Overview of Prognostic Factors in Non-Hodgkin’s Lymphoma

Review Article [1] | October 02, 1998
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The non-Hodgkin’s lymphomas are a biologically heterogeneous group of diseases with varying clinical presentations and outcomes. A number of studies have identified variables that carried independent prognostic significance. Although several staging systems had evolved that incorporated these prognostic variables, they were still unable to predict outcome. Ideally, the object of a staging system is to predict the likelihood of treatment response, time to progression or disease-free survival, and overall survival, and to provide a way to compare the outcome of similar groups of patients among various clinical trials. The need for such a system led to the creation of prognostic models such as the M. D. Anderson Tumor Score and, more recently, the International Prognostic Index. These prognostic models may identify those patients at highest risk for treatment failure, thereby identifying those patients who may require different therapeutic approaches.

Introduction

There are many clinically important prognostic factors in non-Hodgkin’s lymphoma, though only a few have consistently been shown to correlate with prognosis and outcome in multivariate analyses. These prognostic parameters (Table 1) have been incorporated into various proposed staging systems, such as the M. D. Anderson Tumor Score and the International Prognostic Index (IPI).[1,2] Unlike in Hodgkin’s disease, the Ann Arbor staging system is of limited use in predicting outcome in patients with non-Hodgkin’s lymphoma, primarily due to its inability to estimate tumor burden. The Ann Arbor staging system becomes more useful when used in combination with other parameters that estimate tumor burden and which might also reflect, directly or indirectly, the tumor’s biologic features.

Surrogate parameters for tumor burden include an elevated beta-2-microglobulin (ß2M), bulky disease, and the number of extranodal sites.[3-5] Bulky disease in the M. D. Anderson Tumor Score System is defined as any peripheral lymph node or mass ≥ 7 cm, a T3 or T4 lesion (by the TNM system) in the sinus cavity or nasopharynx, or > two-thirds infiltration of the stomach, liver, or other extranodal sites that are difficult to measure. Such estimates of tumor burden, when combined with serum lactic dehydrogenase (LDH) levels and used as a prognostic model, have proven useful in predicting 5-year survival. For example, patients with poor-risk disease as defined by extensive nodal and/or extranodal disease and elevated LDH levels had a 5-year survival of 20%, in comparison with 87% for those good-risk patients with less extensive disease and normal LDH levels.[5]

Beta-2-microglobulin seems to correlate with tumor burden as well, and is an independently significant and easily measured prognostic parameter.[5] The ß2M level has been used together with LDH to identify patients with a poor prognosis; in combination with an elevated serum LDH, an elevated ß2M correlates with an inferior time to treatment failure and survival among patients with aggressive non-Hodgkin’s lymphoma, regardless of Ann Arbor stage.[6]

Swan et al correlated these variables to identify a distinct high-risk group of patients with large-cell lymphoma whose 2-year survival was 19% compared with a 2-year survival of 100% in a low-risk group of patients.[6] In this system, an intermediate prognostic category was observed and consisted of cases with either ß2M or LDH elevation, but not both. This intermediate category is considered undesirable for treatment planning because it is much easier to design or select treatment for patients with either a very favorable or a very unfavorable prognosis, but is more difficult for patients with an intermediate prognosis. The former could be treated with conventional regimens whereas the unfavorable group could be entered on experimental programs.
Estimates of tumor burden have proven to be significant in multivariate analyses and have found their way into some of the more recent staging systems. Ann Arbor stage, an increased β2M and LDH, the presence of constitutional “B” symptoms and bulky disease were incorporated into a staging system known as the M. D. Anderson Tumor Score.[7] One point is assigned for each adverse prognostic feature with the sum representing a “tumor score.” An estimate of tumor burden, the tumor score, correlates with response rates (Table 2).

In a study of 144 patients who were uniformly treated with the CHOP regimen (cyclophosphamide [Cytoxan, Neosar], doxorubicin [Adriamycin], vincristine [Oncovin], and prednisone), those patients with a tumor score of 0 to 2 had a time to treatment failure rate of 83% compared to 24% for those patients with a tumor score of 3 or more.[7] This system incorporated tumor-dependent variables that had been found to be significant in multivariate analyses, were easily reproducible, and correlated with outcome. A major advantage of this system is the definition of only two prognostic categories with no intermediate categories.

