VOLUME 33 · NUMBER 18 · JUNE 20 2015

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

International Pediatric Non-Hodgkin Lymphoma Response Criteria

John T. Sandlund, R. Paul Guillerman, Sherrie L. Perkins, C. Ross Pinkerton, Angelo Rosolen,† Catherine Patte, Alfred Reiter, and Mitchell S. Cairo

See accompanying article on page 2112

John T. Sandlund, St Jude Children's Research Hospital, Memphis, TN; R. Paul Guillerman, Texas Children's Hospital, Houston, TX; Sherrie L. Perkins, University of Utah Health Sciences Center, Salt Lake City, UT; C. Ross Pinkerton, University of Queensland, Brisbane, Queensland, Australia; Angelo Rosolen, University of Padova, Padova, Italy; Catherine Patte, Institut Gustave Roussy, Paris, France; Alfred Reiter, Justus-Liebig-University of Giessen, Giessen, Germany; and Mitchell S. Cairo, New York Medical College, Valhalla, NY.

†Deceased.

Published online ahead of print at www.jco.org on May 4, 2015.

Supported in part by National Cancer Institute Grant No. CA 21765 and the American Lebanese Syrian Associated Charities (J.T.S.) and by grants from the Pediatric Cancer Research Foundation and National Cancer Institute Grant No. 1R13CA171748-01 (M.S.C.).

Presented in part at the Third International Childhood, Adolescent and Young Adult Non-Hodgkin's Lymphoma (NHL) Symposium, Frankfurt, Germany, June 11-13, 2009, and the Fourth International Childhood, Adolescent and Young Adult NHL Symposium, New York, NY, November 1-3, 2012.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Mitchell S. Cairo, MD, New York Medical College, 40 Sunshine Cottage Rd, Skyline Office 1N-D12, Valhalla, NY 10595; e-mail: mitchell_cairo@nymc.edu.

0732-183X/15/3318w-2106w/$20.00

DOI: 10.1200/JCO.2014.59.0745

ABSTRACT

Purpose
Response criteria are well established for adult patients with non-Hodgkin lymphoma (NHL). A revised set of response criteria in adults with NHL was recently published. However, NHL in children and adolescents involves different histologies, primary sites of disease, patterns of metastatic spread, approaches to therapy, and responses to treatment compared with adult NHL. However, there are no standardized response criteria specific to pediatric NHL. Therefore, we developed international standardized methods for assessing response to therapy in children and adolescents with NHL.

Methods
An international multidisciplinary group of pediatric oncologists, pathologists, biologists, and radiologists convened during and after the Third and Fourth International Childhood, Adolescent and Young Adult NHL Symposia to review existing response and outcome data, develop methods for response evaluation that reflect incorporation of more sensitive technologies currently in use, and incorporate primary and metastatic sites of disease for the evaluation of therapeutic response in children and adolescents with NHL.

Results
Using the current adult NHL response criteria as a starting point, international pediatric NHL response criteria were developed incorporating both contemporary diagnostic imaging and pathology techniques, including novel molecular and flow cytometric technologies used for the determination of minimal residual disease.

Conclusion
Use of the international pediatric NHL response criteria in children and adolescents receiving therapy for NHL incorporates data obtained from new and more sensitive technologies that are now being widely used for disease evaluation, providing a standardized means for reporting treatment response.

J Clin Oncol 33:2106-2111. © 2015 by American Society of Clinical Oncology

INTRODUCTION

There have been well-established response criteria for adults with non-Hodgkin lymphoma (NHL).[1,2] In the recently published Lugano classification system, Barrington et al[3] and Cheson et al[4] updated and reported revised response criteria during and after treatment in adults with NHL. Both the prior and more recent reports on therapy response assessment in patients with NHL were developed without input from the pediatric oncology community and did not reference specific pediatric NHL disease entities.[1-4] However, there are major differences in clinical presentation, pathologic subtype, approach to therapy, and evaluation of response to treatment between pediatric and adult NHLs.[5-16] Currently, there are no uniformly agreed on response evaluation criteria for children with NHL. This dilemma prompted an international effort to establish uniform criteria. This proposal represents the consensus of a multidisciplinary international (North America, Europe, and Australia) collaboration of experts in pediatric oncology, hematopathology, radiology, and NHL biology (Third and Fourth International Symposia on Childhood, Adolescent and Young Adult NHL, held in 2009 and 2012, respectively).

