Prognostic Factors in Aggressive Non-Hodgkin’s Lymphomas

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Key Words. Non-Hodgkin’s lymphoma · Prognostic factors

ABSTRACT

Aggressive non-Hodgkin’s lymphoma (NHL) is a biologically heterogeneous disease that can be cured with aggressive chemotherapy treatment. Different clinical, biological, cellular and molecular features have been identified as having prognostic significance on the outcome of NHL patients. The knowledge of these prognostic features can be used in everyday practice in order to predict the prognosis of every new NHL patient and tailor his or her treatment accordingly. The Oncologist 1998;3:189-197

INTRODUCTION

Aggressive lymphomas as classified in the “Revised European American Classification of Lymphoid Neoplasms” (REAL) [1] include diffuse large B-cell lymphoma, anaplastic large cell lymphoma and peripheral T-cell lymphomas (Table 1). In the International Working Formulation [2] these lymphomas of B- or T-cell immunophenotype were classified in the histologic subtypes of diffuse mixed small and large cell (F), diffuse large cell (G), and immunoblastic lymphoma (H). Aggressive lymphomas are composed predominantly of cells that are larger than normal circulating lymphocytes, with a high proliferation fraction and appear to correspond to proliferating stages of antigen-dependent B- or T-cell differentiation. Most aggressive lymphomas arise de novo, but may also develop from a pre-existing low-grade lymphoma.

Diffuse large cell lymphoma is the most common, accounting for 60%-70% of the cases. In decreasing frequency, the remainder of the cases are made up of anaplastic large cell lymphoma and peripheral T-cell lymphoma. Potentially curable with combination chemotherapy, if left untreated, the median survival of patients with these lymphomas is measured in months. Aggressive lymphomas developing from pre-existing low-grade lymphoma are less susceptible to cure. CHOP combination chemotherapy has cured 30% of patients with diffuse large cell lymphomas [3]. Second- and third-generation regimens with predicted five-year survival of more than 55% have been developed later [4-9]. In recent randomized cooperative group studies [10, 11] m-BACOD, ProMACE-CytaBOM and MACOP-B failed to prove that they are more effective than standard-dose CHOP, now considered as the standard therapy. The reasons patients with aggressive lymphomas fail treatment and, consequently, prolonged survival, are failure to achieve complete remission (CR) at initial chemotherapy, and relapse of the tumor. Patients who achieved CR at initial chemotherapy and were free from disease at 24 months were considered cured, but this is not the case, as late relapses can also occur [3, 5, 12].

A variety of factors have been identified as having a prognostic significance on response to treatment, relapse-free and
overall survival in patients with aggressive lymphomas. Some of these factors are: measures of the physiologic reserve of the patient and his or her ability to tolerate intensive chemotherapy treatment; the tumor’s burden and invasive potential, as well as the tumor’s impact on the patient. Based on these prognostic parameters, prognostic indexes have been described [13-19] that could identify newly diagnosed patients as “low-” or “high-risk” [13-17]. Low-risk patients may be effectively treated with currently used chemotherapy regimens, whereas high-risk patients may benefit from experimental treatments, such as high-dose consolidation treatment with hematopoietic stem cell support after CR from initial chemotherapy [20-22], or initial high-dose induction chemotherapy with stem cell support [23].

In this paper we intend to review the factors that could predict the outcome of patients with aggressive lymphomas.

**Parameters Related to the Patient**

**Age**

Advancing age was associated with shorter survival in many studies [14-16, 18, 19, 24-27]. In these studies the age found to be associated with shorter survival varied from above 60 years to above 70 years. Others have failed to identify advanced age as an adverse prognostic factor [28-31]. In one study [32], the CR rate of patients >60 years was comparable with that of patients ≤60 years; the difference in five years’ survival being attributed to causes of death not related to lymphoma or its treatment. In another study, older patients had a poorer outcome because of poor CR rate and more relapses, as the dose intensity received was 50% of the scheduled one [33]. Age per se is not an absolute predictor of survival. Older patients may have other concomitant debilitating diseases that could affect their performance status (PS) and physiologic reserves, rendering them unable to tolerate intensive chemotherapy treatment. Elderly patients with good PS must be treated with full doses of aggressive chemotherapy with curative intent.

**HIV Infection**

Lymphomas in patients with HIV infection may occur early in the course of the disease, possibly being the AIDS-defining criterion, or later in the course of AIDS. Early in the disease the lymphomas are more likely to be Burkitt’s-like, whereas those associated with more severe immunosuppression are diffuse large B-cell lymphomas. Patients with HIV-associated lymphomas frequently present with profound β symptoms, advanced stage disease, and involvement of multiple extranodal sites. The treatment of HIV-associated lymphomas is complicated by the underlying immunodeficiency and associated infections that render patients unable to tolerate intensive chemotherapy. The median survival of these patients is less than a year, and adverse prognostic factors include: a CD4+ count of less than 100/µl, PS >1, large cell lymphomas, prior manifestations of AIDS, increased LDH and age 40 or above [34, 35].

**Parameters Related to Host Tumor Reaction and Host Immune Response**

In Table 2 the prognostic factors related to host tumor reaction and host immune response are listed.

<table>
<thead>
<tr>
<th>Factor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>[5, 13, 16, 18, 19, 26, 31, 44]</td>
</tr>
<tr>
<td>ESR</td>
<td>[31, 41]</td>
</tr>
<tr>
<td>Serum albumin levels</td>
<td>[17, 31]</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>[31, 42, 43]</td>
</tr>
<tr>
<td>β symptoms</td>
<td>[17, 18, 25, 27, 36, 37]</td>
</tr>
<tr>
<td>β-2 microglobulin</td>
<td>[54-56]</td>
</tr>
<tr>
<td>Absence of MHC encoded recognition structures</td>
<td>[37, 52]</td>
</tr>
<tr>
<td>Cytokine production by tumor or host-reactive cells</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>[46]</td>
</tr>
<tr>
<td>IL-10</td>
<td>[47]</td>
</tr>
<tr>
<td>Soluble IL-2 receptors</td>
<td>[48]</td>
</tr>
<tr>
<td>TNF and its soluble receptors p55, p75</td>
<td>[49, 50]</td>
</tr>
</tbody>
</table>

**Erythrocyte Sedimentation Rate (ESR)**

Patients with aggressive NHL usually do not have elevated ESR. Elevated ESR is a well-established prognostic factor in Hodgkin’s disease [38-40] and also has been found to predict for survival in primary gastrointestinal lymphomas [41]. ESR >50mm/h was associated with poor CR rate and survival in patients with aggressive lymphomas [31].

**Serum Albumin Levels**

Serum albumin values have rarely been studied for their prognostic significance, although low serum albumin was associated with low response rate [17] and higher death rate during treatment because of higher hematological toxicity. In a recent study [31], albumin values <3.5g/ml were associated
with poorer CR rate, relapse-free and overall survival only in univariate analysis.

**Hemoglobin Level**

Hemoglobin level less than 12 g/dl is usually considered as anemia. Newly diagnosed patients with hemoglobin value less than 12 g/dl have been found to have an increased death rate during treatment and poorer CR rate [42]. It is also related to shortened relapse-free and overall survival [31]. The shorter survival of anemic patients has been found to be independent of bone marrow infiltration by lymphoma cells [43].

**Performance Status (PS)**

PS is a measure of the functional ability of the patients. It is related to other parameters such as β symptoms, tumor's burden, and other concomitant illnesses and age, being an indicator of how patients tolerate their disease. It has always been found to be a strong prognostic factor in studies addressing its significance for the prognosis of patients with aggressive lymphomas. A PS ≥ 2 of the ECOG scale is an indicator of poor tolerance of the disease and an adverse prognostic factor [5, 13, 16, 18, 19, 26, 31, 44]. Because it is related with other adverse features such as age, β symptoms and anemia, this may be the reason the above parameters do not maintain their independent significance in multivariate analysis, in different studies.

