Guideline updates for non-Hodgkin lymphomas

Sharon Worcester attended the 2014 National Comprehensive Cancer Network annual conference in Hollywood, Florida, and reports on guideline updates for non-Hodgkin lymphomas, which were by Dr Andrew D Zelenetz, vice-chairman of medical informatics at Memorial Sloan Kettering Cancer Center, New York, and chair of the NCCN Non-Hodgkin Lymphomas Guidelines panel.

MYC now included in diffuse large B-cell lymphoma guidelines

The NCCN guidelines for diffuse large B-cell lymphoma have been updated to include the oncogene MYC as an essential component of the immunohistochemistry panel for tumors. The updated guideline also highlights the value of fluorescence in situ hybridization for detecting MYC translocation.

The changes, which are reflected in version 1.2014 of the guidelines, are the result of recent data showing that MYC expression in diffuse large B-cell lymphoma (DLBCL) is associated with poor outcomes in patients receiving CHOP-based therapy (cyclophosphamide, doxorubicin, vincristine, prednisone), according to Dr Andrew D Zelenetz. "We have found is that it's not the expression of MYC in DLBCL, but it seems to be the expression of MYC in conjunction with BCL2. This was originally described in tumors with both translocation of the MYC gene and the BCL2 gene, and these patients had a very, very poor outcome," he said.

This "double-hit" phenomenon with both translocations is relatively uncommon, affecting about 6% of patients, but additional data has emerged showing that actual expression of the MYC protein in more than 40% of cells, coupled with expression of the BCL2 protein in more than 70% of cells on immunohistochemistry (which equates to a double-hit score of 2) confers a far worse outcome than does a score of 0 or 1 in patients with DLBCL undergoing R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), Dr Zelenetz said. Patients with a double-hit score of 2 had a significantly lower response rate and significantly shorter overall and progression-free survival (J Clin Oncol. 2012;30:3460-7).

"This is no longer a minor population of patients. It actually represents about 30% of patients, and, importantly, it does not have a strict correlation with cell of origin," said Dr Zelenetz. He noted that this data is widely cited as the basis for treatment of MYC-positive tumors and is what the data shows, "but it is misinterpreted many times as showing the treatment for double-hit lymphoma. In this series, only 1 or 2 cases actually had a double-hit lymphoma, so this was really the treatment of MYC-positive lymphoma, which we know has very similar outcomes when compared to MYC-positive lymphoma in the absence of BCL2."

"The guidelines are silent on the appropriate treatment here because there literally are no data, and here clinical trials are essential," he said.

New guideline addresses rare TLGLL

T-cell large granular lymphocytic leukemia, or TLGLL, generally has an indolent clinical course, but about two thirds of patients require treatment for related symptoms and disorders, according to Dr Andrew D Zelenetz. TLGLL is a rare disease, representing about 2%-5% of chronic leukemias and it is often found in association with autoimmune disorders, particularly rheumatoid arthritis. TLGLL also is increased in association with B-cell.

According to a new guideline from the NCCN, indications for therapy include severe neutropenia, moderate neutropenia with recurrent infections, symptomatic or transfusion-dependent anemia, autoimmune disorders exacerbated by disease, and B-symptoms. Cytopenias are the most common indication for treatment.

For asymptomatic patients, observation is acceptable because "intervening early doesn't change the overall natural history of the disease," he said. For symptomatic patients, the preference is to do a clinical trial, but based on the limited amount of data for this rare disease, it appears there are a number of useful treatments. For example, numerous studies have demonstrated that methotrexate is associated with about a 50% overall response rate and durability of about 1 year. Across 7 studies, full remission was achieved by about 20% of patients overall.

Cyclophosphamide has also been shown in several studies to have about a 50%-60% response rate, although the numbers are small – only 85 patients

JCSO 2014;12:193-194. ©2014 Frontline Medical Communications. DOI 10.12788/jcso.0046.

were reported on from 6 studies. Data regarding durability are lacking, but the experience at Memorial Sloan Kettering Cancer Center, where Dr Zelenetz is the vice-chair of medical informatics and a professor of medicine, a suggests durability of about 12 months.

