was closed.

Table 1 lists the patients' characteristics. The median age of patients in the trial was 70 years (range, 61–83 years). Twenty-six (47%) were male and 29 (53%) were female. Four patients were stage II (with bulky disease), 51 stage III-IV. Eight patients (14.5%) had bulky disease.

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 (Ethical Committee), and has been registered at ClinicalTrials.gov, http://www.clinicaltrials.gov, NCT00850512.
Table 1. Patients' characteristics (n = 55)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in y (range)</td>
<td>70 (61-83)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (47)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (53)</td>
</tr>
<tr>
<td>Symptoms, n (%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>39 (71)</td>
</tr>
<tr>
<td>B</td>
<td>16 (29)</td>
</tr>
<tr>
<td>Bulky disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (14.5)</td>
</tr>
<tr>
<td>No</td>
<td>47 (85.5)</td>
</tr>
<tr>
<td>LDH level, n (%)</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>50 (91)</td>
</tr>
<tr>
<td>Normal</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (7)</td>
</tr>
<tr>
<td>III</td>
<td>11 (20)</td>
</tr>
<tr>
<td>IV</td>
<td>40 (73)</td>
</tr>
<tr>
<td>aa-IPI score (%)</td>
<td></td>
</tr>
<tr>
<td>High-intermediate (2)</td>
<td>30 (55%)</td>
</tr>
<tr>
<td>High risk (3)</td>
<td>25 (45%)</td>
</tr>
</tbody>
</table>

Abbreviation: LDH, lactate dehydrogenase.

All diagnostic biopsies were reviewed by an expert pathologist (S.P.) from the Seràgnoli Institute, and then were categorized in accordance with the WHO classification (14).

Baseline studies

All the patients enrolled into this trial were required to undergo a full history, physical examination, complete blood cell count with leukocyte differential, platelet count, computed tomography (CT) scan of neck, chest, abdomen, and pelvis (with and without contrast), 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan, and bone marrow aspiration and biopsy. Bulky disease was defined as the presence of a nodal or extranodal mass ≥10 cm on its major diameter, as documented on CT scan. Patients were also tested for serum creatinine, liver function (including hepatitis-B virus antigens and hepatitis-C virus antibodies), uric acid, lactate dehydrogenase, and HIV, and underwent urinalysis and electrocardiography. Patients with a history of impaired cardiac status were further evaluated by echocardiography, and were then considered eligible if the cardiac ejection fraction was within normal ranges.

Treatment plan

Patients were treated by R-CHOP21 chemotherapy every 21 days for 4 cycles; standard doses of 375 mg/m² rituximab, 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 1.4 mg/m² (maximum total dose of 2.0 mg) vincristine were administered i.v. on day 1; 100 mg/day prednisone was given orally for 5 days for each cycle, starting from day 1. Oral allopurinol (300 mg/day) was recommended for at least 15 days as an adjunctive therapy for patients with bulky disease.

If there were <1,500/μL granulocytes or <100,000/μL platelets by the time the next cycle was due, treatment would be delayed for 1 week and then blood counts would be repeated. If blood counts did not recover after 2 weeks, the patient would be treated at 75% of the last dose of cyclophosphamide and doxorubicine received. A subsequent dose re-escalation would be taken into consideration at the discretion of the treating physician.

Granulocyte colony-stimulation factor (G-CSF) was not administered to prevent neutropenia, according to our institutional guidelines; patients who experienced grade 3 or 4 neutropenia or who developed neutropenic fever between cycles of chemotherapy were allowed to receive growth factors, at the discretion of the treating physician.

Restaging

Patients were restaged 3 to 4 weeks after the completion of the fourth cycle of R-CHOP21 chemotherapy, through a complete physical examination, blood testing, CT scan, PET scan, and bone marrow aspiration and biopsy (if bone marrow involvement was documented during baseline evaluation).

Responses were classified according to the revised response criteria for malignant lymphoma (15). Patients achieving at least a partial response after four cycles of R-CHOP21 were considered eligible for further consolidation with 90Y-ibritumomab tiuxetan, provided a granulocyte count and a platelet count greater than 1,500/μL and 100,000/μL, respectively, and a bone marrow lymphoma infiltration not exceeding the 25% of the total marrow cellularity, were assessed on completion of the induction chemotherapy.

Six to 10 weeks after completing the fourth cycle of R-CHOP21 chemotherapy, eligible patients were treated with a single course of 90Y-ibritumomab tiuxetan (Fig. 1). The radioimmunotherapy treatment plan consisted of an initial infusion of rituximab, at a dose of 250 mg/m² on day 1, then repeated on days 7, 8, and 9. The second infusion of rituximab was immediately followed by a weight-based dose of 90Y-ibritumomab tiuxetan (Bayer Schering Pharma), given as a slow i.v. push over 10 minutes. The dose of 90Y-ibritumomab tiuxetan was estimated in 11.1 MBq/kg (0.3 mCi/kg) for patients with a pretreatment platelet count of 100,000/μL to 149,000/μL and 14.8 MBq/kg (0.4 mCi/kg) for those with a platelet count of at least 150,000/μL. In all cases, the maximum total dose was 1184 MBq (32 mCi). 90Y-ibritumomab tiuxetan was routinely administered on an outpatient basis in view of the lack of γ emissions.

Because of the transitory myelosuppression generally observed after the administration of 90Y-ibritumomab tiuxetan, a complete blood cell count with leukocyte differential and platelet count was done in all patients.
on a weekly basis, from the third week after radioimmuno-
therapy until the complete hematologic recovery.

Disease status was evaluated again upon treatment
completion, through physical examination, bone marrow
biopsy (if still positive after induction chemotherapy),
CT scan of neck, chest, abdomen, and pelvis (with and
without contrast), and PET scan; other clinically relevant
information, such as the development of febrile neutro-
penia, the use of antibiotics or G-CSF, or blood transfusion
during cytopenia and the presence of any extrahematologic
toxicity, were also recorded. Patients’ re-assessment was
repeated three months after $^{90}$Y-ibritumomab tiuxetan
infusion.

Safety and tolerability were evaluated by monitoring the
incidence, severity, and type of any adverse event. Adverse
events were defined according to the WHO criteria for toxicity.

Statistical analysis
The primary end point of this study was the assessment
of the response rate (including PET evaluation) associated
with R-CHOP21 plus radioimmunotherapy.

Sample size estimation was carried out by Fleming’s
single-stage procedure (16, 17). Previous experience
shows that the response rate, adjusted for the response
criteria as in par, has been 50%. Defining $\pi_0$ as the propor-
tion of response below the treatment that does not
warrant further investigations and $\pi_a$ as the proportion
of responses beyond which a phase III trial should be
carried out, we set $\pi_0 = 0.6$ and $\pi_a = 0.8$. The number
of patients required, given a type I error ($\alpha$) at 0.05
two-sided and a power of 1-$\beta$ = 80%, was 48, and the
number of successes (responses) was 33. Considering a
drop-out rate of about 10%, the sample size was fixed
at 55. If, at the end of the trial, at least 33 responses
(succeses) were observed, the treatment would be accepted
for a phase III trial (18).

OS and PFS curves were plotted by the Kaplan-Meier
method (19). PFS was defined as the time interval from di-
agnosis to the first observation of disease relapse or death
as a result of any cause. Complete response and partial re-
response rates, as well as the proportion of patients with pro-
gressive disease, are expressed on an intention-to-treat
basis.

Results
Clinical response
At the time of reassessment after four cycles of
R-CHOP21, the overall response rate was 89%, with 32
of 55 (58%) patients achieving a complete response and
17 of 55 (31%) patients achieving a partial response; the
remaining 6 patients had progressive disease.
Forty-eight of 55 patients (more specifically, all the patients with complete response and 16 patients with partial response) were deemed eligible for subsequent consolidation with $^{90}\text{Y}$-ibritumomab tiuxetan. The remaining patient with partial response showed a lymphoma progression two weeks before radioimmunotherapy, and was then considered ineligible for consolidation treatment. There is no record of any patient receiving a reduced dose of $^{90}\text{Y}$-ibritumomab tiuxetan because of persisting thrombocytopenia following R-CHOP21.

The complete response rate after the end of the entire treatment (all the four cycles of R-CHOP21 and the administration of $^{90}\text{Y}$-ibritumomab tiuxetan) was 73% (40 of 55 patients). Four patients remained in partial response and 11 showed disease progression (4 patients previously in partial response and all the 7 ineligible for radioimmunotherapy).

