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ORIGINAL ARTICLE

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Cyclophosphamide, doxorubicin, vincristine, and prednisone versus intensive chemotherapy in non-Hodgkin's lymphoma

Abstract Therapy for aggressive non-Hodgkin's lymphomas has undergone significant evolution in the past 25 years. First-generation combination chemotherapy studies produced complete response (CR) rates of 45–53% together with 30–37% rates of long-term survival. New treatment programs aimed at increasing CR rates were then developed on the assumption that the additional patients who achieved a CR would become long-term disease-free survivors. Initial reports of single-institution pilot studies with third-generation regimens suggested CR and survival rates of 68–86% and 58–69%, respectively; however, after longer follow-up periods, survival rates decreased. Furthermore, confirmatory national phase II trials using these newer regimens produced CR rates of only 49–65% and survival rates of 50–61%. Thus, ultimate conclusions concerning the efficacy of these new regimens awaited the results of prospective randomized trials. The Southwest Oncology Group (SWOG) conducted a randomized trial comparing standard therapy, CHOP, to the third-generation chemotherapy regimens m-BACOD, ProMACE-CytaBOM, and MACOP-B. After 6 years, no difference in the response rate, progression-free survival, or overall survival has been found between CHOP and the third-generation regimens. For example, the 6-year estimates of progression-free survival are CHOP 33%, m-BACOD 36%, ProMACE-CytaBOM 34%, and MACOP-B 32% (P = 0.41). The 6-year overall survival estimates are CHOP 42%, m-BACOD 40%, ProMACE-CytaBOM 46%, and MACOP-B 41% (P = 0.89). Furthermore, we have not identified any subset of patients who survive longer on treatment with the third-generation regimens, and the cost and toxicity of the new regimens are higher. On the basis that $<50\%$ of these patients are cured, the best approach for any patient is an experimental one designed to improve our ability to cure the disease. Examples of this include (l) increasing the dose intensity of drugs used in standard regimens and (2) autologous bone marrow transplantation and/or peripheral stem-cell support as rescue from marrow-ablative chemotherapy. If a patient is not eligible or does not wish to participate in a clinical trial, CHOP, as inadequate as it is, remains the gold standard.

Key words Diffuse large-cell lymphoma · Non-Hodgkin's lymphoma · CHOP · ProMACE · CytaBOM · m-BACOD · MACOP-B

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Introduction

Treatment for the aggressive non-Hodgkin's lymphomas (NHL; identified as intermediate- and high-grade lymphomas under the Working Formulation Classification [25] and primarily considered diffuse large-B-cell lymphoma in the recently reported REAL Classification [15]) currently consists of initial combination chemotherapy for essentially all patients. This results in cure for the vast majority of patients with limited disease, as we have recently reported [19], as well as in a subset of patients with advanced stages of disease. Studies with the initial or first-generation chemotherapy regimens such as cyclophosphamide, vincristine, procarbazine, and prednisone (C-MOPP) or cyclophosphamide, doxorubicin, vincristine, bleomycin, and prednisone (BACOP), conducted by the National Cancer Institute [8], and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), conducted by the Southwest Oncology Group (SWOG) [5], produced complete response (CR)

rates of 40–55% along with 30–35% rates of long-term survival; 10- to 15-year follow-up revealed that there were few late relapses. Therefore, investigators assumed that if they could increase the CR rate, they would increase the long-term survival rate, and several institutions developed new and more complex chemotherapy protocols, which have been termed the second-generation studies [4]. These programs initially reported CR rates of 72–80% and survival rates of 55–62%. Unfortunately, longer follow-up periods revealed that late relapses were occurring in each of these studies.