The International Harmonization Project convened to address these issues in adults with malignant lymphoma, and this group subsequently published its recommendations.[1,2] The more recent

Lugano classification system incorporates [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) findings, immunohistochemistry (IHC) results, and flow cytometric data into response evaluation.[3,4] The Lugano classification does not specify an age range for intended application, but it is based on data primarily derived from populations of adult patients with lymphoma. However, there are some striking pathologic and staging differences between NHL occurring in children and adolescents compared with adults. The spectrum of histologic subtypes occurring in children and adolescents is quite different than that observed in adults, with a predominance of high-grade lymphomas occurring in children and adolescents.[5,7,8,14,16] Children are more likely to present with extranodal disease and have a greater propensity for involvement of the bone marrow (BM) and CNS as compared with adults. However, detection of extranodal disease in kidneys or CNS or diffuse BM involvement can be difficult using FDG-PET alone.[17] With respect to response evaluation modalities, the data on FDG-PET in pediatric NHL are derived from relatively small patient cohorts, particularly with respect to residual masses. However, there is increasingly wider use and acceptance of more sensitive ancillary immunophenotypic and molecular approaches to quantify minimal residual disease (MRD) for the NHL subtypes frequently encountered in children (eg, lymphoblastic lymphoma [LL], Burkitt's lymphoma [BL], anaplastic large-cell lymphoma [ALCL]).[18-24]

The accuracy and precision of response evaluation are directly related to the sensitivity, specificity, and availability of the tools used to make the determination. This has clearly changed and evolved over the years.[24] Subsequent changes have included the use of FDG-PET (available since early 2000s at some pediatric cancer centers), which in most settings has replaced gallium and bone scintigraphy.[25]

There remains controversy on how to interpret FDG-PET findings in children.[17,25,26] A subcommittee of the International Harmonization Project made specific recommendations regarding the use of FDG-PET in adults with NHL, indicated that visual assessment alone using the mediastinal blood pool as a comparator is adequate for determining abnormal FDG uptake, and strongly encouraged the implementation of the attenuation-correction PET technique.[27,28] These criteria for FDG-PET assessment were intended for end-of-treatment evaluation, and it was recommended that the use of FDG-PET for treatment monitoring during therapy be limited to clinical trials or prospective registries. Dunleavy et al[27] also emphasized that the role of FDG-PET is still being defined and made the following observations and recommendations: 1) reports of interim FDG-PET results in the treatment of adults with diffuse large B-cell lymphoma (DLBCL) have prognostic significance; 2) using FDG-PET to guide therapeutic decision making is still under investigation; 3) there are a lack of standardized reporting criteria for FDG-PET with proven reproducibility; and 4) interim FDG-PET should be considered investigational and only used for clinical decision making in the context of a clinical trial. There are also conflicting reports regarding the predictive value of FDG-PET with respect to treatment outcome.[29,30] More recently, Barrington et al[3] reported a new set of recommendations on the use of PET–computed tomography (CT) for staging and response assessment in malignant lymphomas to be used in clinical practice and late-phase clinical trials. These recommendations have been incorporated into the new Lugano classification and are intended both for interim analysis to assess early treatment response and for end-of-treatment analysis to establish remission status.[4] For metabolic response assessment on FDG-PET in the Lugano classification, a visual 5-point scale based on the Deauville criteria is recommended to grade the most intense disease FDG uptake, with a score of 1 representing no uptake above background, a score of 2 representing uptake $\leq$ mediastinum, a score of 3 representing uptake $>$ mediastinum but $\leq$ liver, a score of 4 representing uptake moderately higher than liver, and a score of 5 representing uptake markedly higher than liver and/or new lesions.[31] A score of 1 or 2 represents a complete metabolic response, a score of 3 probably represents complete response (CR) but may be considered as an inadequate response to avoid undertreatment in a de-escalation trial, a score of 4 or 5 with reduced uptake compared with baseline represents a partial metabolic response, a score of 4 or 5 with no significant change from baseline represents no response, and a score of 4 or 5 with an increase in uptake from baseline represents progressive metabolic disease.[4] However, it should be noted that the Deauville criteria were developed and validated on the basis of studies focused on adult DLBCL and follicular lymphoma subtypes and not pediatric NHL subtypes.[3]

