Prognostic Significance of Actual Dose Intensity in Diffuse Large-Cell Lymphoma: Results of a Tree-Structured Survival Analysis

By Larry W. Kwak, Jerry Halpern, Richard A. Olshen, and Sandra J. Horning

While diffuse large-cell lymphoma (DLCL) is considered to be highly curable with current therapy, treatment failures are observed even with intensive combination chemotherapy regimens. In order to study the prognostic significance of actual dose intensity of chemotherapy in DLCL, we retrospectively analyzed 115 previously untreated patients treated at Stanford between 1975 and 1986 with cyclophosphamide, Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH), vincristine, and prednisone (CHOP), methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, and dexamethasone (MABCOD), or methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B). The actual relative dose intensity (RDI), the amount of drug actually administered to each patient during the first 12 weeks of therapy, was calculated as standardized to CHOP and analyzed in addition to clinical factors prognostic for survival by univariate analysis. Multivariate recursive partitioning (tree-structured) survival analysis identified the actual RDI of Adriamycin greater than 75% as the single most important predictor of survival. A model incorporating the actual RDI of Adriamycin and performance status, in combination with serum lactate dehydrogenase (LDH) and extranodal disease, defined three overall prognostic groups of patients with respective 3-year survival rates of 89%, 63%, and 18%. The three prognostic groups remained distinct, even when restricted to complete responders. This model was also predictive of survival when dose intensity was analyzed relative to the optimum dose defined for each of the three regimens and when applied to a subgroup of patients aged 50 years or younger. We conclude that actual RDI is an important prognostic factor for survival in DLCL and that analysis of RDI early in the course of treatment may allow modification of the treatment plan.

clear that the more intensive multidrug regimens are superior to CHOP, delivered at full doses every 3 weeks, to comparable patients. For these reasons, we undertook a survival analysis of 115 patients with DLCL treated at Stanford between 1975 and 1986 with three combination chemotherapy regimens: CHOP, methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, and dexamethasone ([M]BACOD), and methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B).

Using the multivariate statistical approach of recursive partitioning, or tree-structured, survival analysis, we analyzed drug DI, based on the amount of drug actually delivered during the first 12 weeks of therapy, in combination with pretreatment clinical prognostic factors. In the process of this analysis, a model was constructed that produced three distinct prognostic groups with markedly different overall survival.

**PATIENTS AND METHODS**

**Patient Characteristics**

One hundred fifteen previously untreated patients with a histologic diagnosis of DLCL, intermediate grade or immunoblastic, as defined by the Working Formulation, who were seen and treated at Stanford between 1975 and 1986, comprised the study group. Patients were staged according to the Ann Arbor criteria. Initial staging procedures in all patients included complete physical examination, chest radiograph, routine blood counts and chemistry tests, bone marrow biopsy, bipedal lymphangiography, and/or abdominal and pelvic computed tomography. Additional tests were performed as clinically indicated.

Patients in this study received CHOP, (M)BACOD, or MACOP-B treatment in standard doses in 3-week cycles for CHOP and (M)BACOD and weekly for MACOP-B. The high-dose methotrexate in (M)BACOD was given as 1 g/m² on day 14 of each cycle with leucovorin rescue. Selection of treatment regimen was individualized for each patient, but in most cases, reflected the regimen with the best results reported at that time. Thus, the standard therapy for advanced-stage patients with DLCL at Stanford was CHOP before 1981, (M)BACOD between 1981 and 1985, and MACOP-B beginning in 1985. CHOP continued to be used after 1981 for limited-stage patients, especially for those with nonbulky or asymptomatic disease. Patients who received radiation therapy were included in the analysis only if it was given after the completion of chemotherapy.

