The past 20 years have brought significant advances in our ability to manage patients with non-Hodgkin’s lymphoma. More precise classification systems, improvements in diagnosis and staging, and effective new treatments have improved outcomes and made cure a reasonable goal for many patients with these disorders.

From a clinical perspective, the major changes in the management of lymphomas over the past 20 years have been based on increased understanding of these diseases at the biologic level, evolving staging and restaging techniques such as functional imaging, and the emergence of new treatment modalities, particularly monoclonal antibodies and stem cell transplantation. These changes are expertly summarized by Dr. Armitage and colleagues in the accompanying article.

Disease entities have been defined and redefined. The present World Health Organization (WHO) classification is a “work in progress” based on a growing understanding of lymphocyte biology at the cellular and molecular levels. The introduction of gene-expression profiling and tissue microarrays has enhanced this understanding, and data from these techniques are being used diagnostically and for predicting outcome. Although used primarily in the context of clinical trials at the moment, information on the cell of origin in diffuse large B-cell lymphoma (DLBCL) is now becoming a part of routine diagnostic work-up. Many subtypes of lymphoma that were not recognized in the 1980s are included in the WHO classification.

Staging and Treatment
Staging techniques have been refined and improved over this 20-year period. These have included improvements in the sensitivity of routine radiologic techniques such as computed tomography (CT) scanning, and the development of highly sensitive methods for detecting very low levels of lymphomatous involvement of some tissues, including the use of flow cytometry, molecular methods such as polymerase chain reaction (PCR), and fluorescence in situ hybridization (FISH). The advent of functional imaging techniques such as [18-F]-fluorodeoxyglucose positron-emission tomography (FDG-PET), both for initial staging and for restaging, is still under evaluation but is already in widespread use and is changing the paradigm for staging and response assessment.

The effectiveness of new treatments for lymphoma must be assessed against the backdrop of these changes in diagnosis and staging. There is no doubt, for example, that patients entered into studies of diffuse aggressive lymphomas in the mid- to late-1980s represent a much more pathologically heterogeneous group than those included in trials of DLBCL in the past 5 years. These studies included patients with aggressive peripheral T-cell lymphomas—a disease now known to have a worse prognosis than DLBCL. Similarly, the changes in staging techniques mentioned above have almost certainly resulted in a major “stage migration” effect. Studies of “limited-stage” non-Hodgkin’s lymphoma (NHL) performed in recent years likely include a different and probably more favorable patient population than those included in such trials in the 1980s.

Improvements in Outcome
Apparent improvements in outcome for patients with NHL over the past 20 years must therefore be evaluated in the context of changing diagnostic and staging criteria and the resulting patient selection. Despite these factors, recent data suggest that survival for patients with some types of NHL has improved over the past 20 years. This is especially true for DLBCL and low-grade follicular lymphoma.[1,2]

Although the methodology of these studies is imperfect, they provide provocative data suggesting that the natural history of some NHL subtypes has changed. Although changes in chemotherapy and supportive care may have had some impact, this improvement has probably been largely due to the introduction of the monoclonal antibody rituximab (Rituxan) for the treatment of B-cell NHL. Almost
every randomized study comparing combination chemotherapy alone with the same combination plus rituximab has shown improvements in response rates, progression-free survival, and in some cases, overall survival associated with the rituximab-containing arm.

Looking Ahead
Armitage et al provide a comprehensive review of the evolution of diagnostic and treatment approaches to NHL over the past 20 years. Their review also poses some important questions for the early part of the 21st century. As they point out, the current data regarding gene-expression profiling and tissue microarrays are derived from patients treated with CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) or similar chemotherapy, before the widespread use of rituximab. Many studies have demonstrated that biologic risk factors in NHL are, to some extent, treatment-dependent, and that those factors predictive of outcome at diagnosis may have no prognostic significance in the relapse setting. New studies of gene-expression profiling and tissue microarrays are now underway using material from patients treated with rituximab and will be important in future trial stratification.

The authors also make the point that approaches using hematopoietic stem cell transplantation need to be further evaluated, especially in light of improvements in first-line treatment strategies. Patients who suffer relapses after these regimens may prove more difficult to “salvage” with transplant approaches.

The article concludes by looking forward hopefully to the next 20 years. This is an exciting time for those of us involved in the treatment of lymphomas. The buzz phrase in lymphoma management in the mid-1980s was probably “dose intensity,” which turned out to be a disappointing approach. In the early 2000s, the buzz phrase has become “rational therapeutic targets.” Many potential new targets have been identified in recent years using immunohistochemistry, gene-expression profiling, and other molecular techniques. These targets include CD40, mammalian target of rapamycin (mTOR), histone deacetylase, proteasomes, Aurora kinase, and protein kinase C-beta (PKC-β). Early clinical trials of drugs targeting these molecules are ongoing. The incorporation of biologic end points into clinical trials of these new agents to confirm their mechanism of action represents a further move from empiric to rational therapy. As Armitage et al suggest, the outlook for lymphoma patients over the coming 20 years is likely to improve dramatically.

Hodgkin’s Lymphoma
Although not mentioned by Dr. Armitage and colleagues, changes in the management of Hodgkin’s lymphoma over the same period have also been remarkable. The nature of the Hodgkin’s Reed-Sternberg (H-RS) cell is now much more clearly understood. Staging laparotomy, still widely used in the mid-1980s, has been abandoned after randomized trials showed that it did not provide a survival advantage. The recognition of the late toxicities of alkylating agent chemotherapy and extensive radiation therapy fields have resulted in the increasing use of anthracycline-based chemotherapy regimens with diminishing radiation fields and doses. These changes have resulted in improved survival for these patients with substantially lower rates of late toxicity and treatment-related mortality.

As with NHL, gene-expression profiling and other molecular studies may yet uncover new therapeutic targets in this disease. We can look forward to the 2026 edition of ONCOLOGY with excitement and optimism for patients with malignant lymphoma.

—John W. Sweetenham, MD

Disclosures:
The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:
