Molecular pathogenesis of germinal-center derived non-Hodgkin’s lymphoma

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Non-Hodgkin’s lymphoma (NHL) derive from mature B-cells (85% of cases) and in a minority of cases from T-cells. Most B-NHL types derive from germinal center (GO) or post-GO B-cells since they express various GO markers and have undergone hypermutation of IgV genes, a phenomenon apparently restricted to GO B-cells. The pathogenesis of NHL represents a multistep process, involving the clonal accumulation of genetic lesions that affect protooncogenes and tumor suppressor genes. The most common mechanism of genetic lesion is by chromosomal translocations, which alter the pattern of expression of various protooncogenes by juxtaposition of heterologous regulatory sequences. During the last 15 years, significant progress has been made in identifying the protooncogenes associated with various B-cell derived NHL subtypes. In fact, most B-cell derived NHL cases are associated with the deregulated expression by chromosomal translocation of various protooncogenes, including: i) BCL-2 in follicular lymphoma; ii) BOL-1 in mantle cell lymphoma; iii) C-MYC in Burkitt lymphoma; and iv) BCL-6 in diffuse large cell lymphoma (DLCL). The mechanism of chromosomal translocation, the functional consequences of these aberrations on oncogene expression and their role in lymphomagenesis will be reviewed. Emphasis will be on recent findings about the normal and pathological function of the BCL-6 gene, which is expressed in all GO-derived lymphomas and is involved in chromosomal translocations in DLCL. In addition, recent evidence indicates that, although mutations of the promoter region of BCL-6 are found in normal GO B-cells, some mutations found in NHL lead to abnormal BCL-6 regulation in DLCL, follicular lymphoma and Burkitts lymphoma. Finally, novel findings on the molecular dissection of chromosomal abnormalities involving band 1q21, among the most frequent in NHL, will be presented.

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Prognostic factors in mucosa-associated lymphoid tissue lymphomas

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Introduction

Prognostic factors in oncology are developed on the basis of large and preferably uniformly treated patient series in order to predict clinical behavior in terms of overall survival, disease-free survival and reaction to therapy in individual patients. These parameters can be relatively simple clinical parameters, such as age and stage, and can also be tissue-based morphological, immunological and molecular factors. Parameters that may predict prognosis can be related to tumor growth characteristics, to the interaction of the patient with the disease and to the patient’s ability to tolerate therapy. Together, these factors serve to guide the choice of therapy. Modern lymphoma classifications are based on the concept of “lymphoma disease-entities”. These are characterized by a specific morphological and immunophenotypical spectrum and characteristic molecular alterations in combination with a characteristic clinical presentation and course. Also within well-defined entities, such as mucosa-associated lymphoid tissue (MALT) lymphoma, for example, a spectrum of clinical behavior can be found and parameters to predict this behavior may be identified.

Clinical prognostic factors

The International Prognostic Index (IPI), which was initially developed for diffuse large cell lymphomas, has proven to be of value in many types of lymphoma, including MALT lymphoma. Since the IPI is built up of basic factors that describe the growth characteristics and aggressiveness of the tumor (stage, number of extranodal sites, lactate dehydrogenase) and basic characteristics of patients and their ability to tolerate therapy (age, performance status), this broad applicability in lymphoma may be expected. However, stratification on the basis of these general parameters would ignore the specific characteristics of individual lymphoma disease-entities.
A more disease-specific approach to develop clinical prognostic factors would include the characteristic clinical properties of MALT lymphoma. Endoscopic ultrasound examination has been shown to be a highly sensitive technique for analyzing the extent of the disease in the gastric wall in gastric MALT lymphoma. Until now, this parameter has been one of the few to be significantly predictive of the response to therapy in Helicobacter pylori eradication protocols for low-grade gastric MALT lymphoma. In view of the essentially different dissemination pattern of extranodal MALT lymphomas stage, as defined by the Ann Arbor system, may not fully appreciate the impact of different lymphoma localization. Staging systems, specifically tailored to these characteristics, may prove to be a more valuable prognostic factor.

Pathological prognostic factors

In the current model of the evolution of MALT lymphoma, a precursor stage of follicular, H. pylori-associated gastritis, is thought to evolve into low-grade gastric MALT lymphoma and ultimately to proceed to transformation to high-grade disease (diffuse large B-cell lymphoma) on the basis of the accumulation of genomic alterations. In the early phases of lymphoma development, the proliferation of tumor cells is still at least partly dependent on immunological drive, mediated through the presence of H. pylori antigens. Therefore, two important biological transitions that justify different therapeutic approaches should be recognized by pathologists: the transition from low-grade to high-grade disease and the transition from the antigen-dependent to the antigen-independent phase.

Morphologically, the transition to high-grade disease (diffuse large B-cell lymphoma) is marked by dominance of neoplastic blasts in large sheets which are possibly also diffusely intermingled in the infiltrate. These features can be recognized in endoscopic biopsy samples and should be reported to guide the choice of therapy.

The transition from the antigen-dependent to the antigen-independent phase is much more difficult to recognize. Tumors that have progressed to the antigen-independent phase do not require antigen-mediated T-cell help to support the growth of malignant B-cells. Therefore, removal of the source of antigen in the form of bacterial eradication would not be enough to abolish tumor growth and reach remission in these cases. In a small series of patients (n=22), an increased number of neoplastic blasts (up to 10%) without overt sheets of neoplastic blasts, predicted a worse tumor response to therapy in a H. pylori eradication protocol. This suggests that this transition may indeed be morphologically defined.

Immunological and molecular prognostic factors

Many of the known prognostic factors in lymphoma are developed on a trial-and-error basis in large series of patients. Identification of the specific factors that are involved in the development and progression of specific lymphoma entities, however, may help to mark clinically relevant transitions in behavior and may prove to be more essential as prognostic markers. Since the different developmental stages from precursor stages to low-grade and into transformed phases can be recognized, MALT lymphoma is a highly suitable model for identifying these factors. Thus far, p53, bcl-6, c-myc and DCC have been implicated in the transition from low-grade to transformed disease. Recently, it has been suggested that bcl-10 may be involved in the transition into the antigen independent phase or that it may play a role in transformation. Further research will be needed to dissect the different factors that are involved in clinically relevant transitions. This knowledge may form the basis of the development of specifically tailored treatment protocols.

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Prognostic factors in diffuse large B-cell lymphoma

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Introduction

The late 1980s and 1990s have seen a significant increase in our understanding of the immune system and the biology of the non-Hodgkin’s lymphomas (NHL). The diversity of the diffuse large B-cell lymphomas (DLBCL) is more readily appreciated with the acceptance of the revised American European lymphoma (REAL) classification and the soon to be released World Health Organization (WHO) classification. A modified version of the diffuse aggressive B-lineage lymphomas, to include expected provisions to the WHO scheme, is shown in Table 1. Modern classification of NHLs is based on a synthesis of morphology, immunophenotypic findings, molecular genetic studies and cytogenetic features. In difficult cases ancillary studies may be required but at a minimum, the determination of lineage is mandatory. Clinically equivalent cases of peripheral T-cell lymphoma have a much worse prognosis than do DLBCLs.
A number of clinical variables are now well established as prognostic factors useful for predicting outcome in DLBCL. An international prognostic index score (IPI) has been developed that includes age, stage, serum lactate dehydrogenase, number of extranodal sites and performance status, assembled into a score between 0 and 5. Patients with a score of 4-5 do significantly worse than those with an IPI score of 0-1. Thus, the IPI score is a powerful predictor of survival in DLBCL but importantly, these clinical variables are surrogates that fail to define the underlying biologic heterogeneity of the DLBCLs. Pathologic or "biologic" variables have been sought to provide the correlates that underlie the clinical behavior of these lymphomas. The most useful of the pathological prognostic factors are those that contribute to the determination of prognosis beyond the information gleaned from an analysis of the clinical variables alone. Some of the well-characterized independent factors are listed in Table 2, together with their probable mechanism of action. What follows is a brief review of pathologic prognostic factors in DLBCL.

**Morphology**

DLBCLs can be divided morphologically into two principal subsets, centroblastic (large noncleaved) and immunoblastic lymphoma (IBL). Several difficulties arise with classification, in particular, no definitive diagnostic criteria exist to distinguish centroblastic lymphoma from IBL. In practice, many cases reveal a mixture of both cytologic types. Several studies have shown that there is poor interobserver reproducibility for distinguishing the cytologic subtypes of DLBCL. Nonetheless, recent studies suggest that B-cell IBL may have a more aggressive course. Of potential help for resolving this problem, objective criteria that may prove useful for distinguishing centroblastic lymphoma from IBL have been proposed. The postgerminatal center cell derivation of IBL has been used to show that immunoblasts have a characteristic immunophenotype based on the differential expression of Bcl-6, syndecan-1 (CD138) and Epstein-Barr virus (EBV)-related protein LMP-1 (latent membrane protein). IBL is typically Bcl-6 –/CD138+ /LMP-1 + in contrast to centroblasts which are Bcl-6+/CD138–/LMP-1 –. These immunophenotypic criteria are deserving of study in retrospective and prospective clinical trials.

T-cell rich B-cell lymphoma (TCRBCL) is a recognized variant of DLBCL. Recent observations suggest morphologic and phenotypic overlap with histiocytic-rich large B-cell lymphoma and a proposed common histogenesis with nodular lymphocyte-predominant Hodgkin’s disease. The poor prognosis of TCRBCL appears to be related to its propensity to involve the bone marrow, a well-established adverse prognostic factor. Bone marrow positivity is detected in as many as 50-60% of cases.

Discordant small cell lymphoma may be found in the bone marrow at the time of staging in approximately 5% of de novo DLBCL. Interestingly, this finding does not appear to have any impact upon prognosis. However, large B-cell lymphoma involving the marrow at diagnosis is associated with a worse prognosis, as is peripheral blood involvement.

Finally, mediastinal large B-cell lymphoma with sclerosis is included in the WHO classification as a recognized subtype of DLBCL. It is thought to arise from a normal B-cell resident in the thymus. Histological findings include a background of fine sclerosis and a tendency for the neoplastic large B-cells to have moderate amounts of clear cytoplasm. Clinically, this lymphoma shows a female predominance, relatively young age, high serum lactate dehydrogenase, bulky disease associated with superior vena cava syndrome and extension to intrathoracic, extranodal sites. Although still controversial, the majority of published reports suggest a favorable outcome compared with other DLBCLs.

**Bcl-2 expression and rearrangement**

The bcl-2 gene was discovered by virtue of its involvement in the reciprocal translocation, t(14;18), that characterizes the majority of cases of follicular lymphoma. This leads to the constitutive overexpression of normal Bcl-2, a protein found in a variety of tissues and cells throughout the body. Importantly, Bcl-2 protein is expressed in many lymphoproliferative disorders lacking a t(14;18) (i.e., bcl-2 gene rearrangement), in addition to many other cancers. The t(14;18) and its corresponding bcl-2 gene rearrangement can be found in 15-25% of de novo DLBCL cases. This is in contrast to Bcl-2 protein expression which is seen in approximately 25-50% of DLBCL, suggesting that mechanisms other than translocation can upregulate Bcl-2 expression in these lymphomas. Recently, gene amplification has been demonstrated as an alternate mechanism, which results in Bcl-2 overexpression in DLBCL and which appears to occur in cases specifically lacking evidence of a bcl-2 gene rearrangement.

The Bcl-2 protein is antiapoptotic and may interfere with a final, common cell death pathway, normally induced by either chemotherapy or radiation. Thus, lymphomas that overexpress Bcl-2 protein are likely to be relatively radiation- and drug-resistant and associated with treatment failure. Several recent studies have confirmed that the presence of a t(14;18) is not predictive of either overall or failure-free survival in patients with DLBCL, in contrast to Bcl-2 protein expression, which is an independent predictor of outcome in DLBCL. In several of these reports, some cases with a bcl-2 gene rearrangement failed to express Bcl-2 protein, presumably explained by mutations of the open reading frame of the translo-

