Recent Advances in the Treatment of Non-Hodgkin's Lymphomas

Presented by Jeremy S. Abramson, MD, and Andrew D. Zelenetz, MD, PhD

Abstract

Non-Hodgkin's lymphomas (NHL) represent a diverse set of diseases, with different treatment pathways based on the stage and type of hematologic cancer. In their presentation at the NCCN 18th Annual Conference, Dr. Jeremy Abramson and Dr. Andrew D. Zelenetz discuss 3 specific B-cell NHLs: follicular lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia. They provided an overview of the treatment strategies for patients with these hematologic malignancies, and offered highlights from recent clinical trials supporting these recommendations. (*JNCCN* 2013;11:671-675)

Advances in the recent medical literature and updates in the 2013 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for non-Hodgkin's lymphomas (NHL) are primarily limited to follicular lymphoma (FL), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL), reported Jeremy S. Abramson, MD, Director of the Lymphoma Program, Massachusetts General Hospital Cancer Center, Boston, and a member of the NCCN Panel for NHL. After Dr. Abramson addressed therapeutic strategies for both FL and MCL, Andrew D. Zelenetz, MD, PhD, Vice Chair, Medical Informatics, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, and Chair of the NCCN Panel for NHL, discussed those for CLL. As all patients with MCL and CLL are not equal, treatment options often differ in the young and fit versus older and more frail populations.

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Dr. Abramson has revealed that he has served as a consultant for Seattle Genetics. Dr. Zelenetz has revealed that he receives clinical research support from Abbott Laboratories; Celgene Corporation; Cephalon, Inc.; Genentech, Inc.; GlaxoSmithKline; Millennium Pharmaceuticals, Inc.; Onyx Pharmaceuticals, Inc.; Allos Pharm; Calistoga, Pharmacyclics; Plexxikon; Roche; and Seattle Genetics and serves on an advisory board or as a consultant for Abbott Laboratories; Celgene Corporation; Cell Therapeutics, Inc.; Cephalon, Inc.; Genentech, Inc.; GlaxoSmithKline; Allos; Cancer Genetics; Gilead; Seattle Genetics; Roche Laboratories, Inc.; and sanofi-aventis U.S.

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FL: The Optional Role of Maintenance Therapy

Focusing on grades 1 and 2 FL, Dr. Abramson reviewed first-line options, the role of rituximab maintenance, and second-line alternatives. For low-grade FL with a high tumor burden, first-line regimens with a category 1 ranking include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone). However, the "new kid on the block" is the combination of bendamustine and rituximab, which carries an NCCN category 2A recommendation ("based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate"). Dr. Abramson anticipates that this treatment will be promoted to a category 1 ranking (high-level evidence and uniform NCCN consensus) in future NCCN Guidelines given recently published results of the phase III trial supporting its use.

New supporting data regarding choice of upfront treatment regimens for follicular lymphoma were briefly reviewed.[1,2] The Italian FOLL05 trial was a randomized study among 3 upfront treatment regimens: R-CHOP, R-CVP, and R-FM (rituximab, fludarabine, mitoxan-

trone). The 3-year time to treatment failure (TTF) and progression-free survival (PFS) were better with R-CHOP and R-FM when compared with R-CHOP, though R-CVP had the least toxicity. Dr. Abramson added, there was "absolutely no impact whatsoever on overall survival [OS]. What is the import of PFS in a disease with a lengthy natural history if OS is not being impacted?" Both efficacy and toxicity must therefore be carefully balanced in selecting initial therapy. The fludarabine-containing regimen had the most toxicity in this study, including an increased rate of secondary malignancies, and so it should not be used as front-line therapy, cautioned Dr. Abramson.

Bendamustine-rituximab (BR) was compared with R-CHOP in a recently published randomized trial and showed a statistically significant improvement in complete response and PFS favoring BR.[2] Again, no difference was seen in OS at 45 months, but BR was less toxic than R-CHOP therapy, and thus serves as an appealing alternative. Additional data comparing these regimens will be forthcoming from the ongoing BRIGHT study.

First-line consolidation or extended dosing after front-line therapy for grade 1 to 2 FL is optional, according to the NCCN Guidelines. Category 1 options include chemotherapy followed by radioimmunotherapy, or maintenance rituximab for patients who presented with high tumor burden. Supporting data on rituximab maintenance came from the PRIMA trial, which enrolled over 1000 patients with high–tumor-burden FL.[3] The study found that 2 years of rituximab maintenance after initial treatment significantly improved PFS, but did not impact OS or quality of life. For patients with a low tumor burden after rituximab alone, rituximab maintenance is not recommended. This is based on results from the RESORT (ECOG 4402) study, which showed no benefit in time to treatment failure of rituximab maintenance when compared with re-treatment with rituximab at the time of progression.

