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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Reassessing Imaging Surveillance in Diffuse Large B-Cell Lymphoma

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H&O Please provide an overview of diffuse large B-cell lymphoma (DLBCL).

BL DLBCL is the most common subtype of lymphoma in North America and Europe. It commonly presents in patients in their seventh and eighth decades of life. It is a life-threatening disease, with long-term survival rates approaching 65% to 70%. The fundamental treatment strategy involves aggressive initial induction in an attempt to produce a complete response. If a complete response is not achieved, death within a year is highly probable. If a complete response is achieved, a relapse rate of approximately 20% remains.

H&O What is the outlook for patients with relapsed disease?

BL Salvage of relapsed patients has variable success. Response rates to commonly used salvage regimens following anthracycline-based immunochemotherapy induction treatment failure were 45% to 55% in large recent prospective trials, such as the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) LY12 study and the CORAL (Intergroup Collaborative Trial in Relapsed Aggressive Lymphoma) study. In these trials, approximately 25% of patients were reported as free from relapse at 3 to 4 years and 30% to 40% of patients were still alive. Patients who are not candidates for aggressive therapy or patients who do not achieve complete remission fare less well.

H&O What is the current role of imaging surveillance in DLBCL?

BL The clinical guidelines have been changing over time, are not completely consistent (internally or with guidelines for research designs), and are generally vague, which reflects the historic paucity of efficacy evidence available on which to base them. As of late 2013, the National Comprehensive Cancer Network guidelines suggest computed tomography (CT) scans no more often than every 6 months for 2 years after completion of therapy and then as clinically indicated. The European Society for Medical Oncology acknowledges that CT scans at 6, 12, and 24 months after treatment are usual practice without definitive evidence in support of impact on outcomes. Neither society recommends surveillance positron emission tomography (PET) scanning despite it being a somewhat frequent practice, at least in the United States.

H&O What are the potential benefits and main risks associated with surveillance imaging in DLBCL?

BL The theoretical benefits of surveillance imaging are centered around the presumption that surveillance imaging will pick up relapses earlier than waiting for patients to become ill. This would seemingly spare the patient from suffering with symptoms, and perhaps earlier detection of relapsed disease would increase the likelihood of effective salvage therapy.

Medical risks of surveillance imaging include—and are not limited to—radiation exposure, nephrotoxic dye exposure, rare anaphylaxis, and risks associated with unnecessary follow-up testing for false positives.

H&O Can you please discuss the design and setting of the trial you worked on?

BL This study, led by Carrie Thompson and Matt Maurer at the Mayo Clinic in Rochester and Hervé Ghesquière in Lyon, France, was presented at the 2013 American Society of Clinical Oncology meeting (abstract 8504). It utilized a

prospective observational study of patients with newly diagnosed lymphoma embedded in the University of Iowa/Mayo Clinic Lymphoma SPORE (NCI Specialized Program of Research Excellence) Molecular Epidemiology Resource for discovery and a similar lymphoma database in Lyon, France for validation. All patients with DLBCL treated with anthracycline-based immunochemotherapy were identified. Of those who relapsed following a complete remission, medical records were examined to determine how such relapses were detected, including the role for imaging.

H&O What were the key findings?

BL In the discovery cohort of 552 patients with DLBCL who achieved a complete remission following induction treatment and entered post-treatment surveillance, 112 patients (20%) relapsed, as expected, at a median follow-up of more than 4 years. Of those relapses, 64% were evaluated based on self-reports of symptoms prior to the next scheduled follow-up visit and an additional 24% of patients had symptoms or physical examination findings at the time of scheduled surveillance. Surveillance scans (CT or PET) identified only 13 patients with asymptomatic relapses, of which only 9 had the recurrent DLBCL subtype. Thus, of 552 patients entering postremission surveillance, only 1.6% had asymptomatic relapse detected by arbitrary surveillance scanning. The findings were essentially identical to those in 261 patients with DLBCL from Lyon, France.

H&O Are there other studies that have reported similar findings?

On a generally smaller scale utilizing retrospective data, there have been multiple studies demonstrating that most DLBCL relapses occur outside the time frame of a scheduled visit. Prior efforts to demonstrate that earlier detection leads to superior outcomes in these smaller studies have been unsuccessful.

Therefore, it is important to educate patients to be more alert to signs and symptoms of relapse, which include enlarged lymph nodes, night sweats, unexplained fever, and unintentional weight loss. Furthermore, deciding whether to perform surveillance scans and how often should be tailored to each individual patient.

H&O What are the potential implications for clinical care?

BL It might be a bit premature to declare any implications for clinical care until the study has completed the rigor of peer review. If that is achieved, 2 straightforward conclusions emerge.

First, if the goal is to detect relapsed DLBCL early, our greatest opportunity for improvement would be to enhance communication channels with patients to survey for symptoms and signs of relapse. This could be done through careful history and physical exams, and enhanced with interim phone calls or even creative use of electronic communication media.

Second, surveillance imaging, as currently utilized, has minimal efficiency in detection of relapsed DLBCL. Any hypothesis suggesting that scanning more frequently or with more sensitive techniques (ie, PET scans) improves efficacy remains plausible, but should be tested in prospective fashion before being adopted.

H&O What are the biggest remaining challenges?

BL If studies such as these influence guideline authors or payer policies, we need to be clear that there are still many good reasons to obtain imaging in the post-therapy period, such as if patients did not achieve a clear complete response, or to follow up on concerning symptoms or physical exam findings. Similarly, systems will need to accommodate surveillance imaging as appropriate for carefully considered endpoints in well-designed clinical research trials in DLBCL if we hope to continue to move the field forward.

H&O What is your overall outlook for the future?

BL I am hopeful that data such as these will allow us to be more efficient in the use of resources for DLBCL patients without negatively impacting outcomes.

Suggested Readings

Crump M, Kuruvilla J, Couban S, et al. Gemcitabine, dexamethasone, cisplatin (GDP) compared to dexamethasone, cytarabine, cisplatin (DHaP) chemotherapy prior to autologous stem cell transplantation for relapsed and refractory aggressive lymphomas: final results of the randomized Phase III NCIC CTG study Ly12 [ASH abstract 745]. *Blood*. 2012;120(21).

Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol*. 2012;30(36):4462-4469.

Pingali SR, Jewell S, Havlat L, et al. Clinical or survival benefit to routine surveillance imaging for classical Hodgkin lymphoma patients in first complete remission [ASCO abstract 8505]. *J Clin Oncol*. 2013;31(suppl 15).

Shenoy P, Sinha R, Tumeh JW, Lechowicz MJ, Flowers CR. Surveillance computed tomography scans for patients with lymphoma: is the risk worth the benefits? *Clin Lymphoma Myeloma Leuk*. 2010;10(4):270-277.

Thompson CA, Maurer MJ, Ghesquieres H, et al. Utility of post-therapy surveillance scans in DLBCL. J Clin Oncol [ASCO abstract 8504]. *J Clin Oncol*. 2013;31(suppl 15).