Sixty-eight patients were treated with CHOP, 31 with (M)BACOD, and 16 with MACOP-B. The clinical characteristics of these patients are shown in Table 1. There were several differences in age and sex ratio among the groups, whereas the distribution of Eastern Cooperative Oncology Group (ECOG) performance scores was essentially constant across all three groups. Performance status was based on the ECOG scale, in which 0 is associated with no symptoms, 1 with symptoms but continued ability to ambulate, 2 with bedridden status less than 50% of the day, 3 with bedridden status greater than 50% of the day, and 4 with chronic bedridden status and a requirement for assistance for daily maintenance. Overall, approximately one third of patients presented with B symptoms. The (M)BACOD group contained the highest proportion of advanced-stage patients (74%). Overall, the majority of patients were Ann Arbor stage III or IV, and the (M)BACOD and MACOP-B groups contained the highest proportion of patients with elevated pretreatment lactate dehydrogenase (LDH), multiple extranodal sites of involvement, and bulk of disease, defined as the largest dimension of a single tumor mass. The size of the largest mass was determined by review of both the medical record and relevant radiographic studies and included both nodal and extranodal sites. Actual dimensions of masses ≥ 3 cm in diameter were used in the analysis. Sixty-four percent of patients presented with extranodal sites of disease of which the gastrointestinal tract was the most commonly involved extranodal site (19%). Other sites of extranodal disease included pleura (13%), bone marrow (12%), bone (11%), lung (10%), testis (9%), skin (7%), pericardium (6%), kidney (6%), and liver (3%).

All patients underwent restaging with baseline staging procedures during treatment and at the completion of treatment. Bone marrow biopsies were, for the most part, repeated only in patients having positive biopsies on presentation. Complete response was defined as the disappearance of all clinical evidence of disease and either the normalization or stabilization of all laboratory and radiographic abnormalities. To be classified as a complete response, the response had to be maintained for at least 30 days following the completion of therapy. Determination of the number of cycles to complete remission was based on restaging studies described above. A value of zero cycles was assigned to patients who had undergone surgical resection of all gross disease before the initiation of chemotherapy (11 patients).

**DI**

Actual chemotherapy doses were available for all 115 patients. The method of Hryniuk and Bush was used to calculate the DI of each drug actually administered to the patient. For the purposes of this analysis, we considered the amount of each drug, normalized to body surface area (mg/m²), administered during the first 12 weeks of therapy. The period of 12 weeks was selected because (1) the MACOP-B regimen is of 12 weeks duration, (2) if found to be important, DI could then be used to make treatment decisions, including changes in therapy, relatively early in the course of treatment, and (3) a previous study has shown that response during the first three to four cycles of chemotherapy is prognostically significant. Although this method may introduce bias in patients with early disease progression, the primary regimen was changed in only three patients before the 12th week of treatment.

DI was expressed as a decimal fraction of the dose prescribed in a standard regimen over the same time frame (relative DI [RD1]). CHOP was selected as the standard regimen because the group treated with CHOP represented the majority of our patients and also because CHOP remains...
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Table 1. Patient Characteristics by Regimen

| Characteristic                        | CHOP | (M)BACOD | MACOP-B | Total (%)
|---------------------------------------|------|----------|---------|-----------
| No. of Patients                       | 68   | 31       | 16      | 115       |
| Age                                   |      |          |         |           |
| ≤ 50 years                            | 30   | 17       | 11      | 58 (51)   |
| 51-65 years                           | 26   | 13       | 5       | 44 (38)   |
| > 65 years                            | 12   | 1        | 0       | 13 (11)   |
| Sex                                   |      |          |         |           |
| Male                                  | 43   | 16       | 6       | 65 (57)   |
| Female                                | 25   | 15       | 10      | 50 (43)   |
| ECOG performance status               |      |          |         |           |
| 0-2                                   | 60   | 26       | 14      | 100 (87)  |
| 3-4                                   | 8    | 5        | 2       | 15 (13)   |
| B symptoms                            |      |          |         |           |
| Absent                                | 51   | 18       | 7       | 76 (66)   |
| Present                               | 17   | 13       | 9       | 39 (34)   |
| Stage                                 |      |          |         |           |
| I, II                                 | 35   | 8        | 7       | 50 (43)   |
| III, IV                               | 33   | 23       | 9       | 65 (57)   |
| Hemoglobin                            |      |          |         |           |
| < 12                                  | 16   | 11       | 5       | 32 (28)   |
| ≥ 12                                  | 52   | 20       | 11      | 83 (72)   |
| Lactate dehydrogenase                 |      |          |         |           |
| Normal range                          | 29   | 8        | 4       | 41 (36)   |
| Elevated                              | 39   | 23       | 12      | 74 (64)   |
| Bone marrow involvement               |      |          |         |           |
| Yes                                   | 3    | 7        | 4       | 14 (12)   |
| No                                    | 65   | 24       | 12      | 101 (88)  |
| Number of extranodal sites            |      |          |         |           |
| 0-1                                   | 57   | 18       | 10      | 85 (74)   |
| ≥ 2                                   | 11   | 13       | 6       | 30 (26)   |
| Tumor bulk                            |      |          |         |           |
| < 10 cm                               | 53   | 15       | 10      | 78 (68)   |
| ≥ 10 cm                               | 15   | 16       | 6       | 37 (32)   |
| Histology                             |      |          |         |           |
| Immunoblastic                         | 12   | 11       | 6       | 29 (25)   |
| Nonimmunoblastic                      | 56   | 20       | 10      | 86 (75)   |
| Consolidative radiotherapy            |      |          |         |           |
| Yes                                   | 22   | 12       | 10      | 44 (38)   |
| No                                    | 46   | 19       | 6       | 71 (62)   |

