Chemotherapy of Intermediate-Grade Non-Hodgkin's Lymphoma: Is "More" or "Less" Better?

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While it would seem obvious that dose intensity is an important determinant of treatment outcome in aggressive lymphomas, actually there are very few prospective data to support this hypothesis. Circumstantial evidence derived from retrospective analyses suggests that dose intensity is of clinical significance.

Introduction

While it would appear to be intuitively obvious that dose intensity is an important determinant of treatment outcome in aggressive lymphomas, actually very few prospective data support this hypothesis. There is, however, considerable circumstantial evidence that dose intensity may be an important variable in treatment outcome. Unfortunately, this is not adequate to prove the hypothesis.

DeVita et al were among the first investigators to discuss the relationship of dose intensity to lymphoma treatment outcome [1]. These investigators proposed a model to relate the projected relative dose intensities of nine drugs (as defined by a treatment protocol) to the outcome realized by using various other regimens that incorporated some or all of these agents. Using this model, they demonstrated a significant correlation between dose intensity and treatment outcome. Problems inherent in a model such as this, which uses projected dose intensity, include the following:

1. Generally, all agents are considered to be equally effective.
2. There is no way to take into account possible effects related to drug scheduling.
3. The projected dose intensity is usually not fully delivered.

Several authors have attempted to analyze the contribution of dose intensity to outcome in retrospective analyses of completed trials. In a preliminary analysis of results obtained with M-BACOD and m-BACOD (both regimens employing methotrexate [in different doses], bleomycin, Adriamycin, cyclophosphamide, Oncovin, and dexamethasone), Shipp et al reported that delivery of more than 80% of projected doses of doxorubicin, vincristine, and cyclophosphamide (Cytoxan, Neosar) was associated with improvement in remission rates and survival [2]. A subsequent analysis noted, however, that in patients who successfully completed eight cycles of therapy, this relationship of received dose intensity and outcome was no longer observed.

The results obtained with the LNH-84 regimen were reported by Coiffier et al [3]. Received dose intensity data were available for 720 of 737 patients treated. While the authors were unable to show statistically significant differences in outcome, they did demonstrate a trend toward a lower relapse rate in those receiving higher dose-intensive therapy. It should also be noted that a trend toward a higher death rate also was seen in this same group of patients.

Epelbaum et al analyzed a series of 78 patients with diffuse large-cell lymphoma treated with the CHOP (cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone) regimen to ascertain the contribution, if any, of dose intensity to outcome [4]. These authors were able to demonstrate a statistically significant association between survival and the received dose intensity of doxorubicin.

Kwak et al reported results of a multivariate analysis of 115 patients with diffuse large-cell lymphoma treated with three different chemotherapy regimens: CHOP, M-BACOD, and MACOP-B (methotrexate, Adriamycin, cyclophosphamide, Oncovin, prednisone, and bleomycin) at different periods of time [5]. Similar survival curves were noted for each of the three regimens. However, the authors did observe a correlation between average relative dose intensity and the received dose intensities of doxorubicin and cyclophosphamide and survival. Using the statistical technique of recursive partitioning, the authors found that after pretreatment hemoglobin, the dose intensity of doxorubicin proved to be the most discriminating prognostic variable.
The technique of meta-analysis also has been employed in an attempt to define the relationship between dose intensity and treatment outcome. Meyer et al performed a meta-analysis on pooled data from 22 studies, of which 14 were randomized trials [6]. High- and low-intensity treatment groups within the 14 trials, which included 2,366 patients, were pooled and compared. The results of the analysis demonstrated that the relative probability of achieving a complete response was 1.34 in favor of the pooled arm of high dose intensity. Unfortunately, because of the variable length of follow-up, long-term disease-free survival, which is a more meaningful measure of treatment outcome than is complete remission rate, could not be compared in the analysis. The authors correctly point out that any conclusions drawn from this analysis must be accepted with caution because the groups are heterogeneous, the treatments are varied, and considerable assumptions are made at the outset in the performance of such an analysis.

