The 9th Conference on Health Care of the Chinese in North America

Treatment of Lymphoma, American Perspective

Peter J. Rosen, MD, Professor of Clinical Medicine, University of California, Los Angeles

---

Abstract

In recent years there has been an unprecedented increase in the incidence of non-Hodgkin's lymphoma in Western societies which cannot be completely accounted for by the association with HIV lymphomas. The predominant histologies have been follicular lymphoma and diffuse large cell lymphoma. No certain etiologic link is known though speculations abound regarding environmental and infectious factors. At the same time, much progress has been made in the classification and treatment of lymphomas.

Prior classifications of nonHodgkin's lymphoma have suffered because of their total reliance on cytologic and architectural patterns. With the recent revolution in cytogenetics, molecular pathology and immunology, a rational clinical/pathologic classification based on syndrome and pathogenesis is feasible. Recently the REAL and WHO have evolved a treatment classification which takes into account these new biologic factors and clinical presentation, which allows closer collaboration between clinician and pathologist aiding the clinician in treatment planning. It is hoped that these syndrome-based classifications will enable more reproducible diagnosis and treatment assessments.

In the United States and Western countries, B lineage lymphomas predominate with T cell lymphomas making up between 15-20% of cases. In Asian countries the percentage of T cell lymphomas is much higher based in part on the prevalence in some areas of ATLL (HTLV-1 associated leukemia-lymphoma), T/NK nasal lymphoma, AILD lymphomas, and other T cell types.

The management of the low grade lymphomas, which include the follicular lymphoma group, marginal zone lymphomas, small cell lymphocytic lymphomas, and mantle cell lymphomas, continues to be troublesome. Although most of these illnesses have relatively indolent courses, cure has been elusive. Reports of long term remissions utilizing stem cell transplantation have been observed, but there is as yet insufficient data to state that a cure has been achieved. The advent of monoclonal antibody therapy has led to the recent approval by the FDA of a CD20 antibody (Rituxan) for use in relapsed follicular lymphomas. This promising treatment opens up a whole new era of biologic therapies and approaches for the low grade lymphoma group, which will hopefully improve overall outcome. It is yet far too early to assess the eventual impact of this treatment. Nevertheless, it is already apparent that approximately 50% of patients with relapsed follicular lymphoma enter partial or complete response utilizing this treatment approach. Furthermore, preliminary data suggest that combinations of chemotherapy and monoclonal antibody therapy may achieve molecular remissions, which have been uncommonly seen with chemotherapy alone. Whether these molecular remissions will lead to improved survival remains to be

seen. Mantle cell lymphoma, a relatively uncommon type of low grade lymphoma, represents a difficult challenge, since all forms of therapy to date have proven unsuccessful in producing durable remissions. Despite its categorization as a low grade lymphoma, the biologic behavior is much more aggressive with average survival under four years in most series. Cytogenetic translocations have characterized some of the low grade lymphoma entities. The translocation (t14;18) is observed in the follicular lymphoma group in as many as 8590% of cases. This translocation juxtaposes the heavy chain gene on chromosome 14 with a gene encoding the bcl-2 protein on chromosome 18. bcl-2 protein appears to abrogate apoptosis, or program med cell death; and thus this lymphoma may be thought of as an accumulation of cells that fail to undergo natural death. This paradigm suggests that some forms of cancer may be as much a problem in the lack of death as in proliferation. On the other hand, the mantle cell lymphomas are usually associated with the translocation (t11;14). In this instance the heavy chain locus is juxtaposed to a gene, bcl-1, which encodes a cyclin D1 kinase involved directly in cell proliferation.

In the case of the intermediate/high grade non-Hodgkin's lymphomas, much more progress has been made in treatment over the last two decades. For example, localized presentations of intermediate grade non-Hodgkin's lymphoma (non bulky Stage I-II) can be cured in roughly 80% of cases with combined chemotherapy and radiation. A relatively short course of CHOP chemotherapy (3 cycles) combined with involved field radiation therapy can achieve such results with minimal morbidity. For the more generalized presentations of the intermediate and high grade lymphomas (Stage III-IV), CHOP therapy will cure between 30-40% of cases. Those patients who relapse can be salvaged approximately 20-40% of the time with high dose chemotherapy and autologous stem cell transplantation. In these lymphomas the possible contribution of antibody therapy is less clear though responses can be seen. Further studies are necessary to show an adjuvant effect.

Although the T cell lymphomas are less commonly seen in Western societies, the WHO and REAL classifications clearly delineate the unusual natural histories of this complex group. Current strategies for the treatment of the T cell lymphomas are less straightforward than for the B cell counterparts. As a rule T cell lymphomas appear to behave in a more aggressive fashion than the B cell lymphomas and the durability of responses to standard chemotherapy programs appears less. Clearly much work needs to be done in our understanding and treatment of this group of disorders.

It is evident that the rapid evolution in biologic understanding of the lymphomas is already paying dividends in the management and treatment of these disorders. It is not far-fetched to believe that in the next two or three decades a series of observations and treatments will become available, which will totally revolutionize the management of these conditions. It is hoped that this progress will obviate the need for toxic therapies, which have had such a disruptive effect on the lives of patients.