A New Schedule of CHOP/Rituximab Plus Granulocyte-Macrophage Colony-Stimulating Factor Is an Effective Rescue for Patients with Aggressive Lymphoma Failing Autologous Stem Cell Transplantation

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ABSTRACT
From 1999 to 2002, 20 patients with aggressive non-Hodgkin lymphoma, among 28 who failed autologous peripheral blood progenitor cell transplantation, were rescued with cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone (CHOP)/rituximab (RTX) and granulocyte-macrophage colony-stimulating factor (GM-CSF). RTX was administered twice during each course of chemotherapy, before CHOP and after GM-CSF. This cytokine was given to increase the antibody-dependent cell-mediated cytotoxicity and to reduce the leukopenia on the basis of our preliminary data, which suggested that this cytokine can upregulate CD20 expression. The relevant (World Health Organization grade 3-4) toxicity mainly consisted of myelosuppression (neutropenia in 60% of patients). Fifteen patients achieved complete remission (CR) or had a partial response, with an overall response rate of 75% (60% CR and 15% partial response). Six of the 12 patients who achieved CR relapsed: 2 died of progressive disease, 1 died of infectious complications after allogeneic transplantation, and 3 are alive in second CR. Eight patients showed progressive disease: 5 died of progressive disease, 1 of secondary acute leukemia, and 1 of infectious complications after allogeneic transplantation, and 3 are alive in second CR. Eight patients showed progressive disease: 5 died of progressive disease, 1 of secondary acute leukemia, and 1 of infectious complications after allogeneic transplantation, whereas 1 is alive in second CR. At last follow-up, 10 patients are alive, 6 of whom are in complete continuous remission, with a median follow-up of 3 months (range, 3-51 months). The projected 4-year progression-free survival is 31.4%, and the 4-year overall survival is 50%. This new association (RTX, CHOP, and GM-CSF) was feasible in approximately 70% of patients; the overall toxicity was manageable. The good response rate and the promising outcome observed in this subset of patients could be explained by the possible increased synergy between chemotherapy, RTX, and GM-CSF, which should be explored in further studies.

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KEY WORDS
Immunotherapy • Rituximab • Lymphoma • Autologous stem cell transplantation • Failure

INTRODUCTION
Lymphoma patients who relapse after autologous peripheral blood progenitor cell transplantation (ASCT), especially those with aggressive non-Hodgkin lymphoma (NHL), have a very poor prognosis. In this setting, salvage chemotherapy or a second transplantation cannot substantially modify the very poor outcome, which is characterized by a median overall survival (OS) of 3 months for patients with large cell lymphoma [1]. Patients with mantle cell lymphoma (MCL) that relapses after ASCT also have a very poor survival [2,3].

A second transplantation attempt in these patients is rarely feasible. Previous reports suggest that a second autologous transplantation or a conventional allogeneic transplantation after the failure of autologous transplantation is rarely curative. Progressive disease and transplant-related mortality (TRM) are the primary causes of failure with second autologous and allogeneic transplantations, respectively [4].
In the allogeneic setting, the lack of suitable donors and the very high TRM reported with myeloablative conditioning [4-6] consistently reduce the proportion of patients who are candidates for this approach. However, it is very difficult to obtain a sufficient peripheral blood stem cell harvest for a second autologous bone marrow transplantation [7], and even when this procedure is feasible, the efficacy of the second attempt is often limited because of a lack of a graft-versus-tumor effect. In these patients, any salvage options are often jeopardized by both a poor performance status and a low hematologic tolerance to chemotherapy.

Rituximab (RTX) is a highly specific chimeric antibody against the CD20 antigen, which is present in most B-cell lymphomas [8,9]. RTX has demonstrated high activity both in follicular lymphoma as a single agent [10] and in aggressive NHL [11], including MCL [12,13]. In all cases, the combination of RTX with cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone (CHOP) chemotherapy has allowed a significant increase in the response rate in follicular [14] and high grade NHL [15], even though this association has never been tested in the posttransplantation setting as a rescue therapy.

The mechanisms by which RTX induces B-cell death include antibody-dependent cell-mediated cytotoxicity (ADCC) [16], complement-mediated toxicity, and apoptosis against chemoresistant B-lymphoma cells [17]. Moreover, some observations suggest that the outcome of patients who receive RTX can be improved if the number and activity of their immune effector cells (in particular, natural killer cells) are preserved or enhanced [18].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine that strongly increases the number and activity of polymorphonuclear cells and macrophages against opsonized targets [19-21]. Furthermore, some preliminary data suggest that this cytokine can upregulate the CD20 expression on lymphoid B cells in vitro and in vivo [22]. This study evaluated the safety and the activity of an original immunochemotherapeutic approach that included CHOP, RTX, and GM-CSF in a group of patients with aggressive NHL after ASCT failure.

MATERIALS AND METHODS

Patient Characteristics

We observed 28 patients with aggressive NHL after ASCT failure from 1999 to 2002. Twenty (14 with diffuse large cell lymphoma [DLCL] and 6 with MCL blastoid variant) were considered eligible for a salvage protocol including RTX and CHOP chemotherapy.

Exclusion criteria included a poor performance status (>1 according to the World Health Organization [WHO], not due to the underlying lymphoma), poor hematologic count (with platelets <100 000/µL and/or polymorphonuclear cells <1500/µL), leukemic disease with hyperleukocytosis (white blood cell count >50 000/µL), HLA-compatible donor if aged <55 years, previous anthracycline cumulative dose >300 mg/m², cardiac ejection fraction <45%, central nervous system involvement, positive serologic test findings for human immunodeficiency virus, and active hepatitis B. Eight (29%) of the 28 observed patients were not eligible for the following reasons: 3 had previously received an anthracycline cumulative dose >300 mg/m², 3 had a very poor performance status unrelated to the underlying lymphoma, 1 had a poor hematologic count, and 1 refused the treatment. Patient characteristics are shown in Table 1.

Patients were heavily pretreated with a median number of 3 chemotherapy regimens before ASCT: 9 patients with DLCL had previously been enrolled in a protocol of high-dose sequential therapy including the etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B) regimen (a median of 8 weeks with a median cumulative dose of 200 mg/m² doxorubicin), followed by cyclophosphama-
mide 7 g/m² and VP-16 2 g/m² before ASCT. The other 5 patients with DLCL received ASCT for relapse after 12 VACOP-B courses (with a median cumulative dose of 300 mg/m² doxorubicin) and received 2 or 3 dexamethasone, high-dose cytarabine, and Platinol (cisplatin) (DHAP) courses before high-dose therapy; the 6 patients with MCL received ASCT as second-line salvage therapy after 2 or 3 courses of DHAP.

Before enrollment, all patients were required to give their written informed consent; to have confirmation of active CD20/H11001 NHL by biopsy or fine-needle aspiration of an involved site (all biopsy specimens were reviewed by 1 or 2 hematopathologists); to be younger than 70 years of age; to show a relapse, progression, or persistence of disease after ASCT; and to have measurable disease and absence of severe organ dysfunctions (bilirubin <3 mg/dL, creatinine <2 mg/m, alanine aminotransferase and aspartate aminotransferase <3 times the normal values, and carbon monoxide diffusion in the lung >40%) not related to the underlying disease. All patients underwent pretreatment staging studies that included computed tomography of the chest, abdomen, and pelvis; nuclear imaging with gallium scans, fluorine-18-fluorodeoxyglucose positron emission tomography, or both; and unilateral bone marrow biopsies. Our institutional review board approved this study.

**Treatment**

Patients received a scheme of treatment that consisted of a modified CHOP-21 schedule (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² up to a maximal dose of 2 mg on day 4, and prednisone 40 mg/m²/d for 4 days, from day 4 to day 7). Patients also received RTX 375 mg/m² on day 1 and 375 mg/m² on day 14 of each cycle of CHOP. The RTX infusion was interrupted in the event of fever, chills, edema, congestion of the head and neck mucosa, hypotension, or any other serious adverse event and was resumed when such event was no longer observed. GM-CSF was administered subcutaneously at 150 g/d; it was started the day after the end of CHOP (day 5) and was continued for at least 9 days until the second RTX administration (Figure 1). The rationale for GM-CSF administration on the fourth day was based on the well-documented ability of this drug to prevent or reduce neutropenia after chemotherapy, on data supporting increased ADCC by phagocytic cells after GM-CSF administration [20,21], and, finally, on the possibility of upregulating CD20 expression, as suggested also by our preliminary findings [22,23] (Figure 2). Patients were treated every 3 weeks for at least 2 courses before the first evaluation of response.

