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Malignant lymphomas: prognostic factors and treatment

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Non-Hodgkin's lymphomas (NHL) represent a heterogeneous group of lymphoid neoplasms, most of them (85 % of cases) deriving from mature B cells and in a minority of cases from T cells. In 1994, the Revised European-American Lymphoma (REAL) classification based on morphologic, immunophenotypic, genetic and clinical characteristics has been proposed. This system was further modified as now universally accepted World Health Organization (WHO) classification. Among B-cell NHL, the most frequent subtype (30 %) is diffuse large B-cell lymphoma (DLBCL), followed by follicular lymphoma, FL (22 %).

Hodgkin's lymphoma (HL) accounts for 14 % of all lymphomas. The WHO classification includes two HL categories: classical HL (nodular sclerosis, lymphocyte-rich classical, mixed cellularity, and lymphocyte depletion HL), and nodular lymphocyte predominant HL.

The new diagnostic tools for the pathologic study of lymphomas (immunophenotyping, PCR, FISH, gene expression profiling) have permitted more precise disease definition and recognition of factors predicting prognosis. B-cell NHLs are clinically divided into: indolent, aggressive, and very aggressive (Table 1). However, even within histologic subgroups, patients can vary considerably with regard to outcome. The International Prognostic Index (IPI), based on age, performance status (PS), serum lactate dehydrogenase (LDH) level, number of extranodal sites and stage, is able to separate DLBCLs into four clinically distinct groups, with percentages of patients surviving at 5 years ranging from 73 % for the low-risk to 26 % for the high risk subgroup. More recently, a similar prognostic index has been developed for FLs, based on age, LDH, stage, Hb level, and number of nodal areas involved (the FLIPI score). With this prognostic system, FL patients can be stratified into three risk groups, with 10-year survivals of 70 % (low risk), 51 (intermediate risk), and 35 % (high risk).

Therapy of lymphomas strictly depends on a careful risk assessment at diagnosis. Before starting treatment, clinicians should obtain the most precise histological and biological definition of the disease, assess its extension (staging) by pathological and imaging procedures (ultrasonography, CT-scan, PET), and take into account PS and age. New classification schemes based on genetics and biology provide the opportunity to develop disease- and even patient-specific therapies, utilizing more targeted approaches.

In indolent NHL, treatment programs range from "watch and wait" to stem cell transplantation (SCT). A watchful waiting policy may be adopted in elderly patients with asymptomatic disease and low tumor burden. Involved field radiotherapy (IFRT) is the appropriate treatment for the rare cases with localized disease. In patients with advanced stage indolent NHL, chemotherapy (CHT) combined with the anti-CD20 monoclonal antibody rituximab is the recommended treatment. Autologous SCT incorporating a purging in vivo with rituximab is an appropriate approach for relapsed/refractory patients. As a graft-versus-lymphoma effect is operative in FL, reduced-intensity allogeneic SCT may be effective in selected cases. Treatment with radio-immunoconjugates is a further evolution of antibody-based therapy.

As regards aggressive NHLs, patients with localized disease may benefit from brief anthracycline-containing CHT followed by IFRT. For all DLBCL patients, the combination of standard CHT with rituximab (R-CHOP regimen) improves response rate and survival. High risk patients may benefit from intensified therapy with autologous SCT. The role of allogeneic SCT is being evaluated in experimental trials.

Also in HL the primary treatment is risk-adapted by stage, systemic symptoms, elevated ESR and local tumor burden > 10 cm ("bulky disease"). Therapy of early stages and standard risk advanced stages is mainly based on CHT (e.g. three to eight ABVD regimen) +/- IFRT. Patients with high risk advanced stages may benefit from intensified regimens such as the escalated BEACOPP. In patients with HL not cured with standard CHT and RT, high dose CHT plus autologous SCT should be offered.

Standardized criteria for assessment of response, incorporating PET scan imaging, are used to evaluate results of treatment.

Table 1. Revised European-American Lymphoma (REAL) Classification: B-Cell Neoplasms		
Indolent	Aggressive	Very Aggressive
B-cell chronic lymphocytic leukemia/ small lymphocytic lymphoma	Prolymphocytic leukemia	Precursor B-lymphoblastic lymphoma/leukemia
Lymphoplasmacytic lymphoma	Plasmacytoma/ Multiple myeloma	Burkitt's lymphoma /B-cell acute leukemia
Hairy cell leukemia	Mantle cell Lymphoma	Plasma cell leukemia
Splenic marginal zone lymphoma	Follicle center lymphoma, follicular, grade III	
Marginal zone B-cell lymphoma	Diffuse large cell lymphoma	
- Extranodal (MALT) - Nodal	Primary mediastinal large B-cell lymphoma	
Follicle center lymphoma, follicular, grade I-II	High-grade B-cell lymphoma/Burkitt's-like	

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