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<thead>
<tr>
<th>Molecular defect</th>
<th>Marker</th>
<th>Biological principle</th>
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<tbody>
<tr>
<td>Apoptosis</td>
<td>Bcl-2 protein</td>
<td>Decreased apoptosis, relative chemoresistance</td>
</tr>
<tr>
<td>Cell cycle</td>
<td>p53, p21, p27, p16</td>
<td>Loss of growth control</td>
</tr>
<tr>
<td>Proliferative fraction</td>
<td>Ki-67, MIB-1</td>
<td>Increased cell division</td>
</tr>
<tr>
<td>Transcription factor</td>
<td>bcl-6 oncogene</td>
<td>??</td>
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<tr>
<td>Adhesion molecules</td>
<td>CD44, ICAM-1</td>
<td>Gain of mobile phenotype</td>
</tr>
<tr>
<td>Cytokines</td>
<td>TNF-receptor, IL-10</td>
<td>Autocrine loop leading to enhanced growth?</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>P-glycoprotein (mdr-1)</td>
<td>Gain of drug efflux pump</td>
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cated bcl-2 allele. This finding further underscores the lack of a relationship between the presence of the molecular rearrangement and the production of a functional protein. Several additional points regarding Bcl-2 are worthy of note. Expression of Bcl-2 protein is inversely related to proliferative activity in DLBCL, consistent with the hypothesis that Bcl-2 retards entry into the cell cycle. Firstly, these results are difficult to reconcile with the observation that increased mitotic activity is also associated with inferior outcome in DLBCL (see below). Secondly, extranodal DLBCLs have a much lower frequency of Bcl-2 positivity than equivalent nodal histology, a finding that may have an impact upon prognosis.

**Bcl-6 rearrangements**

The bcl-6 gene located on chromosome 3q27 encodes a transcriptional repressor normally expressed by B-cells of the germinal center. As normal B-lymphocytes exit the follicle, there is a commitment to differentiation that is associated with decreased expression of Bcl-6 protein. Therefore, Bcl-6 protein expression is a good marker of the germinal center. The observation that rearrangement of the bcl-6 gene on chromosome 3q27 was an important prognostic marker in DLBCL was initially reported in 1994. These authors described an association with extranodal disease and freedom from disease progression greater than 80% in a series of patients with DLBCL. However, others have been unable to confirm the prognostic significance of bcl-6 rearrangement. Furthermore, the authors of the original report have subsequently published findings suggesting an inverse relationship between bcl-6-gene rearrangement and the presence of additional markers of clonal cytogenetic evolution typically associated with a poor outcome in DLBCL. Thus, the prognostic significance of bcl-6-gene rearrangements in DLBCL remains unresolved.

Reciprocal rearrangements of 3q27 and the immunoglobulin (Ig) genes (14q32, 2p12, 2q11) are common but half of the bcl-6 translocations may involve other non-Ig loci. These latter cytogenetic rearrangements are less frequently detected with Southern blot analysis, creating a problem with false negative results. Of equal importance, bcl-6 gene rearrangements are commonly cryptic (subcytogenetic changes) and can be detected by Southern blot analysis even when the 3q27 breakpoint using routine cytogenetics does not appear to be involved. Thus, studies addressing the prognostic significance of the bcl-6 oncogene in DLBCL are better served by combining both molecular and cytogenetic data. A similar dichotomy exists for the bcl-6 gene and Bcl-6 protein as is seen with the bcl-2 oncogene: there is no clear relationship between the presence of the translocation and expression of the protein. A study to determine the independent prognostic impact of Bcl-6 protein expression in DLBCL has not been reported.

Cell cycle regulation

Mutations of the p53 gene are associated with many solid tumors and a number of lymphoid malignancies. For the indolent B-cell NHLs, p53 mutations are closely correlated with p53 protein expression. Additionally, transformation of follicular lymphoma to DLBCL is clearly linked to mutations in p53 and p16, the latter cell cycle protein which is located on chromosome 9p21 encodes a cyclin-dependent kinase. However, the story for DLBCLs is far less clear. P53 expression is frequently detected in de novo DLBCL without evidence of mutation, suggesting upregulation of wild-type p53 protein in these cases. Wild-type p53 is responsible for increasing the expression of another related protein called p21, a down-stream effector of p53 function normally involved in cell cycle control through the binding and inhibition of cyclin-dependent kinases. P53 mutations have been shown to predict outcome in DLBCL but the data for p53 protein expression are much less clear. A surrogate marker that may be of value for detecting p53 mutations is dual labeling for p53/p21. The cases with the phenotype p53+/p21— appear to be the cases with p53 mutations and an associated poor outcome. Other cell cycle regulatory proteins of potential interest include Mdm2, retinoblastoma protein, p16, p27 and cdc25b. Preliminary data suggests that some of these factors may have prognostic significance in DLBCL.