Experience with FDG-PET imaging in pediatric NHL is relatively sparse compared with adult NHL. Riad et al[32] described a small series of children with BL who were found to have false-positive FDG-PET scans. False-positive FDG-PET scans have been observed in children with benign inflammatory processes,[32] xanthomatous pseudotumour,[33] brown fat, rebound thymic hyperplasia, or infection or as the result of a granulocyte colony-stimulating factor effect. A review of the past decade of publications regarding the use of FDG-PET for therapy response in pediatric lymphoma showed that FDG-PET generally demonstrates high sensitivity and negative predictive value but more variable and modest positive predictive value. Consequently, the significance of new or residual FDG-avid foci in the absence of a growing nodal or extranodal mass on CT or magnetic resonance imaging (MRI) is uncertain.[34] Minimal residual FDG-PET uptake has been the subject of much study and poses a challenge in the interpretation of FDG-PET.[31,35-39] These studies have been conducted primarily in adults, and specific data regarding FDG-PET imaging to determine response in children with NHL undergoing therapy are relatively lacking because of small sample sizes and inconsistent study designs. A recent small study showed that FDG-PET interpreted using the Deauville criteria can help confirm a CR in children with BL at the end of induction chemotherapy by virtue of a high negative predictive value.[40] However, with regard to the evaluation of treatment response in children with BL or other NHL histologies, more data regarding the significance of FDG-PET findings in a residual mass is needed before negative findings can be assumed to confirm a CR, as is now the case in the newly proposed Lugano classification for adult PET-CT–based response determination.[2,4]

MRI is the preferred imaging modality for evaluating CNS disease. CT scan is superior for assessing the lungs, and MRI is superior for assessing the marrow. With growing concern about the risks of cumulative ionizing radiation exposure to children resulting from CT, MRI could be considered as an alternative to CT for evaluating nonpulmonary disease sites, particularly in children with syndromes associated with increased sensitivity to ionizing radiation (eg, ataxia-telangiectasia, Nijmegen breakage syndrome).[41]

METHODS

Response criteria and methodology for determining response were reviewed from the results of multiple childhood and adolescent NHL pediatric cooperative group clinical trials and reports.[5-16,42-44] Morphologic evaluation of a pathologic sample, including a biopsy of a residual mass, or analysis of a BM or

Table 1. International Pediatric NHL Response Criteria

Criterion	Definition
CR	Disappearance of all disease (three designations)
CR	CT or MRI reveals no residual disease or new lesions
	Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques described as supporting data [Table 2])
	BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2])
CRb	Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques described as supporting data [Table 2]), with no new lesions by imaging examination
	BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2])
	No new and/or progressive disease elsewhere
CRu	Residual mass is negative by FDG-PET; no new lesions by imaging examination
	BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2])
	No new and/or progressive disease elsewhere
PR	50% decrease in SPD on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 2]); however, there should be 50% reduction in percentage of lymphoma cells
MR	Decrease in SPD $>$ 25% but $<$ 50% on CT or MRI; no new and/or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 2]); however, there should be 25% to 50% reduction in percentage of lymphoma cells
NR	For those who do not meet CR, PR, MR, or PD criteria
PD	For those with $>$ 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM or CSF

Abbreviations: BM, bone marrow; CR, complete response; CRb, complete response biopsy negative; CRu, complete response unconfirmed; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; MR, minor response; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; NR, no response; PD, progressive disease; PET, positron emission tomography; PR, partial response; SPD, sum of product of greatest perpendicular diameters.

