Intensive Chemotherapy in Aggressive Lymphomas: Updated Results of LNH-80 Protocol and Prognostic Factors Affecting Response and Survival

By Bertrand Coiffier, Paul-André Bryon, Martine Fkrench, Michel Blanc, Catherine Sebban, Françoise Berger, and Jean-Jacques Viala

One hundred patients with aggressive malignant lymphomas treated with the LNH-80 regimen were evaluated for long-term survival and pretreatment characteristics predictive of response and survival. LNH-80 consists of three intensive courses of adriamycin cyclophosphamide viudamine bleomycin (ACVB) followed by sequential consolidation and final intensification. Eighty-four patients went into complete remission (CR), eight had a partial response (PR), three failed to respond, and five died during induction. Twenty-three patients (27%) relapsed, in two of whom a second remission was obtained. Sixty-three patients are currently alive, two of them with disease. Four patients died in CR. Median survival and median freedom from relapse survival were not reached with a median follow-up of 4½ years. Characteristics negatively associated with response in multivariate analysis were: poor performance status, bone marrow involvement, and two or more extranodal sites of disease. Duration of CR was associated with splenic involvement. Three characteristics were negatively associated with survival in multivariate analysis: age, high grade subtypes, and bone marrow involvement.

THE POOR PROGNOSIS associated with aggressive lymphomas has been dramatically improved by intensive combination chemotherapy. Regimens such as M-BACOD, ProMACE-MOPP, MACOP-B, and LNH-80 have been associated with increases of 10% to 30% in complete remission (CR) rates over those attained by CHOP regimens, and a concurrent decrease in relapse rates. Thus a greater number of patients survive 3 years of more. However, the long-term results of these intensive regimens are not known and their superiority is not definitively accepted.

Multicenter randomized studies are currently in progress in the United States and Europe to verify the better results of intensive regimens over those obtained with CHOP regimens. Even with these newer regimens, there are some patients who fail to respond or who relapse prematurely. Prognostic factors have been identified in patients treated with CHOP or newer regimens. This report updates the results of the LNH-80 regimen on 100 patients, with a median follow-up of 4½ years. Results already reported after 2 years of follow-up have been maintained with a plateau over 60%. Factors associated with response and/or survival are specified.

PATIENTS AND METHODS

Patients. One hundred patients with aggressive malignant lymphoma (ML) were treated with the LNH-80 regimen: the 97 patients previously described and three additional patients who had been excluded from the first publication due to the long time interval between diagnosis and treatment. Since they did not receive any chemotherapy or radiotherapy during this interval, they were brought into this study. All the patients were treated in our department between March 1980 and April 1984. All patients had given their informed consent in accordance with local institution guidelines. Entrance criteria for the protocol have been previously described: diagnosis of aggressive ML according to the Working Formulation, stage II or greater for intermediate grade ML, all stages for high grade ML, age <75 years, no contraindication to adriamycin, no previous chemotherapy or radiotherapy.

Of the 100 patients, 69 were males and 31 were females. Median age was 48.5 years (range 11 to 73 years, with three patients <15 and eight patients >65 years). Initial staging procedures included chest radiography, bone marrow aspiration and biopsy, liver function tests, CSF examination, abdominal echography and/or computed tomography (CT). Other examinations were performed as clinically indicated. The clinical presentation was detailed in the earlier report. Briefly, 66 patients had stage IV disease, 48 had B symptoms, 46 a performance status >1, 65 a large tumoral mass, 21 one extranodal site. Lactate dehydrogenase (LDH) was ≥2.5 times the normal level in 29 patients. Bone marrow involvement was present in 34 patients. Morphological subtypes are listed in Table 1.

Treatment. The LNH-80 regimen shown in Fig 1 included three phases of chemotherapy. The induction phase consisted of three courses of ACVB. A fourth course was administered if CR had not been obtained after three courses. The courses were initiated every 15 days or when polymorphonuclears increased to >1,500 x 10^9/L. A consolidation phase of sequential chemotherapy was initiated 1 month after the last ACVB. A final intensification was started 2 months later with two courses of AraCvMB. CNS radiotherapy was administered in cases of initial CNS localization.

Prognostic factors. The factors evaluated for potential prognostic significance included sex, age, performance status, presence of B symptoms, morphologic subtype, immunologic phenotype, sites of involvement, number of extranodal sites of disease, bulky (more than 7 cm in diameter) tumor, serum LDH, alkaline phosphatase and protein levels, complete blood count, and intensity of administered drugs during the induction phase. Performance status was based on the Eastern Cooperative Oncology Group scale: 0 to 4. Pathologic review was done by two hematopathologists (PAB and FB) according to the Working Formulation. Immuneologic phenotypes were determined in 37 patients by light chain characterization or monoclonal antibody typing, either on cell suspensions or on frozen specimens. LDH levels were expressed as multiples of the maximum normal value. Intensity of administered drugs during the induction phase was calculated as the number of milligrams per
expressed as a percentage of the theoretical dose.\textsuperscript{44}

Assessment of response. Response to treatment was assessed at the start of the consolidation phase. CR was defined by the disappearance of all clinical evidence of disease and the normalization of all laboratory values. Some patients with persisting radiographic abnormalities were deemed to be in CR if morphologic examination did not reveal any evidence of lymphoma: these patients were considered to have a persisting necrotic mass.\textsuperscript{15} Partial response (PR) was defined as $>50\%$ reduction in the largest dimension of each site of measurable disease. The failure category comprised progressive disease, transient disease regression, or death during the induction phase.

