Review Article

Prognostic Factors in Aggressive Non-Hodgkin's Lymphoma: Who Has "High-Risk" Disease?

By Margaret A. Shipp

Combination chemotherapy has transformed aggressive non-Hodgkin's lymphoma (NHL) from a fatal disease to one that is now often curable. Complete response rates of 60% to 80% and predicted 5-year survivals of greater than 55% have been obtained with current regimens in pilot single-institution trials. However, many of these regimens (MACOP-B, m-BACOD, ProMACE-CytaBOM) proved to be no more effective than standard-dose CHOP in recent randomized cooperative group studies, raising the disappointing possibility that the favorable pilot results were caused in part by patient selection. This dilemma has focused our attention on the need to compare treatment regimens in comparable patient subgroups and to identify patients with different long-term prognoses to individualize therapy.

The identification of "high-" or "low-risk" patients with aggressive NHL would have important therapeutic implications. "High-risk" patients who are not effectively treated with current regimens are most likely to benefit from new experimental approaches whereas "low-risk" patients may do well with standard therapy and incur substantial toxicity if they are treated with experimental regimens. As noted, the identification of different patient risk groups will also aid in the design and interpretation of therapeutic trials.

This review summarizes recent efforts to develop clinically based pretreatment prognostic factor models to identify patients with aggressive NHL who have different risks for death from their disease. Treatment-related prognostic factors will also be discussed. In addition, the review will highlight more recently described cellular and molecular features that may be directly associated with the biologic heterogeneity of aggressive NHL.

Identification of Clinical Prognostic Factors

Currently, patients with aggressive NHL are staged with the Ann Arbor classification that was originally developed for Hodgkin's disease. This classification schema emphasizes the distribution of nodal disease sites because Hodgkin's disease commonly spreads via contiguous lymph node groups. Because the patterns of disease spread in Hodgkin's and NHL are somewhat different, it is not surprising that the Ann Arbor classification is less accurate in identifying prognostic subgroups of patients with aggressive NHL. For this reason, investigators have attempted to identify clinical prognostic factors that would form the basis of a new classification for aggressive NHL that would be more reflective of the unique biology of this disease.

In previous analyses of relatively small numbers of patients with aggressive NHL, a variety of pretreatment clinical characteristics were consistently associated with survival: age at diagnosis; systemic (B) symptoms; performance status; serum LDH; number of nodal and extranodal sites of disease; tumor bulk; and the distinction between localized and advanced stage disease according to the Ann Arbor classification (Table 1). These clinical characteristics were thought to reflect three basic features: (1) the tumor's growth and invasive potential (lactate dehydrogenase [LDH], stage, mass size, number of nodal and extranodal sites of disease, bone marrow [BM] involvement); (2) the patient's response to the tumor (performance status, B symptoms); and (3) the patient's ability to tolerate intensive therapy (performance status, BM involvement, age) (Table 1).

The prognostic significance of age deserves special mention. As expected, age at diagnosis was more commonly identified as a prognostic factor in studies that included large numbers of older patients. In an early South-west Oncology Group Trial, elderly patients who received automatic dose reductions because of age had significantly lower complete response rates than elderly patients who received full-dose therapy. In a subsequent Nebraska Lymphoma Group trial, elderly patients treated with full-dose therapy had complete response rates and therapy-related toxicities that were comparable with those of younger patients; however, fewer elderly patients survived 5 years because this group had an increased incidence of death because of unrelated causes. Additional series of elderly patients from Canada and Denmark had higher death rates caused by both the lymphoma itself and the toxicity of the administered chemotherapy. These studies highlight the tendency to treat elderly patients with lower doses of chemotherapy to reduce treatment-related toxicity while emphasizing the fact that older patients benefit from full-dose therapy.

Development of a Predictive Model Based on Clinical Pretreatment Prognostic Factors

Early prognostic factor models. Many investigators have identified the clinical pretreatment variables associated with survival in univariate analyses of their own series of patients with aggressive NHL. Features that retained independent significance in multivariate analyses of survival were often used to develop prognostic factor models.