**Tumor cell proliferation**

There are conflicting reports regarding the effect of tumor cell proliferation on clinical outcome in DLBCL. Several methodologies have been used to assess the proliferation rate but more recent studies have utilized immunohistochemistry with either Ki-67 or the paraffin-equivalent, MIB-1. One study reported that a proliferation rate of >80% was associated with poor survival in previously untreated patients with aggressive NHLs, whereas another study found that patients who achieved a good response to treatment were less likely to relapse if they had a tumor cell proliferation of >80%. These data are in conflict and perhaps importantly, are also discordant with recent data concerning Bcl-2. Two studies have reported that Bcl-2 protein expression in DLBCL tends to correlate with a low proliferative index, a finding that is in agreement with preclinical models. Thus, the proliferation rate and Bcl-2 protein expression data are at odds with each other and would suggest that tumors with a low proliferation rate are less sensitive to chemotherapy than are rapidly proliferating tumors. Well-organized, multinational studies will be required to answer this question definitively.

**Adhesion molecules**

Few studies of adhesion molecule expression in DLBCL have been performed but hold promise to be useful predictors of outcome. Specifically, both CD44 and intercellular adhesion molecule-1 (ICAM-1) expression have been shown to correlate with disease dissemination and a poor outcome in DLBCL. Further studies of other patient cohorts and additional adhesion molecules will be of interest, as the development of certain primary extranodal NHLs may correlate with the expression of a specific marker profile.

Other factors have been considered as potential prognostic markers in DLBCL including major histocompatibility complex molecule expression, tumor-infiltrating lymphocytes, cytokine production by neoplastic large B-cells and drug resistance markers. However, more studies will be required before they can be established as significant predictors of outcome in DLBCL.

**Prognostic factors in mantle cell lymphoma**

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Definition and general characteristics

Mantle cell lymphoma (MCL) is a lymphoproliferative disorder, which is derived from a subset of naive pregerminal center cells, characterized by a proliferation of atypical lymphoid cells with a monoclonal B-cell phenotype and coexpression of CD5 (1, 2). Architecturally, MCL usually shows a diffuse or vaguely nodular lymphoid proliferation effacing the lymph node architecture. Transitional areas between nodular and diffuse patterns are common but, in rare cases, nodularity may be prominent and may lead to a misinterpretation as follicular lymphoma (3). A mantle zone pattern has been recognized in some tumors in which the atypical lymphoid cells expand the mantle cell area surrounding a reactive “naked” germinal center (4, 5). However, some nodules may be solid without evidence of residual germinal centers and may represent the malignant counterpart of primary follicles or, alternatively, a massive infiltration and obliteration of the original germinal center. Two cytological variants have been identified, typical and blastic. Typical cases show a monotonous proliferation of small to intermediate-sized lymphoid cells with rounded nuclei and scarce cytoplasm. Occasional cases may show a predominance of small lymphocytes with condensed chromatin and rounded nuclei and only rare cells with irregular or indented nuclei. Proliferative activity in typical cases may vary, but it is usually less than 1-2 mitoses per high power field. Blastic variants include a spectrum of intermediate to large cells with round or irregular nuclei and finely dispersed chromatin. Some cases may have pleomorphic nuclei and a more heterogeneous population of cells. Blastic variants have a higher proliferative activity and a more aggressive clinical evolution (2).

MCL is genetically characterized by 11q13 translocations and bcl-1 rearrangement (6, 7). This alteration leads to a constant overexpression of cyclin D1, which plays an important pathogenetic role, probably deregulating cell cycle control by overcoming the suppressor effect of retinoblastoma protein (Rb) and p27Kip1 (8-11). Detection of cyclin D1 may be used as a highly specific marker of MCL.

Different studies have analyzed the prognostic significance of a number of pathological, genetic, molecular and clinical parameters in MCL. 

Pathological parameters

Architectural pattern

Three different architectural patterns have been recognized in MCL: mantle zone, nodular and diffuse. Although identification of these patterns is important in the differential diagnosis of MCL, its prognostic value is controversial, due in part to the lack of clear definitions and the frequent presence of a mixture of these patterns in the same case. A mantle zone pattern has been associated with more frequent localized disease, a higher proportion of complete remissions and longer survival in some studies (17). However, the number of cases with this particular pattern has been very low in most series, precluding confirmation of these results (18-20). Moreover, in older series without detailed molecular or immunophenotypic confirmation, other types of B-cell lymphoma such as MALT lymphomas, may have been included. No clear differences in survival have been observed between cases with a nodular or diffuse pattern (19, 20), although a trend favoring improved survival for nodular cases has been seen (21).

