Intensive Therapy With Peripheral Blood Progenitor Cell Transplantation in 60 Patients With Poor-Prognosis Follicular Lymphoma


Intensive therapy, mainly with purged autologous bone marrow transplantation (ABMT), has been proposed in recent years as consolidation treatment in young patients with follicular lymphoma. Reported experience with transplantation of peripheral blood progenitor cells (PBPC) is, so far, limited. The feasibility and the therapeutic efficacy of intensive therapy followed by unpurged autologous PBPC reinfusion were evaluated in 60 patients with poor-prognosis follicular lymphoma. Twelve patients were in first partial remission (PR), 34 were in second partial or complete remission (CR), and 14 were in subsequent progression. At the time of the procedure, 39 patients (65%) had persistent bone marrow involvement, 49 patients (82%) were in PR, and 16 patients had presented with a histologic transformation (HT). PBPC were collected after chemotherapy followed by granulocyte (G) colony-stimulating factor (CSF) or granulocyte-macrophage (GM)-CSF in 50 patients. Conditioning regimens included high-dose chemotherapy alone (14 patients); mainly the BCNU, etoposide, ara-cytine, melphalan (BEAM) regimen, or cyclophosphamide with or without etoposide plus total body irradiation (46 patients). The median time to reach a neutrophil count greater than 0.5 × 10^9/L was 13 days. There were five treatment-related deaths, with four being associated with a delayed engraftment and all occurring in patients in third or subsequent progression. At a median follow-up of 21 months, 48 patients were still alive, 18 relapsed, and seven died of lymphoma progression. Estimated 2-year overall survival (OS) and failure-free survival (FFS) rates were 86% and 53%, respectively, without a plateau. Patients treated in PR1 or PR2/CR2 had a significantly longer rate of OS and FFS than those treated in subsequent progression (P = .002 and P = .001, respectively), whereas age, response to salvage treatment, presence or absence of residual bone marrow involvement, or conditioning regimen had no influence on outcome. Patients with HT tended to have a worse FFS rate (P = .04) without an OS difference. Along with an unusual rate of engraftment failure, the poor FFS observed in heavily pretreated patients suggests that intensive therapy should be performed early in the course of the disease. Given the high percentage of patients intensified in PR with residual bone marrow involvement, our results are comparable with those achieved with ABMT published to date. Prospective trials are warranted to compare this strategy with standard therapy in patients with relapsing or PR follicular lymphoma.

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Although follicular lymphomas are characterized by a relatively indolent course, they remain an incurable disease in spite of various therapeutic approaches. Median survival ranges from 6 to 10 years in recent studies, with a constant annual rate of relapse and death. In recent years, prognostic factors have been better defined, and the notion that a complete clinical remission is associated with a longer outcome has emerged. Recently, the use of intensive therapy supported by autologous bone marrow transplantation (ABMT) has been investigated in these patients, especially for those aged less than 60 years with recurrent disease. In the experience of St Bartholomew’s Hospital (London, UK), this strategy seems to be able to prolong remission duration. However, this longer time-to-progression survival and the possible impact on overall survival have not been proven in randomized controlled trials. Furthermore, the optimal modalities of this therapeutic approach and, particularly, the influence of in vitro treatment of the bone marrow on disease recurrence remain unknown. In the experience of the Dana-Farber Cancer Institute (Boston, MA), antibody-mediated purging eliminated lymphoma cells detectable by polymerase chain reaction (PCR) in hematopoietic stem cell harvests in about half of the patients who had a breakpoint involving the bcl-2 translocation, and disappearance of bcl-2-rearranged cells after in vitro treatment was the single most important prognostic factor for freedom from recurrence. On the other hand, disappearance of bcl-2-rearranged cells has rarely been achieved in the experience of the St Bartholomew’s Hospital, and the impact of successful purging on further outcome is not clear. Furthermore, the overall survival rates from the two centers are the same.

