Ten Years of Progress in the Treatment of Non-Hodgkin's Lymphoma

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Over the past decade considerable progress has been made in understanding the different types of non-Hodgkin's lymphoma (NHL), including the genetic abnormalities specific to these lymphomas and the optimal clinical management. The initial NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NHL in 2001–2002 were very basic and included broad recommendations regarding the diagnosis and therapy for 8 different histologic types of NHL. The guidelines were 48 pages in length and represented a prototype that has been refined over the past decade. Major additions and modifications have included new information on molecular data, prognostic factor indices, testing used for response to therapy, new therapies, response criteria, and survivorship issues.

Some of the changes over the past decade are outlined in Table 1. Examples of molecular data found to be helpful for prognosis or deciding therapy include those from testing for the 17p abnormality in chronic lymphocytic leukemia/small lymphocytic lymphoma or the t(11;18) in gastric marginal zone lymphoma. Various prognostic factor indices have been developed over this time, including the Follicular Lymphoma International Prognostic Index (FLIPI) and the Mantle Cell Prognostic Factor Index (MIPI), which were added to the guidelines. A decade ago, gallium scans and lymphangiograms were still in the guidelines and have now been replaced by PET scans. With the widespread use of PET scans, the response criteria was modified to include the use of PET scans in patients with appropriate histologic subtypes, such as diffuse large B-cell lymphoma (DLBCL). Multiple new drugs and combinations have been added to the guidelines based on the scientific evidence available. This included the use of rituximab for an increasing number of histologic types of B-cell lymphomas, starting with just follicular lymphoma, and then in combination with chemotherapy for DLBCL (2004) and mantle cell lymphoma (2005). New agents added to the guidelines during the past decade include bortezomib, bendamustine, lenalidomide, and, more recently, agents specific for some subtypes of NHL, such as romidepsin or pralatrexate for peripheral T-cell lymphoma. In many cases, clinical trials are listed as the first option for the treatment of some subtypes of NHL when standard therapy options produce results that are not optimal. As we have become more successful in treating some types of lymphoma, long-term survivors have faced several issues, such as fertility, that have also been more recently addressed in the guidelines.

Additional guidelines have been added over the past decade to assist in the treatment for patients with rare types of NHL, including HIV-associated NHL, mycosis fungoides, peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma, posttransplant lymphoproliferative disorders, and Waldenström's macroglobulinemia. Many of the different histologies have guidelines and recommendations for therapies that are very specific based on the individual subtype of lymphoma and the affected patient population.

When either new antineoplastic agents are approved by the FDA or significant clinical information becomes available about a new drug or combination therapy, the NCCN Guidelines for NHL have been quickly updated to incorporate this information. The future of clinical care for patients with lymphoma will be highly invested in the identification of genetic abnormalities and pathways that can be targeted by new agents. Rather than being one-size-fits-all, personalized therapies

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will become an important aspect of lymphoma care in the near future. The NCCN Guidelines will continue to reflect the important changes in clinical care and research regarding lymphoma therapies.

Table 1 Examples of Modifications to the NCCN Guidelines From 2002–2012		
Year	Modifications	New Guidelines Added
2002	Fludarabine, cyclophosphamide, rituximab (FCR) added for CLL	HIV-related NHL
2003	Ki-67 added to the mantle cell lymphoma prognostic index	None
2004	Groupe d’Etudes des Lymphomes Folliculaires criteria for follicular prognosis added	Splenic marginal zone lymphoma
2005	Follicular Lymphoma International Prognostic Index (FLIPI) added	None
2006	Follicular lymphoma grades 1–2 separated from follicular lymphoma 3	Primary central nervous system lymphoma
2007	Revised response criteria using PET added	PTCL
2008	CLL with del(17p) treatment recommendations added	Mycosis fungoides/Sézary syndrome
2009	Rituximab: hepatitis B reactivation concern added	Primary cutaneous B-cell NHL
2010	Bendamustine + rituximab for first-line treatment of follicular lymphoma added	Adult T-cell leukemia/lymphoma
2011	Principles of radiation therapy linked to the guidelines	Natural killer/T cell Posttransplant lymphoproliferative disorder
2012	Cyclophosphamide, etoposide, doxorubicin, vincristine, prednisone (CHOEP) added for PTCL	Hairy cell leukemia T-cell prolymphocytic leukemia

Abbreviations: CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin’s lymphoma; PTCL, peripheral T-cell lymphoma.