If the absolute neutrophil count was <1.5 x 10⁹/L or the platelet count was <1 x 10⁹/L, chemotherapy administration was delayed for up to 2 weeks, and then

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**Table 2. Toxicity**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PS 1-2 (WHO)</th>
<th>PS 3-4 (WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Neutropenia</td>
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<td>60</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>Extrahematologic toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
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</tr>
<tr>
<td>Mucositis</td>
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<td>0</td>
</tr>
<tr>
<td>Liver toxicity</td>
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<td>5</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
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<td>0</td>
</tr>
<tr>
<td>Neurologic toxicity</td>
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</tr>
<tr>
<td>Renal toxicity</td>
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<td>0</td>
</tr>
<tr>
<td>Lung toxicity</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

PS indicates performance status.

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**Figure 1.** Schedule of treatment in 20 patients with aggressive lymphoma and failed ASCT. Doxo indicates doxorubicin; CTX, cyclophosphamide; VCR, vincristine; ANC, absolute neutrophil count; sm, square meter; MPDN, prednisone.
The treatment was stopped. The doses of RTX were not modified, and RTX was also continued when CHOP was stopped. Treatment was stopped if lymphoma progressed, if the patient declined to continue, or at the discretion of the investigator in cases of intercurrent illness or adverse events.

Patients showing disease progression after 2 courses of treatment were excluded from further treatment. The responders (complete remission [CR] or partial response [PR]) received 2 more courses of CHOP/RTX/GM-CSF or 3 more courses of RTX alone in case of poor hematologic tolerance, at the dose of 375 mg/m² at day 7, every 21 days, together with daily GM-CSF from day 1 to day 11 (second step of therapy; Figure 3).

Patients achieving clinicoradiologic CR did not receive any further treatment. Patients in PR after the second step of therapy were treated at the clinician’s discretion (local radiotherapy or allogeneic transplantation in case of HLA-matched sibling availability).

**Response to Treatment and Adverse Events**

The first tumor response assessment was performed after at least 2 courses of chemotherapy (including 4 doses of RTX), and the final restaging was performed at the end of treatment. The responses were classified as CR, PR, or progressive disease according to the International Workshop criteria [24].

CR was defined as the disappearance of all lesions and radiologic or biological abnormalities observed at diagnosis and the absence of new lesions. An unconfirmed CR was defined as a CR with the persistence of some radiologic abnormalities, which had to be regressed in size by at least 75%. PR was defined as the regression of all measurable lesions by more than 50%, the disappearance of no measurable lesions, and the absence of new lesions. Progressive disease was defined as the appearance of a new lesion, any growth of the initial lesion by more than 25%, or growth of any measurable lesion that had regressed during treatment by more than 50% from its smallest dimensions.

All adverse events reported by the patient or observed by the investigator were collected from the case-report form in predefined categories. An adverse event was defined as any adverse change from the patient’s baseline condition, whether it was considered related to treatment or not. Each event was graded according to the WHO toxicity criteria.

**Statistical Analysis**

Because of the scarcity of data in patients with aggressive lymphomas treated after ASCT failure, the safety and efficacy evaluation of this schedule was powered by basing our statistical design on the historical experience reported in 54 patients with refractory or relapsing aggressive lymphoma (DLCL or MCL) rescued with RTX alone (375 or 500 mg/m²). Coiffier et al. [11] reported an overall response rate (ORR) of 32%, with a CR rate of 9% and a treatment-related death rate of 4%.