CSF sample remains the standard approach to determine response. However, the findings of more sensitive pathologic techniques, including sensitive molecular and immunophenotypic approaches, should be considered and, in some cases, used to define the response evaluation. For example, immunophenotyping by IHC or flow cytometric analysis is useful for determining whether suspicious cells are in fact lymphoma. For example, in ALCL, occasional large cells that are CD30 and/or ALK positive in a biopsy or BM sample may be considered residual disease, assuming the diagnostic sample is also positive for both markers.[45,46] Similarly, use of sensitive flow cytometric approaches are well accepted for detection of MRD in LL in blood and marrow.[16] Use of other more sensitive detection methods to identify residual disease is more controversial, particularly in cases where suspicious cells are not observed in biopsy materials. For example, positive cytogenetic findings from a tumor biopsy or BM sample are not used to indicate induction failure, but we would advocate that such findings should be indicated in the response designation as supporting data. The finding of positive cytogenetics is unusual in the setting of negative morphologic evidence of disease. However, MRD testing (by either flow cytometric or molecular method), which can detect one in 10,000 to one in 100,000 cells, is more commonly observed, and inclusion of these data is not required or considered in the current standard NHL response evaluation systems in the literature. MRD technology has been successfully developed for the major pediatric NHL subtypes.[18-23] This includes flow cytometric determination of MRD for precursor T-LL,[18] polymerase chain reaction (PCR) detection of immunoglobulin gene rearrangements for mature B-cell lymphomas (eg, BL, DLBCL),[22,23] and quantitative PCR screening for the *NPM-ALK* fusion transcript in t(2;5)-positive cases of ALCL.[19,20] If positive MRD results are obtained, we do not recommend that the major response evaluation category be changed (eg, from CR to partial response [PR]), but we do suggest that this information be included in the response description as supporting data.

RESULTS

International Pediatric NHL Response Criteria

On the basis of a review of scientific evidence, consensus among the experts of this panel, recommendations of the International Harmonization Project in Lymphoma, and more recent revised response criteria,[1-4] we propose the following criteria for response assessment in children and adolescents receiving treatment for NHL (Table 1). We have elected to use the change in the sum of the products of the largest diameter and the perpendicular diameter (SPD) for each tumor mass, as measured by CT or MRI, as the measure of tumor size change, with the understanding that there may be cases where this is somewhat imprecise because of irregularly shaped tumor masses or disseminated disease with multiple tumor masses (Table 1). In cases with multiple masses, up to six of the most representative nodal or extranodal masses should be selected for measurement, as suggested in the new Lugano classification for adults.[1-4] To grade FDG uptake for metabolic response assessment on PET, a reproducible method should be used, such as the Deauville criteria visual 5-point scale recommended in the Lugano classification[4] or a more quantitative measure like the change in the maximum standardized uptake value. This will facilitate analysis and potential validation of these methods in subsequent clinical trials of pediatric NHL.

CR

The CR designation will be used to indicate the disappearance of all disease; however, there will be subclassification of this designation to indicate how this designation was determined.

CR. The CR designation indicates the complete disappearance of all disease, as confirmed by physical examination, CT, or MRI and examination of CSF and BM. Specifically, the CT or MRI should be free of residual mass or evidence of new disease. FDG-PET should be negative (Deauville criteria score of 1, 2, or 3 [unless score of 3 is considered as inadequate response to avoid undertreatment, such as in de-escalation trial]). If a residual or new mass is present but has been completely resected and is negative for disease by pathologic evaluation of morphology, a CR designation is still assigned. Evaluation of BM and CSF should be negative for morphologic evidence of disease