Hence, whereas these retrospective analyses have, in some cases, suggested a correlation between dose intensity and outcome, they do have to be interpreted cautiously, in large part, because they are retrospective. Although there is circumstantial evidence that dose intensity may be an important predictor of outcome, there is very little direct evidence available from prospective studies. Four of the regimens in the model proposed by DeVita-m-BACOD, ProMACE/CytaBOM (prednisone, methotrexate, Adriamycin, cyclophosphamide, etoposide, cytarabine, Oncovin, and methotrexate) ProMACE-MOPP (prednisone, methotrexate, Adriamycin, cyclophosphamide, etoposide, mechloretamine, Oncovin, procarbazine, and prednisone) and MACOP-B have greater projected dose intensity than CHOP. These regimens have been studied extensively in clinical trials. In this review, we will focus on results obtained in phase II and III studies employing these regimens. It should be noted that, in many of the earlier phase II studies, received dose intensity data was not reported, and thus, the database is incomplete. It should also be noted that none of the phase III studies we will review that employed these four regimens or CHOP were prospectively stratified by dose intensity. Finally, we will review the single prospective phase III study that has directly tested the question of dose intensity and has been reported in the literature. Key terms that will be used in this article are defined in Table 1.

**Phase II Studies**

**m-BACOD**

M-BACOD is a regimen that was developed and piloted at the Dana-Farber Cancer Institute [7]. The regimen employs high-dose methotrexate with leucovorin rescue given at mid-cycle, that is, at the time of maximal bone marrow suppression secondary to the myelotoxic drugs that are given at the beginning of the cycle (see Table 2). Although this regimen proved to be effective and appeared to be a significant improvement over prior chemotherapy regimens, it was also costly and required hospitalization.

The m-BACOD regimen, which employs moderate-dose methotrexate (see Table 2), was therefore piloted by the same group, and results similar to those seen with the high-dose regimen were achieved [8]. Of the 134 patients with diffuse histiocytic or undifferentiated lymphoma who were treated, 75% had either stage III or IV disease. The median age of the treated patients was 49 years. Eighty-two patients (62%) achieved a complete response and 62 (76%) of these remain in complete remission with a median follow-up of 3.6 years. The predicted 1-, 3-, and 5-year survival rates were 80%, 63%, and 60% respectively. The disease-free survival rate at 5 years for patients achieving a complete response was 74%.

As noted above, in a preliminary analysis of the data, Shipp et al noted a correlation between dose intensity and outcome. This correlation, however, was no longer found to be of importance when patients completing eight cycles of therapy were analyzed.

The Southwest Oncology Group (SWOG) conducted a confirmatory phase II trial of the m-BACOD regimen [9]. By study design, patients were stratified at registration as having either normal or impaired bone marrow reserve. Of the 106 eligible patients, 28 were in the impaired category and received decreased doses of cyclophosphamide and doxorubicin. In the study population as a whole, 76% had diffuse large-cell lymphoma, 75% had stage III or IV disease, and 46% had B symptoms. The overall complete response rate was 56%. There was, however, a marked difference in complete response rates in the normal and marrow-impaired groups. At 3 years, 64% of the normal marrow group who achieved a complete response were disease-free, as compared with 29% in the marrow-impaired group. It should be noted that despite decreased dosages, the marrow-impaired group experienced toxicity similar to those treated with full-dose therapy.

The relative dose intensity on the normal marrow reserve arm was .76 for cyclophosphamide, .75 for...
doxorubicin, .90 for vincristine, .85 for dexamethasone, and .55 for methotrexate. On the impaired-marrow reserve arm, as would be expected, the values for all drugs were lower. In addition to being given decreased doses of cyclophosphamide and doxorubicin by study design, patients with marrow impairment also had more dose reductions and treatment delays, as compared to patients with normal marrow reserve.