The use of peripheral blood progenitor cells (PBPC) may have theoretical advantages compared with bone marrow cells. First, hematologic recovery is more rapid with PBPC than with bone marrow cells. Second, peripheral blood may be less contaminated by tumor cells, although this has not been proven. Third, this strategy remains feasible in heavily pretreated patients, especially in those who have received previous pelvic radiotherapy. The reported experience with high-dose therapy followed by PBPC reinfusion is, so far, very limited in patients with follicular lymphoma.

We present here the results obtained in 60 patients with follicular lymphoma treated with high-dose therapy and PBPC support in three French centers. The vast majority of these patients were in the second or a subsequent phase of their disease and had persistent bone marrow involvement at the time of the procedure.

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PATIENTS AND METHODS

Patients. Sixty patients, aged 20 to 58 years (median age, 47 years), treated between August 1990 and April 1994 in Lyon-Sud (34 patients), Paris-St-Louis (18 patients), and Créteil (eight patients), France, form the basis of this analysis. The clinical characteristics of these patients are listed in Table 1. Patients were considered to have a large tumor burden if they had at least one of the following criteria, as determined by an analysis of the literature and a previous study: any nodal or extranodal tumor mass with a diameter larger than 7 cm; involvement of at least three nodal sites, each of which had a diameter larger than 3 cm; systemic symptoms; substantial splenic enlargement; serous effusion; orbital or epidural involvement or ureteral compression; and leukemic presentation. In a previous study, patients with characteristics at diagnosis and treated with a CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone)-like chemotherapy regimen with or without interferon experienced a median event-free survival of 28 months and an estimated median overall survival of about 60 months.

Twelve patients were in first partial remission. In all cases but one, intensive therapy was used because of the presence of a large tumor burden if they had at least one of the following criteria, as determined by an analysis of the literature and a previous study: any nodal or extranodal tumor mass with a diameter larger than 7 cm; involvement of at least three nodal sites, each of which had a diameter larger than 3 cm; systemic symptoms; substantial splenic enlargement; serous effusion; orbital or epidural involvement or ureteral compression; and/or leukemic presentation. In a previous study, patients with such characteristics at diagnosis and treated with a CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone)-like chemotherapy regimen with or without interferon experienced a median event-free survival of 28 months and an estimated median overall survival of about 60 months.

Thirty-four patients were in second partial or complete remission. In all cases but one, intensive therapy was used because of the presence of a large tumor burden if they had at least one of the following criteria, as determined by an analysis of the literature and a previous study: any nodal or extranodal tumor mass with a diameter larger than 7 cm; involvement of at least three nodal sites, each of which had a diameter larger than 3 cm; systemic symptoms; substantial splenic enlargement; serous effusion; orbital or epidural involvement or ureteral compression; and/or leukemic presentation. In a previous study, patients with such characteristics at diagnosis and treated with a CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone)-like chemotherapy regimen with or without interferon experienced a median event-free survival of 28 months and an estimated median overall survival of about 60 months.

Adverse prognostic factors as defined above were present at diagnosis in 23 of them (68%). Ten patients had presented with a histologic transformation (HT) as second progression of their disease. Fourteen patients were in subsequent progression.

Initial treatment was chlorambucil or prednimustine in seven patients (12%), CHVP regimen (cyclophosphamide 600 mg/m², doxorubicin 25 mg/m², teniposide 60 mg/m², prednisone 40 mg/m²/d × 5 days) with (11 patients) or without (six patients) interferon-α2b in 17 patients (28%), standard-dose or high-dose CHOP in 23 patients (38%), multiling regimens without anthracyclin in six patients (10%), fludarabine monophosphate in four patients (7%), interferon-α2b in two patients (3%), and radiotherapy in one patient (2%). At the time of intensive therapy, all patients except two had received at least one anthracyclin-containing regimen. Seven patients had received localized radiotherapy.

Sixteen patients (27%) had experienced HT in the course of their disease. Forty-nine patients (82%) had a history of previous bone marrow involvement, and 38 patients had persistent marrow involvement at the time of stem cell harvest (63%). Twenty-five patients (42%) had reached a complete remission in the course of their disease before intensive therapy.

