B-Cell Non-Hodgkin Lymphoma: Targeting in on the Future

B-cell non-Hodgkin lymphoma (B-cell NHL) is composed of a heterogeneous group of clonal lymphoproliferative disorders. According to the 2008 World Health Organization classification of lymphomas, this group includes more than 30 different disease subtypes.

Approximately 70,000 patients with NHL are diagnosed annually in the United States, with approximately 85% of these originating from B cells. Thirty years ago, the Working Formulation Classification stratified lymphomas into three categories based on clinical outcomes: low, intermediate, and high grade. While this approach has been helpful in determining prognosis and guiding treatment decisions, several advances have been made in molecular biology and genetics that have brought about significant changes in the classification and prognostication of lymphomas. In addition, novel treatments have been introduced that have changed our approach to B-cell NHL and have altered the prognosis in several subtypes of this disease. This issue of Cancer Control highlights many of these updates in the molecular pathogenesis and management of B-cell NHL, with a particular focus on targeted therapies.

In the first article, Dr Ayala focuses on treatment of B-cell NHL with hematopoietic cell transplantation (HCT). Most patients with B-cell NHL can be managed with conventional doses of chemotherapy and immunotherapy. However, selected patients with relapsed or refractory disease can benefit from high-dose chemotherapy followed by hematopoietic cell rescue. A recent report suggested that approximately 5,000 lymphoma patients are treated with HCT in North America annually. Thus, the evolving role of autologous HCT in distinct subtypes of B-cell NHL is the focus of this timely article, as well as indications for allogeneic transplantation.

The next article, by Dr Bello and colleagues, is devoted to follicular lymphoma (FL). Low-grade FL is the most common indolent B-cell NHL worldwide, with a median overall survival of approximately 10 years. Significantly more aggressive biological behavior is observed in FL grade 3, which is usually managed as an intermediate-grade B-cell NHL. Currently, the treatment of FL remains highly individualized and is based on clinical judgment. However, newer prognostic systems and tests, including gene expression profiling and next-generation sequencing, may help guide treatment decisions in the future. The US Food and Drug Administration (FDA) has approved the use of several effective therapeutic agents for FL over the past 15 years, including rituximab, yttrium-90 ibritumomab tiuxetan, iodine-131 tositumomab, and bendamustine. Recently, a new generation of small inhibitor molecules and monoclonal antibodies demonstrated promising efficacy in clinical trials. These include CAL-101, a p110-delta selective phosphatidylinositol-3-kinase inhibitor, as well as epratuzumab (anti-CD22), GA101 (anti-CD20), and MEDI-551 (anti-CD19). The authors discuss in detail the mechanism of action of these novel agents, as well as the results of clinical studies evaluating their effectiveness.

Dr Tombleson and coauthors provide a thorough report on their experience with bendamustine, with a main focus on management and prevention of infusion-related reactions. In the 4 years since this rediscovered drug was approved for B-cell NHL in the United States, bendamustine has become an important part of the frontline armamentarium. It is currently under investigation in various types of hematologic and nonhematologic malignancies. Thus, understanding the infusion-related reactions associated with bendamustine therapy is critical in our treatment of patients with B-cell NHL.

Another exciting field of research for the treatment of B-cell NHL, both indolent and aggressive, is radiomunotherapy (RIT). The two RIT agents approved by the FDA for the treatment of NHL are yttrium-90 (90Y)-ibritumomab tiuxetan and iodine-131 (131I)-tositumomab. These sophisticated and potent targeted therapies have been shown to improve outcomes for patients with low-grade FL. Although initially available only in larger centers, RIT is now becoming a more commonly available treatment. Dr Tomblyn reviews the evidence behind these indications for the approved RIT agents.

The most common type of NHL in the United States is diffuse large B-cell lymphoma (DLBCL). Drs Cultrera and Dalia discuss the most important steps that led to the use of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) as the gold standard for the treatment of DLBCL. The successful introduction of the anti-CD20 monoclonal antibody rituximab was an important breakthrough in the therapy of B-cell NHL. This ushered malignant hematology into a new era of research focused on targeted therapy. Newer monoclonal antibodies such as obinutuzumab, veltuzumab, epratuzumab, and blinatumomab have shown efficacy in clinical studies in the treatment of DLBCL. In addition, the role of agents that modulate the tumor microenvironment is discussed as another promising area of targeted therapy.

The past decade has produced several advances in the diagnosis and molecular stratification of different
NHL subtypes. In the next article, Dr Perry and colleagues from the internationally recognized Lymphoma and Leukemia Research Center at the University of Nebraska discuss new molecular tests, with a particular focus on the subclassification of DLBCL. While the clinical relevance of these new molecular tests is not clear, it does appear that we are getting closer to a better understanding of how to use these tests to guide our treatments.

We then turn our attention to a less common type of NHL, mantle cell lymphoma (MCL). Dr Shah and coworkers provide a thorough description of this NHL as a “protean” condition. This term refers to the Greek god Proteus, known for being able to change shapes. This is a suitable adjective for an NHL type that has features of both low-grade and aggressive lymphomas. The authors discuss the current recommendations on the management of MCL with regard to patient age and performance status. They also discuss promising novel agents in the field.

Finally, Dr Sokol and coauthors provide an excellent review of primary cutaneous B-cell lymphoma (PCBCL), a heterogeneous group of rare clonal B-cell lymphoproliferative disorders. By definition, this category involves the skin but lacks any evidence of extracutaneous involvement at the time of diagnosis. Low-grade primary cutaneous NHLs have an excellent prognosis in contrast to the aggressive entity, primary cutaneous diffuse large B-cell lymphoma, leg type. This article reviews the challenges in diagnosing and staging these conditions as well as the prognostic systems used in the management of PCBCL.

This is indeed an exciting time in the management of B-cell NHL. With technology expanding exponentially, our diagnostic, prognostic, and therapeutic techniques are also improving. Hopefully, in the relatively near future, we will be able to offer novel nonchemotherapy regimens with high efficacy and low toxicity to our patients with B-cell NHL, thus improving their quality of life and long-term outcome.

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