**Cytokine Production by Tumor or Host Reactive Cells**

Interleukin 6 (IL-6) is a cytokine produced by a variety of cell types including both benign and malignant B- and T-lymphocytes. IL-6 is a growth factor for multiple myeloma cells, and increased IL-6 level predicts for poor outcome in multiple myeloma patients [45]. In a study of 58 patients with aggressive lymphomas, elevated serum IL-6 levels at diagnosis were associated with other adverse disease features such as β symptoms, elevated β-2-microglobulin levels, poor PS, low albumin level and increased ESR. Patients with elevated IL-6 levels had poor relapse-free and overall survival [46].

IL-10 is a cytokine produced by monocytes, macrophages, and B- and T-cells. It has immunosuppressive properties inhibiting macrophage activity, antigen-specific T-cell activation, and production of IFN-γ by NK cells. In one study [47], serum IL-10 levels were measured in 153 patients with NHL of all histologic subtypes according to the International Working Formulation. The percentage of patients with detectable serum IL-10 was comparable in the different histologic subtypes as well as in B- and T-cell NHL. The percentage of patients with high IL-10 levels was not significantly different in patients with different disease stages. Serum IL-10 level did not correlate with other prognostic factors such as age, PS, number of extranodal sites of disease, LDH value, and tumor mass. The prognostic significance of IL-10 was studied in 70 patients with high or intermediate grade NHL. Patients with detectable serum IL-10 had significantly shorter progression-free and overall survival. In multivariate analysis, IL-10 had an independent prognostic significance for progression-free survival and marginal significance for overall survival, when analyzed with the factors of the International Prognostic Index (IPI).

Soluble IL-2 receptor levels were found to be associated with clinical stage, tumor burden, and the presence of β symptoms, thus having prognostic significance for survival in aggressive lymphomas [48].

Tumor necrosis factor (TNF) is one of ten known members of a family of ligands that activates a corresponding family of structurally related receptors. With the exception of TNF and lymphotoxin α, each member of the ligand family binds to a specific receptor. TNF and lymphotoxin α engage two receptors—the 55kd and the 75kd TNF receptors. By proteolytic cleavage of the membrane-bound receptors, these are shed in the circulation as soluble proteins. Elevated plasma levels of TNF and both of its soluble receptors (p55 and p75) in patients with aggressive lymphomas were associated with other prognostic factors such as elevated LDH and β2-microglobulin levels, Hb <12 g/dl, stage III-IV disease, bulky tumor, poor PS, β symptoms, albumin <3.5 g/dl, and predicted for poor relapse-free and overall survival [49, 50].

Low serum albumin level, β symptoms, elevated ESR, and anemia in patients with aggressive lymphomas could be explained by cytokine release in the circulation. This is the reason why elevated IL-6, TNF and its soluble receptors correlate with these disease features. TNF and IL-6 can induce weight loss and fevers. IL-6 is an inducer of hepatic fibrinogen synthesis, the major determinant of ESR, and inhibits the hepatic synthesis of albumin, causing hypoalbuminemia. Anemia in NHL patients without bone marrow infiltration could be explained in part by high levels of TNF in these patients by analogy to hairy cell leukemia, in which increased TNF values contribute to hematopoietic failure [51].

Tumor antigens could be recognized by the immune system when they are associated with major histocompatibility complex (MHC) molecules. The absence of MHC-encoded recognition structures could limit host-tumor immunosurveillance. Patients whose tumors lacked HLA-DR had significantly shorter survivals than patients with HLA-DR+ tumors [37, 52].

β2-microglobulin is a small extracellular protein that is a structural component of MHC class 1 molecules. MHC class I molecules are heterodimers composed of an extremely polymorphic 45 kd α chain and β2-microglobulin. β2-microglobulin is synthesized by all nucleated cells and plays an important role in the proper folding of the 45 kd class I α chain. Pretreatment β2-microglobulin levels correlate strongly with
tumor burden in multiple myeloma and are a strong prognostic factor for survival [53]. Elevated serum β2-microglobulin levels are associated with high tumor burden and shortened survival in patients with aggressive NHL [54, 55]. β2-microglobulin level is one of the parameters that predicts the risk of relapse for complete remission patients [56].

**Factors Related to the Tumor and Its Invasive Potential**

Table 3 shows the parameters related to the tumor and its invasive potential. These parameters have been found to have prognostic significance in the outcome of patients with aggressive lymphomas.