Dr. Abramson reflected on the role of rituximab maintenance in first remission for patients with high tumor burden. "Maintenance therapy with rituximab does not save lives in FL," he acknowledged. However, for patients with a high tumor burden after rituximab and chemotherapy, maintenance rituximab may be considered given the improvement in PFS and only minimal increase in toxicity. When selecting a maintenance or consolidation strategy, "My preference would be maintenance rituximab as opposed to radioimmunotherapy," noted Dr. Abramson, based on the lack of data supporting radioimmunotherapy consolidation after initial rituximab-containing chemotherapy. "However, as neither consolidation approach has been shown to improve OS, the option is by no means mandatory and should be discussed individually with patients weighing the risks and benefits."

As in past NCCN Guidelines, numerous options are listed as acceptable second-line treatment regimens in follicular lymphoma, including R-CHOP, radioimmunotherapy, rituximab alone, and R-fludarabine-based regimens. Stem cell transplant may also be considered in highly selected patients.

The 2013 Guidelines also added lenalidomide with or without rituximab as a new treatment option for follicular lymphoma, which has a category 2A ranking. Supporting data are from the randomized CALGB 50401 trial comparing lenalidomide alone to lenalidomide plus rituximab.[4] The overall response rate was higher with lenalidomide and rituximab than with lenalidomide alone (73% vs 51%). In addition, the 2-year event-free survival was better with the combination treatment (44% vs 27%), which Dr. Abramson called "very encouraging in relapsed/refractory disease." The combination of lenalidomide and rituximab is now being studied in the first-line setting as well.

MCL: Treatment Differs for Young and Fit Patients Versus Older and More Frail Patients

Decisions regarding induction therapy for MCL center on whether patients are young and fit or older and infirm, with more aggressive approaches reserved for those better able to tolerate them. The NCCN Guidelines offer a lengthy list of aggressive induction therapies; as no one regimen has been shown to be superior to another, Dr. Abramson added, they are all category 2A recommendations. Featured options for younger and more fit patients include 1) hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine and rituximab; 2) the Nordic regimen (dose-intensified induction immunochemotherapy with rituximab and cyclo-

phosphamide, vincristine, doxorubicin, prednisone alternating with rituximab and high-dose cytarabine followed by autologous stem cell transplantation; and 3) R-CHOP alternating with R-DHAP followed by autologous stem cell transplantation, among others.

The Nordic regimen was studied in a phase II trial by Geisler et al.[5] The 10-year follow-up data on the use of intensive immunochemotherapy and autologous stem cell transplantation (ASCT) in untreated MCL showed an encouraging PFS of 55% and OS of 57%. "These are excellent numbers in MCL," noted Dr. Abramson.

The first randomized trial evaluating the role of cytarabine-containing induction therapy in MCL compared R-CHOP to R-CHOP alternating with R-DHAP (rituximab plus dexamethasone, cytarabine, cisplatin), each regimen followed by ASCT.[6] The authors confirmed that high-dose cytarabine with R-CHOP significantly improved TTF and OS, "This OS difference has been difficult to demonstrate in prior randomized trials in advanced-stage MCL," added Dr. Abramson, and validates the inclusion of cytarabine-containing induction therapy before ASCT in young fit patients with MCL. Unanswered questions in MCL include whether one cytarabine-containing induction regimen is superior to another, whether maintenance rituximab has a role in the treatment of younger patients, and incorporation of numerous emerging novel agents with encouraging activity in MCL including lenalidomide, ibrutinib, and idelalisib.

For older or more-frail patients who are not candidates for aggressive treatment, the NCCN panel recommends less-intensive therapies such as R-CHOP followed by rituximab maintenance and BR. Dr. Abramson briefly reviewed the most current supporting data for these options.

A recently published large study by the European Mantle Cell Lymphoma Network[7] compared R-CHOP and R-FC (rituximab, fludarabine, cyclophosphamide) for first-line therapy in older patients with MCL, followed by a second randomization to maintenance therapy with either interferon-alfa or rituximab. R-CHOP was superior to R-FC as initial treatment. As was previously demonstrated in FL, the fludarabine-containing regimen should not be considered a first-line regimen in MCL due to excess toxicity, he added. Furthermore, the researchers noted a marked difference in OS favoring maintenance rituximab in the R-CHOP patients. "Four years later, over 80% of these patients remain alive and well," reported Dr. Abramson. However, it is difficult to extrapolate these findings to patients treated with other regimens, he cautioned. Thus, "maintenance is only recommended after R-CHOP, making it an appealing standard of care for our older patients."

Results from the German StiL NHL1 study including older patients with mantle cell lymphoma were recently published.[8] The authors found that the median PFS was longer in MCL patients treated with BR than with R-CHOP (35.4 vs 22.1 months. As previously noted, a PFS benefit was also observed in follicular lymphoma as in well as in Waldenström's macroglobulinemia. However, although it appeared to be a well-tolerated regimen, no difference was seen in OS.