Coiffier et al prospectively applied several of these prognostic systems from various single institutions to patients receiving the LNH-84 regimen and identified groups of good- and poor-risk patients. (The LNH-84 regimen includes doxorubicin, cyclophosphamide, vindesine [Eldisone, Enisone], bleomycin [Blenoxane], prednisone, and methotrexate.) Although the ability of each system to predict prognosis was roughly equivalent, a commonly accepted definition of tumor burden remained elusive.[8] Serum LDH levels and Ann Arbor stage remained the most important variables, although β2M was not included as a variable. Coiffier then proposed a prognostic index based on LDH and three measurements of tumor burden (tumor size, the number of extranodal sites, and Ann Arbor stage). Other prognostic variables such as serum albumin levels and bone marrow involvement did not seem to add to the prognostic capability beyond the aforementioned variables.[9]

The International Non-Hodgkin's Lymphoma Prognostic Factors Project also reviewed pretreatment clinical prognostic factors in order to develop a system that might correlate with future outcome for newly diagnosed patients with non-Hodgkin's lymphoma. The resulting International Prognostic Index (IPI) has proven to be particularly useful in predicting outcome, and is widely used. Both prospective and retrospective analyses of other data have confirmed the utility of this prognostic model.[10]

The IPI incorporates advanced age (defined as greater than 60 years old), advanced stage (Ann Arbor III or IV), elevated LDH, poor performance status, and greater than one extranodal disease site. For example, patients with only one or fewer adverse prognostic features are classified as being low risk, with a complete response rate of 87%, and a 5-year overall survival rate of 73%. Patients with low-intermediate and high-intermediate risk have complete response rates of 67% and 55%, and 5-year survival rates of 51% and 43%, respectively. Patients with high risk disease have a projected complete response rate of only 44%, with a 5-year survival rate of 26%. Variations of the IPI scale, such as an age-adjusted IPI score, have also been found to be quite sensitive.[2]

The IPI has proven useful in predicting outcome in patients with both aggressive and low-grade lymphoma and has even proven to be useful among patients with mantle cell lymphoma.[11] Both the M.D. Anderson tumor score and the IPI are shown in Table 2 and Table 3 along with projected response rates and survival estimates. The only drawback of the IPI is the fact that there are a large number of cases that fit into the intermediate risk categories, making treatment selection problematic.

**Other Relevant Prognostic Factors**

**Bone Marrow and Central Nervous System Involvement**

Patients with lymphoma involving the bone marrow, testes, or those with a lymphoblastic or Burkitt’s lymphoma are at greatest risk for central nervous system (CNS) involvement. Given the poor prognosis of CNS or lepto-meningeal lymphoma, it is important to search for central nervous system involvement in such patients at presentation and to incorporate CNS prophylaxis into the treatment plan whenever indicated. Similarly, bone marrow involvement is considered to be an adverse feature
and may occur in approximately 10% of all patients with histologically aggressive non-Hodgkin’s lymphoma at the initial staging evaluation. While bone marrow involvement has been shown to be prognostically important, it does not significantly add to the utility of existing prognostic models such as the IPI, and is therefore not generally included.

The presence of divergent histology in the marrow is an interesting phenomenon with prognostic ramifications.[12] Robertson et al described 50 patients with diffuse large-cell lymphoma of lymph nodes and evidence of bone marrow involvement. Forty-eight percent had large-cell lymphoma, 38% had small cleaved-cell lymphoma, and 14% had mixed histology in the marrow. Those with large-cell lymphoma in the bone marrow had a low complete remission rate (16.7%), a high risk of CNS involvement (33%), and a poor 5-year overall survival (12%). Those with small-cleaved-cell lymphoma in the bone marrow had a higher complete remission rate (89.4%), a lower rate of CNS involvement (5%), and a better 5-year survival rate (79%). However, those patients with small-cleaved-cell lymphoma in the marrow had a continuous rate of relapse with a progression-free survival of only 30% at 5 years and 15% at 8 years, reminiscent of the situation with indolent non-Hodgkin’s lymphoma.[12]

Host-Dependent Variables

Chronologic Age

Age is an important prognostic factor in most studies and an independent variable in multivariate analyses.[2,13-16] The bulk of the data analyzed cite age as an adverse feature, although a few reports cite comparable outcomes among elderly and younger patients when dose intensity is maintained.[17] Dose-intensity does not seem to be the only determining factor in the elderly, though.

A Southwest Oncology Group study found that patients over 60 years of age had lower response rates and higher relapse rates.[14] The survival among elderly patients was lower, even when differences in dose intensity were taken into consideration. A study from d’Amore et al revealed that the 7-year survival was 35% for patients older than 70, while survival for younger patients was 57%; survival among the elderly remained inferior even when stratifying for non-lymphoma related deaths.[18] Further analysis of this elderly population revealed other independent prognostic parameters such as stage, the presence of constitutional symptoms, and elevated LDH.