The Ann Arbor staging system was originally developed for the staging of Hodgkin’s disease and is used also for the staging of NHLs despite their different biologic behavior. For instance, Hodgkin’s disease is an essentially nodal disease, extranodal involvement being a late event in the natural history of the disease. NHLs, however, frequently present with primary extranodal localizations, and they more readily infiltrate bone marrow. Stage is always related to outcome, with patients with stage III or IV disease having a poorer CR rate and survival [17, 18, 28, 31, 37, 44, 57].

Patients with extranodal sites of disease may have either a localized lymphoma with involvement of only one site, with or without dissemination, or disseminated disease. The number of extranodal localizations is a reflection of the disease’s propensity to disseminate. Two or more extranodal sites involved by disease is one of the most important prognostic factors [5, 13-15, 17, 19, 27, 44, 57]. Specific extranodal sites involved by disease have been identified as sites with prognostic significance, with bone marrow involvement being one of these [17, 31, 42, 44, 58, 59]. Bone marrow infiltration was subdivided into infiltration by large cells similar to those seen in the lymph node and infiltration by small cells. Patients with large cell lymphoma and bone marrow involvement by small cell lymphoma have a higher risk of relapse, but a longer survival than patients with involvement by large cells [60-62].

A measure of the tumor’s aggressiveness and burden is the diameter of the largest tumoral mass. Poor outcome has been shown to exist with large tumors in one involved site. The diameter of the largest tumor with prognostic significance in different studies varies from above 5 cm to above 10 cm [4, 13-15, 17]. Vitolo et al. [63], and Pereira et al. [36] found that bulky abdominal disease >10 cm was associated with poor response to therapy and poorer survival. Others [29, 31], and, most importantly, the IPI study [19] could not find an association between the maximum diameter of a tumoral mass in a single site and survival in multivariate analysis. Consolidation radiotherapy is often employed in sites with bulky disease after combination chemotherapy. However, as relapses in patients with bulky disease are not confined only to these sites, and, as studies in which “adjuvant” or no radiotherapy failed to demonstrate any advantage for this treatment [9], “adjuvant” radiotherapy to sites of prior bulky disease cannot be considered as standard treatment in aggressive lymphoma patients.

In lymphoproliferative diseases the LDH level is a marker of increased cell turnover and correlates with tumor burden. Increased LDH level has been recognized as an important factor that affects CR rate [17, 31, 36, 63] relapse-free [17, 63] and overall survival [17, 19, 25, 29, 31, 36, 63].

Controversial reports have been published in the international literature with regard to the significance of immunophenotype and outcome in aggressive NHL. T phenotype was associated with poor CR rate and survival, at least in patients with stage IV disease [64]. Similarly, others [37, 65] reported that patients with aggressive T-cell lymphomas relapsed from CR more frequently than patients with B-cell disease. T immunophenotype is associated with more advanced stage disease, β symptoms, poorer PS, and extranodal involvement of sites such as skin, liver, and nose, whereas B-cell lymphomas affected the gastrointestinal tract and Waldeyer’s ring as extranodal involvement. Similar outcome of patients with B- or T-cell immunophenotype has also been reported [66]. In a recent study [67] the authors stratified patients with B- or T-cell lymphomas according to the different risk groups of the IPI and found that T-cell immunophenotype was associated with significantly poorer survival, retaining an independent prognostic value in multivariate analysis.

**Proliferative Activity**

The tumor cell proliferation rate can be measured by flow cytometric DNA assessment, tritiated thymidine uptake, or by

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**Table 3. Prognostic factors related to the tumor and its invasive potential**

