

Editorial

The lymphomas in 1998: from cell biology to therapy

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Introduction

Lymphoproliferative disorders are a very heterogeneous group of neoplastic diseases, which originate from malignant transformation of cells of the lymphoid system. Within broad limits, they include at least four main types of diseases: Hodgkin's disease, the so-called non-Hodgkin's lymphomas, the chronic lymphoid leukemias and the neoplasms of mature B antibody-producing cells, such as Waldenström macroglobulinemia and multiple myeloma. Although many exceptions are recognized, the great variability of biological characteristics and clinical expression of lymphoproliferative disorders can be related to maturation arrests at different specific points in the normal ontogenic process of immunocompetent cells. Correlation of markers characteristics of malignant lymphocytes with those of normal cells is thus important for purposes of classification and can aid in diagnosis and prognosis. The complex nosology of lymphoproliferative disorders, moreover, does in fact tend to group diseases of similar clinical behavior, proliferative potential, preferential sites of involvement, natural history and response to therapy.

The great majority of lymphoproliferative disorders encountered in the clinical practice are derived from B or T cells, most frequently at mature stages of their differentiation. The clinical characteristics of all these lymphomas demonstrate a wide range. Lymphomas with a follicular (or nodular) histological pattern of growth have a "low-grade" clinical behavior,

acting as though their primary physiopathology involves the persistence of long-lived cells, rather than a proliferation of activated cells. The diffuse large cell and immunoblastic B-cell lymphomas, on the other hand, have an intermediate to "high grade" pattern of growth and spread, corresponding to a high turnover rate and shorter cell cycle time. These different scenarios begin in the last years to be partly explained on the basis of functional cell characteristics, such as¹ their activation manifested by the production of cytokines and growth factors by the cells themselves and by the appearance on the cell surface of growth factor receptors and² the presence of adhesion molecules on the cell surface membrane. The expression of such integrins has been postulated to explain, for instance, the tendency to lymph node homing in well-differentiated lymphocytic lymphoma, as compared to its leukemic counterpart, chronic lymphocytic leukemia.

Hodgkin's disease

Hodgkin's disease, firstly described by Thomas Hodgkin in 1832, is a unique malignancy that has become a prototype for curable neoplasms. From the point of view of pathology, Hodgkin's disease has classically been divided into four types: lymphocyte predominance, nodular sclerosis, mixed cellularity and lymphocyte depletion. The nodular sclerosis type constitutes 70-80% of cases of Hodgkin's disease and classically presents in young

women with mediastinal and cervical node disease. Mixed cellularity disease, on the other hand, occurs predominantly in older males and is more commonly widespread. Recent studies suggest that the lymphocyte predominance Hodgkin's disease is a clinically distinct B cell lymphoma, often presenting with isolated enlargement of a peripheral lymph node.

Unlike most other human tumors, the nature of the malignant cell in Hodgkin's disease, the Reed-Sternberg (RS) cell, remains controversial. *In vitro* studies indicate that it is an end-stage, non-proliferating cell, and that the most proliferative or clonogenic cell is a small, less conspicuous mononuclear cell. The proportion of RS and their mononuclear variants in affected tissues correspond to the clinical grade of malignancy. The expression of the CD30 antigen on RS cell support the hypothesis that they are derived from activated lymphocytes. According to the most recent reports, T-lymphocyte origin is suggested at least for some cases of nodular sclerosis and mixed cellularity Hodgkin's disease, while a B-lymphocyte origin is likely in nodular lymphocyte predominance, which in many cases seems to arise in progressively transformed germinal centers.

Treatment modalities are well-defined for Hodgkin's disease. Patients with early stage disease (non-bulky stage I and IIA) are managed with radiotherapy. Treatment confined to the involved area is sometimes used for localised lymphocyte predominant disease. The remaining cases receive at least mantle or inverted Y radiotherapy, resulting in cure in 60-70% of cases. Patients with more extensive or symptomatic disease and those for whom initial radiotherapy fails receive combination chemotherapy. About two thirds of patients receiving chemotherapy will remain permanently free of disease as a result of this treatment. At the time of relapse, treatment may comprise further chemotherapy or high dose chemotherapy with bone marrow or peripheral blood stem cell transplant as a rescue. Long term studies suggest that the overall cure rates for Hodgkin's disease are stable at 70-80%, although it is hoped that high dose chemotherapy may improve these figures. Late toxicity, such as particularly secondary tumors, myelodysplastic syndromes and acute leukemia, remains a problem for patients that have been treated with wide field radiothera-

py or chemotherapy. Patients with early stage disease are increasingly being managed with limited radiation fields combined with brief courses of chemotherapy in an attempt to avoid this complication. Even in patients with advanced-stage diseases, recent trials have shown that new alternating regimen protocols provide superior failure-free survival, with greater acute toxicity but significantly fewer secondary malignancies.