the standard of comparison for the second and third generation combination chemotherapy regimens. Average RDI for the combination of drugs was calculated by taking the arithmetic mean of RDI of the four individual drugs for each patient. The projected RDIs for each drug and the four-drug average for each of the regimens standardized to CHOP are shown in Table 2. These are based on 100% of the calculated dose for that particular regimen without any delays in treatment. From these calculations, it is apparent that the regimen with the highest DI of cyclophosphamide is CHOP, while MACOP-B has the highest DI of Adriamycin. The following assumptions were made in calculating actual RDI: (1) a maximum value of 1.00 was allowed for the RDI of prednisone/dexamethasone when calculating average RDI, since no clear dose-response relationship exists for steroids given in therapeutic doses, (2) 1 mg of dexamethasone was equivalent to 6.7 mg of prednisone, based on relative glucocorticoid activity, (3) the capping off of vincristine doses at 2.0 mg for CHOP meant that the RDI of this drug for patients treated with (M)BACOD varied with body surface area above 1.43 m², (4) for two patients who had RDI of a single drug greater than 1.00 (other than prednisone), a value of 1.00 was assigned when calculating average RDI, and (5) three patients treated with (M)BACOD received higher doses of methotrexate, between 1 and 3 g/m². A maximum value of 1.50 was assigned to the RDI of this drug when
calculating average RDI (for each regimen as its own standard).

Statistical Methods

Survival curves were calculated from the date of initiation of treatment according to the actuarial method of Kaplan and Meier. The generalized Wilcoxon test of Gehan was used to assess whether survival differed between patient groups. The ability of each variable alone to predict survival was tested by a univariate Cox model. Multivariate Cox analyses with up to eight variables were also done. For a particular model, each variable was treated separately, and up to five variables were tested in combination for their additional prognostic significance beyond that of the other variables in the model.

A new and important aspect of our work is the use of a “tree-structured” survival analysis. The method, also termed “recursive partitioning,” is based on extensions by Gordon and Olshen and others of classification and regression trees. With this method, the entire patient group is divided into two subgroups as defined by the patient characteristic (eg, systemic symptoms) that identifies the subgroups most different in prognosis. These two subgroups are again partitioned (each subgroup being split on the same or other prognostic factors that provide the greatest difference in prognosis), thus creating a tree-structure. This process is continued until no further subdividing is worthwhile for prognostic purposes. In sum, the tree-growing paradigm for each group (1) examines every allowable split on each prognostic factor and (2) selects (creates subgroups) the best of these splits. The best splits were selected by computing a log-rank statistic for the survival differences. The prognostic factors, their values, and the subgroups for which the survival differences were greatest were further selected, using a criterion that compared the horizontal distance between the survival functions in each subgroup pair. Kaplan-Meier survival curves were made for each distinct group identified by our model, and pairs of these curves were compared with Gehan’s generalized Wilcoxon test.

Cross-validation, which estimates how well a tree will do on future data, was also used. This sample reuse method deletes a random patient group from the data, constructs a tree on the remaining data, and uses the group left out as “new data” on which to test the tree. The technique has a built-in method for handling missing data, of which there is very little in our study group (LDH was missing in a single patient).

RESULTS

Response and Survival Data

Figure 1A shows the Kaplan-Meier survival curve for the total group of 115 patients. The actuarial 5-year survival is 58% with a median follow-up of survivors of 3 years (range, 8 months to 7.5 years). The survival of the patients is stratified by regimen in Fig 1B. As shown, when the three regimens were compared for survival in this retrospective, nonrandomized analysis, no statistically significant differences were observed. Complete response (CR) rates were high for all three groups, although the (M)BACOD regimen was associated with a somewhat lower CR rate (68%) compared with the other two regimens (CHOP, 87% and MACOP-B, 94%). The lack of observable differences in survival may relate to relatively small patient numbers and to the fact that the regimens, for the most part, were not used concurrently. Differences among the three groups in patient characteristics that may influence survival are noted in Table 1 and further analyzed below.