<table>
<thead>
<tr>
<th>Factor</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Stage</td>
<td>[17, 18, 28, 31, 37, 44, 57]</td>
</tr>
<tr>
<td>≥2 extranodal sites</td>
<td>[5, 13-15, 17, 19, 27, 44, 57]</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>[17, 31, 42, 44, 58, 59]</td>
</tr>
<tr>
<td>Tumor &gt;10 cm in one site</td>
<td>[4, 13-15, 17, 36, 63]</td>
</tr>
<tr>
<td>T-cell lymphomas</td>
<td>[37, 64, 65, 67]</td>
</tr>
<tr>
<td>LDH</td>
<td>[17, 19, 25, 29, 31, 36, 63]</td>
</tr>
<tr>
<td>Tumor proliferation rate</td>
<td>[37, 68]</td>
</tr>
<tr>
<td>CD44v/CD44v expression</td>
<td>[69, 70]</td>
</tr>
<tr>
<td>bcl-2 rearrangements, overexpression</td>
<td>[72, 73, 74]</td>
</tr>
<tr>
<td>Bax expression</td>
<td>[75]</td>
</tr>
<tr>
<td>Bcl-6 rearrangements</td>
<td>[82]</td>
</tr>
<tr>
<td>p53 mutations</td>
<td>[84]</td>
</tr>
<tr>
<td>MDR-1 expression</td>
<td>[86]</td>
</tr>
</tbody>
</table>
the nuclear proliferation antigen Ki-67. High proliferative activity correlated with poorer survival in aggressive lymphoma patients [37]. In a prospective study [68], 60 of 899 patients who were enrolled on a treatment-directed study were evaluated for the tumor’s proliferative activity. There were no significant differences in prognostic risk distribution between the 60 patients studied and the remaining 839, nor in overall three-year survival. Eighteen percent of patients whose tumors expressed Ki-67 ≥80% survived one year, whereas 82% of patients having a Ki-67 index <80% survived one year (p = 0.0004). Of the 60 patients, 41 were aggressive lymphomas, Working Formulation histologic subtypes, diffuse large cell, and immunoblastic. The one-year actuarial and three-year estimated survival of patients with Ki-67 ≥80% (seven patients) was 29%, while the one-year actuarial and three-year estimated survival of patients with Ki-67 <80% (34 patients). Ki-67 was a statistically significant independent prognostic factor in multivariate analysis with the factors of the IPI.

Adhesion Molecule Expression

NHLs express a variety of adhesion receptors. These adhesion receptors regulate normal lymphocyte trafficking and tissue-specific positioning. Cutaneous lymphocyte antigen, α4β7, α(E)β7, and L-selectin mediate the positioning of normal lymphocytes in the skin, mucosa, epithelium, and lymph nodes, respectively. The lymphocyte homing receptor (CD44) facilitates the binding of lymphocytes to high endothelial venules and extravasation of lymphocytes to nodal areas. Expression of CD44 is related to lymphoma aggressiveness and dissemination. Fifty-one percent of patients with a lymphoma having a high CD44 antigen expression had stage III-IV disease, whereas only 12% with low or negative CD44 antigen expression had stage III-IV disease [69]. Similarly, patients with lymphomas expressing high levels of CD44 had poor response to treatment and overall survival [69].

A total of 20 exons provide the coding information of the CD44 gene locus, but only nine of these are predominantly expressed as the so-called standard form CD44 (CD44s). CD44 variant isoforms (CD44v) are obtained by alternate RNA splicing. Variant isoforms containing exon 6v (CD44-6v) have been found to be predominantly involved in tumor dissemination. Variant isoforms containing CD44-6v in combination with other variant exons were observed predominantly in aggressive lymphomas and were associated with a shorter survival. Multivariate analysis indicated CD44-6v as an independent adverse prognostic factor [70].

Genetic Lesions

The genome of lymphoma cells is characterized by a few chromosomal abnormalities, mainly chromosomal translocations, but chromosomal deletions and mutations also occur. At the molecular level, chromosomal translocations result in proto-oncogene activation, chromosomal deletions and mutations resulting in the inactivation of tumor suppressor genes.