Table 2. Supporting International Pediatric NHL Response Criteria Data

Supporting Information	Description
BM involvement	Currently defined by morphologic evidence of lymphoma cells; this applies to any histologic subtype; type and degree of BM involvement should be specified*
BMm	BM positive by morphology (specify percentage of lymphoma cells)
BMi	BM positive by immunophenotypic methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
BMc	BM positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
BMmol	BM positive by molecular techniques
CNS involvement	
CSF status	CSF positivity is based on morphologic evidence of lymphoma cells; CSF should be considered positive when any number of blasts is detected; CSF may be unknown; as with BM, type of CSF involvement should be described whenever possible
CSFm	CSF positive by morphology (specify No. of blasts/μL)
CSFi	CSF positive by immunophenotype methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
CSFc	CSF positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
CSFmol	CSF positive by molecular techniques
RM	
RMm	Tumor detected by standard morphologic evaluation
RMi	Tumor detected by immunophenotypic methods (immunohistochemical or flow cytometric analysis)
RMc	Tumor detected by cytogenetic or FISH analysis
RMmol	Tumor detected by molecular techniques

Abbreviations: BM, bone marrow; FISH, fluorescent in situ hybridization; NHL, non-Hodgkin lymphoma; PB, peripheral blood; RM, residual mass.
*Same approach should be used for PB involvement (ie, PBm, PBi, PBc, PBmol).

as well for the CR designation. Detection of disease using more sensitive techniques, such as immunophenotyping or molecular techniques should be indicated as supporting data, as summarized in Table 2. There should be no new and/or progressive disease (PD) elsewhere.[2]

CR biopsy negative. The CR biopsy negative (CRb) designation is for patients who otherwise meet the CR designation but have a residual mass on CT or MRI that is biopsied (not resected) and found to be negative for disease based on pathologic evaluation of morphology. If disease is detected by more sensitive tools (eg, molecular techniques, flow cytometry, IHC, cytogenetics), this should be indicated as supporting data, as summarized in Table 2. Although a biopsy of a residual mass that is negative for viable tumor provides some reassurance, there is always a possibility of sampling error. Thus, a CRb designation is included until there are more data showing that a negative biopsy is equivalent to a negative morphologic examination of a completely resected residual mass and/or until there are adequate PET data to confidently exclude the need for biopsy of a PET-negative residual mass. The decision to biopsy an FDG-PET–positive bone lesion is a clinical judgment based on symptoms and level of concern about risk associated with biopsy of a weight-bearing long bone.

CR unconfirmed. The CR unconfirmed designation is applied in otherwise CR cases in which a residual mass on CT or MRI is negative by FDG-PET imaging. BM and CSF must be morphologically negative for tumor. There should be no new and/or PD elsewhere.

PR. The PR designation is assigned when there has been $\geq$ 50% decrease in the SPD by CT or MRI. The FDG-PET imaging results may be positive (Deauville score of 4 or 5 with reduced lesional uptake compared with baseline). Morphologic detection of disease in a biopsy sample of the mass may be present. There may also be persistent morphologic detection of disease in the BM and CSF if this finding was present at diagnosis; however, there should be a 50% reduction in the percentage of lymphoma cells. There should be no new and/or PD elsewhere.

Minor response. The minor response designation is assigned in cases where the decrease in the SPD is $>$ 25% but $<$ 50%. Morphologic detection of disease in a biopsy sample of the mass may be present. There may also be persistent morphologic detection of disease in the BM and CSF, if this finding was present at diagnosis; however, there should be a 25% to 50% reduction in the percentage of lymphoma cells. There should be no new and/or PD elsewhere.

No response. The no response designation will be applied for those patients whose residual lesions do not meet the criteria for CR, PR, minor response, or PD.

PD. The PD designation is applied for any patient with $>$ 25% increase in the SPD of residual lesions, Deauville score 4 or 5 on FDG-PET with an increase in lesional uptake from baseline, or documentation of new lesions. PD also applies to any patient who develops new morphologic evidence of BM or CNS disease.