Another study from the Groupe d’Etudes des Lymphomes de l’Adulte (GELA) shows an impressive ranking of survival according to age. In this study, 3-year survival rates were over 65% for patients aged younger than 50 years, less than 55% for those aged 50 to 65, and less than 40% for those over 65 years old, respectively.[19] Other studies confirm a higher mortality during treatment, possibly due to an increased likelihood of regimen-related toxicity and comorbid medical conditions.

Some reports have shown that elderly patients who achieve a significant treatment response seem to do as well as their younger counterparts, although there are concerns about increased toxicity in the elderly.[15,16] In summary, age seems to confer an adverse prognosis for higher treatment-associated morbidity and mortality, lower remission rates, and shortened survival.

Time to Achievement of Complete Response

Although not considered pretreatment prognostic variables, the time to achievement of a complete response and chemosensitivity are all of prognostic importance. Patients who fail to achieve a complete remission by the third cycle of CHOP chemotherapy have a worse prognosis than those who achieve a rapid complete remission.[20] The persistence of clinically or radiographically identifiable disease after three to six courses of chemotherapy has been used in some studies as an indication to change therapy or even as a point at which to proceed to high-dose chemotherapy and autologous stem-cell rescue. Changing treatment based on time to treatment response remains controversial, particularly given questions regarding the significance of residual abnormality on CT scans as well as the accuracy and reproducibility of gallium scans. Post-treatment variables, though prognostically important, are not helpful for assessing prognosis at initial presentation and are
difficult to separate from the prognostic parameters in the IPI.

It seems obvious that patients who achieve a complete remission should enjoy a better survival than those who do not. While patients whose best response is less than a complete remission may have a long progression-free survival, particularly for the indolent lymphomas, it is essential to achieve complete remission in order to cure the patient. The prognosis for those with aggressive or highly aggressive lymphomas and chemorefractory disease is quite poor, with a 1-year survival of less than 10%.

**Prognostic Factors in High-Dose Chemotherapy**

The management of patients with recurrent lymphoma is often difficult, and prognostic factors may prove particularly useful in identifying those who would benefit from high-dose chemotherapy and stem-cell support. Chemosensitivity to standard dose salvage therapy before transplant is the most important factor in determining who might benefit from high-dose chemotherapy and stem-cell transplant.[21] Extensive pretreatment, the presence of bulky disease, elevated LDH levels, and other factors denoted in the IPI are helpful in evaluating prognosis with dose intensive therapy.[22-25]

A study from the University of Nebraska confirmed the importance of these prognostic factors in a multivariate analysis [22], with reports of a 10% survival among those classified as having a poor prognosis compared to 40% for those in the more favorable prognostic group. Other clinical factors of prognostic significance for high-dose chemotherapy include assessments of tumor burden, such as tumor bulk, the number of extranodal sites, elevated LDH, and stage at diagnosis.[5,23-28] Disease burden (eg, greater than three sites of disease or bulky disease) may adversely affect outcome despite limited stage disease.[29] A retrospective study showed the IPI to be an important predictor of prognosis for those patients undergoing high-dose chemotherapy.[28]

**Other Tumor-Related Variables**

**Immunophenotype**

The prognostic importance of immunophenotype had been controversial for some time, with conflicting reports about whether T-cell lymphomas of aggressive histologic types had an equivalent or inferior outcome in comparison to the B-cell lymphomas of aggressive histologic type.[30-32] The T-cell lymphomas tended to be a heterogeneous group and the importance of phenotype outside of the context of the IPI had been less clear until recently. The IPI Project did not assess the impact of T-cell phenotype, in part due to the limited amount of data.[2]

In a recent analysis, we found that a diagnosis of peripheral T-cell lymphomas (PTCL) was an important prognostic variable for failure-free survival independent of the IPI.[33] Patients with T-cell lymphomas had more adverse features at presentation. For example, patients with T-cell lymphomas had a greater likelihood of advanced disease and high LDH when compared to those with B-cell lymphomas, but the effect of T-cell phenotype on outcome was independent of this. The only exceptions were the Ki-1 anaplastic large-cell lymphomas, which seemed to have a more favorable outcome and thus do not appear to share the same poor prognosis as the rest of the PTCLs.

The most recent study by Gisselbrecht et al confirmed the findings that the T-cell phenotype is generally an adverse prognostic feature, even when accounting for IPI variables.[34] Patients with aggressive non-Hodgkin’s lymphoma treated according to the LNH87 protocol were analyzed according to immunophenotype in an analysis of 288 patients with T-cell lymphoma (15%), and 1,595 patients with B-cell lymphomas (85%) (Table 4).

