The Crucial Role of Imaging for Response-Adapted Management of Lymphoma

Written by Toni Rizzo

Computed tomography (CT) is the gold standard for assessing lymphoma response to therapy. This session addressed the role of imaging in guiding the treatment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (nHL), with a focus on the use of positron emission tomography (PET)/CT for response evaluation.

David Hodgson, MD, MPH, University of Toronto, Toronto, Ontario, Canada, addressed the issues involved in the transition from risk- to response-adapted therapy for customizing the intensity of therapy for lymphoma. The standard approach to treatment selection has been based on patient risk according to the stage of disease and other prognostic factors.

The shift to response-adapted therapy began with the Children's Oncology Group observation that early treatment response on CT indicated a good prognosis [Friedman DL et al. *J Clin Oncol.* 2014]. Patients with intermediate-risk lymphoma were evaluated after receiving 2 cycles of chemotherapy. Rapid early responders (RERs; 60% tumor reduction on CT) received another 2 cycles, after which those who had a complete response (CR; 80% reduction) were randomized to radiotherapy or no radiotherapy. Slow early responders (SERs) were randomized to 2 additional chemotherapy cycles, and all received radiotherapy. Four-year event-free survival (EFS) was significantly better in the RERs (87.4% vs 78.5%; $P=.0001$). EFS was similar in RERs receiving and not receiving radiotherapy (87.9% vs 84.3%) but not significantly different between SERs receiving and not receiving chemotherapy dose intensification (79.3% vs 75.2%; $P=.11$). When stratified by PET response, dose intensification improved 4-year EFS from 54.6% to 70.7% in PET-positive patients ($P=.05$).

The EuroNet-Pediatric Hodgkin Lymphoma (PHL)-C1 study [NCT00433459] used a combination of CT volume reduction and PET response to determine selection for radiotherapy. Patients with ≥50% CT volume response did not receive radiotherapy. PET-negative patients were unlikely to receive radiotherapy. Based on this system, rates of overall survival (99%), progression-free survival (88%), and EFS (87%) were high.

The predictive value of interim CT and PET for predicting outcomes of treatment in adults with HL has also been evaluated. Studies of adult HL indicate that omitting radiotherapy based exclusively on end-of-chemotherapy PET response increases the risk of relapse. The clinical significance of this increase is not clear. Relapse is less likely to occur with more aggressive chemotherapy. The use of interim PET and CT for treatment selection in patients with early-stage HL may be better than either alone [Kostakoglu L et al. *Leuk Lymphoma*. 2012].

The usefulness of PET and CT for evaluating response and prognosis in patients with diffuse large B-cell lymphoma (DLBCL) has also been evaluated in clinical studies (Table 1).

Imaging is a critical component of determining the prognosis of patients with HL and DLBCL. Fluorodeoxyglucose (FDG)-PET and CT are critical for staging DLBCL and for evaluation of response and prognosis. The PET response at the end of chemotherapy is more useful for prognosis than the interim response. However, current treatment options are not advanced enough to use this information for treatment selection in an evidence-based manner.

Steve Y. Cho, MD, University of Wisconsin, Madison, Wisconsin, USA, discussed response evaluation in lymphoma with FDG-PET, visual response criteria, and quantitative response criteria. FDG-PET is currently used for initial staging, treatment assessment, and patient-specific risk-adapted therapy. FDG uptake varies in different types of lymphoma [Allen-Auerbach A et al. *Radiol Clin North Am.* 2008].

The International Harmonization Project (IHP) of the International Working Group (IWG) developed updated recommendations for response criteria, incorporating PET, immunohistochemistry, and flow cytometry in the definitions of response for HL and nHL [Cheson BD et al. *J Clin Oncol.* 2007; Juweid ME et al. *J Clin Oncol.* 2007].

According to the IWG recommendations, CT criteria should be followed in variably FDG-avid or PET-negative lymphomas. In FDG-avid (HL, DLBCL) or baseline PET-positive lymphomas, the new IHP PET response guidelines should be followed. The interpretation of the revised criteria is shown in Table 2 [Schöder H, Moskowitz C. *Radiol Clin North Am*. 2008].

Consensus was reached at the 11th International Conference on Malignant Lymphoma, Lugano, Switzerland, in 2011 to update the guidance on the use of PET/CT for staging and response assessment for FDG-avid lymphomas in clinical practice [Barrington SF et al. *J Clin Oncol.* 2014; Cheson BD et al. *J Clin Oncol.* 2014]. A summary of the Lugano classification is shown in Table 3.