With a probability of early termination of 55%, the following rules were established for the prelimi-
nary evaluation of safety and efficacy in the first 15 patients: with an observed rate of CR < 2 in 15 or with a treatment-related death rate > 1 in 15, the study should be stopped. We hypothesized that our schedule could obtain a CR rate > 29% (> 20% than the historical data); therefore, the expected sample size (considering α = .05 and β = .20) was 20 patients with a minimax Simon design [25].

OS and progression-free survival (PFS) were calculated from the day the CHOP/RTX/GM-CSF treatment started until death due to any cause or last follow-up. The probabilities of survival and relapse were estimated and plotted by using the Kaplan-Meier method. Data were analyzed by using the SPSS statistical package (SPSS Inc., Chicago, IL).

RESULTS

The median time from transplantation to the initiation of treatment in the 20 patients was 8 months (range, 2-72 months). The 4 scheduled courses of CHOP/RTX/GM-CSF were given to 15 patients (75% of enrolled patients), and 5 patients showed disease progression after the first or second cycle. These patients were included in the response and outcome analysis according to intention-to-treat criteria. Two patients who achieved a PR after 4 courses of CHOP/RTX/GM-CSF received 2 additional courses, followed by the second step of therapy. One patient in PR after the 4 courses of chemoimmuno-therapy withdrew from the protocol because of persistent aplasia and eventually had progressive disease; among the 12 patients in CR, 8 patients with unconfirmed CR after the 4 courses of CHOP/RTX/GM-CSF received the second step of therapy as previously planned.

Toxicity

All 20 patients were included for the toxicity evaluation of 73 courses of CHOP/RTX/GM-CSF, followed in 10 patients by the second step of immunotherapy, for a total of 176 RTX infusions. The GM-CSF administration was interrupted in 3 patients because of intolerance and was replaced by granulocyte colony-stimulating factor. These 3 patients developed an
acute syndrome after the first GM-CSF dose, with chills and fever in 1 case and severe bone pain and chest pain (without evidence of coronary disease) in the other 2 patients. RTX was generally well tolerated. We observed 1 grade 4 tumor lysis syndrome and 2 grade 1 to 2 episodes of hypotension after the first infusion of RTX. The grade 3 to 4 adverse effects were consistent with the expected toxicity of CHOP chemotherapy. We did not observe any toxic deaths. The most relevant (WHO 3-4) toxicity was hematologic: 1 patient, with a long disease history and heavy pretreatment, withdrew from the protocol because of persistent marrow aplasia.

Sixty percent of patients developed severe neutropenia, and 50% and 40% of patients experienced severe anemia and thrombocytopenia, respectively. The grade 3 to 4 extrahematologic toxicity mainly consisted of infectious complications (15%): we observed 1 Pseudomonas aeruginosa sepsis, 1 P. aeruginosa pneumonitis, and 1 radiologically documented pneumonitis. Grade 1/2 and grade 3/4 hematologic and extrahematologic toxicities are reported in Table 2.

**Response and Survival Analysis**

Fifteen patients responded to treatment, with 12 (60%) CRs and 3 PRs (ORR, 75%), whereas 5 patients were classified as nonresponders. Six patients are still in complete continuous remission (CCR) with a median follow-up of 31 months (range, 3-51 months).

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**Table 4. Clinical Outcome of the 20 Patients According to the Initial Characteristics and the Secondary Therapy Given after CHOP/RTX/GM-CSF Failure**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>Histology</th>
<th>IPI</th>
<th>Time ASCT Prior CHOP-RTX (mo)</th>
<th>Response CHOP-RTX</th>
<th>Outcome</th>
<th>Secondary Therapy</th>
<th>Status at Last Follow-Up</th>
<th>Follow-Up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>MCL</td>
<td>3</td>
<td>15</td>
<td>CR</td>
<td>Relapse</td>
<td>Allotransplantation</td>
<td>Death</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>DLCL</td>
<td>3</td>
<td>12</td>
<td>CR</td>
<td>Relapse</td>
<td>No therapy</td>
<td>Death</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>MCL</td>
<td>5</td>
<td>5</td>
<td>CR</td>
<td>Relapse</td>
<td>No therapy</td>
<td>Death</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>MCL</td>
<td>7</td>
<td>72</td>
<td>CR</td>
<td>Relapse</td>
<td>LPD + RTX</td>
<td>CR</td>
<td>49*</td>
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<tr>
<td>5</td>
<td>28</td>
<td>DLCL</td>
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<td>5</td>
<td>CR</td>
<td>CCR</td>
<td>No therapy</td>
<td>CR</td>
<td>51*</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
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<td>Relapse</td>
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<td>48*</td>
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<tr>
<td>7</td>
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<td>38*</td>
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<td>Allotransplantation</td>
<td>Death</td>
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<td>No therapy</td>
<td>CR</td>
<td>31*</td>
</tr>
</tbody>
</table>