**Ki-67**

Lymphomas whose proliferative index is elevated, as shown by the proliferative antigen Ki-67, have been confirmed to have a particularly poor prognosis in multivariate analysis. Miller et al observed that patients with a high proliferative index as characterized by a Ki-67 of ≥ 80% had a poor survival
at 1 year, compared with those patients with a low proliferative index (18% vs 82% 1-year survival respectively).[35] However, only a small fraction (18%) of all patients with aggressive NHL had a high proliferative index. Recent trials have attempted to explore whether or not a more aggressive treatment approach might improve survival.

**BCL-2 Gene Rearrangement and Protein Expression**

Bcl-2 gene rearrangement, characterized by the t(14;18)(q32;q21) translocation, is found in up to 90% of follicular lymphomas, but may also occur in 20% to 30% of large-cell lymphomas.[36] It is not yet clear whether the t(14;18) abnormality in diffuse large-cell lymphomas indicates a de novo event or transformation from a previous follicular histology. However, patients with bcl-2 positive aggressive histology lymphoma do not seem to follow the natural history of low-grade lymphomas.

The prognostic significance of bcl-2 gene rearrangement in aggressive non-Hodgkin’s lymphoma has been studied. Bcl-2 gene rearrangement and expression has been cited as an unfavorable prognostic feature by some, but this has not been a consistent finding. Yunis et al. observed that only 7 of 23 patients with bcl-2 rearrangement achieved a complete remission, compared to 21 of 26 complete remissions among bcl-2 negative patients.[37] However, a number of other studies have not observed an impact on disease-free or overall survival among such patients.[38,39]

For example, Gascoyne et al. studied 139 patients with advanced, aggressive non-Hodgkin’s lymphoma for whom the bcl-2 gene rearrangement status was known. He observed similar results for bcl-2 rearranged patients and bcl-2 germline patients, with relapse-free survivals of 43% and 51%, respectively, 8-year disease-free survivals of 42% and 47%, respectively, and comparable overall survival.[36] The bulk of the available literature suggests that the presence of bcl-2 gene rearrangement does not carry independent prognostic significance.

Bcl-2 protein expression may occur in the absence of bcl-2 gene rearrangement and its prognostic significance has also been studied. The frequency of bcl-2 protein expression among patients with aggressive non-Hodgkin’s lymphoma has been difficult to assess, with between 34% and 69% of patients being positive, according to the assay and the cut-off used, the prognostic importance of which was unclear.[40,41] The GELA group studied a series of patients whose lymphomas stained strongly for bcl-2 protein (42% of patients) and observed an adverse outcome, with significantly inferior disease-free and overall survival.[42] Other investigators have reported similar observations and their data suggest that bcl-2 protein expression carries an adverse prognosis, even when stratified for IPI score and immunophenotype.[36,39,43]

**BCL-6**

A cytogenetic abnormality in chromosome 3q27 has been identified among diffuse large-cell lymphomas and has shown to have prognostic significance, suggesting the presence of a gene, which was later identified as bcl-6. Offit et al. identified bcl-6 gene rearrangement in 23% (23 of 102) of patients with B-cell diffuse large-cell lymphoma.[44] Among those with the bcl-6 rearrangements, 19 of the 23 showed primary extranodal involvement of the stomach, lung, skin, muscle, bowel, kidney, liver, or pancreas; two had primary splenic lymphoma; and only one had bone marrow involvement. The bcl-6 positive patients were older (62.2 years vs 54.1 years), had a better 3-year freedom from progression (82% vs 56%), and had a better 3-year survival (86% vs 56%). In multivariate analysis, bcl-6 was found to be a significant and independent variable for relapse-free and overall survival.

**Mantle Cell Lymphoma**

The utility of the IPI score has been suggested in patients with mantle cell lymphoma also.[10] In the M. D. Anderson experience, histology can be prognostically important in mantle cell lymphoma as well. For example, the mantle zone variant seems to carry a more favorable prognosis than the diffuse and blastoid subtypes.[45] A high proliferative phase as characterized by a Ki-67 of ≥ 10% has also been associated with a worse outcome. There are little data regarding other prognostic factors in mantle cell lymphoma, primarily due to the relatively rare nature of this disorder.[45]
Indolent Lymphoma

Prognostic factors for follicular lymphoma are more difficult to define, due to the long natural history of the disease and the difficulty in following a group of such patients. Nevertheless, prognostic parameters have been described for follicular center cell lymphomas. The most important prognostic parameter appears to be stage, with stage I patients achieving the best long-term survivals.[46-48]

A study from the Princess Margaret Hospital [49] grouped patients according to age, stage, constitutional symptoms, and tumor bulk. The first group consisted of stage I or II patients who were younger than 70 years old and whose maximum lymph node size did not exceed 5 cm; the second group contained stage II patients with lymph nodes greater than 5 cm in greatest diameter; and the third group consisted of patients who were 70 years of age and older. The 10-year disease-free survival was 75% in the first group, 58% in the second group, and less than 20% in the third group. Patients with stage I or II disease comprise only about 15% of those with follicular lymphoma, though, and the primary challenge has been to identify clinically relevant prognostic factors among those with stage III and IV disease.