From the Department of Medicine, Dana Farber Cancer Institute and Harvard Medical School, Boston, MA.

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Address reprint requests to Margaret A. Shipp, MD, Department of Medicine, Dana Farber Cancer Institute and Harvard Medical School, 44 Binney St, Boston, MA 02115.

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predictive for an individual patient’s risk for death.\textsuperscript{19-22,24-27} Although the specific clinical features used in these prognostic factor models differed, all models incorporated parameters of disease volume and extent of tumor involvement at presentation. For example, an early prognostic factor model in patients treated with either M- or m-BACOD was based on pretreatment performance status, largest mass size, and number of extranodal sites of disease.\textsuperscript{19} Another early prognostic factor model in patients treated with CHOP-bleomycin used “tumor burden” (the number of extranodal and extensive nodal sites of disease) and serum LDH.\textsuperscript{20} A similar prognostic factor model in patients treated with the LNH-84 regimen incorporated tumor size, numbers of extranodal sites of disease, collapsed Ann Arbor stage, and serum LDH.\textsuperscript{23} In each model, an individual patient’s risk was related to the number of adverse factors present at diagnosis. The above-mentioned models were similarly predictive for outcome in a large series of uniformly treated patients, suggesting that the models used slightly different parameters to identify similar patient subgroups.\textsuperscript{32}

The International Index. To develop a widely accepted prognostic factor model for patients with aggressive NHL, 16 single institutions and cooperative groups in the United States, Europe, and Canada recently participated in the International Non-Hodgkin’s Lymphoma Prognostic Factors Project.\textsuperscript{33} In this project, patients with aggressive NHL who were treated with a doxorubicin-containing combination chemotherapy regimen between 1982 and 1987 were evaluated for pretreatment clinical features predictive for overall survival and relapse-free survival. Clinical features that were independently associated with survival included age, LDH, performance status, stage, and number of extranodal disease sites (Table 2). These features were incorporated into a model that identified groups of patients with different risks for death (Table 3).\textsuperscript{33} Because the relative risk associated with each of the clinical features was comparable (Table 2), an individual patient’s relative risk for death was determined by adding the number of adverse prognostic factors present at diagnosis (Table 3). The relative risk for death in patients with each possible number of adverse prognostic factors was determined and groups of patients with similar relative risk (low-risk [L], low-intermediate [L-I], high-intermediate [H-I], or high [H] risk) were identified (Table 3).\textsuperscript{31}

In 2,031 patients of all ages, a model (International Index) based on age, stage, serum LDH, performance status, and number of extranodal disease sites identified four risk groups with predicted 5-year survivals of 73\%, 51\%, 43\%, and 26\%, respectively (Tables 2 and 3).\textsuperscript{31} Because younger and older patients had significantly different outcomes and patients \( \leq 60 \) years were more likely to be candidates for intensive experimental regimens, an age-adjusted model for patients \( \leq 60 \) years of age (age-adjusted International Index) was also developed.\textsuperscript{31} In 1,274 younger patients, the clinical features that were independently associated with survival included stage, LDH, and performance status (Table 2). An age-adjusted model based on these three features (Table 2) identified four risk groups of patients \( \leq 60 \) years of age with predicted 5-year survivals of 83\%, 69\%, 46\%, and 32\% (Table 3).\textsuperscript{31}

To determine whether younger patients had better outcomes because they presented with less extensive disease, the clinical characteristics of patients \( \leq 60 \) and \( > 60 \) years of age were compared (Table 4). Equal percentages of younger and older patients presented with advanced stage disease, multiple extranodal sites of involvement, elevated serum LDH, and nonambulatory performance status (Table 4), suggesting that the disease at diagnosis was similar in the two age groups.