IPI indicates International Prognostic Index; F.U., follow-up; NR, no response; LPD, liposomal pegylated doxorubicin.

*Alive and well.

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**Figure 4.** OS in 20 patients with aggressive NHL. CI indicates confidence interval.

**Figure 5.** PFS in 20 patients with aggressive NHL. CI indicates confidence interval.
Eight patients experienced disease progression: 5 died of progressive disease, 1 died of infectious complications after receiving an allogeneic transplant, 1 died of secondary acute myeloid leukemia, and 1 is alive and in second CR after receiving an allogeneic transplant from an HLA-identical sibling.

Six of the 12 patients who achieved CR relapsed: 2 died of progressive disease, 1 died of infectious complications after allogeneic transplantation, and 3 are alive and achieved a second CR (2 after a liposomal anthracycline-based regimen and 1 after an allogeneic transplantation). The ORR was 71% in the 14 patients with DLCL and 83% in the 8 MCL patients, with a 64% and 50% CR rate, respectively. Nevertheless, despite this apparently similar response rate, all 5 MCL patients who were responsive to the chemotherapy eventually relapsed or progressed within a median time of 14 months, compared with the 3 relapses observed in the 9 DLCL patients who achieved CR.

All 20 patients were evaluable for clinical outcome with a median follow-up of 31 months (range, 3-51 months). Ten patients died; 7 of these died of progressive disease (6 with DLCL NHL and 1 with MCL). As far as the other 3 patients affected by MCL are concerned, 1 died of pneumonia, 1 died of sepsis after allogeneic transplantation performed after the relapse, and 1 died of secondary acute leukemia.

At the last follow-up, 10 patients were alive, among whom 2 were affected by MCL and 8 by DLCL. Six patients were still in CR, and 4 achieved a subsequent CR: 2 after allogeneic transplantation and 2 after RTX/liposomal anthracycline–based regimens. These data are summarized in Tables 3 and 4.

The projected 4-year OS was 48% (95% confidence interval, 28%-69%; Figure 4), and the 4-year PFS was 30% (95% confidence interval, 14.5%-52%; Figure 5). In the 14 patients with DLCL, the OS was 58%, with 43% PFS (Figures 6 and 7).

**DISCUSSION**

The first attempt at rescue therapy with RTX alone achieved only a 31% ORR in pretreated aggressive NHL [11]. After the demonstration that the RTX association with CHOP was very effective as up-front therapy both in patients with indolent NHL [14] and in those with aggressive NHL [11,26], many other attempts to improve the response rate have been tested that associate RTX with other chemotherapy regimens [27].

We decided to modify the timing of RTX administration during CHOP therapy, basing our schedule on the hypothesis that RTX can sensitize lymphoma cells to chemotherapy [17] and that GM-CSF administration can increase RTX activity, both by upregulating CD20 expression [19,20] and by enhancing ADCC [21-23]. Moreover, in vivo and in vitro experiments suggest that low doses of GM-CSF can stimulate and expand both the natural killer compartment and ADCC [19-21]. Many patients showed a poor hematologic tolerance to chemotherapy after ASCT, and profound immune suppression was documented in all of them even 1 or 2 years after ASCT [28].