**ProMACE-CytaBOM**

The ProMACE-CytaBOM regimen was developed and piloted at the National Cancer Institute (NCI) [10]. Investigators at the NCI had previously developed the ProMACE-MOPP regimen, an intensive, multidrug regimen in which cycles are repeated every 28 days (see Table 2). In the ProMACE-CytaBOM regimen, several nonmyelosuppressive agents with antitumor activity in lymphoma are given on day 8 to allow recovery from the myelosuppressive effects of day 1 agents in time to permit each cycle to be given every 3 weeks instead of every 4. By administering a complete cycle every 3 weeks, six full cycles can be delivered in 18 weeks, instead of the 24 weeks required to deliver six cycles of the ProMACE-MOPP regimen, thereby achieving a 25% increase in the dose intensity of the regimen.

One large phase II study of this regimen, conducted by the SWOG [11], involved 97 previously untreated patients with stage II, III, or IV disease (median age, 54.5 years). Of these patients, 29% had stage II disease, 49% had B symptoms, and 60% had diffuse large-cell histology. Of the 97 patients, 78 were assessable for response. A complete response was attained by 51 patients (65%). The projected overall 3-year survival was 57%, and the failure-free survival was 37%. Among the patients achieving a complete response, 50% were alive and without disease at 3 years. Compared with patients who had stage III and IV disease, patients with stage II disease had superior overall survival ($P = .057$), failure-free survival ($P = .045$), and relapse-free survival ($P = .0033$).

In this cooperative group setting, 84% of all treatment courses were delivered precisely according to protocol specifications. The average actual dose delivered was compared with the ideal dose as initially described for the regimen. The ratio of actual dose to ideal dose varied between .80 to .87 for all drugs except vincristine, which had a ratio of .64.

**MACOP-B**

The MACOP-B regimen was developed and studied extensively at the British Columbia Cancer Agency in Vancouver [12]. It consists of 12 weeks of continuous therapy with doxorubicin and cyclophosphamide given during odd-numbered weeks alternating, on even-numbered weeks, with vincristine and either bleomycin or moderate-dose methotrexate with folic acid (leucovorin) rescue (see Table 2). Oral prednisone is given throughout the 12 weeks of therapy. Prophylactic trimethoprim-sulfamethoxazole and either cimetidine or ranitidine are given as well.

The Vancouver study entered 126 patients. Eligibility criteria included a diagnosis of diffuse large-cell lymphoma, which included a variety of histologic subtypes, and stage III or IV disease (or stage I or II if the tumor was bulky or B symptoms were present). Complete responses were achieved in 84% of patients. The actuarial overall survival at 8 years was 62%, and the failure-free survival at the same time point was 52%.

The initially reported excellent results with MACOP-B prompted a series of phase II studies of this regimen conducted in both single-institution and cooperative group settings. Schneider et al treated 70 assessable patients at Memorial Sloan-Kettering Cancer Center with the MACOP-B regimen [13]. Patients who were previously untreated and had stage II, III, or IV intermediate-grade or immunoblastic lymphoma were eligible. It should be noted that consecutive patients were not entered into this study because eligible high-risk patients were randomized to a study of MACOP-B vs autologous bone marrow transplantation as first therapy if they had no bone marrow involvement, were < 50 years of age, and had a very good performance status. Patients who had AIDS, ARC, or were HIV-positive were not eligible for transplantation, and thus were assigned to MACOP-B. Overall, a complete response was achieved in 54% of the treated patients; rates of complete response varied from 52% in the 49 patients with diffuse large-cell lymphoma to 58% in the 21 patients with other histologic subtypes. Of the patients with diffuse large-cell lymphoma, eight were HIV-positive. These patients had a complete response rate similar to that in HIV-negative patients with the same histology. HIV-positive patients had a much higher mortality (75% vs 49%), however, secondary to causes other than lymphoma. Median survival of these patients was only 10.6 months. Excluding the HIV-positive patients, 54% of the patients with diffuse large-cell histology remained in complete response at 25 months. Survival at 3 years was 56% for the entire group of patients.

