Perspectives on Recent Non-Hodgkin's Lymphoma (NHL) Data

Summary Article

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A series of 5 expert interviews were conducted, focusing on lymphoma subtypes such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, mantle cell lymphoma, peripheral T-cell lymphomas, and chronic lymphocytic leukemia/small lymphocytic lymphoma, based on the latest data presented at the 2010 Annual Meeting of the American Society of Clinical Oncology® (ASCO) and the 15th Congress of the European Hematology Association (EHA). Each interview was with an expert clinician/clinical scientist and focused on the major advancements and continuing problems in the care of patients with these 5 major subtypes of lymphoid malignancy. This summary article provides highlights from those expert interviews.

Diffuse Large B-Cell Lymphoma *(Discussant, Dr. Izidore Lossos, University of Miami)*

Since the addition to rituximab to standard chemotherapy regimens, DLBCL is now curable in more than 50% of patients who develop this disease. While patients with localized disease have a higher chance to be cured than those with widespread disease, all patients have some chance for cure. New insights into the biology of DLBCL have shown that a variety of genetic subtypes exist, and they do not all have the same chance for benefit from the available therapies. Research aimed at better understanding this lymphoma and improving available treatments continues at a rapid pace.

One of the important recent studies in DLBCL was the CORAL study.[1] In this study, patients with relapsed DLBCL were randomly assigned to receive therapy with rituximab plus ICE (ifosfamide, carboplatin, and etoposide) or DHAP (dexamethasone, cytarabine,

and cisplatin) for 3 cycles followed by a transplant. The goal of the study was to see if the pretransplant, standard-dose chemotherapy had an important impact on the eventual outcome. Part way through the study, rituximab became part of the primary therapy of patients with DLBCL. Neither standard-dose salvage regimen was superior. However, an analysis of patients who had initially been treated with rituximab and then relapsed vs those whose initial therapy did not contain rituximab was interesting. The cure rate was approximately 50% lower in patients who had had rituximab initially and subsequently came to transplant vs those whose first exposure to rituximab was part of the preparation for transplant. The presumed explanation for this is that the initial use of rituximab cured a higher proportion of patients and that the patients who relapsed were more refractory. It is important to remember that approximately 25% of patients were still cured with the transplant.

A recent report in the *Journal of Clinical Oncology* (JCO) tested the hypothesis that dose-dense CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) would improve the outcome for patients with DLBCL.[2] As part of this study, patients underwent early restaging with PET scans, and those who had persisting disease were switched to an alternate chemotherapy regimen. However, a positive PET scan had to be confirmed by biopsy. The surprising result of the study was that the majority of positive interim PET scans did not show persisting lymphoma on biopsy, and patients who had a negative biopsy had as good an outcome as those whose PET scan was negative. The place of interim PET scans in patients with DLBCL remains uncertain.[3] It may be that in patients who receive initial therapy with rituximab, the value of interim PET scans is less than it had been previously. At any rate, patients with a positive interim PET scan should undergo biopsy before therapy is switched.

A number of new drugs are active in patients with DLBCL. Lenalidomide* has been shown to cause objective responses in approximately 20%-25% of patients with relapsed or refractory DLBCL, including those patients who failed a previous transplant.[4] An occasional patient achieves a complete remission. A Syk inhibitor R778* was administered to 6 patients with DLBCL, and 5 had an objective response.[5] It may be that these and other drugs will eventually find their way into the initial treatment of patients with DLBCL, either in combination with existing chemotherapy regimens or as maintenance treatment.

Patients with germinal center B-cell type DLBCL have a much better survival than those with the activated B-cell type. It is now known that patients with the activated B-cell type DLBCL consistently overexpress the NF-kappa-B pathway. Inhibitors to this pathway have been developed and are entering clinical trials. Recently, a group of investigators from the National Cancer Institute reported the addition of bortezomib to the dose-adjusted EPOCH-R (etoposide, doxorubicin, vincristine, prednisone, cyclophosphamide, and rituximab) regimen.[6] They showed a benefit of this approach in patients with the activated B-cell type of DLBCL. In addition, protein kinase C beta signaling is highly expressed in the activated B-cell type of DLBCL, and an inhibitor to this pathway, enzastaurin,* has been developed.[7] A clinical trial of the use of this drug as an adjuvant to patients with activated B-cell type DLBCL after initial chemotherapy is underway.

Follicular Lymphoma (*Dr. Jonathan Friedberg, University of Rochester*)

Follicular lymphoma is the second most common subtype of lymphoma; in the United States, it is almost as frequent as DLBCL. While patients with a high proportion of transformed, or large, cells are generally treated as if they had DLBCL, patients with predominately small-cell follicular lymphoma have a relatively indolent course, and the best treatment for these patients has been a point for debate for many years.