Increased serum LDH and β2M levels adversely affect prognosis in the low-grade lymphomas, possibly due to an association with greater tumor burden.[50,51] Expression of Ki-67 and an increase in the percentage of cells in S phase have also been associated with an adverse prognosis.[52]

A number of features have been examined for possible prognostic significance in patients with advanced stage low-grade lymphoma, including tumor characteristics, clinical features such as B symptoms, and cytogenetic and molecular data. Among patients with low-grade lymphoma, the degree of nodularity has been associated with a more favorable prognosis, though some controversy persists.[53] Much of the controversy can be traced to difficulties in defining the extent of nodularity and how or whether to subdivide those with mixed presentations of both small and large cells. It does appear, though, that those with a predominance of large cells tend to have a more aggressive clinical course. Interfollicular fibrosis and infiltration with CD4+ T-cells have been described as favorable features, and CD4+ T-cell infiltration has been correlated with the unusual event of spontaneous regression.[54]

Clinical features associated with failure-free survival include large peripheral lymph nodes, degree of marrow involvement, and gender (in that order), while the number of extranodal sites, large peripheral lymph nodes, gender, and degree of marrow involvement were important for cause-specific survival.[48] Response to initial therapy has been reported to be an important prognostic variable as well. Several studies confirm a superior survival among complete responders as compared with those patients who did not achieve a complete response to therapy.[55,56]

Tumor burden, response to therapy, and other clinical factors are also important in patients with low-grade lymphoma. As in patients with aggressive lymphomas, evaluation of tumor burden in patients with low-grade lymphoma has been performed using Ann Arbor stage, disease bulk, marrow involvement, β2M, and the number of extranodal sites. More than one site of extranodal disease, advanced age, and poor performance status are also adverse prognostic features (Table 5).[48]

The IPI prognostic model has been examined in the indolent lymphomas to determine its correlation with outcome. In a study of patients with low-grade lymphoma, Lopez-Guillermo et al examined the prognostic value of the IPI, which had been studied in patients with aggressive disease. There was a significant correlation with survival, with a 10-year survival of 75% for those categorized as low risk, 50% for intermediate-risk patients, and 0% for high-risk patients.[57] No correlation was observed for treatment response. However, only 11% of patients were classified as high risk. The sensitivity of this system is low in predicting prognosis for indolent non-Hodgkin’s lymphoma.

The presence of constitutional symptoms, male gender, and low hemoglobin level have also been associated with a poor outcome in patients with indolent lymphomas, though these have been questioned as having independent prognostic significance.[46-48,58,59]
The cytogenetic abnormality t(14;18) is associated with follicular lymphoma and the clinical course appears to be fairly indolent for those patients in whom this is the sole chromosomal abnormality at presentation. Additional karyotypic abnormalities are generally unfavorable, particularly structural abnormalities of chromosome 17 which is an adverse prognostic factor in multivariate analyses.[60]

Up to 85% of patients with follicular center cell lymphoma may have circulating bcl-2 rearranged cells as detected by polymerase chain reaction.[61] Although this finding does not seem to carry an adverse prognosis in such patients as a whole, it has been associated with risk of graft contamination, recurrence rates, and overall survival in patients who undergo high-dose chemotherapy and autologous stem-cell transplant. [62,63] We have recently observed that the molecular breakpoint has important prognostic implications. The complete response rate of germline patients was significantly lower than that of MBR and mcr rearranged patients. Estimated 3-year failure-free survival for mcr, MBR and germline cases was 95%, 76%, and 57%, respectively (P < .001). The associated bcl-2 breakpoint site with outcome was independent of serum β2M and LDH in its correlation with failure-free survival.[64]

**Conclusion**

Prognostic factors have become increasingly important in assessing the newly diagnosed patient with non-Hodgkin's lymphoma. In order to improve survival, it is necessary to identify those patients at low risk for remission with conventional approaches and consider placing them on clinical trials using risk-appropriate regimens. Current laboratory and clinical investigations offer new opportunities to learn about both disease biology and to identify better ways to predict outcome for patients with lymphoma.

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