Finally, the same institutions developed third-generation regimens such as cyclophosphamide, doxorubicin, vincristine, bleomycin, methotrexate, and dexamethasone (m-BACOD) [24]; cyclophosphamide, doxorubicin, etoposide, cytarabine, vincristine, bleomycin, methotrexate, and prednisone (ProMACE-CytaBOM) [9]; and cyclophosphamide, doxorubicin, vincristine, bleomycin, methotrexate, and prednisone (MACOP-B) [17], and early reports suggested CR and survival rates of 68–86% and 58-69%, respectively. SWOG subsequently conducted a series of phase II confirmatory trials using the latter three regimens [7, 18, 27]. Both CR and survival rates were lower than initially reported; CR rates varied from 49% to 65% and survival rates from 50% to 61%. Since the results of these studies were closer to those obtained with the first-generation regimens in a national cooperative group setting, ultimate conclusions concerning the efficacy of these new regimens awaited the results of prospective randomized trials.

Comparative trials of standard chemotherapy regimens

To determine definitively the relative merits of the first- and third-generation regimens (Table 1), SWOG and the Eastern Cooperative Oncology Group (ECOG) conducted SWOG-8516 (Intergroup 0067) between May 1986 and June 1991 [10]. This study, which was designated the National High Priority Lymphoma Trial, enrolled 1138 previously untreated patients with bulky stage II, stage III, or stage IV intermediate- or high-grade NHL who were randomized to receive treatment with either standard therapy (CHOP) or one of the third-generation chemotherapy regimens (m-BACOD, ProMACE-CytaBOM, or MACOP-B).

Each treatment regimen was given exactly as initially described and the treatment arms were well balanced for patient characteristics. No significant difference has been found in the overall response or CR rates between treatment arms, with the median follow-up for all patients exceeding 5 years. The 6-year estimates of progression-free survival are CHOP 33%, m-BACOD 36%, ProMACE-CytaBOM 34%, and MACOP-B 32% (P = 0.41); the 6-year overall survival estimates are CHOP 42%, m-BACOD 40%, ProMACE-CytaBOM 46%, and MACOP-B 41% (P = 0.89). Furthermore, we have not identified any subset of patients who survive longer on treatment with the third-generation regimens. The received dose-intensity data were comparable to the data previously published for these regimens, but the cost and toxicity of the new regimens were higher. Fatal toxicities have been observed in 1% of patients treated with CHOP, in 5% of those treated with m-BACOD, in 3% of those treated with ProMACE-CytaBOM, and in 6% of those treated with MACOP-B. All individual pairwise comparisons between CHOP and these third-generation regimens reached identical conclusions.

ECOG and Cancer and Acute Leukemia Group B have reported the results of treating 325 diffuse mixed or diffuse large-cell lymphoma patients who were randomized to CHOP or m-BACOD [12]. After a median follow-up period of 4 years, there was no difference in CR, time to treatment failure, or survival. However, more severe and life-threatening pulmonary, infectious, and hematologic toxicity was observed after therapy with m-BACOD.

The Spanish Cooperative Group compared CHOP and ProMACE-CytaBOM [20], and no significant difference was reported. The New Zealand Lymphoma Study Group reported the results of a prospective randomized trial in which 304 patients were treated with either the third-generation regimen MACOP-B or CHOP [6]. The dose modifications and schedules of both regimens were as originally described. Of the 125 patients treated with MACOP-B, 64 (51%) achieved a CR as compared to 65 of 111 (59%) treated with CHOP (P = 0.3). The estimated failure-free survival at 4 years is 44% for MACOP-B and 32% for CHOP; the estimated survival at 4 years was 56% for MACOP-B and 51% for CHOP (P = 0.69). Hence, no significant difference in CR, failure-free survival, or overall survival rates was found between CHOP and MACOP-B.

New therapeutic approaches

On the basis of similar failure-free and overall survival rates obtained with lower cost and less severe toxicity as described in each of the randomized trials outlined above, CHOP remains the gold standard for chemotherapy treatment for patients with advanced-stage intermediate- or high-grade NHL. However, on the basis that $<50\%$ of these patients are cured, the SWOG Lymphoma Committee believes that new treatment approaches for patients with advanced-stage NHL of aggressive histology must be developed. Newer therapeutic approaches include (l) increasing the dose intensity of drugs used in standard regimens and (2) autologous bone marrow transplantation (ABMT) and/or peripheral stem-cell support as rescue from marrow-ablative chemotherapy.