To more specifically compare outcomes in younger and older patients, patients older than 60 years were also analyzed according to the age-adjusted International Index (Table 3). Similar numbers of younger and older patients fell into each of the four risk groups (Table 3, B and C). Although patients older than 60 years of age had complete response (CR) rates that were similar or only slightly lower than those of patients \( \leq 60 \) years, the older patients were

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<th>Table 2. Prognostic Factors for Survival in International Index Patients</th>
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<td>Relative Risk</td>
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<td>Age ( \leq 60 ) yrs, ( &gt; 60 ) yrs</td>
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| A. Patients of all ages |
| B. Patients \( \leq 60 \) yrs of age |
| Stage I/II v III/IV | 2.17 | <.001 |
| LDH \( <1 \text{ v} \geq 1 \) | 1.95 | <.001 |
| Performance status \( 0, 1 \text{ v} 2-4 \) | 1.81 | <.001 |

The subset of factors that retained independent prognostic significance were included in the International Index patients of all ages (A) and patients \( \leq 60 \) years of age (B). The only factor that retained independent prognostic significance in patients of all ages (A) but not in patients \( \leq 60 \) years of age (B) was the number of extramedullary sites of disease (patients \( \leq 60 \) years of age: \( \leq 1 \text{ site} > 1 \text{ site} \), relative risk 1.20, \( P = .134 \)).

Abbreviation: nl, normal.
much less likely to maintain their complete remissions (compare RFS of CRs, Table 3, B and C). The age-related differences in relapse rates, which were most striking in low- and low-intermediate-risk patients (Table 3, B and C), translated into significant age-related differences in survival in these risk groups (Fig 1). In contrast, high-intermediate- and high-risk patients ≤ and >60 years of age had more comparable long-term survivals (Fig 1).

The previously described correlation between outcome and chemotherapy dose in elderly patients prompts speculation that certain patients older than 60 years of age may have had more durable CRs because they received less intensive treatment. In addition, older patients may have had blunted host immune responses to their disease. As we reduce the toxicity of chemotherapy with hematopoietic growth factors, prophylactic antibiotics, and platelet support, it will be easier to treat older patients with full-dose regimens and to explore additional approaches to maintaining CRs in this age group.

In both the International Index and the age-adjusted index, the increased risk for death resulted from both a lower CR rate and a higher rate of relapse from CR (Table 3). Because patients with an increased risk of relapse might be candidates for intensive experimental "consolidation" therapy with peripheral blood stem cell or autologous BM support, the pretreatment clinical features predictive for relapse from CR were also identified. As in earlier studies, stage, serum LDH, and age were the features most closely correlated with the durability of CR. Each of the clinical features associated with an increased risk for relapse from CR was also associated with a decreased likelihood of achieving an initial remission, suggesting that the achievement and durability of a CR are related parameters that should be considered together in approaches to "high-risk" patients.

Although the International Index and earlier prognostic factor models were specifically developed to predict outcome in patients with aggressive NHL, such models may also be useful in lymphoma patients with more indolent histologies. For example, the model developed by Coiffier et al also predicted survival in a smaller series of follicular lymphoma patients and the International Index predicted survival in a larger series of similar patients (Fig 2). Furthermore, the International Index also predicted survival and relapse from CR in a recently described series of patients with low-grade (small lymphocytic, follicular small cleaved, and follicular mixed) lymphoma.

TREATMENT-RELATED PROGNOSTIC FACTORS

It is important to distinguish pretreatment clinical features that can be used to determine upfront therapy from parameters that are more directly associated with response to treatment. Although treatment-related parameters cannot be used to guide decisions regarding induction therapy, they provide important prognostic information regarding the chemosensitivity of an individual patient's disease.

