

## EDUCATION SESSION 5: NON-HODGKIN'S LYMPHOMA



# Biologic Prognostic Features in Non-Hodgkin's Lymphoma and Their Implications

*Bertrand Coiffier*

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of cancers, this heterogeneity resulting from the numerous histologic entities, the lymphoma's locations in nodal or extranodal sites, its capacity to remain localized or to disseminate throughout the body, and the patient's age and associated diseases. The prognostic implications of this heterogeneity must be known before therapeutic options are proposed and, as a result of the multiplicity of lymphoma entities and of the possible lymphoma manifestations, it is difficult to accurately predict the outcome of therapy in individual patients. Defining subgroups among large numbers of patients with histologically similar lymphomas and similar clinical manifestations is, however, likely to lead to identification of meaningful prognostic indicators.

The first prognostic factor corresponds to the histologic entity; among the different entities described in the REAL classification [1] or the WHO classification [2], response to treatment, time to progression, or survival do not have the same correlations [3]. Indolent lymphomas are characterized by their slowly increasing tumour burden, a good response to treatment but a rarity of complete responses, a longer survival, and their potential to transform into aggressive lymphoma. They comprise follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma, marginal zone lymphoma, and cutaneous T-cell lymphoma. Aggressive lymphomas are characterized by the converse characteristics: a rapidly growing tumour, the possibility to reach a CR, and a cure for some patients and a short survival for the others. They comprise diffuse large B-cell lymphoma (DLCL), peripheral T-cell lymphoma, anaplastic large cell lymphoma, Burkitt's lymphoma, and lymphoblastic lymphoma. Mantle cell lymphoma (MCL) is an indolent lymphoma by its clinical characteristics but it does not respond to currently available therapeutics and has a short survival.

Independently of the lymphoma entity, a variety of clinical and biological features has been identified as being associated with response to treatment and survival. The features that have most frequently been associated with the ability to achieve complete remission and with a long sur-

vival reflect the tumour's growth and invasive potential, the patient's response to the tumour, and the patient's ability to tolerate intensive therapy.

Parameters associated with large tumour mass and a poorer outcome are: high number of nodal sites, high number of extranodal sites, certain specific locations, large tumour diameter, disseminated stage, high serum LDH level and high  $\beta$ 2-microglobulin level. If disseminated stage is usually associated with a poor prognosis, it is somewhat difficult to apply to NHL because of the extranodal primary localizations and the weak correlation between extranodal involvement and outcome in some lymphoma subtypes. Disseminated stage seems to be the only parameter associated with a high risk of late relapse. A poor outcome has been associated with large tumours, but the cutoff to define "large" varies from 5 to 10 cm, depending on the study. Large tumours are thought to be associated with an increased risk of development of more aggressive clones of lymphoma cells, but this adverse risk factor often does not persist in multiparametric analyses.

Lymphoma cells may appear in any organ or lymph node. Although some of these extranodal sites are associated with a poorer outcome in retrospective studies, multiparametric analyses have always shown that poorer outcome was a function of the number of extranodal sites rather than secondary to a specific location. Patients with bone marrow involvement have a poorer outcome. However, bone marrow involvement is present in more than 70% of patients with FL, SLL, or MCL and, in these tumours, may not modify the prognosis. However, patients with Burkitt's lymphoma or lymphoblastic lymphoma and bone marrow involvement have a considerably worse prognosis. Only 20–25% of patients with DLCL have bone marrow involvement at the time of diagnosis but they have poorer responses to therapy and shorter survivals than those without bone marrow involvement. For DLCL patients, bone marrow infiltration was subdivided into infiltration by large cells, similar to those seen in the lymph nodes, and by small cells. Patients with DLCL and bone marrow infiltration with small cells have a higher risk of relapse but a longer sur-

vival than patients with large cell involvement.

Above normal levels of LDH have been identified as a prognostic factor in lymphoma patients in almost all published prognostic analyses. Moreover, the higher the LDH level, the poorer is the outcome. The adverse prognosis associated with a high  $\beta$ 2-microglobulin serum level was recognized in lymphoma patients years ago, but this parameter has not been widely used. The putative importance of the  $\beta$ 2-microglobulin level has been recognized and applied to prognostic analyses in several centers, and, like LDH level, it appears to be one of the parameters that predict the risk of relapse for patients.

The parameters associated with a patient's response to the tumour include B symptoms, performance status, serum albumin and haemoglobin levels, all of them well correlated. They probably reflect the same phenomenon, cytokine secretion by either tumour cells or the patient's immune cells in response to the tumour.