In patients with a suitable donor, a second allogeneic transplantation can offer a better chance of cure than a second ASCT, thanks to the potential graft-versus-leukemia effect, but this procedure is affected by a very high TRM [29]. Recently, the use of reduced-intensity conditioning regimens has reduced TRM with a very promising OS and PFS, even in heavily pretreated patients with hematologic malignancies [30]. The role of reduced-intensity conditioning after ASCT failure has been recently investigated in 38 patients with lymphoproliferative malignancies [31]. This approach was feasible, with a 20% TRM at 14 months, 53% OS, and 50% PFS; nevertheless, only a minority of patients, after ASCT failure, could benefit from this approach.

The role of RTX as salvage therapy after ASCT failure has not been extensively investigated in pa-
Preliminary data on the efficacy of rituximab in the posttransplantation setting have been reported. Patients with CD20⁺ DLCL [32]; recently, 17 patients received RTX alone after ASCT failure, with a 54% ORR, but the median duration of response was only 13 months [33]. More recently, 28 lymphoma patients received RTX after ASCT (n = 16) or allogeneic stem cell transplantation (n = 12); 9 patients who did not achieve CR after stem cell transplantation converted to CR after RTX [34].

In a second report, a heterogeneous population including 55 patients with NHL and Hodgkin disease received RTX plus GM-CSF after ASCT. Among the 33 patients with B-cell lymphoma, 14 had primary refractory disease, 12 had relapsed disease, and 7 had high-risk disease in first CR [35].

A third report evaluated the efficacy and toxicity of RTX plus GM-CSF after ASCT in 35 patients with DLCL (n = 25), MCL (n = 3), or other subtypes of B-cell lymphoma. With a median follow-up of 30 months, the 2-year event-free survival rate was 83%, and OS was 88%. The third report, although it confirms the feasibility of the association RTX plus GM-CSF in the posttransplantation setting, also highlights the need for further studies to optimize the timing and duration of therapy.

**Figure 8.** Computed tomographic scan of a young woman after a DLCL relapse 6 months after ASCT, with mediastinal bulky disease involving the lung and pleural effusion (A) after 4 courses of CHOP/GM-CSF/RTX (B). The same patient (C and D) showed extensive liver and renal involvement at relapse. E and F, Complete regression of lymphoma. The patient is in CCR 4 years after the end of therapy.
setting, does not answer the question of whether this association could be worthwhile in patients whose ASCT fails; indeed, 34 of 35 patients had chemosensitive disease before ASCT, and an amendment of the protocol also allowed enrollment of patients in CR before ASCT [36].

Our approach, tested in a homogeneous setting, was feasible in most (20 of 28) patients with aggressive lymphoma whose ASCT failed. We did not observe severe or fatal cardiotoxicities, probably because we included only patients with a relatively low cumulative dose (<300 mg/m²) of doxorubicin.

In the 14 patients with DLCL, the outcome seems to be better than reported in previous experiences, thus suggesting that this schedule could effectively eradicate the disease in a relevant proportion (6/14) of patients. Indeed, we observed a long CCR in patients with DLCL relapsing with bulky disease and extra nodal sites after high dose sequence followed by ASCT (Figure 8). Conversely, although they showed a very high ORR, none of the 6 MCL patients maintained a CCR.

In conclusion, our study shows that this new schedule represents an effective salvage treatment for lymphoma patients with failed ASCT, who are often not eligible for allogeneic transplantation. More data are needed to confirm the synergy between GM-CSF and RTX, but in our opinion, this association should be now considered for all patients with CD20+ DLCL and failed ASCT who lack a suitable donor or who are not eligible for an allogeneic bone marrow transplantation.

In many centers, the anthracycline-based regimens plus RTX are increasingly used as up-front treatment for young patients with CD20+ DLCL, and it is not uncommon to observe many patients who have received a heavy cumulative anthracycline dose after their first- or second-line therapy fails. In this case, although the re-treatment with RTX can be safe and effective in patients with bulky disease [37], if the previous cumulative dose of doxorubicin is >400 mg/m², rescue therapy with CHOP/RTX plus GM-CSF could generate some concerns about the high risk of cardiotoxicity or acquired drug resistance. For this reason, we think that the introduction of liposomal anthracyclines (instead of conventional doxorubicin) in the same schedule could be an attractive alternative option for this subset of patients.

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REFERENCES