To determine which patient populations would be good candidates for more intensive therapy, it is necessary to determine whether there are known prognostic factors that are capable of separating patients with a good prognosis from those with a poor prognosis. The International Non-Hodgkin's Lymphoma Prognostic Factors Project has recently presented a predictive model for aggressive lymphomas [16]. Five factors were independently associated with poor survival, including an age of >60 years, stage III or

IV disease, two or more extranodal sites, a poor performance status, and abnormal serum levels of lactate dehydrogenase (LDH). Patients were grouped into low-, low-intermediate-, high-intermediate-, or high-risk categories on the basis of the presenting number of poor risk factors. Patients with one risk factor, if any, were found to be at low risk, patients with two risk factors were at low-intermediate risk, patients with three risk factors were at high-intermediate risk, and patients with four or five risk factors were at high risk. When patients on SWOG-8516 were analyzed according to this prognostic index, statistically significant differences in both failure-free and overall survival could be detected among the four prognostic groups. However, when these four risk groups were analyzed according to the chemotherapy regimen they received, there was no significant difference between the curves obtained for any of the regimens in any of the risk groups.

Dose intensification of standard chemotherapy regimens

With the availability of colony-stimulating factors (CSFs), the ability to maximize dose intensity has been improved as compared to the doses that can be delivered without CSF support. Hence, one very rational approach to maximizing the efficacy of therapy is to dose-escalate the drugs given in standard regimens with CSF support. SWOG is undertaking a randomized phase II study of dose intensified CHOP and dose-intensified ProMACE-CytaBOM with granulocyte-CSF support. In both arms the doses of cyclophosphamide and doxorubicin are escalated to approximately twice the normal dose intensity of each regimen to determine whether the results appear better than those of prior studies employing these drugs at conventional doses. A similar phase I study that escalated the doses of cyclophosphamide and doxorubicin in 30 patients newly diagnosed with bulky, advanced-stage, aggressive NHL has recently been described [25] and showed that initial CR rates were high; however, the follow-up period was very short.

High-dose therapy with stem-cell rescue

High-dose chemotherapy with autologous bone marrow support has become established as an effective salvage therapy for selected patients with refractory or relapsed diffuse aggressive lymphoma. In several phase II series, 20–25% of treated patients have achieved prolonged disease-free survival employing this approach [1, 2, 13, 22]. Although there has been considerable variability in the selection criteria of these studies, several consistent findings have been observed. The patients who are likely to achieve a CR and possible cure are those who respond well to initial therapy, who respond well to salvage therapy pretransplantation, and who undergo transplantation with minimal, if any, residual disease. Patients progressing on salvage therapy and those who respond poorly to initial therapy are unlikely to benefit. A variety of regimens has been used and shown to be effective.

The results of an important randomized trial called the Parma trial, which compared ABMT with salvage chemotherapy for patients in relapse with chemotherapy-sensitive NHL, have just been published [23]. At 5 years the rate of event-free survival was 46% in the transplantation group and 12% in the group receiving only salvage chemotherapy ($P = 0.001$), and the overall survival rates were 53% and 32%, respectively ($P = 0.038$). This study definitively established the role of ABMT as the primary therapy for relapsing chemotherapy-sensitive lymphoma.

The role of ABMT as initial therapy for patients judged to be at high risk for treatment failure with conventional therapy remains to be defined. Few randomized studies comparing ABMT with conventional therapy have been completed.

The Groupe d'Etudes des Lymphomes des l'Adulte (GELA) reported on a subset of 727 patients treated using the LNH87 protocol [14]. In this analysis, 370 patients who had achieved CRs with induction therapy were randomized to a consolidation phase in which patients were randomized to sequential chemotherapy or ABMT. Only one patient died of transplant-related complications. At a median follow-up of 21 months, the overall 2-year survival rate was 62% and the disease-free survival rate was 58%. Overall survival and disease-free survival did not differ between the consolidation arms ($P = 0.089$). A subsequent retrospective subset analysis revealed a relapse-free and overall survival benefit for patients who were reclassified as having the high-intermediate- and high-risk characteristics according to the International Index. Whether this subset of patients truly benefits from high-dose therapy cannot be determined at this time because a retrospective analysis of this type cannot be considered statistically valid; however, it is useful for generation of a new hypothesis. Prospective randomized trials in those two subsets of patients will be required to answer the question definitively.