Univariate Analysis of Clinical Features for Survival

Eleven pretreatment clinical factors were evaluated individually for the entire group of 115 patients as prognostic indicators of survival (Table 3). ECOG performance status, number of extranodal sites of disease, and Ann Arbor stage, all analyzed as continuous or ordered variables, were significant (P < .05), with poor performance status, greater number of extranodal sites, and more advanced stage each associated with an
adverse effect on survival. Bone marrow involvement and the presence of B symptoms were also associated with a significantly adverse effect on survival. Hemoglobin and LDH, both analyzed as continuous variables, were of borderline statistical significance, as was sex, in favor of females. Single factors not predictive for survival included age and bulk, analyzed as continuous variables, histology (intermediate grade vs immunoblastic), and specific nodal or extranodal sites of involvement other than bone marrow. The small number of patients involved in each specific site of involvement may have precluded the full analysis of its influence on survival.

The effect of consolidative radiation therapy on survival was also evaluated. Thirty patients had been selected to receive radiation therapy to sites of initial bulky disease following the achievement of CR and completion of chemotherapy. When they were compared with patients having an initial mass $\geq$ 5 cm who had not received consolidative radiation therapy in CR ($n = 23$) a significant difference in survival was observed in favor of radiotherapy (Table 3), suggesting a beneficial role for radiation therapy as an adjunct to chemotherapy in this setting.

The time interval required to achieve CR was also examined as a variable for survival. Among the 96 patients (83%) who achieved a CR, the number of cycles of chemotherapy required to
Table 3. Factors Prognostic for Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>$&lt; 0.01$†</td>
</tr>
<tr>
<td>No. extranodal sites</td>
<td>$&lt; 0.01$†</td>
</tr>
<tr>
<td>Stage</td>
<td>$0.02$†</td>
</tr>
<tr>
<td>Marrow involvement</td>
<td>$0.02$</td>
</tr>
<tr>
<td>B symptoms</td>
<td>$0.04$</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>$0.06$†</td>
</tr>
<tr>
<td>Sex</td>
<td>$0.07$</td>
</tr>
<tr>
<td>LDH</td>
<td>$0.08$†</td>
</tr>
<tr>
<td>Age</td>
<td>$0.17$†</td>
</tr>
<tr>
<td>Histology</td>
<td>$0.68$</td>
</tr>
<tr>
<td>Bulk</td>
<td>$0.98$†</td>
</tr>
<tr>
<td>Consolidative radiotherapy $(n = 53)$</td>
<td>$0.01$‡</td>
</tr>
<tr>
<td>No. cycles to CR $(n = 96)$</td>
<td>$0.61$†</td>
</tr>
</tbody>
</table>

* $p$ values were determined by an approximate likelihood ratio statistic for a Cox proportional hazards model.
† Indicates when the corresponding factor was analyzed as a continuous or ordered variable.
‡ Analysis included patients with initial bulky mass $\geq 5$ cm who did $(n = 30)$ or did not $(n = 23)$ receive radiation therapy following achievement of complete remission.

achieve CR, analyzed as a continuous variable, was not of prognostic significance (Table 3). These results should be interpreted with caution, however, as not all patients were restaged at the same time points in their therapy, and some patients may have achieved CR at time points somewhat earlier than indicated by formal restaging.

Relative DI

Shown in Table 2 are the median actual RDI and the corresponding projected RDI of each drug and of the four-drug average for each of the regimens, standardized to CHOP, based on doses of chemotherapy received by each of the 115 patients during the first 12 weeks of therapy as described above. With the exception of six patients, there were no arbitrary dose reductions for advanced age or poor performance status. The most frequent reason for dose attenuation or treatment delay was leukopenia (8%), or an episode of fever with absolute neutropenia associated with a prior cycle of treatment (12%). Liver dysfunction necessitated dose attenuation of Adriamycin in two patients, and prednisone was removed from the regimen of one patient because of severe mental status changes and in another patient because of severe muscle weakness. Neurotoxicity associated with vincristine resulted in dose attenuations or deletions of this drug from the regimen of 11% of patients. However, patients in all three treatment groups received close to full projected doses as shown by the small differences between projected and actual RDI for each of the drugs within each regimen.