Supporting Response Data

The recommended collection of additional response data beyond current conventional data collection is summarized in Table 2. These additional data largely reflect information obtained using newer or more sensitive technologies to detect MRD. Although these data are not incorporated into our recommended response evaluation criteria outlined in this report, they will likely be used in future recommendations for pediatric NHL response evaluation.

DISCUSSION

The international pediatric NHL response criteria described in this consensus statement provide a more uniform and accurate means of defining treatment response in children and adolescents with NHL and allow for systematic collection of supporting data generated by ancillary testing (Table 2) that may, in the future, become important criteria in defining response. The major response designations will be established by CT or MRI of involved sites in conjunction with morphologic evaluation of BM and CSF, if involved at diagnosis. With growing concern about the risks of cumulative ionizing radiation

exposure to children resulting from CT, MRI could be considered as an alternative to CT for evaluating nonpulmonary disease sites. The lack of universal availability of FDG-PET is accounted for in this system; however, in centers where FDG-PET is available, the results will be used and designated accordingly.

This response evaluation system will be revised as additional evidence about the utility, reproducibility, and impact of data from FDG-PET and more advanced immunophenotypic and molecular tools become available. For example, the need for a CR unconfirmed designation may become unnecessary (as in revised Cheson criteria and Lugano classification),[2-4] if sufficient evidence becomes available that FDG-PET–negative masses reflect a true CR in children and adolescents with NHL. Pathologic evaluation of a residual FDG-PET–negative mass provides the most direct evidence as to whether a true CR has been achieved, whereas lack of progression or relapse at the site of the residual FDG-PET–negative mass would provide indirect evidence of CR status. More sensitive molecular and immunophenotypic tools for disease detection will also be helpful in further refining response criteria. Among children with acute lymphoblastic leukemia, MRD as detected by PCR or flow cytometry is now reported as a subdesignation of response in marrows that are otherwise morphologically free of disease.[47,48] Similarly, MRD evaluations of peripheral blood and BM in NHL are now possible for children and adolescents with the major pediatric lymphoma subtypes,[18,19,21-23] and this information can now be included in the description of response evaluation as supportive data. Additional refinements in the description of response evaluation will be required as more sensitive tools are developed for pathologic detection of disease and evidence as to their utility in defining outcomes emerges.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: Sherrie L. Perkins
Data analysis and interpretation: Sherrie L. Perkins
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI-sponsored international working group. J Clin Oncol 17:1244, 1999

2. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

3. Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32:3048-3058, 2014

4. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 32:3059-3068, 2014

5. Abromowitch M, Sposto R, Perkins S, et al: Shortened intensified multi-agent chemotherapy and non-cross resistant maintenance therapy for advanced lymphoblastic lymphoma in children and adolescents: Report from the Children's Oncology Group. Br J Haematol 143:261-267, 2008

6. Brugières L, Pacquement H, Le Deley MC, et al: Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: A report from the French Society of Pediatric Oncology. J Clin Oncol 27:5056-5061, 2009

7. Burkhardt B, Woessmann W, Zimmermann M, et al: Impact of cranial radiotherapy on central nervous system prophylaxis in children and adolescents with central nervous system-negative stage III or IV lymphoblastic lymphoma. J Clin Oncol 24:491-499, 2006

8. Cairo MS, Gerrard M, Sposto R, et al: Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 109:2736-2743, 2007

9. Cairo MS, Sposto R, Gerrard M, et al: Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (≥ 15 years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: Results of the FAB LMB 96 study. J Clin Oncol 30:387-393, 2012

10. Gerrard M, Cairo MS, Weston C, et al: Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: Results of the FAB/LMB 96 international study. Br J Haematol 141:840-847, 2008

11. Goldman S, Smith L, Anderson JR, et al: Rituximab and FAB/LMB 96 chemotherapy in children with stage III/IV B-cell non-Hodgkin lymphoma: A Children's Oncology Group report. Leukemia 27:1174-1177, 2013