A report at the recent ASCO® meeting detailed the results of the PRIMA [Primary Rituximab and Maintenance] study in patients with follicular lymphoma.[8] The great majority of patients in the study had follicular lymphoma grade 1 or grade 2. Patients received a standard combination chemotherapy regimen in combination with rituximab to induce remission, and then were randomly allocated to maintenance rituximab for 2 years with the drug administered at 2-monthly intervals, or observation. The results showed a highly significant improvement in remission duration with maintenance rituximab, at a cost of minimal toxicity.

In a previous report, investigators from Switzerland reported 2 different schedules of rituximab as a single agent for patients with follicular lymphoma.[9] One involved the drug weekly for 4 weeks followed by observation, and the other had the same initial treatment followed by 4 maintenance doses administered every other month. The duration of remission was better in the patients who had received maintenance rituximab, and this benefit was maintained for a follow-up of 8-10 years. The explanation for this persisting benefit is unclear but might have to do with alteration in the tumor microenvironment.

There are a variety of new drugs that are being used in the treatment of patients with follicular lymphoma. Ofatumumab* and GA-101* are antibodies directed against CD20. While it was hoped that these agents would prove superior to rituximab, to date, studies have not borne out this hope.

Bendamustine is an active drug in follicular lymphoma, and a randomized trial that was recently reported from Germany suggested that bendamustine plus rituximab might be superior to CHOP plus rituximab.[10] Further studies with this drug are ongoing. Other agents that are targeting Bcl2 and the PI3 kinase pathway appear to have activity in patients with follicular lymphoma. Radioimmunoconjugates have been known to be active for many years but have not been widely utilized. An intergroup trial in the United States that compared R-CHOP vs CHOP followed by the radioantibody tositumumab has not yet been reported. A positive study could alter standard therapy. Two drugs that were developed for the treatment of multiple myeloma -- lenalidomide and bortezomib -- are active in follicular lymphoma, and clinical trials are ongoing testing the place of these agents in the initial therapy of patients with this disease. Over the next few years, it is possible that one or more of these new agents will alter our standard approach to patients with this common subtype of lymphoma.

Mantle Cell Lymphoma *(Discussant: Dr. John Leonard, New York Hospital and Cornell Medical Center)*

Mantle cell lymphoma represents approximately 5%-10% of all non-Hodgkin's lymphomas. It is a disease that is predominately seen in elderly men but can affect all age groups and both genders. The disease is rarely localized at presentation, has a high incidence of bone marrow involvement, and frequently involves the gastrointestinal tract. This lymphoma, while not generally rapidly growing, has responded poorly to therapy, and remissions, when they occur, have not been durable.

A recent report from German investigators that studied bendamustine plus rituximab vs CHOP plus rituximab included approximately 60 patients in each arm.[10] The results suggested that bendamustine plus rituximab might be superior in progression-free survival and tolerability.

Whether patients with mantle cell lymphoma should always be treated with intensive regimens is unclear. A report in the JCO suggested that approximately 20% of untreated patients might go at least several months, and in some cases several years, without progression.[11] Patients with a normal lactate dehydrogenase (LDH) and lymphomas with a low Ki67 level are particularly likely to do well with observation. Whether this is appropriate in younger patients is less clear. Currently, most oncologists would treat younger patients with an intensive chemotherapy regimen that includes rituximab and, frequently, follow this with an autologous hematopoietic stem cell transplant.

New drugs offer the hope to improve the treatment of patients with mantle cell lymphoma. Lenalidomide, bortezomib, mTOR inhibitors*, and PI3 kinase inhibitors* all have demonstrated a potential to improve our ability to treat patients with mantle cell lymphoma. Both lenalidomide and bortezomib have shown a high level of activity, and studies are ongoing trying to incorporate these drugs into the earlier treatment of patients with this disease. It is important to remember that some younger patients with mantle cell lymphoma are candidates for allogeneic hematopoietic stem cell transplantation, and this treatment can be curative.

