Curability of Relapsed Childhood B-Cell Non-Hodgkin's Lymphoma After Intensive First Line Therapy: A Report From the Société Française d'Oncologie Pédiatrique

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The very high cure rate in advanced B-cell non-Hodgkin's lymphoma in children using intensive multiagent therapy has been previously reported by the French Société Française d'Oncologie Pédiatrique lymphoma Malin B type (LMB) group. To address the issue of salvageability in an unselected group of patients who had all received the same front-line therapy, the outcome of relapses following the LMB 84 (216 patients) protocol have been reviewed. Fourteen percent of patients achieving complete remission (CR) relapsed, ie, 27 of 195. Relapse sites comprised the central nervous system (CNS) alone (6 cases), lung or mediastinum (2 cases), abdomen (8 cases), head and neck (2 cases), or multifocal (9 cases). There were three early deaths due to disease. Twenty-four patients received rescue chemotherapy regimens and 15 were treated with high-dose chemotherapy and bone marrow rescue (1 allogeneic). Of these, 9 were in second CR, 4 in second partial remission, and 2 treated during progressive disease. One died in CR from treatment-related toxicity. Ten relapsed patients received autologous marrow transplant and 4 are alive disease free and probably cured. Two of the long-term survivors had some delay during initial chemotherapy due to toxicity and two were isolated CNS relapses. Twelve of 27 patients did not proceed to megatherapy (12 of 12 died).

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In children, small noncleaved high-grade lymphomas are invariably B-cell lymphoblastic (Kiel classification) and usually of the Burkitt subtype. In the last decade, survival from advanced-stage disease in children has dramatically increased from 25% to 80%. This improvement has been achieved through the use of dose escalation of the agents known to be active in this disease, such as cyclophosphamide, methotrexate, and cytarabine. It has been clear since the first reports of the use of high-dose therapy with autologous bone marrow (BM) rescue that this strategy was able to cure some patients with relapsed Burkitt's lymphoma and to increase survival in some initially bad prognosis patients when given as consolidation of first-line therapy.

The salvage rate in large series is around 40% at 3 years, but because of major selection of patients in all published series, confusion still exists as to the precise role of high-dose therapy and autologous BM transplantation (ABMT) in Burkitt's lymphoma. The object of this study is to review all relapses in an unselected group of patients treated with the Société Française d'Oncologie Pédiatrique (SFOP) lymphoma Malin B type (LMB) 84 protocol to try and define the role of second-line therapy including megatherapy in this group of patients for whom there is mean follow-up of more than 4 years.

Patients and Methods

Two hundred sixteen patients from 31 centers were included in the LMB 84 trial between January 1984 and September 1987, as previously reported in detail. One hundred sixty-seven had Murphy stage III and 34 had Murphy stage IV. One hundred ninety-five of the 216 patients had reached complete remission (CR) after induction (90%). Among these 195 patients, 27 relapsed and are the subject of this report. One of the 27 patients had already received high-dose chemotherapy with ABMT administered to consolidate initial partial remission (PR). Three of the relapses were initially stage II head and neck disease, 17 were stage III, and 7 were stage IV. Fifteen relapsed during therapy and 12 relapsed having completed treatment. Six relapses were isolated to the central nervous system (CNS), 12 were local relapses with or without BM involvement, and 7 relapses were multisystem.

The initial histologic diagnosis was small noncleaved high-grade lymphoma (lymphoblastic; Kiel classification). The B lineage was confirmed by immunophenotyping with expression of surface Ig in 107 cases. Supportive evidence came from the presence of characteristic 8;14, 2;8, or 8;22 translocations in 25 of the 216 cases. Large-cell lymphomas, ie, large-cell anaplastic lymphoma, malignant histiocytosis, or pure histiocytic lymphoma, were not included. One hundred sixty-two slides were reviewed centrally by Drs Caillou, Bayle, and Gentilhomme: 154 were small noncleaved Burkitt type, 3 small noncleaved non-Burkitt type, 1 immunoblastic, 1 lymphoblastic, and 3 small cell unclassified. Fifty-four slides were not reviewed and diagnosed in individual centers as small noncleaved Burkitt (n = 50), small noncleaved non-Burkitt (n = 1), and nonclassified small cell (n = 3).