When evaluated separately as continuous variables for the entire group of 115 patients, average RDI, as well as the RDI for cyclophosphamide and Adriamycin were significant ($P < .05$) for survival (Table 2). The RDIs for vincristine and prednisone were not significant for survival in this analysis. Similarly, the RDI for methotrexate and bleomycin evaluated for the 47 patients treated with (M)BACOD or MACOP-B had no significant effect on survival ($P > .05$, data not shown).

Tree-Structured Survival Analysis (Multivariate Recursive Partitioning)

The covariates selected for this analysis were (1) the pretreatment clinical factors that were prognostically significant in the univariate analysis (ECOG performance status, number of extranodal sites, stage, marrow involvement, B symptoms, and LDH), (2) age, sex, and bulk, which were not statistically significant in the univariate analysis but were included because other retrospective analyses have found these factors to be prognostically important, (3) average RDI and the RDI for cyclophosphamide and Adriamycin, and (4) treatment regimen.

Tree-structured survival analysis identified the RDI of Adriamycin greater than 75% as the first split point (Fig 2). This divided the patients into groups of 92 and 23 patients; superior survival was associated with the group who received higher doses of Adriamycin (Fig 3A). The significance of actual DI as a determinant of survival was further supported by the identification of average RDI (all four drugs) and RDI of cyclophosphamide as the surrogate covariates. The term surrogate covariate refers to the covariate that best predicts the best split.32

The less favorable group (those with RDI of Adriamycin $\leq 75\%$) of patients was best further subdivided by pretreatment LDH resulting in two terminal subgroups (Fig 2, subgroups I and II). Patients with RDI of Adriamycin $\leq 75\%$ and pretreatment LDH greater than 1.4 $\times$ normal formed a particularly poor prognostic group (Fig 3B). The surrogate covariate for this node was stage.
Figure 2 shows that patients who received greater than 75% RDI of Adriamycin were best further subdivided by ECOG performance status. Patients with poor initial performance scores (ECOG 3 or 4) despite greater than 75% RDI of Adriamycin (subgroup III), had a very poor prognosis as demonstrated in Fig 3C. The surrogate covariates for this node were number of extranodal sites and age.

The favorable group of patients with RDI Adriamycin greater than 75% and good performance status was then further subdivided by the number of extranodal sites of disease. As shown in Fig 2, this generated the most favorable subgroup (IV) of all patients, and a second subgroup (V) with an intermediate prognosis. These results are shown in Figure 3D. The surrogate covariates for this node were age and the RDI of Adriamycin and cyclophosphamide.

The resulting five subgroups of patients at each terminal node divide naturally into three groups.
overall prognostic groups. The survival curves of these three groups are shown in Fig 4. The favorable group (3-year survival, 89%) consists of those patients with RDI of Adriamycin greater than 75%, ECOG performance status 0 to 2, and no extranodal disease (subgroup IV). The poor-prognostic group (3-year survival, 18%) consists of those patients with RDI of Adriamycin ≤ 75% together with significantly elevated LDH (subgroup II), or poor performance status, regardless of DI (subgroup III). The intermediate group (3-year survival, 63%) consists of the remaining patients: those with RDI of Adriamycin ≤ 75% without significantly elevated LDH (subgroup I), and those with RDI Adriamycin greater than 75% and good performance status, but at least one extranodal site of disease (subgroup V). The CR rates for the three groups were 97% for the favorable, 84% for the intermediate, and 60% for the poor prognostic groups. It is important to note that 60% of the patients in the poor prognostic group achieved CR, as it suggests that the effect of the variables we have identified on survival is not solely related to the ability to achieve a CR. This point is further illustrated by the survival curves in Fig 5, which show that the three prognostic-group comparisons maintain statistical significance when this model is applied only to the 96 patients who achieved a CR.

One of the aims of this study was to identify a subgroup of younger patients with poor prognosis who may be candidates for very aggressive or investigational therapy, such as bone marrow transplantation. To this end, we applied the model to the subgroup of patients aged ≤ 50 years (n = 58). The analysis for this subset of patients was not as extensive, in part because of the smaller number of patients, and the majority of the patients fell into a favorable prognostic group; that is, high RDI of Adriamycin and good performance status (Fig 6A). However, using the same covariates with slightly different split points, it was possible to identify a small subgroup of patients at high risk for failure (Fig 6B). The characteristics of this poor prognostic group (actuarial 2-year survival, approximately 20%) were (1) RDI of Adriamycin ≤ 85% and LDH greater than 1.1 times normal or (2) ECOG performance status 3 or 4, despite a high RDI of Adriamycin.