Verdonck et al. [26] recently published a comparison of CHOP chemotherapy and ABMT in slowly responding patients with newly diagnosed, aggressive NHL. Patients who did not have a CR after three cycles of CHOP chemotherapy were randomized to either ABMT or five more cycles of CHOP. Of the 286 patients entering the trial, 106 were classified as slow responders, and 69 of these patients underwent randomization. There was no difference at 4 years with regard to overall survival (85% versus 56%), disease-free survival (72% versus 60%), or event-free survival (53% versus 41%) between the patients randomized to CHOP and those randomized to ABMT. The authors concluded that early application of ABMT did not improve the outcome in these slowly responding patients.

In a trial conducted by Gianni et al. [11], 75 patients with high-risk aggressive NHL were randomized to treatment with MACOP-B ($n = 37$) or with a novel high-dose chemotherapy regimen requiring hematopoietic progenitor-cell autotransplantation ($n = 38$). By using a cross-over design the authors sought to determine not only which was the most effective therapy but also which was the best

Table 1 Randomized trials comparing CHOP with third-generation regimens (CALGB Cancer and Leukemia Group B, NS not significant)

Trial	Treatment	n	Survival	Probability	Reference
ECOG/CALGB	CHOP	174	48% at 5 years		
	vs			P = 0.5	[12]
	m-BACOD	151	49% at 5 years		
Spanish Cooperative	CHOP	76	43% at 4 years		
Group	vs			P = NS	[20]
	ProMACE-CytaBOM	72	56% at 5 years		
Australia/New	CHOP	111	51% at 4 years		
Zealand Cooperative	vs			P = 0.69	[6]
Group	MACOP-B	125	56% at 4 years		
SWOG/ECOG	CHOP	225	42% at 6 years		
	vs				
	m-BACOD	223	40% at 6 years		
	vs			P = 0.89	[10]
	ProMACE-CytaBOM	233	46% at 6 years		
	vs				
	MACOP-B	218	41% at 6 years		

therapeutic strategy, i.e., whether initial or salvage high-dose therapy would result in better overall patient survival. The toxic death rate in the high-dose arm of the study was initially high (16%) but decreased on modification of the treatment regimen. In all, 38 patients were randomized to high-dose therapy and 37 to MACOP-B. After a median follow-up period of 43 months there were statistically significant improvements in relapse-free survival (93% versus 68%; P = 0.05) and freedom from progression (88% versus 41%; P = 0.0001) in favor of the high-dose therapy arm. However, overall survival was not statistically improved (73% in the high-dose arm versus 62% in the MACOP-B arm). Although this study is promising, the small number of patients enrolled make it difficult to know whether the results can be attributed to imbalances in patients' prognostic factors. Future confirmatory trials are required.

The recommendations of a consensus conference on intensive chemotherapy plus hematopoietic stem-cell transplantation in malignancies have recently been published [3]. The sections dealing with relapsed lymphomas are now outdated because, as discussed previously, the Parma study demonstrated the superiority of ABMT over conventional salvage therapy [23]. However, the consensus conference recommendations on the initial use of ABMT remain relevant, i.e., they recommend that for high- or intermediate-grade NHL a randomized trial of conventional therapy versus high-dose therapy with bone marrow and/or peripheral stem-cell support be developed for those patients defined to be in poor-prognosis groups.

Conclusions

The majority of patients with advanced-stage intermediate- or high-grade NHL are not cured with conventional therapy. Unfortunately, increasing the CR rate has not resulted in a major increase in the number of patients cured. Therefore, each treating physician must recognize the inadequacy of current therapy and urge all eligible patients to participate in well-designed clinical trials. As the best therapy remains to be defined, the best approach for the patient is an experimental one designed to improve our ability to cure the disease. If a patient is not eligible or does not wish to participate in a clinical trial, CHOP, as inadequate as it is, remains the gold standard against which all new therapies must be compared.

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