T-Cell Lymphoma (*Discussant: Dr. Julie Vose, University of Nebraska)*

The peripheral T-cell lymphomas make up approximately 10% of all non-Hodgkin's lymphomas. They represent a wide variety of pathologic and clinical syndromes and, in the past, have not been a major focus for clinical trials. A recent international study showed that the new World Health Organization classification is clinically relevant and reproducible and offers the opportunity to improve our ability to study patients with these complex disorders.[12]

A recent study reported the SMILE regimen for patients with extranodal NK/T-cell lymphoma, nasal-type.[13] This regimen incorporates steroids, methotrexate, ifosfamide, L-asparaginase, and etoposide. This disease is quite responsive to radiotherapy but has been previously relatively resistant to chemotherapy regimens. However, the SMILE

regimen showed an overall response rate of 74% and 38% complete responders. Many patients with this lymphoma present with localized disease involving the nose and nasopharynx. In these patients, radiotherapy is a key part of the regimen, and many clinicians would favor radiotherapy being administered before chemotherapy.[14]

A large international trial showed that for patients who did not have an anaplastic large-cell peripheral T-cell lymphoma, there was no clear benefit to incorporating doxorubicin into the initial treatment regimen.[12] There is an ongoing effort by investigators around the world to identify new drugs active in the peripheral T-cell lymphomas and to develop better regimens. Some drugs that show promise include etoposide, pralatrexate, and HDAC inhibitors. It is extremely important that clinical trials are completed with these new approaches in order to identify better regimens.

The place of hematopoietic stem cell transplantation in the treatment of patients with peripheral T-cell lymphomas has been somewhat controversial.[15,16] However, many clinicians today suggest autologous hematopoietic stem cell transplantation in first remission for patients with the aggressive peripheral T-cell lymphomas, possibly excluding anaplastic large cell lymphoma. The retrospective look at data from the recent international study suggested a modest benefit to adjuvant transplantation in initial remission.[12] Some patients with recurrent peripheral T-cell lymphoma can benefit from autologous transplantation, but in a young patient, allogeneic hematopoietic stem cell transplantation might be preferable.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma *(Dr. William Wierda, MD Anderson Cancer Center)*

Asymptomatic patients who present with chronic lymphocytic leukemia are frequently followed without treatment, and some of these patients will never require therapy. This seems particularly true of those whose only cytogenetic abnormality at diagnosis is an abnormality involving 13q. In most patients, with the exception of those who present with genetic abnormalities involving 17p, this disease follows a relatively indolent course, and patients usually respond to chemotherapy regimens when they are initially administered. However, the best treatment approach has been uncertain. A recent trial from German investigators involving more than 800 patients compared fludarabine and rituximab with a 3-drug regimen incorporating fludarabine, cyclophosphamide, and rituximab (FCR).[17] The FCR regimen showed an improvement in overall survival in addition to complete response rate and progression-free survival.

Another recent study from the Cancer and Leukemia Group B reported the long-term follow-up of patients who were treated with single-agent fludarabine vs single-agent chlorambucil as part of their initial therapy.[18] The use of fludarabine rather than chlorambucil resulted in an improved overall survival.

Patients older than 65-70 years of age who present with chronic lymphocytic leukemia frequently do not tolerate aggressive chemoimmunotherapy regimens such as FCR. In these patients, the use of chlorambucil or bendamustine, or reducing the dose of fludarabine-containing regimens all might be appropriate in specific patients.

Certain genetic abnormalities have important therapeutic implications. For example, patients with an 11q deletion appear to benefit from alkylating agent-containing regimens. Unfortunately, patients with a 17p deletion seem to do badly with all regimens. Although they respond to alemtuzumab, it is unclear that an initial regimen including alemtuzumab is superior to FCR. Many clinicians would move quickly to allogeneic hematopoietic stem cell transplantation in a young patient who presents with a 17p deletion.

The relative merits of FCR and bendamustine plus rituximab have not been studied.[19] There is a trial ongoing in Germany comparing these 2 approaches in the upfront setting. At the present time, in a younger, fit patient, FCR is the favored initial therapy.

Approximately 10% of patients who develop chronic lymphocytic leukemia will undergo transformation to DLBCL at some point in their course. This is referred to as Richter's transformation. These patients usually present with localized, rapidly enlarging lymphadenopathy, systemic symptoms, and elevated serum LDH levels. PET imaging often shows a very high standardized uptake value (ie, greater than 10). The best treatment for these patients is unclear. Investigators in Houston have used the OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab) regimen to try to cytoreduce patients and then proceed with allogeneic hematopoietic stem cell transplantation as soon as possible. However, Richter's transformation remains a serious clinical problem.

In conclusion, major advances continue to occur in our understanding of lymphomas and our ability to treat patients suffering from these diseases. At the present time, a patient who develops one of these diseases has some chance for extended survival free from lymphoma. This goal can be achieved regularly in patients with DLBCL but less frequently in the other subtypes. Even so, clinical trials are pointing the way to improve the survival of patients suffering from all of these malignancies.

**The US Food and Drug Administration has not approved this medication for this use.*

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