Thus, this single-institution study confirmed the activity of MACOP-B. However, the complete response rate observed was considerably less than that seen in the original Vancouver study.
The SWOG enrolled 131 patients (median age, 53.5 years) into a phase II study of the MACOP-B regimen; 109 of these patients were assessable [14]. Eligibility criteria were the same as for the ProMACE-CytaBOM trial conducted by the SWOG (detailed above). In the MACOP-B study, 30% of patients had stage II disease, and 63% of all treated patients had diffuse large-cell histology. Of the evaluable patients, 54% achieved a complete response; 51% of patients were projected to be alive at 3 years, and 63% of patients achieving a complete response remained free of disease at that same time point.

The ratio of actual to planned dose intensity varied from .76 for bleomycin to .92 for methotrexate. The relative dose intensity was .84 for vincristine, .88 for doxorubicin, and .89 for cyclophosphamide. The average actual dose intensity was 85% of the planned dose intensity. In 72% of the patients, average relative dose intensity was over .80.

Thus, the response rates and survival in the SWOG trial of MACOP-B were lower than had been reported in the Vancouver trial. The response rates were similar to those reported by Schneider et al and, in fact, were similar to results that had been seen in the SWOG studies of the CHOP regimen.

**Randomized Trials**

**ProMACE-MOPP vs ProMACE-CytaBOM**

In a single-institution study, 193 patients with stage II, III, or IV follicular large-cell, diffuse large-cell, diffuse-mixed, immunoblastic, or diffuse small- non-cleaved-cell (non-Burkitt's) lymphomas were randomized to receive either ProMACE-MOPP (99 patients) or ProMACE-CytaBOM (94 patients) [10]. Responding patients received at least six cycles of therapy or two cycles after a maximum clinical response.

The median follow-up of patients on this study was 5 years at the time of reporting. Of the 99 patients treated with ProMACE-MOPP, 73 (74%) achieved a complete response, and 30 of these (41%) have relapsed. Deaths occurred in 45 patients (45%) treated with this regimen, 42 from uncontrolled lymphoma, 2 from treatment-related causes, and 1 unrelated to lymphoma or its treatment.

By comparison, 81 (86%) of 94 patients randomized to ProMACE-CytaBOM achieved a complete response, and 22 (27%) of the complete responders have relapsed. In this treatment group, 31 (33%) of the patients have died, 22 from uncontrolled lymphoma, 6 related to treatment (all from *Pneumocystis carinii* pneumonia), and 3 from causes unrelated to lymphoma.

The complete response rate for ProMACE-CytaBOM was significantly higher than that achieved with ProMACE-MOPP ($P = .048$). The plateau of the disease-free survival curve was at 54% for the ProMACE-MOPP arm and 69% for ProMACE-CytaBOM arm ($P = .082$). The plateau of the survival curve was at 53% for ProMACE-MOPP and 69% for ProMACE-CytaBOM ($P = .046$).

The actual mean dose intensity of doxorubicin was 42% higher in ProMACE-CytaBOM than in ProMACE-MOPP, and the actual mean dose intensity of cyclophosphamide, etoposide, and vincristine were augmented by 43%, 40%, and 29%, respectively, suggesting that one possible explanation for the observed differences between the two regimens may be that regimens with higher dose intensities are more effective.

**MACOP-B vs ProMACE-MOPP**

In a prospective, randomized, multicenter trial conducted by the Italian Non-Hodgkin's Lymphoma Cooperative Study Group, 221 patients were randomized to receive either MACOP-B or six cycles of ProMACE-MOPP [15]. Patients eligible for the study included those with diffuse intermediate- to high-grade NHL with stage II bulky, III, or IV disease. The median age of the patients was 46 years on the MACOP-B arm and was 50 years on the ProMACE-MOPP arm. Patients with bone marrow involvement and/or bulky disease received central nervous system prophylaxis with intrathecal methotrexate. On the ProMACE-MOPP arm, 104 patients were assessable for response, as compared with 93 on the MACOP-B arm; results were reported on an intention-to-treat basis for 114 patients on the ProMACE-MOPP arm and 107 on the MACOP-B arm.