The most frequent deletion involves the long arm of chromosome 6 (6q) and is associated with adverse prognosis [71]. The t(14;18)(q32;q21) chromosomal translocation, the genetic hallmark of follicular lymphomas, results in the activation of the 18q21 gene, the bcl-2 gene. The consequence of the translocation is the presence within the cells of high levels of bcl-2 protein. Bcl-2 is a member of a family of apoptotic regulators which also includes Bax and bcl-x. Bax protein promotes apoptosis. The inherent ratio of bcl-2 to Bax determines the functional ability of bcl-2. Bcl-2 is believed to contribute to oncogenesis by blocking programmed cell death, thereby extending cell survival. Overexpression of bcl-2 protein also prevents cell death induced by nearly all cytotoxic drugs and γ irradiation. Moreover, expression levels of the bcl-2 family of proteins change as tumors become more malignant or after treatment suggesting that expression of these survival proteins is critical not only for tumor development, but also for tumor progression and resistance to therapy. Up to 30% of aggressive NHLs have the t(14;18) chromosomal translocation [71]. The expression of bcl-2 protein is not restricted to lymphomas carrying the t(14;18) chromosomal translocation. Other mechanisms for bcl-2 overexpression include chromosomal amplification at 18q, and deletion of a nonconserved region (residues 51-85) of the bcl-2 gene.

Bcl-2 protein expression has been found in 44%-55% of aggressive lymphomas [72-74]. It was associated with stage III-IV disease [72] and primary nodal disease [73]. The relapse rate was higher in patients with bcl-2 expression and was the only significant factor in multivariate analysis for relapse [73]. The disease-free survival for patients with tumors expressing bcl-2 was significantly poorer and remained an independent prognostic factor in multivariate analysis [72-74]. The overall survival was also lower in patients with bcl-2-expressing tumors [72-74], but a significant effect on overall survival was documented in only one study in which eight-year follow-up data were available and patients have received a uniform treatment [74].

Overexpression of Bax protein promotes apoptosis. Bax protein expression was not of prognostic significance in the outcome of patients with aggressive lymphomas, although a trend for Bax negative to relapse sooner and die faster than patients whose tumors contained Bax was noted [75]. However, patients whose tumors were both Bax and bcl-2 negative experienced significantly lower eight-year relapse-free (29% versus 61%, p < 0.01) and lower eight-year overall survival (29% versus 63%, p = 0.05) when compared with
that Bax promotes apoptosis.

Chromosomal translocations with breaks at 3q27 juxtapose several chromosomal sites to 3q27, including 14q32 (IgH), 2p12 (Igκ), and 22q11 (Igλ), resulting in the rearrangement of the \textit{bcl-2} gene. The coding domain of \textit{bcl-6} is unaffected by the translocation, whereas the 5′ regulatory region is either completely removed or truncated. The result is that heterologous promoters are juxtaposed to the \textit{bcl-2} coding domain, leading to its deregulated expression. Apart from translocations, the \textit{bcl-6} gene may be altered by multiple, often biallelic, mutations clustering in its 5′ non-coding region [76]. The combined frequency of mutations and rearrangements approaches 100% of aggressive lymphoma cases, suggesting that structural alterations of the 5′ non-coding region of the \textit{bcl-6} gene are necessary for the development of these tumors [76].

Rearrangements of \textit{bcl-6} have been found in 27%-45% of aggressive B-cell lymphomas [77-79], 45% of CD30+ anaplastic large T-cell or null-cell type, but not in peripheral T-cell lymphomas [80], and in 20% of patients with AIDS-associated lymphomas [81]. In a study of 102 patients with aggressive B-cell lymphomas, \textit{bcl-6} rearrangements were found in 23 patients and rearranged \textit{bcl-2} in 21 cases [82]. Patients with \textit{bcl-6} rearrangements were more likely to present with extranodal disease. Freedom from progression at 36 months was 82% for patients with rearranged \textit{bcl-6}, 31% for patients with rearranged \textit{bcl-2}, and 56% for patients with germline \textit{bcl-6} and \textit{bcl-2}. The overall survival was also significantly better for patients with \textit{bcl-6} rearrangements. In multivariate analysis, \textit{bcl-6} rearrangement was an independent prognostic factor for survival and freedom from disease progression.

Mutations of the tumor suppressor gene \textit{p53} located on the short arm of chromosome 17 were first described in Burkitt’s lymphoma and later found to be related to the histologic transformation of follicular lymphomas. \textit{p53} mutations were also associated with advanced stage disease [83]. \textit{p53} is a critical component of a cell cycle checkpoint that causes either G1 arrest or apoptotic cell death after DNA damage. Transcription of the \textit{Bax} apoptotic gene is upregulated by \textit{p53}, suggesting that \textit{Bax} is involved in a \textit{p53}-regulated pathway for induction of apoptosis. \textit{p53} mutations have also been implicated in drug resistance.