12. Le Deley MC, Rosolen A, Williams DM, et al: Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: Results of the randomized ALCL99-vinblastine trial. J Clin Oncol 28:3987-3993, 2010

13. Lowe EJ, Sposto R, Perkins SL, et al: Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: Final results of Children's Cancer Group Study 5941. Pediatr Blood Cancer 52:335-339, 2009

14. Patte C, Auperin A, Gerrard M, et al: Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: It is possible to reduce treatment for the early responding patients. Blood 109:2773-2780, 2007

15. Reiter A, Schrappe M, Ludwig WD, et al: Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: A BFM group report. Blood 95:416-421, 2000

16. Sandlund JT, Downing JR, Crist WM: Non-Hodgkin's lymphoma in childhood. N Engl J Med 334:1238-1248, 1996

17. Kluge R, Kurch L, Montravers F, et al: FDG PET/CT in children and adolescents with lymphoma. Pediatr Radiol 43:406-417, 2013

18. Coustan-Smith E, Sandlund JT, Perkins SL, et al: Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: A report from the Children's Oncology Group. J Clin Oncol 27:3533-3539, 2009

19. Damm-Welk C, Busch K, Burkhardt B, et al: Prognostic significance of circulating tumor cells in bone marrow or peripheral blood as detected by qualitative and quantitative PCR in pediatric NPM-ALK-positive anaplastic large-cell lymphoma. Blood 110:670-677, 2007

20. Damm-Welk C, Schieferstein J, Schwalm S, et al: Flow cytometric detection of circulating tumour cells in nucleophosmin/anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: Comparison with quantitative polymerase chain reaction. Br J Haematol 138:459-466, 2007

21. Mussolin L, Damm-Welk C, Pillon M, et al: Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. Leukemia 27:416-422, 2013

22. Mussolin L, Pillon M, d'Amore ES, et al: Minimal disseminated disease in high-risk Burkitt's lymphoma identifies patients with different prognosis. J Clin Oncol 29:1779-1784, 2011

23. Shiramizu B, Goldman S, Kusao I, et al: Minimal disease assessment in the treatment of children and adolescents with intermediate-risk (stage III/IV) B-cell non-Hodgkin lymphoma: A Children's Oncology Group report. Br J Haematol 153:758-763, 2011

24. Sandlund JT: Burkitt lymphoma: Staging and response evaluation. Br J Haematol 156:761-765, 2012

25. Shankar A, Fiumara F, Pinkerton R: Role of FDG PET in the management of childhood lymphomas: Case proven or is the jury still out? Eur J Cancer 44:663-673, 2008

26. Nakatani K, Nakamoto Y, Watanabe K, et al: Roles and limitations of FDG PET in pediatric non-Hodgkin lymphoma. Clin Nucl Med 37:656-662, 2012

27. Dunleavy K, Mikhaeel G, Sehn LH, et al: The value of positron emission tomography in prognosis and response assessment in non-Hodgkin lymphoma. Leuk Lymphoma 51:28-33, 2010 (suppl 1)

28. Juweid ME, Stroobants S, Hoekstra OS, et al: Use of positron emission tomography for response assessment of lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 25:571-578, 2007

29. Cahu X, Bodet-Milin C, Brissot E, et al: 18F-fluorodeoxyglucose-positron emission tomography before, during and after treatment in mature T/NK lymphomas: A study from the GOELAMS group. Ann Oncol 22:705-711, 2011

30. Palmer J, Goggins T, Broadwater G, et al: Early post transplant (F-18) 2-fluoro-2-deoxyglucose positron emission tomography does not predict outcome for patients undergoing auto-SCT in non-Hodgkin and Hodgkin lymphoma. Bone Marrow Transplant 46:847-851, 2011

31. Meignan M, Gallamini A, Haioun C: Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma 50:1257-1260, 2009

32. Riad R, Omar W, Sidhom I, et al: False-positive F-18 FDG uptake in PET/CT studies in pediatric patients with abdominal Burkitt's lymphoma. Nucl Med Commun 31:232-238, 2010