All relapses from the LMB 84 protocol were registered in the SFOP data center. All relapses were small noncleaved high-grade lymphoma with B-lineage immunophenotyping. At the time of relapse, a second-line chemotherapy rescue protocol was administered according to the individual group policy. Thirteen patients received etoposide and high-dose cytarabine (CYVE) and 3 received etoposide and cisplatin as previously reported. Fourteen received COPADM as in the original LMB 84 regimen, 2 received MIME, and five received other regimens or no treatment.

Whenever possible, BM was harvested after one course of rescue therapy, except in the one case in which an allogeneic donor was available. High-dose therapy was scheduled 3 weeks after the second course of conventional rescue. The high-dose therapy regimen de...

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pended on the policy of the individual BMT team. BEAM (BCNU, etoposide, cytarabine, melphalan) was used in 8 cases; BEAC (BCNU, etoposide, cytarabine, cyclophosphamide) in 2 cases; high-dose busulphan, cyclophosphamide in 3 cases; and high-dose busulphan, cyclophosphamide, and melphalan in 2. Total body irradiation (TBI) was added in one case and cranial irradiation boost added to another in both of whom the BEAM regimen was used. CNS-directed therapy at relapse consisted of intrathecal methotrexate, cytarabine, and hydrocortisone, the number of injections depending on the presence of overt CNS disease. Apart from patients receiving TBI or cranial irradiation mentioned above, no radiotherapy was electively used in these relapsed patients.

After high-dose therapy, consolidation patients were isolated in sterile rooms with decontamination policies depending on the individual transplant center.

Survival was calculated using the Kaplan-Meier method and toxic deaths were included as events in all the curves. CR was defined as complete disappearance of all previously measurable disease for at least 4 weeks and a PR was 50% reduction in all disease. Any additional lesion or a 25% increase of a previously defined site of disease was defined as progressive disease (PD).

RESULTS

Response to second-line chemotherapy. Three patients were not evaluable because of early death. One patient was diagnosed to have relapsed after fatal interstitial pneumonitis, 1 died within 24 hours of diagnosis with PD, and 1 died 7 days after diagnosis with multisystem disease. Of the 13 patients who received the CYVE regimen, 6 had CR, 5 PR, and 2 PD. In the 3 who received etoposide, cisplatin regimen there was 1 CR, 1 PR, and 1 PD. Two of 4 who were reinduced with COPADM achieved CR and 2 progressed on treatment. One of three receiving MIME achieved a CR. One received a modification of the CYVE, but was not evaluable for response due to early CR of a CNS relapse with CNS-directed therapy.

It was intended that all responding patients should receive consolidation treatment with high-dose therapy and BM rescue. This strategy was followed in all but one patient, a child who had CNS, liver, and marrow relapse on treatment but achieved a PR with CYVE. Instead of high-dose therapy, he achieved CR after megatherapy, 1 progressed, and 1 was not evaluable due to toxic death associated with interstitial pneumonitis on day 39.

The median time to reach 1 × 10⁹/L white blood cells after ABMT was 23 days, 0.5 × 10⁹/L polymorphs 20 days, 0.2 × 10⁹/L polymorphs 19 days, and 50 × 10⁹/L platelets 30 days. Morbidity was acceptable with 1 reversible candida pneumonitis, 1 prolonged BM recovery, and 1 hemorrhagic cystitis.

As shown in Fig 1, the survival of the 12 patients who were not submitted to high-dose therapy was 0 of 12, with a median survival of 43 days after relapse. In those who were able to be transplanted, there was 4 of 15 event-free survival at 4 years. All 4 long-term survivors received BEAM as high-dose therapy regimen and were all in second CR before ABMT. None of the initial stage II patients are among the long-term survivors and the only allografted patient had rapid disease progression and died. Event-free survival after BMT of the 13 patients with “sensitive relapses,” ie, those achieving a PR or CR after second-line chemotherapy, is 4 of 13, and of the 9 patients, 4 are in second CR. Details concerning the 4 long-term survivors are given in Table 1. The overall survival in the 27 patients who relapsed after the LMB 84 regimen is 4 of 27 at 4 years.