The overall response rate for the entire treatment was 80%, including 73% complete response and 7% partial response. The therapy with $^{90}\text{Y}$-ibritumomab tiuxetan therefore substantially improved the complete response rate (Table 2). In particular, the addition of $^{90}\text{Y}$-ibritumomab tiuxetan improved the overall best response (from partial response to complete response) in 8 (50%) of the 16 patients in partial response after the R-CHOP21-only regimen.

Among the complete-response patients, 4 experienced a disease relapse after 6, 8, 12, and 14 months, respectively. At the median follow-up time of 18 months (range, 9-25 months), 4 patients experienced a disease relapse and 12 had a lymphoma progression, yielding an estimated 2-year DFS of 85% and an estimated 2-year OS of 86% (Fig. 2).

**Safety**

There were no treatment-related deaths. The R-CHOP21 regimen was well tolerated by most of the patients. Reversible hematologic toxicities constituted most of the adverse events, with grade 3 hematologic toxicity in 21 (39%) patients and grade 4 in 7 (13%) patients, mainly consisting of neutropenia. Four patients (9%) developed febrile neutropenia, and two of them required hospitalization and i.v. antibiotic treatment.

Regarding $^{90}\text{Y}$-ibritumomab tiuxetan, there were no infusion-related reactions. Adverse events after $^{90}\text{Y}$-ibritumomab tiuxetan treatment were primarily hematologic and transient; no patient discontinued treatment because of an adverse event. The severity of the hematologic toxicity (expressed as the lowest, i.e., nadir, concentration of granulocytes, platelets, and hemoglobin reached after radioimmunotherapy) and its duration are reported in Table 3. Grade 3 to 4 thrombocytopenia and neutropenia occurred in 19 patients (39.5%) and 23 patients (48%), respectively. Seven patients (14.5%) received G-CSF; only three patients (6.2%) received platelet transfusions, and none received RBC transfusions.

No patient showed a thyroid-stimulating hormone elevation, nor did any secondary malignancies occur.

**Discussion**

This study was aimed at establishing the feasibility, tolerability, and efficacy of a sequential treatment with

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**Table 3. Hematologic toxicity after radioimmunotherapy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (range)</th>
<th>Nadir (range)</th>
<th>Interval from baseline to nadir (range)</th>
<th>Median duration of grade 3-4 nadir (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>3,500 cells/mm$^3$ (1,550-6,120)</td>
<td>700 cells/mm$^3$ (210-2950)</td>
<td>37 d (22-59)</td>
<td>30 d (12-65)</td>
</tr>
<tr>
<td>Platelets</td>
<td>233,000 cells/mm$^3$ (154,000-498,000)</td>
<td>37,000 cells/mm$^3$ (10,000-121,000)</td>
<td>32 d (19-38)</td>
<td>21 d (9-52)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.1 g/dL (11.4-15.2)</td>
<td>11.3 g/dL (8.9-13.0)</td>
<td>41 d (20-55)</td>
<td>/</td>
</tr>
</tbody>
</table>

Abbreviation: ANC, absolute neutrophil count.
Table 4. First-line consolidation treatment with $^{90}$Y-ibritumomab tiuxetan

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients' subset</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>CR after induction</th>
<th>CR after $^{90}$Y-IT</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. (10)</td>
<td>Untreated mantle cell-lymphoma</td>
<td>4×R-CHOP + $^{90}$Y-IT</td>
<td>56</td>
<td>Not reported</td>
<td>42%</td>
<td>71% FFS at 18 months</td>
</tr>
<tr>
<td>Zinzani et al. (11)</td>
<td>Untreated DLBCL, age ≥60 years</td>
<td>6×CHOP + $^{90}$Y-IT</td>
<td>20</td>
<td>75%</td>
<td>95%</td>
<td>75% PFS at 2 years</td>
</tr>
<tr>
<td>Hamlin et al. (12)</td>
<td>Untreated DLBCL, age ≥60 years</td>
<td>6×CHOP + $^{90}$Y-IT</td>
<td>39</td>
<td>Not reported</td>
<td>Not reported</td>
<td>78% PFS at 2 years</td>
</tr>
<tr>
<td>This study</td>
<td>Untreated DLBCL, age ≥60 years</td>
<td>4×R-CHOP + $^{90}$Y-IT</td>
<td>55</td>
<td>58%</td>
<td>73%</td>
<td>85% PFS at 2 years</td>
</tr>
</tbody>
</table>

NOTE: CR, complete response; $^{90}$Y-IT = $^{90}$Y-ibritumomab tiuxetan; FFS, failure-free survival.

four cycles (instead of the conventional six) of R-CHOP, delivered every 21 days, followed by the administration of $^{90}$Y-ibritumomab tiuxetan as a frontline therapy in elderly untreated DLBCL patients. Patients up to age 83 tolerated the planned sequential treatment regimen well.