\textit{p53} mutations in the cells of aggressive B-cell lymphomas were associated with older age, advanced clinical stage, and elevated LDH [84]. Only 27% of patients with \textit{p53} mutations achieved CR, whereas 76% of wild-type \textit{p53} achieved CR. The estimated five-year survivals were 16% for patients with \textit{p53} mutations and 64% for patients with wild-type \textit{p53}. Multivariate analysis showed \textit{p53} mutation as an independent prognostic factor for survival. \textit{p53} mutations were associated with a low CR rate and poor survival in patients who were classified as being of low or low intermediate risk according to the IPI risk groups, having no effect on the CR rate and survival of patients with IPI high intermediate and high risk groups [84].

The \textit{MDR-1} gene encodes a transmembrane protein (Pgp) that functions as a drug efflux pump. Cancers that overexpress Pgp are likely to accumulate less drug and thereby become drug resistant. \textit{MDR-1} expression is relatively low in untreated NHL patients (10%-20%), but increases in patients with recurrent disease (50%-70%) [85]. In a recent report [86] \textit{MDR-1} expression was associated with resistance to chemotherapy and poor outcome.

### The International Prognostic Index (IPI)

In 1993 the International NHL Prognostic Factor Project developed the IPI [19]. Patients with aggressive lymphomas treated with a doxorubicin-containing chemotherapy regimen were evaluated for pretreatment clinical features predictive for relapse-free and overall survival. Clinical features that were independently associated with survival included age, PS, LDH, stage, and number of extranodal disease sites. A patient’s relative risk of death was calculated by adding the number of adverse prognostic factors present at diagnosis. Four groups of patients with similar relative risk, low (zero to one adverse factor), low intermediate (two adverse factors), high intermediate (three adverse factors) and high (four to five adverse factors) with predicted five-year survivals of 75%, 51%, 43%, and 26%, respectively, were identified (Table 4).

For patients under 60 years, the age-adjusted index was also developed, based on stage, PS and LDH. The predicted

<table>
<thead>
<tr>
<th>IPI risk group (all patients)</th>
<th>Number of risk factors</th>
<th>CR rate (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>87</td>
<td>75</td>
</tr>
<tr>
<td>Low intermediate</td>
<td>2</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>High intermediate</td>
<td>3</td>
<td>55</td>
<td>43</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
<td>44</td>
<td>26</td>
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<table>
<thead>
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<th>Age-adjusted IPI risk group (patients &lt;60 years)</th>
<th>Number of risk factors</th>
<th>CR rate (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>92</td>
<td>83</td>
</tr>
<tr>
<td>Low intermediate</td>
<td>1</td>
<td>78</td>
<td>69</td>
</tr>
<tr>
<td>High intermediate</td>
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<td>57</td>
<td>46</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>46</td>
<td>32</td>
</tr>
</tbody>
</table>

![Table 4. The international non-Hodgkin’s lymphoma prognostic index](http://theoncologist.alphamedpress.org/)
five-year survivals of the four risk groups, low (no risk factors), low intermediate (one risk factor), high intermediate (two risk factors) and high (three risk factors) were 83%, 69%, 46%, and 32%, respectively (Table 4). Subsequent studies have validated the prognostic significance of IPI in aggressive [31, 87, 88] as well as in low-grade lymphomas [88, 89].

In the IPI study, however, the then-known prognostic factors—serum albumin levels and β2 microglobulin—either were not included in the analysis (serum albumin levels), or did not show prognostic significance (β2 microglobulin), because few patients had pretreatment measurements. Since the development of the IPI, other factors have been found to be of prognostic significance in aggressive lymphomas. Some of them are associated with other known clinical prognostic factors but maintain independent prognostic significance in multivariate analysis, so they have to be taken into consideration for the assessment of prognosis of individual patients with aggressive NHL.

**REFERENCES**