DISCUSSION

Relapses are now a rare event in childhood B-cell non-Hodgkin’s leukemias (NHLs) in which intensive multiagent regimens are used. Only 14% of a group of 216 patients in this LMB 84 study relapsed. An earlier review of the natural history of Burkitt’s lymphoma in Europe and North Africa reported one-third of relapses to be in the CNS, one-third at primary site, and one-third in the multisystem.16,17 Although the overall relapse rate has dramatically declined with current regimens, the proportion of each relapse site is essentially unchanged. Although it has been claimed that isolated CNS relapse may be curable in some patients,19 in general, there are little published data indicating significant salvage rates in which BM or primary sites are involved. A wide range of salvage chemotherapy regimens have been devised for the treatment of relapsed high-grade lymphoma in adults,19,20 but in the experience of the SFOP group, CYVE has the highest response rate (85%, including 46% CR).12

The first question raised by this study is the likelihood of achieving a good second remission having relapsed after initially intensive treatment. The fact that 6 of 13 patients who received CYVE achieved a CR and 5 a PR, indicates that this disease remains relatively chemo-sensitive. The issue of whether some patients who achieve a CR with conventional second-line therapy may be cured without megatherapy cannot be answered by these data, but are the question of a large randomized study in adults.21 Historical experience within the French group suggests that the majority of patients will relapse unless further intensification is administered. This
study confirms that patients with PD should not be put into megatherapy programs, as although responses may occur, these are likely to be of short duration. However, sensitive relapses may benefit from further dose escalation, as appeared to be the case in 4 of the 9 who achieved a second CR. Overall, these data are not as good as the 40% cure rate reported in an early Lyon series, presumably reflecting patient selection.

Many different drug combinations are used in high-dose therapy regimens, but the BEAM regimen is well tolerated and has clear activity in refractory disease. The high failure rate even in sensitive relapses remains disappointing (4 CNS, 2 local, and 4 multisystem relapses). New phase II studies are required to try and increase the efficacy of the consolidation regimen in these patients.

Survival did not appear to differ according to the site of relapse or the time of relapse from diagnosis. Two of 8 CNS relapses are cured, 1 of 9 local relapses, and 1 of 9 multisystem relapses. One of 10 off therapy is a long-term survivor, whereas 3 of 16 who relapsed on treatment are cured. It should be noted that 2 of 4 long-term survivors had some delay during...

### Table 1. Details Concerning the Four Long-Term Survivors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Therapy</th>
<th>Date of Relapse (localization)</th>
<th>Rescue Protocol (response)</th>
<th>Conditioning Regimen (BMT)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EJ</td>
<td>LMB 84</td>
<td>7 mo (mediastinal)</td>
<td>MIME (CR)</td>
<td>BEAM (auto)</td>
<td>CCR</td>
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<td></td>
<td></td>
<td>Delay between COPADEM 1 and 2 because of interstitial pneumonitis and resuscitation (30 d)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CJ</td>
<td>LMB 84</td>
<td>3 mo (CNS)</td>
<td>VP16-CDDP + MTX (CR)</td>
<td>BEAM (auto)</td>
<td>CCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delay between COPADEM 1 and 2 (+8 d) and between COPADEM 2 and CYM (+7 d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EK</td>
<td>LMB 84</td>
<td>6 mo (multisystem)</td>
<td>CYVE (CR)</td>
<td>BEAM (auto)</td>
<td>CCR</td>
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<td></td>
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<td>Without any modification</td>
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</tr>
<tr>
<td>ED</td>
<td>LMB 84</td>
<td>3 mo (CNS)</td>
<td>CYVE (CR)</td>
<td>BEAM (auto)</td>
<td>CCR</td>
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<td>Without any modification</td>
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Abbreviations: MIME, methylgag, ifosfamide, methotrexate, etoposide; MTX, methotrexate; CDDP, dichloroacaminoplatinum; VP16, etoposide; COPADEM, cyclophosphamide, vincristine, prednisone, adriamycin, methotrexate; CYM, cytosine, methotrexate; CCR, continuous complete remission; Auto, autologous BMT.
initial chemotherapy due to toxicity and this may have contributed to their initial relapse (Table 1). However, the numbers are too small to conclude to what extent this increased the likelihood of subsequent salvage.

Investigational therapies for relapsed high-grade lymphomas include antibody-targeted therapy, antisense oligonucleotide therapy, and immunotherapy. However, at the present time, dose escalation remains the only method capable of achieving long-term survival and probable cure. It appears that around 15% of those who relapse after moderm treatment programs are still curable, provided effective conventional rescue regimens are followed with minimal delay by consolidation using high-dose therapy with BM rescue. For the present time, the latter should be restricted to patients who achieve a second CR or at least a second PR as the short-term morbidity is unjustified in patients in whom progression-free survival is likely to be short. In the complete responders, the cure rate may be as high as 30% and therapeutic nihilism at the time of relapse of Burkitt’s lymphoma is not necessarily justified in all patients.

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