An alternative method of analyzing DI would be to consider the amount of drug delivered during the first 12 weeks of therapy relative to the optimum dose defined for each regimen. Such an approach would allow more general application to other regimens used in the treatment of DLCL. While it is understood that 75% of the optimum Adriamycin dose in one regimen may not be equivalent to that in another regimen, considering each regimen as its own standard

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**Fig 4. Actuarial survival curves and CR rates for favorable-, intermediate-, and poor-prognosis patients identified by tree-structured survival analysis in Fig 2. The respective 3-year survival rates are 89%, 63%, and 18%. The favorable group consists of terminal subgroup IV, the intermediate group consists of subgroups I and V, and the poor prognosis group consists of subgroups II and III.**
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Fig 5. Actuarial survival curves of the three prognostic groups of patients restricted to patients who achieved CR (96 patients).

Gehan P-values
1 vs. 2  0.044
1 vs. 3 < 0.001
2 vs. 3  0.002

Fig 6. (A) Recursive partitioning survival analysis applied to patients aged ≤ 50 years (58 patients). Numbers in squares indicate number of patients in each subgroup. (B) Actuarial survival curves of the four terminal subgroups grouped by prognosis. The majority of patients exhibited favorable prognosis (49 patients). Characteristics of the poor-prognosis group (nine patients) were RDI of Adriamycin ≤ 85% together with LDH > 1.1 times normal or ECOG performance status 3-4 despite RDI of Adriamycin > 85%.

Gehan P-values
1 vs. 2 < 0.001
also would reflect indirectly the impact of additional drugs in the regimen not included in CHOP (e.g., bleomycin, methotrexate). When this approach was used in calculating DI, the RDI for Adriamycin, cyclophosphamide, and the average RDI (four or six drugs) were again highly significant for survival in univariate analysis ($P < .01$, data not shown). Moreover, when these values of RDI were incorporated into the multivariate model, again three overall prognostic groups were generated (Fig 7).

In order to more fully assess the confounding of RDI with other prognostic variables, the clinical features of the 23 patients with RDI Adriamycin less than 75% were separately evaluated. Six (26%) were older than 65 years of age, five (22%) had an ECOG performance status of 3 or 4, 14 (61%) had stage IV disease, 11 (48%) had pretreatment LDH greater than 1.5 x normal, four (17%) had more than two extranodal sites of disease, and six (26%) had tumor bulk greater than 10 cm in diameter. However, when evaluated individually, less than one half of patients (11 of 23) had more than two adverse prognostic clinical factors, as defined by the results of the univariate analysis in Table 3. The reasons for Adriamycin dose attenuation or delay in therapy in these patients were leukopenia or fever with neutropenia associated with a prior cycle of therapy (nine patients), cholestasis, which was idiopathic or associated with chronic active hepatitis (two patients), patient preference (three patients), and arbitrary dose reduction due to advanced age (one patient). The remaining eight patients received fewer than 12 weeks of their primary chemotherapy regimen because of disease progression (three patients) or early termination of chemotherapy following CR (four patients), and one patient received cyclophosphamide, vincristine, and prednisone (CVP) as his first cycle of chemotherapy.

Because of the suggestion from our data that lower doses of Adriamycin tended to be associated with M-BACOD and this therapy was administered to patients with poor-prognostic features, the model was applied to the population excluding those treated with M-BACOD. Poor performance status or RDI of Adriamycin less than 75% together with LDH greater than 1.4 x normal continued to define a prognostic group with significantly worse survival ($P < .001$, data not shown).

**Multivariate Proportional Hazards Regression Analysis of Survival**

The same covariates were also included in multivariate Cox regression analyses for survival. Only a single patient had to be excluded from these analyses because of missing data (pretreatment LDH was not available). Table 4...