Pretransplant status. All patients except one responded to salvage treatment, but only 10 patients were in complete remission (CR). Forty-nine patients were in partial remission (PR), 37 with a minimal disease defined as reduction of the tumor masses to 2 cm or less. Twenty-five patients (42%) had residual bone marrow involvement as the only site of residual disease.

PBPC collection. At the time of PBPC collection, none of the patients had cryogenic evidence of blood involvement by lymphoma cells. In those patients with previous blood involvement, immunologic studies were performed to search for a monoclonal B-cell fraction and were negative. Peripheral mononuclear cells (MNC) were collected after a cycle of cytotoxic chemotherapy followed in 50 cases by granulocyte (G) colony-stimulating factor (CSF; 28 patients) or granulocyte-macrophage (GM)-CSF (22 patients). The chemotherapy regimen used for PBPC mobilization was high-dose cyclophosphamide in 30 patients, a CHOP or CHOP-like regimen in 15 patients, high-dose cyclophosphamide plus etoposide in eight patients, and another cytotoxic regimen in seven patients (with mitoxantrone in five patients; without anthracyclin or mitoxantrone in two patients). The collections were performed daily to obtain at least 2 × 10⁸ MNC per kilogram in 1990 and 1991 and at least 4 × 10⁸ MNC per kilogram in the following period, with at least 2 × 10⁹ colony-forming units/ganulocyte-macrophage (CFU-GM) per kilogram in both cases in Lyon-Sud, France. The minimum requirements for CFU-GM were, respectively, 2 × 10⁸ and 4 × 10⁹ CFU-GM per kilogram in Paris-St-Louis and Créteil, France.

A median MNC number of 4.25 × 10⁹/kg (range, 0.85 × 10⁹ to 16 × 10⁹) and a median CFU-GM number of 9.95 × 10⁹/kg were collected after a median number of 3.5 aphereses (range, one to nine). The MNC were then cryopreserved without any in vitro manipulation in the patient's serum with 10% dimethyl sulfoxide (DMSO) in the vapor phase of liquid nitrogen. In two patients (Lyon-Sud), the number of MNC and CFU-GM collected were below the planned thresholds; considering the poor prognosis of their disease (both patients had experienced HT, and one had been previously treated with ABMT), intensification was performed.

Conditioning regimen. Conditioning regimens are shown in Table 2. Forty-six patients received cyclophosphamide plus etoposide (43 patients) and total body irradiation (TBI) as conditioning regimen. Because of extensive previous therapy, one patient in third progression of his disease received TBI as a single dose of 8 Gy; in other patients, TBI was administered at a dose of 10 or 12 Gy, whether fractionated or unfractiected according to each center's policy. However, because of previous radiotherapy or extensive pre-

Table 1. Characteristics of the 60 Patients With Follicular Lymphoma Treated With Intensive Therapy and PBPC Support

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>Patients in CR1</th>
<th>Patients in CR2/PR2</th>
<th>Patients in CR3rd Phase</th>
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* Criteria of the GELF-86 protocol.25
INTENSIVE THERAPY WITH PBPC IN FCL PATIENTS

vious chemotherapy, 14 patients received a pretransplant regimen consisting of high-dose chemotherapy only. Median time from PBPC collection to intensive therapy was 43 days (range, 9 to 376 days). Thirty-three patients received no further treatment between PBPC collection and high-dose therapy, and 27 patients received at least one course of chemotherapy (median, one; range, one to six) during this interval. Fifty-two patients received a hematopoietic growth factor after PBPC reinfusion (GM-CSF, 30 patients; G-CSF, 22 patients) until neutrophil recovery.

Response criteria. Engraftment failure was defined as the absence of persistent recovery of neutrophil count greater than 0.500 \times 10^9/L. CR was defined as the disappearance of all sites of disease including bone marrow. PR was defined as a reduction of more than 50% in the largest diameter of each measurable site of disease, or as the persistence of bone marrow infiltration as the only residual site of disease. Otherwise, the patient was considered as nonresponding. Response was assessed 3 months after high-dose therapy with clinical examination, computed tomography (CT) scan, bone marrow aspirate, and biopsy.