Of the 114 patients randomized to ProMACE-MOPP, 56 (49.1%) achieved a complete response, as compared with 56 (52.3%) of the 107 patients randomized to MACOP-B. With a median follow-up of 41 months, the overall 3-year survival rates were 45.2% for ProMACE-MOPP and 52.3% for MACOP-B. Progression-free survival at 3 years was 36.4% for the ProMACE-MOPP- treated patients and 36.1% for the MACOP-B-treated patients. Disease-free survival at 3 years for responding patients was 52.3% on the ProMACE-MOPP arm and 50.3% on MACOP-B. None of the differences in complete response rate, 3-year survival, progression-free, or disease-free survival was statistically significant.

The actual dose of drug delivered was accurately calculated for all patients except seven MACOP-B
patients and two ProMACE-MOPP patients. Most of the patients received more than 90% of the projected dose intensity. The numbers of patients who received less than 75%, between 75% to 90%, and more than 90% of the projected dose intensity in the two regimens are uneven, but the response rates and percentages of relapse overlap.

A similar analysis was performed, considering the percentage of projected dose intensity (actual dose intensity) of the two drugs with the clearest dose-response relationship, namely, cyclophosphamide and doxorubicin. According to this analysis, again, no statistically significant differences between the two treatment groups with regard to response or relapse were evident. In addition, survival did not differ significantly between the groups.

Hence, despite the superiority of MACOP-B in terms of projected average relative dose intensity (relative to a hypothetical combination of nine drugs delivered as full doses continuously), MACOP-B is not more effective than ProMACE-MOPP. The authors conclude, therefore, that the projected average relative dose intensity does not influence clinical outcome. Also, when patients were stratified according to the relative dose intensity (ratio between actual and projected dose intensity for either regimen), no difference in terms of response rate was evident among patients receiving 75%, between 75% to 90%, and more than 90% of relative dose intensity; nor were there any differences in relapse rates observed.

**m-BACOD vs CHOP**

The Eastern Cooperative Oncology Group (ECOG) performed a prospective randomized trial to compare standard therapy, CHOP, with m-BACOD [16]. Of the 392 patients screened, 325 had stage III or IV, diffuse-mixed or diffuse large-cell lymphoma and had had no prior treatment and thus were eligible for participation.

The CHOP regimen was administered as had been previously described, except that from 1984 to 1986, patients over age 60 received a 25% reduction in the calculated doses of cyclophosphamide and doxorubicin. After 1986, all patients received full-dose therapy from the time of treatment initiation. m-BACOD, as given in this study, differed from that originally reported, in that only eight cycles of therapy were given (as compared with the 10 cycles in the original report).

Complete responses were noted in 88 (51%) of 174 patients treated with CHOP and 85 (56%) of 151 patients treated with m-BACOD \( (P = .32) \). With a median follow-up of 4 years, 91 patients treated with CHOP and 71 treated with m-BACOD have died. After 2 and 5 years, survival rates were 59% and 48%, respectively, for CHOP, and 62% and 49%, respectively, for m-BACOD. There was no significant difference between the two treatments with respect to overall survival \( (P = .49) \), time to treatment failure, or duration of complete response.

The authors calculated the normalized dose intensity (ratio of the actual dose intensity to the designed dose intensity) for cyclophosphamide and doxorubicin. They found the median normalized dose intensity of cyclophosphamide to be greater in CHOP than in m-BACOD. Approximately 25% of the patients treated with CHOP received more than 100% of the normalized dose intensity of cyclophosphamide because of the dose escalation specified in the protocol. The median dose of doxorubicin, expressed as a percentage of the designed dose, was higher for CHOP than for m-BACOD.

From the results of this study, it is clear that m-BACOD affords no advantage over CHOP with regard to complete response rate or outcome. Because there was more associated toxicity with m-BACOD, the authors concluded that CHOP would have to be considered the preferable therapy, given a choice between these two regimens.