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**Fig 7. Actuarial survival curves of the three prognostic groups in Fig 4 with DI calculated relative to the optimum dose defined for each regimen. The three groups remain distinct when DI is standardized to regimens other than CHOP.**

1. **FAVORABLE (36 PTS)**
2. **INTERMEDIATE (58 PTS)**
3. **POOR (21 PTS)**
Table 4. Multivariate Proportional Hazards Regression Analysis of Survival

<table>
<thead>
<tr>
<th>Effect of clinical factors</th>
<th>ECOG PS</th>
<th>No. extranodal sites</th>
<th>LDH</th>
<th>Marrow</th>
<th>Sex</th>
<th>Age</th>
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<tbody>
<tr>
<td>Effect of RDI</td>
<td>ECOG PS</td>
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<td>LDH</td>
<td>RDI</td>
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<tr>
<td>Effect of regimen</td>
<td>ECOG PS</td>
<td>No. extranodal sites</td>
<td>LDH</td>
<td>CHOP</td>
<td>M-BACOD</td>
<td>MACOP-B</td>
</tr>
</tbody>
</table>

| Abbreviations: PS, performance status; Adria, Adriamycin; Ctx, Cytoxan (cyclophosphamide; Bristol-Myers Co, Evansville, IN). |

describes the results of selected Cox regression analyses based upon the clinical factors that were prognostically significant in the univariate analyses (Table 3), variables identified in the tree-structured analyses, and the three regimens used.

Among the pretreatment clinical factors found to be significant in the univariate analysis or tree-structured analyses, only ECOG performance status consistently retained additional significance beyond that of various combinations of factors ($P < .05$). Of interest, sex in favor of females also was found to be significant in combination with a number of pretreatment clinical factors ($P = .02$). The individual RDI of Adriamycin and cyclophosphamide, as well as the average RDI, also retained significance independently ($P = .02, .04, .07$, respectively), and in combination ($P = .048$ by the likelihood ratio test), when analyzed together with ECOG performance status. These results with proportional hazards regression support the tree-structured analysis model, especially with regard to the independent significance of RDI of Adriamycin. Treatment regimen provided no significant additional prognostic information, when analyzed with RDI and performance status.

**DISCUSSION**

There has been increasing interest in the concept of DI with respect to cancer chemotherapy. Retrospective studies of chemotherapeutic regimens for a variety of cancers have reaffirmed the importance of dose in achieving a maximum therapeutic effect in responsive tumors and have highlighted the implications of this concept for the design and analysis of future clinical trials. In our analysis of 115 patients with DLCL, we have shown that actual RDI, as measured during the first 12 weeks of therapy, is an important prognostic factor for survival. Using a tree-structured analysis, the characteristic that generated two patient groups most different in prognosis was the actual RDI of Adriamycin. Univariate analysis and multivariate Cox regression analysis also confirmed the impact of actual RDI on survival in DLCL.

DI has been shown to be important in the treatment of lymphomas. Carde et al reported that DI during the first three cycles of mechlorethamine (nitrogen mustard), vincristine, prednisone, and procarbazine (MOPP) chemotherapy was significantly related to outcome in Hodgkin’s disease. Using a hypothetical nine-drug regimen as the standard of comparison, DeVita et al at the National Cancer Institute (NCI) used DI analysis to calculate projected DIs for a variety of treatment programs used in the management of diffuse aggressive lymphomas. They found a strong correlation of average RDI (based on nine drugs) to long-term survival, but no relationship of outcome to separately calculated two-drug average RDI for Adriamycin and cyclophosphamide. While our analysis confirms a correlation between average RDI and outcome, there are several important differences between the NCI analysis and our study, which may explain the discrepancy with regard to the individual RDI of Adriamycin and cyclophosphamide. First, the availability of specific data on actual doses of drugs delivered to each of the 115 patients in our study allowed precise calculation
and subsequent analysis of actual DI. It is important to emphasize the difference between actual and projected DI. Actual DI may vary significantly from projected DI for individual patients because of the nature of dose adjustments based on drug toxicity or other factors. Clearly, actual DI is the datum of greater importance and would be expected to correlate much more closely with outcome than DI calculated from an intended protocol.\textsuperscript{35} Second, initial dose reductions up to 50% were allowed for patients over age 65 treated with CHOP in the Southwest Oncology Group (SWOG) studies cited in the study by DeVita et al. The effect of these dose reductions on actual DI could not have been reflected in calculations of projected DI, and this factor may, at least in part, explain the lack of correlation of the two-drug average RDI with outcome. Third, two assumptions made when using the DI method to calculate average RDI of two drugs, (1) that both drugs in a multidrug regimen are equally effective and (2) that the effects of the individual drugs are additive, are avoided in a multivariate analysis in which the RDI of Adriamycin and cyclophosphamide are treated as separate variables. Finally, calculations of DI for CHOP in the NCI study were based on 4-week cycles; at Stanford CHOP is routinely administered every 3 weeks as originally described by McKelvey et al.\textsuperscript{24}