Statistical methods. Overall survival (OS) was defined as the time from reinfusion of PBPC to death or date of last visit. Failure-free survival (FFS) was defined as the time from reinfusion of PBPC to the time of disease progression, last follow-up, or death from any cause. Survival distributions were estimated using the product-limit method of Kaplan-Meier.23 The statistical significance of observed differences in the distributions of OS and FFS were assessed using the log-rank test.

RESULTS

Clinical toxicity and hematopoietic recovery. There were five treatment-related deaths (8%): intraalveolar hemorrhage (one patient), failure to engraftment (four patients). These four patients reached an absolute neutrophil count of greater than 0.5 \times 10^9/L between 15 and 24 days posttransplant, but neutropenia thereafter relapsed. They then died of infectious complications between day 64 and 168, with an absolute neutrophil count of less than 0.5 \times 10^9/L and were considered as engraftment failures. They were all in third or subsequent phase of their disease, and they were older than 45 years. The number of MNC collected in these four patients ranged from 2.06 \times 10^9/kg to 3.35 \times 10^9/kg, and the number of CFU-GM from 2 \times 10^8/kg to 5.6 \times 10^8/kg. No other major adverse event was observed. The median time to reach a neutrophil count of greater than 0.5 \times 10^9/L was 13 days (range, 9 to 32 days). A platelet count of greater than 50 \times 10^9/L was reached after a median time of 19 days (range, 9 to 1,163+ days). One patient developed a myelodysplastic syndrome 25 months after the procedure; he had been extensively treated with a first high-dose therapy with TBI and bone marrow stem cell support 3 years earlier.

Assessment of response after high-dose therapy. Fifty-six patients were assessable for response. CR was obtained in 46 patients (77%), PR in nine patients (15%), and one patient had a rapidly progressive disease.

OS and FFS. At the time of analysis, median follow up after intensive therapy was 21 months. Forty-eight patients were still alive. Apart from the five procedure-related deaths, seven patients died of recurrent lymphoma. Eighteen patients have had a lymphoma recurrence after a median time of 14 months (range, 2 to 31 months). Estimated 2-year OS and FFS rates were 86% (95% confidence interval [CI], 76% to 96%) and 53% (95% CI, 37% to 69%), respectively (Fig 1). No plateau was observed.

Prognostic factors for OS and FFS. There was no corre-
loration between OS and FFS and any of the following parameters: age, response to salvage treatment (CR vs PR), presence of a residual bone marrow involvement (Fig 2), previous CR at any time, time from diagnosis to intensive therapy (less or more than 30 months), or conditioning regimen with or without TBI. The results are similar when the analysis is confined to the subgroup of patients intensified after relapse. There was no significant difference in OS or FFS between patients intensified in PR2/CR2 and in PR1, but this latter group comprises only 12 patients. However, patients who received intensive treatment at a later stage of the disease, ie, in third or subsequent progression, have clearly a poorer OS and FFS (log-rank tests: P = .002 and P = .001, respectively; Fig 3). Patients with histologic transformation did not have a statistically different OS but did have a significantly shorter FFS (log-rank test: P = .04; see Fig 4). FFS was shorter for patients with a tumor mass of ≥2 cm at time of intensification compared with those with no detectable residual disease or a tumor mass of less than 2 cm, but this difference was not statistically significant.

**Patients with previous HT.** Sixteen patients received intensive therapy after they had experienced an HT. Two died of treatment-related toxicity. Among the remaining 14 patients, eight have relapsed after a median time of 14 months; two had an aggressive histology at that time, whereas six had returned to a follicular histology. Among these last six patients, four are still alive and on therapy at 2, 15, 25, and 34 months after relapse.