**MACOP-B vs CHOP**

The New Zealand Lymphoma Study Group reported results of a prospective randomized trial comparing the third-generation regimen MACOP-B to CHOP [17]. Of the 340 patients enrolled in the study, 236 were eligible. Patients with bulky stage I or stages II, III, and IV disease were eligible. Eligible histologies included diffuse small-cleaved cell, diffuse mixed small- and large-cell, follicular large-cell, diffuse large-cell, and immunoblastic lymphoma. The dose modifications and schedule of both the MACOP-B and CHOP regimens were as originally described. Responding patients received at least six cycles of CHOP or two cycles after achieving a complete response. MACOP-B was administered over the prescribed 12-week period. Median age of patients was 54 years on the MACOP-B arm and 53 years on the CHOP arm.

Of the 125 patients randomized to MACOP-B, 64 (51%) achieved a complete response, as compared with 65 (59%) of 111 patients randomized to CHOP \( (P = .3) \). Complete response rates for patients with diffuse mixed, diffuse large-cell, and immunoblastic histologies were 54% with MACOP-B and 59% with CHOP. Estimated failure-free survival at 4 years was 44% for MACOP-B and 32% for CHOP. Fifty-two patients on each arm have died. Estimated survival at 4 years was 56% for MACOP-B and
51% for CHOP ($P = .69$). Hence, there was no significant difference in rates of complete response, failure-free, or overall survival between CHOP and MACOP-B.

The average relative dose intensity was .91 for the MACOP-B-treated patients and .90 for the CHOP-treated patients. Protocol therapy could not be completed in 27% of the MACOP-B patients and 14% of the CHOP patients. However, there was no significant difference in complete response rates between MACOP-B and CHOP among those patients who completed the protocol therapy (60% vs 65%).

Hence, as was seen in the ECOG trial, the efficacy of a newer, more complex chemotherapy regimen was equivalent to that of standard CHOP therapy. Toxicity was significantly greater, however, with MACOP-B, and thus, based on this study, it cannot be considered to offer any advantage over CHOP for patients with diffuse aggressive lymphomas.

**CHOP vs m-BACOD, ProMACE-CytaBOM, and MACOP-B**

In an intergroup trial, 1,138 previously untreated patients with bulky stage II, stage III, or stage IV disease and intermediate- or high-grade histology were randomized to one of four treatment arms: CHOP, m-BACOD, ProMACE-CytaBOM, or MACOP-B [18]. A total of 899 patients were eligible for the study. Each of the regimens was administered exactly as had been described in the prior phase II studies. The median age of patients was 54 years, and 25% of the patients were over age 64. With a median follow-up of 49 months at the time of reporting, no differences were observed among the four treatment arms with respect to complete response or overall response rates. Complete response rates were 44% for CHOP, 48% for m-BACOD, 56% for ProMACE-CytaBOM, and 51% for MACOP-B.

Because assessment of complete response is difficult due to persistent abnormalities on CT scans after treatment, the time to treatment failure, which is a measure of time to progression, relapse, or death from any cause, was analyzed as a more accurate estimate of the fraction of patients cured by initial therapy. At 3 years, 43% of all eligible patients were estimated to be alive without disease. By treatment arm, 43% on the CHOP arm, 43% on the m-BACOD arm, 44% on the ProMACE-CytaBOM arm, and 40% on the MACOP-B arm were projected to be alive without disease at 3 years ($P = .35$). Projected overall survival at 3 years for all eligible patients was 52%; by treatment arm, these values were 49% on MACOP-B, 51% on m-BACOD, 53% on ProMACE-CytaBOM, and 55% on CHOP ($P = .90$). Dose intensity was calculated for all patients in this study. Although comparable data were not available from the initial trials of m-BACOD and MACOP-B, they were available from a trial of ProMACE-CytaBOM. When the dose intensity of ProMACE-CytaBOM was compared with that in the study of Longo et al, according to their definition of dose intensity, the data were comparable. The dose intensities of the three third-generation regimens in this study were also comparable to the intensities of these regimens in the initial phase II trials conducted by the SWOG.