Nevertheless, several limitations, outlined in recent reviews, remain with all studies using the DI approach.\textsuperscript{35-37} Among these is the assumption that drug scheduling is relatively unimportant. In addition, it remains to be seen to what extent DI correlates with outcome independent of total dose. For example, among 121 patients with DLCL treated with at least eight cycles of m- or M-BACOD chemotherapy, no relationship was found between survival and the percentage of the total prescribed dose of each drug actually administered.\textsuperscript{13}

One of our goals in evaluating this series of patients with DLCL was the identification of prognostic groups that would have implications for the design of randomized therapeutic trials and for determination of optimal therapy for individual patients. The actual RDI of Adriamycin and performance status, in combination with pretreatment LDH and the number of extranodal sites of disease, defined three groups of patients with markedly different survival. The identification of these prognostic groups underscores the predictive power of the novel statistical approach of recursive partitioning, or tree-structured, survival analysis. In contrast to multivariate proportional hazards regression analysis, this method only identifies prognostic factors that are present in actual patients, rather than a hypothetical patient who might possess multiple significant factors. The analysis presented here illustrates the prospective use of tree-structured analysis and, once the prognostic groups have been identified, the ease with which a given patient may be properly assigned to one of them. Other advantages of this approach include that very few assumptions are necessary to use it (and hence its broad applicability), its automatic identification of interactions (ie, synergistic effects among the variables included for analysis), and the natural way that it handles missing data.\textsuperscript{30,32,38}

The tree-growing paradigm of examining nearly every allowable split on each variable and selecting the best of these splits at each point has been successfully applied to a variety of classification data,\textsuperscript{39-44} and in several of these applications, performance of tree-based classifiers on test subjects has proved superior to that of logistic regression. When directly compared with other methods, tree-based analyses have usually been somewhat more accurate, and have only rarely performed less well. For instance, clinical factors predictive for myocardial infarction, outcome of hypoxic coma, multiple markers for lung cancer diagnosis, lymphocyte markers and assays for immunosuppression classification, and patient characteristics predictive of findings at laparotomy in Hodgkin’s disease have all been identified using this statistical method.

The three risk groups generated in the model were also prognostic when limited to the population of complete responders. The relatively high CR rate of 60% in the poor prognostic group suggests that the remissions among the three risk groups were not equally durable. These results are in contrast to the observation that the improvement in overall survival observed between two generations of chemotherapy regimens relates solely to the ability of the regimens with greater DI to induce higher CR rates.\textsuperscript{22} RDI and the clinical prognostic factors we have identified may not only exert their influence on the achieve-
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The favorable prognostic group (3-year survival, 89%) appears to be effectively treated with existing chemotherapy regimens. Significant improvements over existing survival rates for this group of patients may be difficult to demonstrate and achieve without substantial additional toxicity. Conversely, the poor prognostic group (3-year survival, 18%) requires alternative therapy. Several reports have suggested a role for high-dose therapy and autologous bone marrow transplantation in selected patients with relapsed non-Hodgkin's lymphoma. Younger patients at high risk for treatment failure may be candidates for primary bone marrow transplantation following cytoreductive chemotherapy to CR or minimal disease status, if they can be confidently identified early on. This approach as reported by Gulati et al appears very promising.

The comparison of nonconcurrent groups, variation in length of follow-up, and differences in patient characteristics among the three chemotherapy treatment groups may obscure the impact of treatment on survival. In our study, no significant differences in survival among the three treatment regimens could be demonstrated by univariate, multivariate recursive partitioning or Cox regression analysis. Valid comparison of these three regimens is the goal of a large prospective randomized study being conducted by the Southwest Oncology Group.
Our analysis supports the concept that drug dose is directly related to therapeutic effect, as DI measured during the first 12 weeks of therapy was a strong predictor of overall survival in our patients with DLCL. Despite the fact that this is a retrospective analysis that should be interpreted accordingly, some of the P values in Figs 3 to 7 are so striking that we feel that "real" differences have been identified that would be validated by future data. If these results are confirmed by others, then actual DI should be included in the analysis and reporting of future clinical trials of DLCL, and considered in the selection of alternative or consolidative therapies.

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