Non-Hodgkin's lymphomas

Non-Hodgkin's lymphomas arise from malignant transformation of B lymphocytes in 85% of cases and T cells in most of the rest. Histopathologically, these disorders comprise an admixture of clonal malignant cells with variable amount of reactive lymphoid cells and stroma. All classifications of non-Hodgkin's lymphomas rely on the distinction of cytological types of neoplastic cells, based on nuclear and cytoplasmic characteristics, as well on the proposed relationship of these cell types with normal counterparts in the lymphoid tissue. The Rappaport classification was introduced in 1956 as an alternative to the old subdivision into lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma. In this classification lymphomas are subdivided into two main groups, nodular and diffuse, with well-differentiated and poorly differentiated lymphocytic, mixed and histiocytic varieties. This classification scheme has been largely superseded, as rapid developments in immunology have allowed a combined morphologic-immunophenotypic definition of lymphoma (so-called Kiel classification and Lukes-Collins classification): these proposals recognize the presence of separate B and T lineage lymphomas and the existence of low-grade and high-grade clinical types. The Working Formulation is the result of an international multi-institutional clinicopathologic study, proposed in 1982 as a common basis for comparison of data obtained in clinicopathologic studies. It has been criticized for excluding immunophenotypic considerations, but its categories represent clinicopathologic entities well recognized by clinicians. Very recently a new Revised European-American classification of Lymphomas (so-called REAL classification) has been published. It includes a number of new clinicopathologic enti-

ties and incorporates clinical features and immunohistochemistry in the diagnostic process. It must now be tested by the broad community of pathologists and clinicians.

The management of non-Hodgkin's lymphomas is less defined and depends on histologic type as well as on clinical characteristics. In low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia treatment is generally adjusted to the natural course of the disease. Cure can be rarely achieved, and the median overall survival in most series is five to eight years. Prognosis relates to age (poorer when older) and particularly to the extent of disease judged in terms of bulk of tumor. Patients who are well with non-threatening disease may initially be watched without treatment, in occasions for many years. Initial treatment, when needed, generally comprises an alkylating agent – usually intermittent chlorambucil – with or without steroids for four to six months and will often be highly successful in causing disease regression; relapse is, however, inevitable. Intermediate grade non-Hodgkin's lymphomas, on the other hand, are curable cancers in about 40% of cases. The standard chemotherapy for these forms is a combination of cyclofosamide, doxorubicin, vincristine, and prednisolone (CHOP regimen), sometimes supplemented by radiotherapy. High grade lymphomas are rare (less than 5%) and includes rapidly progressive cancers of children and young adults. Treatment is required urgently with intensive combination chemotherapy.

Extra-nodal lymphomas or maltomas (mucosal associated lymphoid tumors) were first described about 15 years ago. These are indolent lymphomas that arise most commonly in the stomach, thyroid, parotid, and lung. They often evolve from a pre-existing inflammatory or autoimmune disease (for example, gastritis related to *Helicobacter pylori* or Sjögren's syndrome). These tumors have been successfully managed with local resection or radiotherapy or both. There is, however, increasing evidence suggesting that gastric maltoma can be controlled or cured by use of appropriate antibiotics, a highly unusual example of malignant regression by treatment of infection. The maltomas can progress to intermediate grade tumors. In addition, they can metastasise, usually to the other maltoma sites described above.

Promising new treatments for lymphomas are being evaluated. They include high dose chemotherapy with stem cell rescue, new chemotherapeutic agents, like fludarabine, treatment with monoclonal antibodies directed against B cell antigens, antisense nucleotides and idiotype vaccines.

High-dose therapy with autologous stem cell rescue is the standard of care for relapsed intermediate and high-grade non-Hodgkin's lymphomas, but its role in low-grade lymphomas is still to be proven. Preliminary results support the possibility of prolonged remission following high-dose therapy, but the potential for prolonged survival or cure remains uncertain.

Monoclonal antibodies can be used alone or coupled to a toxin or to a therapeutic dose of a radioisotope and can target the malignant lymphoid cell. Among these monoclonal antibodies, rituximab is a molecularly synthesized chimeric monoclonal antibody which recognizes the CD20 antigen expressed on normal B cells and more than 90% of malignant B-cell lymphomas. Based on results of the first clinical phase III trials (minimal toxicity with a single agent response rate approximating 50%), rituximab was approved in USA in 1997 for use of patients with recurrent low-grade or follicular lymphomas. Preclinical trials have suggested a synergy between the antibody and several cytotoxic agents, including doxorubicin, cis-platinum, and etoposide.

Antisense nucleotides are short, single-stranded DNA molecules that bind to the "sense" RNA message and are used to block production of the *bcl2* gene at the transcription level. Overexpression of *bcl2* is an important part of the malignant transformation that leads to some non-Hodgkin's lymphomas and may decrease the efficacy of therapies that induce apoptosis. The strategy of this oncogene block has already shown clinical efficacy.

Finally, since the immunoglobulin molecule is expressed as a unique receptor on clonal B-cell malignancies, it can serve as a tumor-specific antigen for immunotherapy. The tumor-specific variable regions of these immunoglobulins are called the idiotype. An adjuvant idiotype vaccine approach is now pioneered in the hope of inducing antitumor immune responses.

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