Hence, in this large, prospective, randomized study, once again, the efficacy of CHOP was found to be equivalent to the newer regimens. The toxicity profile, as well as cost, would also favor the use of CHOP over any of the three regimens to which it was compared.

**Summary**

As noted above, in the model proposed by DeVita et al, ProMACE-MOPP, ProMACE-CytaBOM, m-BACOD, and MACOP-B are all regimens with dose intensities superior to CHOP. It is clear from the data, however, that in randomized trials, none of these regimens has been shown to be superior to CHOP. Furthermore, the poor showing does not appear to be related to inadequate delivery of drugs in these regimens. With the exception of the study reported by Longo et al, there are few compelling data to suggest that the more dose-intensive regimens are of benefit in terms of outcome in these diseases. It should be pointed out, once again, that none of these studies prospectively studied the question of dose intensity, and hence, all of the data presented thus far suffer from the various inadequacies inherent in retrospective analyses.

**Randomized Trial Focusing on Dose Intensity**

Meyer et al recently reported the results of a prospective randomized trial in which patients received BACOP (bleomycin, Adriamycin, cyclophosphamide, Oncovin, and prednisone), either given in standard dosages or in a regimen in which the dose of doxorubicin was increased, compared to standard-dose therapy [6]. This study entered 238 previously untreated patients with advanced-stage intermediate- or high-grade lymphoma, ranging in age from 16 to 70 years. By study design, all patients received standard doses of all drugs in cycle 1; the dose of doxorubicin in the standard arm was 25 mg/m². Patients who were randomly assigned to standard therapy received the same doses as they had received in cycle 1 during all subsequent cycles. Patients randomly
assigned to escalated therapy received doxorubicin in a dose of 40 mg/m² in subsequent cycles if they did not develop granulocytopenia during the initial cycle. The mean weekly dose intensity of doxorubicin was significantly higher on the escalated- as compared to the standard-dose arm (13.5 vs 10.4 mg/m²/wk), as was the mean total dose of doxorubicin (296 vs 231 mg, \( P < .001 \)). Because of granulocytopenia occurring in the first cycle, only 56 of 119 patients randomized to the escalated arm (47%) actually received higher-dose therapy. With a median follow-up of 65 months, there were no differences observed in response rate, overall survival, or disease-free survival between patients receiving escalated doses and those treated with standard doses. Likewise, analyzing only the subset of patients who received escalated drug doses, no differences were seen. Toxicity was, however, greater in the escalated arm of therapy.

The authors thus concluded that escalating the doxorubicin doses in the BACOP regimen did increase toxicity but did not improve outcome. They pointed out, however, that while the projected dose intensity of doxorubicin was 50% greater in the escalated as compared to the standard arm, the mean received dose intensity was only 30% greater than in the standard arm. This difference in projected and actual dose intensity was due, in large part, to the patients randomized to escalated therapy who never actually received it because of neutropenia occurring in the first cycle.

It should be pointed out that a prospective randomized trial addressing the issue of dose intensity provides a higher level of evidence regarding the issue of dose intensity than do the retrospective analyses detailed above. The results obtained in this study are consistent, however, with the randomized trials described above in which regimens that are more dose intense did not produce superior outcome when compared with a standard regimen, such as CHOP.

**Conclusions**

Based on the available data, the answer to the question posed in the title of this article, "Is 'more' or 'less' better?" remains unknown. Clearly, at the dose levels tested, there appears to be relatively little impact of dose intensity on outcome. This does not mean, however, that dose intensity is not a determinant of outcome. Rather, we may be observing results from trials in which what is being considered dose-intense therapy really is not different enough from standard therapy for any impact to be realized.

Several groups are now beginning to report preliminary results of very-dose-intense therapy used as first-line therapy in this disease. These preliminary results are encouraging. However, longer follow-up is needed before we can abandon what is now considered standard therapy.

**References:**