Cytological variants

Different studies have shown that blastic morphology is clearly associated with poor prognosis in patients, with a median survival of 16-18 months, significantly shorter than the 50 months in patients with typical morphology (18, 20). These patients also have a poor response to therapy and usually fail to obtain complete remission. Blastic morphology is associated with other parameters associated with poor prognosis such as high proliferative activity (18), increased cytogenetic alterations (16) and molecular alterations in tumor suppressor genes (12, 13, 22).

Proliferative activity

Several studies have shown that an increased mitotic index is an important prognostic parameter. The exact mitotic index for which prognostic significance may be shown varies, but generally, a mitotic rate higher than 1.5-2.5 mitoses per high power field indicates a more aggressive course (18, 20). Differences between studies may be due to methodological aspects. Similarly, a high proliferative index, recognized by Ki-67/MIB-1 immunostaining, has also been associated with a poor prognosis (21, 23). In fact, mitotic index, S-phase detected by flow cytometry, and Ki-67 labeling are significantly associated in MCL (10). Interestingly, in multivariate analysis different prognostic parameters, including blast morphology, lose their significance whereas mitotic index remains an independent prognostic factor, indicating that it may be one of the most important predicting factors in these tumors (18). It will be necessary to determine the more appropriate and reproducible method to assess proliferation in these tumors.

Genetic parameters

Classic cytogenetic studies have identified additional chromosome abnormalities besides the 11q13 translocations in MCL. Tetraploid clones and aberrant karyotypes have been associated with blastic variants (24). However, these studies are limited and no correlation with the biological behavior of the tumors has been described. Two
recent studies using FISH (15) and comparative genomic hybridization (16) have indicated that the degree of karyotype complexity and the number of chromosomal gains in particular were associated with shorter survival of the patients. Interestingly, the prognostic significance of the number of chromosomal gains was also found when the survival analysis was restricted to patients with typical morphology. In addition, gains in chromosome 3q, 12q and losses in 9p were significantly associated with a shorter survival of the patients.

**Molecular parameters**

Different studies have analyzed the molecular alterations of MOL. Cyclin D1 expression levels are variable in different cases (8). Cyclin D1 plays an important role in the control of G1 phase by binding to CDK4 and 6. These complexes inactivate the suppressor effect of retinoblastoma on the cell cycle progression. However, the relationship between cyclin D1 expression levels and the proliferative activity of the tumors is not clear, suggesting that other mechanisms may be involved in the proliferative activity of MCL. p53 gene mutations and p16 inactivation have been associated with shortened survival of the patients but these alterations are also closely related to both blastic morphology and a high proliferative rate (12, 13, 25). Interestingly, alterations of these genes have been detected in occasional cases with typical morphology that showed a high proliferative activity and a short survival, similar to cases with blastic morphology (14, 25).

**Clinical parameters**

The main clinical parameters associated with poor prognosis in published series are advanced age (>65-70 years), poor performance status, advanced stage, splenomegaly, peripheral blood involvement, high lactate dehydrogenase and low albumin serum levels, bulky disease and anemia (2, 18, 20, 23). The International Prognostic Index has been found to be of prognostic value in some series (26, 27) but not in others (18, 28), probably because most of the patients fall into high-risk categories. Multivariate analysis including clinical and pathological parameters seem to indicate that proliferative activity and performance status of the patients may be independent prognostic factors.

In conclusion, MCL is an aggressive lymphoproliferative disorder with poor response to therapy, frequent relapses, and a short median survival. However, the range of survival may vary from less than 18 months to more than 50 months and a small group of patients may even show a relatively long survival. The parameters associated with this clinical evolution are not well known. Different studies suggest that blastic morphology, proliferative activity, genetic alterations in tumor suppressor genes and different genetic alterations are associated with the prognosis of the patients. The relative impact and independence of these parameters are not clear. Further cooperative studies including larger series of patients are needed for a better understanding of the mechanisms involved in the biological evolution of these tumors.

**References**