**DISCUSSION**

Although follow up is still short, this study is the largest reported so far on intensive therapy with PBPC support in patients with follicular lymphoma. As in patients with aggressive lymphoma, this approach is feasible even in patients with advanced disease and/or with residual bone marrow involvement. The use of mobilized PBPC allows a more rapid hematologic recovery than bone marrow stem cells, with a 13-day median time to reach a neutrophil count of ≥0.5 x 10^9/L. However, our treatment-related death rate is 8%, which is higher than reported in most studies with PBPC transplantation, although a comparable or even higher toxicity has been reported in heavily pretreated patients. This toxicity is largely due to engraftment failures (6.5%): all of them occurred in patients who were at least in third progression of their disease with extensive previous treatments. A major concern is the fact that in these four patients, the amount of MNC and CFU-GM collected seemed to be in keeping with our usual thresholds. Therefore, these two parameters do not appear to be useful in selecting candidates for high-dose therapy with PBPC support, at least not in heavily pretreated patients. Other parameters such as the count of CD34+ cells, which has not been performed systematically in this study, may help in selecting candidates for this treatment among heavily pretreated patients. Along with toxicity, the shorter FFS observed in heavily pretreated patients suggests that intensive therapy should be performed early in the course of the disease.

It is difficult to compare our results with those published to date on intensive treatment followed by ABMT. In the original report from the Dana Farber Cancer Institute, 3-year disease-free survival after myeloablative treatment followed by purged ABMT was approximately 50% for low-grade lymphoma patients. In this series, 30 patients of 69 had residual bone marrow involvement at the time of the procedure. In the report from St. Bartholomew’s Hospital, which only included follicular lymphoma patients in relapse, 3-year freedom-from-recurrence survival was approximately 50%, with a median follow-up of 3.5 years. Only 30 of the 64 patients were in PR at time of intensive therapy, and only seven had residual bone marrow involvement, which is a much lower proportion than in our report for both parameters. Given the high proportion of patients in PR and/or with residual marrow involvement in our study, our results seem comparable with those reported in these two series. Furthermore, in the present study, FFS did not differ for patients receiving high-dose therapy while in PR or in CR, and the presence of residual bone marrow involvement had no influ-
ence on outcome. This contrasts with data obtained after purged ABMT\(^1\) and may suggest a specific interest for intensive therapy with PBPC support in this subset of patients. Indeed, this must be confirmed with a longer follow up.

Another important point is that patients treated after HT have a relatively good outcome, with the same OS as patients who retained a low-grade histology. This point is largely controversial. In a report from the Nebraska Medical Center, patients receiving transplants after HT had a very poor outcome.\(^2\) This poor outcome was also confirmed in a small group of patients from the European Bone Marrow Transplant Group Registry.\(^2\) This contrasts with the Dana-Farber Cancer Institute experience, in which there was no difference in the disease-free survival between patients with low-grade and patients with a transformed lymphoma.\(^1\) Patients with follicular lymphoma and HT have a very poor outcome with standard chemotherapy: in our experience, median survival was 7 months for all patients and 20 months for patients who could be treated with a CHOP-like regimen.\(^3\) These results suggest that the adverse prognosis associated with HT may be modified by intensive therapy with PBPC support. Notably, the majority of patients intensified after HT who subsequently relapsed returned to a low-grade histology.

In recent years, our policy has been to propose intensive therapy for young patients with recurrent disease or in first partial remission if adverse prognostic factors were present at diagnosis, but many questions remain unresolved. A study of minimal residual disease in patients bearing a polymerase chain reaction-amplifiable breakpoint after PBPC transplantation and during follow up is in progress in our institutions.\(^2\) A prospective randomized study comparing standard chemotherapy and a CHOP regimen followed by intensive therapy with TBI as consolidation has been initiated by our group. In young patients with recurrent disease, the comparison with historical control groups may suggest an improved relapse-free survival.\(^8\) It remains unclear, however, whether this treatment is able to prolong OS. If this intensive therapy is to be considered for patients with HT who respond to salvage chemotherapy, further experience with a longer follow up is needed for relapsing patients or for first-line patients.

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Intensive therapy with peripheral blood progenitor cell transplantation in 60 patients with poor-prognosis follicular lymphoma

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