Time to CR. In 1986, Armitage et al identified the time required to achieve CR as an important prognostic variable in aggressive NHL. In their series, only 40% of patients who required more than 5 cycles of standard therapy to achieve CR remained disease free whereas 80% of patients who needed ≤3 cycles of therapy to achieve CR re-
mained disease free at 2 years. Engelhard et al subsequently identified time to CR as the most important prognostic determinant of overall survival in their series of 548 patients with aggressive NHL. These data clearly correlate rapid responses with more favorable outcomes.

However, it is difficult to evaluate time to CR using standard radiographic techniques because patients with bulky tumors frequently have residual abnormalities of uncertain significance on plain films and CT/MRI scans. For this reason, Kaplan et al used gallium-67 citrate (Ga-67) imaging to distinguish between residual viable tumor and scar tissue and to assess early responses to therapy in patients with aggressive NHL. Patients with gallium-avid tumors were reevaluated after 4 to 6 cycles of therapy and at the completion of their regimen. Only 24% of the patients who had persistent gallium uptake midtreatment achieved long-term responses, whereas 70% of patients who were gallium-negative after 4 to 6 cycles maintained durable CRs. In more recent studies in which “high-risk” patients with aggressive NHL were imaged with Ga-67 after 2 of 4 planned cycles of high-dose induction therapy, patients with negative postcycle 2 gallium scans were significantly more likely to have durable complete remission. Our own experience suggests that gallium scans provide the most useful information when they are performed with “double dose” (8 to 10 mCi) radioisotope and 72- to 96-hour views and interpreted in conjunction with standard radiographic studies by a committed radiologist.

Dose intensity and schedule. As noted, early studies highlighted significant differences in survival rates of elderly patients who were treated with “full-dose” or “dose-reduced” induction therapy. The doses of cyclophosphamide and doxorubicin administered in the first 12 weeks of therapy were also the factors most closely associated with survival in 115 patients with aggressive NHL treated with CHOP, M-BACOD, or MACOP-B at Stanford University. Similar patients who received reduced doses of cyclophosphamide on the LNH-84 regimen also had decreased CR rates and increased rates of relapse from CR. These data suggest that there may be a minimum dose of therapy required to achieve optimal results in aggressive NHL and that certain patients may benefit from dose escalation of the most active drugs in this disease.

In additional ongoing studies, Wilson et al, Sparano et al, and others are evaluating whether a change from a bolus to infusional schedule of administration reduces the development of resistance to several of the agents commonly used to treat aggressive NHL.

CELLULAR AND MOLECULAR FEATURES ASSOCIATED WITH PROGNOSIS IN AGGRESSIVE LYMPHOMA

It is important to recognize that the clinical features incorporated into predictive models in aggressive NHL are, in part, surrogate variables for the biologic heterogeneity of this disease. For example, it is the biologic features associated with having an elevated serum LDH rather than the
with high CD8+ T-TIL were missing similar MHC determinants in patients with aggressive NHL. Tumor cell proliferation has also been evaluated in aggressive NHL using the nuclear proliferation antigen, Ki-67. In patient groups that were similar in age, stage, tumor burden, LDH, therapy, and CR rate, the percentage of Ki-67+ cells was closely correlated with median survival (>60% Ki-67+ cells, median survival of 8 months v <60% Ki-67+ cells, median survival of 39 months, P = .003) and was an independent factor in multivariate analysis. Ki-67 expression was similarly associated with survival in B-lineage diffuse small cell lymphomas.

**IMMUNOPHENOTYPIC CHARACTERISTICS**

B- versus T-cell phenotype. Although the majority of aggressive NHLs are of B-cell origin, up to ~20% of these tumors have a T-cell phenotype. Controversy remains regarding the prognostic significance of immunophenotype in this disease. To date, morphologic distinctions between diffuse large cell and B- and/or T-cell immunoblastic lymphomas have not been associated with significant differences in outcome. Similarly, the distinction between B- and T-cell disease had no prognostic significance in a recent series of patients with aggressive NHL from Stanford. However, Coiffier et al and Slymen et al recently reported that patients with T-cell aggressive NHL relapsed from CR more frequently than patients with B-cell disease (eg, T-cell v B-cell, 43% v 29% relapse from CR, P < .001).