Data are also very limited with respect to cyclosporine, with outcomes reported only for 123 patients across 10 studies, but the findings suggest a response rate of about 50%. Providers should keep in mind that it takes time for patients to respond to this treatment and that it is important to persist for a number of weeks before a response will be seen. In a patient who is tolerating treatment, one should continue the drug, even if no response has been seen after 4 to 8 weeks, he said. Another possible treatment is alemtuzumab. "We don't have great data, but it looks like immunosuppressive treatments provide some tools for the clinician to treat these patients, and sometimes with durable results," Dr Zelenetz said.

Primary cutaneous T-cell lymphoproliferative disorders

The treatment of patients with lymphomatoid papulosis depends on the presentation, according to new NCCN guidelines for managing primary cutaneous CD30+ T-cell lymphoproliferative disorders. No treatment is needed in patients with lymphomatoid papulosis (LyP) who present without symptoms because spontaneous remission is extremely common in this disease, and these patients typically won't have problems with progressive disease, said Dr Andrew D Zelenetz. But for those who are symptomatic, topical or systemic treatments are useful in some cases. Topical steroids "are effective, but not great," with reported response rates in the 50%-60% range.

Bexarotene is another treatment option, although experience with the drug is quite limited. The largest series included only 11 patients. Unpublished data from that series at Memorial Sloan Kettering Cancer Center show a response rate of 45% at a maximum oral dose of 600 mg daily, Dr Zelenetz said. However, where there is a response, it is "dramatic and quite obvious," although treatment duration needs to be adequate before a patient is considered a nonresponder; the median duration of treatment in the 11-patient series was 35.5 weeks.

In a series of 57 patients from Memorial Sloan Kettering Cancer Center (including the 11 treated systemically with bexarotene), 16 received no therapy; 19 received topical treatment with steroids (13), bexarotene (2), UVB (2), cryotherapy (1), or nitrogen mustard (1); and 5 received systemic treatment with methotrexate. At follow-up, 14% of patients had no evidence of disease, and, with the exception of 1 who died of another cause, the remaining patients were alive with disease, Dr Zelenetz said.

LyP is a rare CD30+ cutaneous lymphoproliferative disorder characterized by self-healing cropped or generalized eruptions of papules that come and go on the trunk or proximal extremities. In rare cases, they present as solitary lesions. "The death rate from LyP is zero, so this is a very manageable disease. One should not overtreat these tumors," he said.

At the other end of the spectrum of CD30+ lymphoproliferative disorders addressed in the new NCCN guidelines is anaplastic large cell lymphoma (ALCL). Primary cutaneous ALCL is characterized by skin-only presentation that is often localized but which can be disseminated in some cases. Lesions also tend to be larger and "more piled up" than those seen with LyP. "You can get clustering in a specific area, but we don't tend to have these big crops of lesions that we see with LyP," Dr Zelenetz said.

The pathology is also different, with diffuse infiltration of the subcutaneous tissue. The cells are large and anaplastic, and there is intense expression of CD30. The course of disease is usually indolent, with progression to extracutaneous sites in about 10%-15% of cases. Nodules or tumors in cases of ALCL are less likely than LyP lesions to regress spontaneously, Dr Zelenetz said.

This disease must be distinguished from a skin presentation of systemic ALCL, he noted. "In anaplastic large-cell lymphoma that's systemic, you will have multiple nodules all over and happen to have skin disease. With primary cutaneous ALCL, you have skin only or skin and some regional lymph nodes but nothing beyond that." These primary cutaneous tumors do extremely well nevertheless, with cumulative survival rates of more than 90%. However, patients with systemic ALCL, have much lower cumulative survival, in the range of 25%.

As with LyP, treatment for primary cutaneous ALCL is based on presentation.

For solitary or grouped lesions, the preferred treatment is surgical excision if needed for diagnosis or radiation if the diagnosis is already established. Methotrexate is the preferred treatment for multifocal lesions.

The subtype that includes regional lymph nodes is typically treated with very mild chemotherapy, including methotrexate or pralatrexate. Radiation can be used for locoregional disease, Dr Zelenetz said.

An exception to the rule that patients with primary cutaneous ALCL do well is in cases of extensive limb disease. Patients with involvement of a single limb – usually lower extremity, but not always – have poor survival, and their disease is refractory to chemotherapy and radiation. It is not clear why there is a distinction in this presentation, but it is important to be aware of it, he said.

Dr Zelenetz is a scientific adviser for Cancer Genetics Inc and Gilead has received consulting fees, honoraria, and/or other support from numerous drug companies.