Issues not clearly addressed in the new criteria include pediatric HL and nHL, as well as spleen, bone marrow (BM), lung, and visceral involvement. A study in children with HL compared the results of initial staging with BM biopsy vs

Table 1. Studies of PET and CT for Evaluating Response and Prognosis in DLBCL

Methods	Results and Conclusions
FDG-PET and prognostic index for DLBCL [Adams HJA et al. *Eur J Haematol.* 2014]	
73 patients treated with R-CHOP Determine prognostic value of whole-body SUV_{max}, whole-body MTV, and whole-body TLG with pretreatment FDG-PET/CT	Whole-body SUV_{max}, MTV, and TLG did not provide prognostic information in addition to NCCN-IPI for PFS and OS IPI remains most important prognostic tool in DLBCL
Interim PET to Predict Treatment Failure [Carr R et al. *J Nucl Med.* 2014]	
327 patients treated with 6 to 8 cycles of R-CHOP ± RT 45% with IPI score 2 to 3 45% with stage IV disease	Interim PET predictive of EFS and OS End of chemotherapy PET had more prognostic value than interim PET
FDG-PET and ASCT outcome [Dickinson M et al. *Br J Haematol.* 2010]	
FDG-PET response after salvage chemotherapy and pre-ASCT in 39 patients with relapsed/refractory DLBCL	3-y PFS: PET positive, 35%; PET negative, 81% ($P = .003$) OS: PET positive, 39%; PET negative, 81% ($P = .01$) PET response predicted outcome of ASCT in DLBCL

ASCT, autologous stem cell transplantation; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FDG, fluorodeoxyglucose; IPI, International Prognostic Index; MTV, metabolic tumor volume; NCCN, National Comprehensive Cancer Network; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; R-CHOP, rituximab + cyclophosphamide + hydroxydaunorubicin + oncovin + prednisolone; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis.

Sources: Adams HJA et al. *Eur Haematol.* 2014; Carr R et al. *J Nucl Med.* 2014; Dickinson M et al. *Br J Haematol.* 2010.

FDG-PET to diagnose BM involvement [Purz S et al. *J Clin Oncol.* 2011]. BM biopsy and FDG-PET results were positive in 7 of 175 patients. FDG-PET found BM involvement in 45 patients, 32 of whom had a typical multifocal pattern. Most of the skeletal lesions disappeared after chemotherapy in 38 of 39 follow-up PET scans. MRI and CT did not detect BM involvement in patients with a negative FDG-PET scan.

Results of a study in patients with newly diagnosed DLBCL suggested that FDG-PET/CT had limited value for detecting BM involvement [Hong J et al. *Ann Hematol.* 2011]. Focal hypermetabolism of hematopoietic BM on FDG-PET/CT had no impact on survival.

A study comparing the different published criteria in HL patients treated with an interim response-adapted approach confirmed the high negative predictive value of PET/CT for treatment outcome in HL [Le Roux PY et al. *Eur J Nucl Med Mol Imaging.* 2011].

False-positive FDG-PET can be caused by a variety of factors: infectious and inflammatory processes, thymic hyperplasia, activated brown adipose tissue, physiologic bowel and urinary activity, skeletal muscle, myocardium, gynecologic physiology, and granulocyte-colony stimulating factor–activated BM.

Table 2. Interpretation of Revised Criteria for Lymphoma

Criteria	Interpretation
Residual mass ≥ 2 cm	Uptake greater than mediastinal blood pool is abnormal, regardless of location
Residual lesions < 2 cm	Any uptake greater than surrounding background is abnormal
New lung nodules and CR elsewhere	Consider infection or inflammation
Residual liver/spleen nodules	> 1.5 cm: abnormal if SUV ≥ surrounding liver or spleen < 1.5 cm: abnormal if SUV > liver or spleen Diffuse spleen > liver: abnormal unless recent cytokine therapy
Bone	Focal uptake abnormal

CR, complete response; SUV, standardized uptake value.

Adapted from *Radiol Clin North Am.*, Vol 46, Schöder H et al, PET imaging for response assessment in lymphoma: potential and limitations, Pages 225-241. Copyright (2008), with permission from Elsevier.

Table 3. Consensus Summary of the 11th International Conference on Malignant Lymphoma

Lugano Classification Summary
PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity
A CMR even with a persistent mass is considered a complete remission (residual CT size at CMR is an issue undergoing evaluation)
PR requires a decrease > 50% in the SPDs of up to 6 representative nodes or extranodal lesions. Positive disease by CT criteria requires only an increase in the SPDs of a single node by 50%
Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding following treatment
Judicious use of follow-up scans may be considered in indolent lymphomas with residual intraabdominal or retroperitoneal disease

CMR, complete metabolic response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FDG, fluorodeoxyglucose; HL, Hodgkin lymphoma; PET, positron emission tomography; PR, partial response; SPD, sum of the product of the greatest perpendicular diameters.

Source: Cheson BD et al. *J Clin Oncol.* 2014.

Dr Cho concluded that the most important visual response criteria are the Deauville 5-point scale, liver and mediastinal blood pool references, and the new Lugano classification. Response assessment at the end of therapy is better validated than midtherapy response assessment. Nodal disease is more relevant than nonnodal disease. The role of CT and quantitative PET response criteria is evolving in terms of optimizing therapy for patients with lymphoma.