Major histocompatibility complex (MHC) molecules. Patients with drug-induced or infection-associated immunodeficiency clearly have an increased risk of developing aggressive NHL. Because "tumor antigens" may be recognized in association with MHC molecules, several investigators have postulated that the absence of MHC-encoded recognition structures could limit host tumor immunosurveillance in this disease. In a small series of large cell lymphoma patients stratified for clinical characteristics, Miller et al found that patients whose tumors lacked HLA-DR had significantly shorter median survivals than patients with HLA-DR+ tumors (0.5 years v 2.8 years, P = .003). Although a similar trend was noted in a subsequent Eastern Cooperative Oncology Group study, the differences in survivals of patients with HLA-DR+ and HLA-DR- tumors did not achieve statistical significance. Investigators at University of Arizona followed up on their earlier observations by correlating tumor expression of class I and class II MHC determinants with the numbers of CD8+ Tumor infiltrating lymphocytes (TIL) in patients with aggressive NHL. Sixty-eight percent of the tumors with low CD8+ T-TIL counts were missing one or more class I or class II HLA determinants, whereas only 20% of tumors with high CD8+ T-TIL were missing similar MHC determinants (P = .0004), prompting speculation that the loss of tumor MHC molecules might result in low T-TILs. Decreased numbers of host tumor T-TILs were also linked with shortened survival in B-lineage diffuse small cell lymphomas.

β2 Microglobulin is a small extracellular protein that is noncovalently associated with α chain of the class I MHC gene; the protein is also detectable in serum. Swan et al have correlated elevated serum β2 microglobulin levels with high tumor burdens and shortened survival in patients with aggressive NHL. Although increased serum β2 microglobulin levels have not yet been linked to decreased lymphoma cell surface β2 microglobulin or deficient antitumor responses, serum β2 microglobulin is an easily measured parameter that has been incorporated into a predictive serologic classification system for aggressive NHL.

Adhesion molecule expression. The lymphocyte homing receptor (LHR, Hermes antigen, CD44) facilitates the binding of lymphocytes to high endothelial venules and permits the extravasation of lymphocytes into nodal areas. In early studies, LHR-negative aggressive lymphomas were less likely to disseminate than lymphomas with increased LHR expression (Fig 3). In additional studies, Horst et al found that 51% of patients with CD44+ lymphomas but only 12% of patients with CD44- lymphomas presented with advanced stage disease. Not surprisingly, patients whose tumors had increased levels of CD44 expression also had shorter survivals. These data prompt speculation that this adhesion molecule may promote the dissemination of aggressive lymphomas. In fact, an aggressive lymphoma cell line transfected with the "hematopoietic" CD44 isoform metastasized more frequently in nude mice than CD44- parental cells. Additional preliminary studies suggest that extranodal and advanced-stage aggressive NHLs also express CD44 vari-
duced chemosensitivity of murine and human lymphoma cell lines to many of the drugs in current lymphoma regi-
were also elevated in aggressive lymphomas without disease-free survival (DFS) (bel-2+ patients v bel-2- or
transgenic animals, the follicular hyperplasia evolved into (t[14;18]) chromosomal translocation developed
follicular hyperplasia. In a large percentage of these transgenic animals, the follicular hyperplasia evolved into
immunoblastic lymphoma and in half of these immunoblastic lymphomas, c-mye alleles were rearranged.91
These data prompt speculation that in certain aggressive NHLs, tumor progression may be related to the aberrant
expression of specific genes that regulate both cell death (bcl-2) and cell growth (myc).99 Because bcl-2 protein levels
were also elevated in aggressive lymphomas without (t[14;18][q32;q21]), mechanisms other than chromosomal translocation may also result in pathogenetically relevant bcl-2 overexpression.92 In a recent series of 371 patients with aggressive NHL, increased bcl-2 expression was significantly more common in patients with advanced stage disease; bcl-2 over-expression was also closely linked with reduced disease-free survival (DFS) (bcl-2+ patients v bcl-2- or –/+ patients, 57% v 75% 2-year DFS P = .006).93 These observations are of particular interest because Miyashita and Reed94,95 have correlated bcl-2 over-expression with reduced chemosensitivity of murine and human lymphoma cell lines to many of the drugs in current lymphoma regimens. In the subset of aggressive NHLs with the [14;18][q32;q21] translocation, a polymerase chain reaction-based technique has been used to amplify the translocation and detect minimal residual disease.96-97
Chromosomal translocations involving 3q27 and several other loci have been identified in 8% to 12% of diffuse lymphomas.98-101 Ye et al102 recently cloned a gene from the 3q27 breakpoint and identified it as a putative zinc finger transcription factor, bcl-6. The bcl-6 gene was truncated within its 5' noncoding region in 33% of diffuse LCL sam-