Statistical methods. Duration of remission was calculated from the onset of the consolidation phase to the first objective evidence of relapse. Survival duration was calculated from the beginning of the start of the consolidation phase to the first objective evidence of relapse. Survival curves were estimated by the method of Kaplan and Meier.\textsuperscript{16} Univariate analyses were performed using the $\chi^2$ and log-rank tests.\textsuperscript{17} Any factor significant at the 0.10 level were evaluated individually as possible prognostic indicators of response to therapy. The response rates associated with some of these factors are shown in Table 3. Statistically significant ($P < .05$) factors negatively associated with response to therapy were age $>50$ years, poor performance status, bulky disease, bone marrow, hepatic, splenic, or pleural involvement, hemoglobin $<100 \text{ g/L}$ and LDH $>2.5$ times the normal level.

There is no statistical difference between intermediate and high-grade lymphomas for response and relapse rates ($P > .10$) and for survival duration ($P > .05$).

RESULTS

Eighty-four patients (84\%) achieved CR. Five patients (5\%) died during the induction phase, eight patients (8\%) presented a PR, and three patients (3\%) failed to respond. Two of the eight PR patients were alive at 2 years, but none were alive at 4 years. Of the 84 CR patients, 23 (27\%) relapsed 5 to 56 months after diagnosis. Only six of the patients relapsed after 18 months, and two more of them relapsed after 3 years. CNS relapse was observed in two of the ten patients with initial CNS localization, but in none of the others. Results according to histologic subtype and immunologic phenotype are presented in Tables 1 and 2. Nineteen of the 23 patients who relapsed were rebiopsied: A histologic progression was seen in five patients and a follicular pattern was seen in two.

Sixty-three patients (63\%) are currently alive, two with disease and two in a stable second CR of $>3$ years. Four patients died in CR: one case each of CMV encephalitis, interstitial pneumonia, staphylococcus septicemia, and acute myeloblastic leukemia (18 months after diagnosis). Overall treatment mortality rate was 9\% (five patients during induction and four in CR). Overall survival and freedom from relapse (FFR) survival are presented in Fig 2. Median survival and median FFR survival were not reached with a median follow-up of 4.5 years.

Prognostic indicators of response to chemotherapy. Forty-five clinical or biological factors determined at diagnosis were evaluated individually as possible prognostic indicators of response to therapy. The response rates associated with some of these factors are shown in Table 3. Statistically significant ($P < .05$) factors negatively associated with response were age $>50$ years, poor performance status, bulky tumor, two or more extranodal sites of involvement, bone marrow, hepatic, splenic, or pleural involvement, hemoglobin $<100 \text{ g/L}$ and LDH $>2.5$ times the normal level.

Single factors not predictive of response to therapy

<table>
<thead>
<tr>
<th>Table 1. Results of Treating 100 Patients With the LNH-80 Regimen, According to Histologic Subtypes Defined in the Working Formulation</th>
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<td>Histologic Subtypes</td>
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<tr>
<td>Intermediate grade (%)</td>
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<td>Follicular large cell</td>
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<td>Diffuse large cell</td>
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There is no statistical difference between intermediate and high-grade lymphomas for response and relapse rates ($P > .10$) and for survival duration ($P > .05$).
included sex, morphologic subtype, immunologic phenotype, stage, B symptoms; digestive, head and neck, cutaneous, pulmonary, pericardiac, osseus, or neurologic localization; presence of a large mediastinal or abdominal mass; decreased level of proteins, albumin, gammaglobulins, platelets, or polymorphonuclear leukocytes; increased level of gammaglobulins, lymphocytes, lymphoblasts, or creatinine; accelerated sedimentation rate, and drug intensity of induction chemotherapy.

The factors associated with response according to univariate unadjusted analysis were further examined by multivariate logistic regression analysis. All the factors having prognostic significance were known for all the patients except the LDH level. Factors found to be significantly associated with poor survival were bone marrow involvement (P = .02), hemoglobin level <100 g/L (P = .07). The presence of a residual necrotic mass in patients without the LDI-1 level. The two studies gave the same results: poor performance status, bone marrow involvement, and two or more extranodal sites remained statistically significant (P < .05).

None of the factors studied was statistically associated with relapse in univariate or multivariate analyses. Drug intensity during the induction phase had borderline significance (P = .07). The presence of a residual necrotic mass in 16 patients was not associated with a greater risk of relapse (P = .15).