33. Otto M, Shulkin BL, Kundu M, et al: Histiocyte-rich xanthomatous pseudotumor mimicking relapse on positron emission tomography imaging in an adolescent with primary mediastinal diffuse large B-cell lymphoma. J Pediatr Hematol Oncol 34:232-235, 2012

34. Sioka C: The utility of FDG PET in diagnosis and follow-up of lymphoma in childhood. Eur J Pediatr 172:733-738, 2013

35. Barrington SF, Qian W, Somer EJ, et al: Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 37:1824-1833, 2010

36. Gallamini A, Fiore F, Sorasio R, et al: Interim positron emission tomography scan in Hodgkin lymphoma: Definitions, interpretation rules, and clinical validation. Leuk Lymphoma 50:1761-1764, 2009

37. Gallamini A, Hutchings M, Rigacci L, et al: Early interim 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: A report from a joint Italian-Danish study. J Clin Oncol 25:3746-3752, 2007

38. Hutchings M, Mikhaeel NG, Fields PA, et al: Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. Ann Oncol 16:1160-1168, 2005

39. Le Roux PY, Gastinne T, Le Gouill S, et al: Prognostic value of interim FDG PET/CT in Hodgkin's lymphoma patients treated with interim response-adapted strategy: Comparison of International Harmonization Project (IHP), Gallamini and London criteria. Eur J Nucl Med Mol Imaging 38: 1064-1071, 2011

40. Bailly C, Eugène T, Couec ML, et al: Prognostic value and clinical impact of (18)FDG-PET in the management of children with Burkitt lymphoma after induction chemotherapy. Front Med (Lausanne) 1:54, 2014

41. Sandlund JT, Hudson MM, Kennedy W, et al: Pilot study of modified LMB-based therapy for children with ataxia-telangiectasia and advanced stage high grade mature B-cell malignancies. Pediatr Blood Cancer 61:360-362, 2014

42. Galardy PJ, Hochberg J, Perkins SL, et al: Rasburicase in the prevention of laboratory/clinical tumour lysis syndrome in children with advanced mature B-NHL: A Children's Oncology Group report. Br J Haematol 163:365-372, 2013

43. Gerrard M, Waxman IM, Sposto R, et al: Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood 121:278-285, 2013

44. Goldman S, Smith L, Galardy P, et al: Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow-positive Burkitt lymphoma/leukaemia: A Children's Oncology Group report. Br J Haematol 167:394-401, 2014

45. Morris SW, Kirstein MN, Valentine MB, et al: Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 263:1281-1284, 1994

46. Morris SW, Xue L, Ma Z, et al: Alk+ CD30+ lymphomas: A distinct molecular genetic subtype of non-Hodgkin's lymphoma. Br J Haematol 113:275-295, 2001

47. Coustan-Smith E, Sancho J, Behm FG, et al: Prognostic importance of measuring early clearance of leukemic cells by flow cytometry in childhood acute lymphoblastic leukemia. Blood 100:52-58, 2002

48. Coustan-Smith E, Sancho J, Hancock ML, et al: Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. Blood 96: 2691-2696, 2000

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

International Pediatric Non-Hodgkin Lymphoma Response Criteria

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

John T. Sandlund
No relationship to disclose

R. Paul Guillerman
Consulting or Advisory Role: PTC Therapeutics, Vertex Pharmaceuticals

Sherrie L. Perkins
No relationship to disclose

C. Ross Pinkerton
No relationship to disclose

Angelo Rosolen
No relationship to disclose

Catherine Patte
No relationship to disclose

Alfred Reiter
No relationship to disclose

Mitchell S. Cairo
No relationship to disclose

Acknowledgment

We thank Lauren Harrison, RN, MSN, and Erin Morris, RN, for their expert editorial assistance in the preparation of this article. We dedicate this article to Angelo Rosolen, MD, who unfortunately passed away after its completion.