Current and Future Treatments for CLL

Dr. Zelenetz briefly reviewed the influence of prognostic markers on the time to first treatment. To treat or not to treat; that is the question in CLL, Dr. Zelenetz remarked. "Any patient with Binet C or Rai high-risk disease should be an automatic candidate for treatment," he stated. On the other hand, those with Binet A or Rai low-risk disease should be observed. In addition, those with Binet B and Rai intermediate-risk disease who have signs or symptoms that meet the International Workshop on CLL criteria (eg, massive splenomegaly, B symptoms, lymphocyte doubling time < 6 months, or progressive marrow failure[9]) should receive treatment.

Various risk factors help to determine which patients with CLL may require treatment start due to disease progression. These factors include unmutated immunoglobulin heavy chain variable (*IGHV*) gene, chromosomal deletions 11q or 17p, the number of involved lymph node sites, and lactate dehydrogenase levels.[10] Although 17p deletion is a known prognostic marker, "it is not the presence of 17p deletion alone that is a risk factor for disease progression," revealed Dr. Zelenetz. "*IGHV* mutation status is very important [in determining risk] for time to first treatment." Patients with unmutated status will require treatment earlier. Wierda et al[10] developed a multivariable model that incorporates these prognostic factors to identify patients at high risk for disease progression. Scores on this nomogram can offer a median treatment-free estimate for a given person.

More than half of patients with CLL will present between the ages of 65 and 84, said Dr. Zelenetz. As a result, an important change in the NCCN Guidelines is the recognition of therapeutic options based on the patient's physiologic and functional status ranging from frail with significant comorbidity, elderly/less fit with some comorbidity, to fit with no major comorbidity. The Cumulative Illness Ratings Scale (CIRS) is useful for guiding treatment strategies according to the presence and extent of comorbidity.[11] Based on a patient's CIRS score, 1 of 3 treatment approaches is indicated (Figure 1).[11] For example, those with a low CIRS score (1 to 2) are physically fit, have no significant morbidities, and have excellent renal function regardless of age. Thus, they would belong in the group of patients Dr. Zelenetz termed "go go" and would receive standard treatment with chemoimmunotherapy regimens such as R-FC (rituximab, fludarabine, and cyclophosphamide).

Supporting data on R-FC came from a randomized phase III trial (CLL8) that found a significant improvement in OS with R-FC over fludarabine and cyclophosphamide.[12] "However, this regimen is not for the faint of heart, as it results in significant cytopenias," noted Dr. Zelenetz.

Patients with a moderate CIRS score (2 to 3) would belong in the "slow go" group and should receive less-intensive treatment. For these patients (who do not have 17p deletion), the NCCN Guidelines include first-line regimens such as chlorambucil with or without rituximab, bendamustine with or without rituximab, cyclophosphamide and prednisone with or without rituximab, and lenalidomide as possible options. Patients with a high CIRS score (3 to 4) would be considered in the "no go" group, whose status precludes aggressive treatment; palliative therapy may be appropriate for these patients.

- **The general rules for severity rating are:**
  - 0→No problem affecting that system.
  - 1→Current mild problem or past significant problem.
  - 2→Moderate disability or morbidity and/or requires first line therapy.
  - 3→Severe problem and/or constant and significant disability and/or hard to control chronic problems.
  - 4→Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.
- **Online calculator: http://farmacologiaclinica.info/scales/CIRS-G/**

Our patient has an index of 2.8 (maximum 4)

Figure 1 Cumulative Illness Rating Scale for CLL Patients. Reprinted from Miller et al;[11] with permission.

New investigational targeted therapies are on the horizon in CLL. Three different types of agents have all shown promising early results in CLL as well as in other types of indolent NHLs. First, the PI3K-delta inhibitor idelalisib (GS-1101 or CAL 101) has produced rapid responses in lymph nodes and subsequent responses in peripheral blood in patients with relapsed/refractory CLL, reported Dr. Zelenetz. It appears to be active as a single agent as well as in combination with rituximab and/or bendamustine, and it appears to retain activity in cases with 17p deletion.

Another investigational agent, the Bruton's tyrosine kinase inhibitor ibrutinib, has shown promising single-agent activity in terms of extended PFS and OS outcomes in older patients with previously untreated CLL and in patients with relapsed/refractory disease.[13] This agent appeared to be well tolerated and maintained its activity in patients with poor prognostic features such as unmutated *IGHV* status, 17p deletion, and 11q deletion. Ibrutinib is given as continuous treatment until disease progression, which Dr. Zelenetz called "a change in the treatment paradigm of CLL."

Interestingly, both of these investigational agents are associated with rapid lymph node responses and an initial rise in peripheral blood lymphocytes, followed by subsequent resolution of lymphocytosis. Finally, the second-generation Bcl-2 inhibitor ABT-199 has shown "dramatic responses" in both peripheral blood and lymph nodes, which improve with time. The optimal dosing schedule is currently under investigation following several reports of significant and fatal tumor lysis syndrome.

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