**Prognostic indicators of survival.** The clinical and biological factors examined for their value in predicting response were also assessed for their relation to survival (Table 4). Single factors statistically associated with short survival were bone marrow involvement (P < .01) (Fig 3), LDH >2.5 times the normal level (P = .02), age >50 years (P = .02), hemoglobin level <100 g/L (P = .03), and more than one extranodal site (P = .05). Poor performance status and peripheral T cell phenotype had borderline significance: P value < 0.05 in the Wilcoxon test, and <0.10 in the Mantel-Cox-Savage test. None of the other factors tested was statistically associated with poor survival, particularly age, morphologic subtype, stage, B symptoms, hepatic, splenic, digestive, or neurologic localization, and drug intensity during the induction phase.

All the factors with some significance were included in a multivariate Cox regression analysis without the stepwise selection (Table 5). The analysis was performed on two sets of patients: all 100 patients, and the 95 for whom LDH was known. Factors found to be significantly associated with poor survival were increasing age, high grade subtypes, and bone marrow involvement.

The prognostic score described by Shipp et al in their study with the M/m-BACOD regimens was applied to our patients. This score was based on the performance status, the diameter of the largest mass, and the number of extranodal sites of disease; it divided patients into three subgroups with a predicted 5-year survival rate of 68%, 55%, and 24%.
The score was a statistically significant indicator of prognosis. Poor performance status, and presence of B symptoms. Poor performance status, bone marrow involvement, and two or more extranodal sites of disease were found to be negatively associated with response. Age, high grade subtypes, and bone marrow involvement were adversely associated with survival. Marrow involvement was one of the most important prognostic factors, as had also been reported for the CHOP regimen. Our 100 patients were evaluated for prognostic factors that could be predictive of response and survival. Poor performance status, bone marrow involvement, and two or more extranodal sites of disease were found to be negatively associated with response. Age, high grade subtypes, and bone marrow involvement were adversely associated with survival. Marrow involvement was one of the most important prognostic factors, as had also been reported for the CHOP regimen, but not in the M/m-BACOD study.

The prognostic factors we found to be significant had been reported in several previous studies on prognostic factors in ML. Poor performance status and presence of B symptoms had been recorded as indicators of low response rate and/or poor survival. Age was considered an indicator of poor survival in most of the studies, but the dividing line was variable: 55 years, 55 and 65 years, 60 years. Visceral localizations as liver, spleen, pleura were occasionally associated with inferior survival. Superior to those obtained with CHOP and CHOP-like regimens. A large proportion of patients will probably be cured, but 3 to 5 more years are required before the results can be considered definitive. These results are the best reported with a follow-up >3 years: the M/m-BACOD regimens have achieved a median survival of 68 months with a 5-year survival rate of 50% for large cell ML, the ProMACE-MOPP/CytaBOM regimens and the MACOP-B regimen have not been updated as yet, but the MACOP-B regimen was reported to give good results only in large cell ML.

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significant prognostic factors in our study. While our results and those of Shipp et al. suggest that it is not the tumor mass that is of little consequence in our series. Only the presence of two or more large tumor masses was associated with poor prognosis and disappeared in multivariate analyses. In contrast with earlier studies that suggested an adverse prognostic significance, the tumoral mass and the number of extranodal sites...  

Although the score described by Shipp was found to have some prognostic significance, the tumoral mass and the number of extranodal sites of disease were not the most significant prognostic factors in our study. While our patients had more indices of poor prognosis, their predicted 5-year survival rates were higher than Shipp's, with a small difference for the best prognostic group (77% vs. 68%), but a large difference for the poor risk patients (52% vs. 24%). This would appear to reflect the better results with our regimen than with the M/m-BACOD, but the actual difference, if any, could only be proved by a randomized study. Drug intensity during the induction phase was of borderline significance for predicting CR duration. It seems to us that drug intensity in our regimen is one of the factors responsible for the better results obtained, but it is difficult to demonstrate due to its low variation in our patients: those who received 75% of the theoretical dose received more adriamycin or cyclophosphamide per month than in CHOP or M/m-BACOD regimens.

The prognostic significance of the immunologic phenotype had rarely been addressed, probably because peripheral T cell lymphomas were rarely recognized in the past. Whether peripheral T lymphomas have the worst prognosis has been much debated and no firm conclusions can be drawn from the literature. Immunological phenotype is not correlated with other prognostic factors. The poor prognosis of our peripheral T cell lymphoma patients was essentially due to the large number of patients who died in induction, failed to respond, and relapsed during the first months of CR: median survival was only 14 months. The intensive regimen did, nevertheless, yield the best survival rates for peripheral T cell lymphomas compared with other forms of treatment.

The LNH-80 regimen applied to 100 patients with aggressive ML can be credited with keeping 63 of them alive with a median follow-up of 4½ years. These results are the best published so far for this disease. Our results are currently being tested in a multicenter randomized study of the LNH-84 protocol in France and Belgium. More than 750 patients have already been included and the initial results will soon be communicated.

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Identification of prognostic subgroups of patients with large-cell lymphoma treated with m-BACOD or M-BACOD. Ann Intern Med 104:757, 1986


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