tants including an isoform associated with the metastatic spread of epithelial malignancies.71
The lymphocyte function-associated antigen, LFA-1 (CD 11a/18) has also been implicated in lymphocyte adhesion
and migration.64 Although the absence of LFA-1 was linked with shortened survival in an early study of a small number
of patients with aggressive NHL,72 this adhesion molecule was not correlated with clinical behavior in additional larger
series.69,73

Karyotypic abnormalities. Several chromosomal abnormalities have been identified in aggressive NHL, although
there is no single karyotypic abnormality that is a hallmark for this disease. After early conflicting reports,74-75 Cowan et
al56 showed that DNA ploidy did not have predictive value. Karyotypic abnormalities in general77,78 and specific dele-
tions and abnormalities of the short arm of chromosome 17 and 7 have been associated with adverse outcomes in aggressive
NHL.79,80,81 abnormalities involving chromosomes 1, 2, 3, 6, 11, 12, 14, and 18 have also been described.77,78,81,82
A substantial percentage (up to 30%) of aggressive NHLs also have the ([t(14;18)[q32;q21]) characteristic chromo-
somal translocation of follicular lymphomas.83,84 This chromosomal translocation results in inappropriately elevated
levels of the 18q21 gene product, bcl-2, 85-87 which blocks progranulated cell death (apoptosis) in B lymphocytes.88-90
McDonnell and Korsemeyer91 found that transgenic mice bearing a bcl-2 Ig minigene that structurally mimics the
([t(14;18)[q32;q21]) chromosomal translocation developed follicular hyperplasia. In a large percentage of these
transgenic animals, the follicular hyperplasia evolved into immunoblastic lymphoma and in half of these immu-
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ples but was not altered in other lymphoid malignancies such as follicular, Burkitts, and small lymphocytic lymphomas.
102 bcl-6 transcripts were identified in mature B cells but not pre-B cells, plasma cells, T cells, or other hematopoietic cell
types,102 prompting speculation that bcl-6 may be a proto-
ocogene that functions to control normal B-cell differentiation and specifically contributes to the pathogenesis of diffuse large cell lymphoma. For these reasons, lesions in bcl-6 may also have prognostic significance in aggressive NHL.

SUMMARY

As the above-mentioned cellular and molecular parameters and newly identified biologic features are evaluated in larger numbers of patients with aggressive NHL, the biologic heterogeneity of this disease will be better appreciated. With a more complete understanding of the disease, it is likely that we will substitute biologic variables for clinical surrogate features in our prognostic factor models and target these biologic variables for therapy in specific subsets of patients. In the meantime, widely accepted clinical models such as the International Index and the age-adjusted index will aid in the identification of specific patient risk groups and the ongoing comparison of different therapeutic approaches. Early restaging with sensitive techniques like Ga-67 citrate scans may also identify patients with suboptimal responses to induction therapy at timepoints when additional therapeutic alternatives may be most effective.

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MA Shipp