Outcomes for lymphoma patients may differ, depending on whether the patients have previously had diseases not related to the lymphoma and on their age at the time of diagnosis. In a Southwest Oncology Group study, older patients had worse outcomes because they responded less well to treatment and relapsed more often. This poorer outcome was related to a decrease in chemotherapy dose intensity. In other studies, more elderly patients were observed to die during the first courses of treatment, whereas those who responded did not have a higher relapse rate. It was then concluded that elderly patients are more likely to develop complications after chemotherapy because of their age and the possible existence of co-morbidities. The cut-off between young and old patients is between 60 and 65 years for patients with DLCL [4]. However, if the tolerance to the treatment decreases with age, it is not perfectly correlated to the numeric age but rather with physiologic age. In an international review, the oldest patients were predominantly female and had a poorer performance status but other main prognostic parameters such as stage, number of extranodal sites, or LDH level were not statistically different according to age distribution [5]. Bone marrow involvement was observed in only 19% of the youngest patients compared to 30–36% in older patients.

A number of investigators have used the subset of clinical features that retained independent significance in multivariate analysis of their patients to develop prognostic factor models predictive of an individual patient's risk of shortened survival. Although the specific clinical features used in the prognostic factor models differ, each model incorporates features that reflect the volume of disease and the extent of tumour involvement at diagnosis, confirming the primary importance of these factors. An international classification system was then developed. This International Prognostic Index (IPI) is based on age, tumour stage, serum LDH level, performance status, and number of extranodal disease sites, and renders it possible to identify four risk groups corresponding to the number of adverse parameters. In young patients an age-adjusted IPI based on

tumour stage, serum LDH level, and performance status also identified four risk groups. In both models, the increased risk of death was the result of both a lower rate of complete responses and a higher rate of relapses. The IPI may also be effectively applied to patients presenting with lymphoma subtypes other than DLCL [3, 6]. The IPI and the age-adjusted IPI have proven significantly more accurate than the Ann Arbor classification in predicting long-term survival.

Since the serum  $\beta$ 2-microglobulin level was measured in only a few centres for patients included in the IPI project, the IPI could not incorporate this important prognostic indicator. However, the MD Anderson Cancer Center team has developed models that included  $\beta$ 2-microglobulin level and other important parameters [7], and proposed an index based on LDH and  $\beta$ 2-microglobulin level that has proven helpful in distinguishing between good-risk and poor-risk patients, regardless of their lymphoma subtype.

The IPI incorporates in its definition only surrogate markers of profound alterations of the cellular biology of tumour cells, particularly the mechanisms involved in the control of mitosis or of the host response machinery to the cancer. Since the time of its description, and in the future, biological or genetic alterations have been, and will be, described that may replace all or some of the classical parameters [8]. These putative parameters include gene alterations of cell-cycle regulator proteins (bcl-2, p53, Rb, p16, p21), cytokines (TNF, IL-6), adhesion molecules (CD44, ICAM-1), angiogenic peptides (VEGF), and transmission factor expression.

## References

1. Harris NL, Jaffe ES, Stein H, et al: A revised European-American Classification of Lymphoid neoplasms. A proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361-1392.
2. Jaffe ES, Harris NL, Diebold J, Muller-Hermelink HK: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: A progress report. *Amer J Clin Pathol* 1999;110:s8.
3. The Non-Hodgkin's Lymphoma Classification Project: A clinical trial of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 1997;89:3909-3918.
4. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993;329:987-994.
5. The Non-Hodgkin's Lymphoma Classification Project: Effect of age on the characteristics and clinical behavior of non-Hodgkin's lymphoma patients. *Ann Oncol* 1997;8:973-978.
6. Bastion Y, Coiffier B: Is the International Prognostic Index for aggressive lymphoma patients useful for follicular lymphoma patients? *J Clin Oncol* 1994;12:1340-1342.
7. Swan F, Velasquez WS, Tucker S, Redman JR, Rodriguez MA, McLaughlin P, Hagamaister FB, Cabanillas F: A new serologic staging system for large-cell lymphomas based on initial  $\beta$ 2-microglobulin and lactate dehydrogenase levels. *J Clin Oncol* 1989;7:1518-1527.
8. Salles G: Towards new prognostic factors in diffuse large cell non-Hodgkin's lymphoma. *Ann Oncol* 1996;7:993-996.