Coiffier et al. (1) showed that the addition of rituximab to CHOP21 can improve the survival outcomes in elderly patients with DLBCL, without significant increase in toxicity, if compared with CHOP21 alone. To better define whether combining dose-dense CHOP14 with rituximab improves results in elderly patients further, 1,222 patients were enrolled in the RICOVER-60 trial, and then were randomized to receive six or eight cycles of CHOP14 with or without rituximab (2). The results obtained with six cycles of R-CHOP14 clearly indicate this to be the preferred treatment for elderly patients, with which other approaches should be compared. However, to become the worldwide standard of care for elderly patients, R-CHOP14 must be confirmed to be superior to R-CHOP21, as the ongoing GELA and MRCI trials in France and Great Britain (5, 20) are supposed to do.

Despite markedly superior outcomes in first-line treatment following the addition of rituximab to the CHOP regimen, with dose-dense/dose-intense regimens also playing a potential role (2, 3, 21–23), the prognosis for patients older than 60 still remains poor, with a 7-year OS rate of 53%, as reported in one study (21). At least 30% to 50% of these patients with an advanced-stage DLBCL will fail to attain a remission with primary therapy, or will experience disease relapse after achieving a remission. Occasionally, asymptomatic patients can be managed with a watch-and-wait approach if they are not candidates for aggressive therapy, and only selected patients may experience prolonged remissions with involved-field radiation therapy. The vast majority of patients, however, will require a second-line (salvage) chemotherapy. Alternative treatment approaches should therefore be addressed at reducing the risk for disease relapse, for example by improving first-line therapeutic strategies, particularly in older patients not eligible for autotransplant.

Recently, on the basis of the “consolidation” concept experienced with $^{90}$Y-ibritumomab tiuxetan in follicular lymphomas, some reports have also pointed out the positive role of $^{90}$Y-ibritumomab tiuxetan in elderly DLBCL patients (refs. 11, 12; Table 4) after a chemotherapy or chemoimmunotherapy induction. Early results have indicated that $^{90}$Y-ibritumomab tiuxetan consolidation has a favorable tolerability profile, with low infection rates and a manageable hematologic toxicity. In addition, responses have improved after consolidation, and OS and DFS rates seem to be very encouraging. The objective of consolidation therapy is to rapidly improve the response to induction therapy, not only by converting a partial response to a complete response, but also by reducing the relapse risk of responders. For this reason we decided to use all the therapeutic approaches (chemotherapy, immunotherapy, and radioimmunotherapy) reducing conventional chemotherapy (from six to four courses) and its related toxicity in this subset of elderly patients.

By the end of this sequential combined treatment, 40 patients (73%) had achieved a complete response and 4 (7%) a partial response, with an estimated 2-years PFS of 85%. More importantly, among the 16 patients who achieved a partial response with R-CHOP21, 8 (50%) could improve their remission status after treatment with $^{90}$Y-ibritumomab tiuxetan. Toxic effects were generally mild and transient, without any aspect of cumulative toxicity.

Early results of the DENSE-R-CHOP14 in elderly DLBCL patients suggest that dose-dense rituximab can improve the outcome of elderly poor-prognosis patients (24): A complete response rate of 81% and 1-year EFS of 74% have, in fact, been obtained.

These data are comparable with our results after only four R-CHOP21 courses and subsequent consolidative radioimmunotherapy, thus confirming the pivotal role of $^{90}$Y-ibritumomab tiuxetan in elderly DLBCL patients.
In addition, we wanted to show the specific utility of this sequential politreatment schedule in reducing, at the same time, the global number of chemotherapy courses in such a subset of high-risk DLBCL patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Clinical Cancer Research

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