Response Assessment in Pediatric Non-Hodgkin Lymphoma

9

Tony H. Truong and Veronique Minard-Colin

Introduction

Through national and international collaboration, the outcome of children with non-Hodgkin lymphoma (NHL) has greatly improved over the past half century [13]. Advances in risk stratification and response assessment have facilitated therapeutic decisions by maximizing therapy in those with the most advanced and resistant diseases, while sparing toxicity and late effects in those with more favorable ones. An ongoing challenge remains the accurate determination of response and remission status, such that subsequent therapy can be individually modified to the patient's disease based on their response to treatment.

Response assessment is the clinical, biopathological, and radiological evaluation of a patient to determine if active residual disease remains either at an interim time point during treatment or at the end of the therapy. The methods used for response assessment are closely linked to those used to assess extent of disease during staging at the time of initial diagnosis. Clinical examination of sites of disease such as residual lymphadenopathy, hepatosplenomegaly, and extra-nodal disease sites are useful at the bedside but lack sensitivity. Follow-up assessments often include repeat staging evaluations, such as imaging and, if applicable, bone marrow aspirates and biopsies and lumbar punctures for cerebrospinal fluid (CSF) involvement. Imaging modalities remain the primary method to assess response status since these tumors are often not evident by other means.

T. H. Truong (✉)
Department of Oncology and Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada
e-mail: tony.truong@ahs.ca

V. Minard-Colin
Department of Pediatric and Adolescent Oncology, Gustave Roussy, Villejuif, France

If residual lesions are identified on follow-up imaging, a major dilemma is whether these represent sites of active residual disease or benign processes such as tumor necrosis and/or inflammatory fibrosis. If there is sufficient concern, the gold standard and often recommended approach is a biopsy.

Different study groups have evaluated the importance of response determination among the various NHL subtypes. In B-NHL, both the Société Française d'Oncologie Pédiatrique (SFOP) LMB and Berlin–Frankfurt–Münster (BFM) studies have demonstrated that residual disease following three cycles of therapy leads to an increased risk of relapse. Intensification of chemotherapy or mega-dose chemotherapy followed by hematopoietic stem cell rescue has resulted in improved outcomes [17, 20]. Among patients with lymphoblastic lymphoma (LBL), the COG A5971 study showed that a radiologic response at two weeks significantly correlated with event-free survival (EFS) and overall survival (OS) [25]. In BFM 90–95 studies, patients with <70% reduction in the size of their mediastinal mass by end of induction day 33 had therapy intensified [19]. In anaplastic large cell lymphoma (ALCL), early response assessment after one course by PCR evaluation may identify patients with a very high risk of treatment failure [10].

Based on a combination of radiographic and histological findings, conventional definitions of response use the designations of complete response (CR), partial response (PR), no response (NR), and progressive disease (PD). CR often refers to the complete absence of any disease detected clinically or radiographically by some pre-specified measure of residual size of the baseline lesion. Partial response encompasses a wide range of definitions between CR and stable disease (SD), also known as "no response." Progressive disease often refers to increasing size of the baseline mass or new sites of disease not present at diagnosis. These definitions are quite varied and often specific to certain diseases or collaborative groups, making comparison across diseases and clinical trials a challenge.

O. Abla, A. Attarbaschi (eds.), *Non-Hodgkin's Lymphoma in Childhood and Adolescence*,
https://doi.org/10.1007/978-3-030-11769-6_9

Response Assessment by Pathology and Molecular Biology

Histological confirmation remains the gold standard to differentiate active residual disease from tumor necrosis or inflammatory scar tissue. In the SFOP LBM89 study, 126 out of 551 patients had radiologic evidence of residual masses. Of these, 113 patients underwent either biopsy or excision of the mass, but only 12 had viable tumor cells (10.6%) [17]. In LMB96, 23 of 657 patients (3.5%) had histologically proven residual disease at remission assessment [4]. For those with active residual disease after three courses of chemotherapy, the success of intensification of therapy suggests that repeat biopsy for these questionable masses may be justified [17].

Sometimes, the decision to resect or biopsy a residual mass may be complicated by several factors, including the patient's underlying condition, the location of the mass, the ease/difficulty of the procedure, and the risks involved. In general, a resection or biopsy should only be attempted if it will change the management approach. Resections are preferred to reduce tumor burden and improve diagnostic yield from pathology, but sometimes may not be feasible or dangerous (e.g., lesions in the gastrointestinal tract). Oopherectomy should be avoided and lesions in the visceral organs need only be sampled with a biopsy. If diagnostic tissue is not obtained, serial biopsies may be attempted if the benefit of knowing the result outweighs the risk involved.

Morphological assessment with the identification of tumor cells is the mainstay for determining residual disease. However, the evaluation of viability of residual cells may be challenging since necrotic tumor cells may still stain positive for B-cell markers such as CD20. The incorporation of highly sensitive measures such as immunophenotyping by flow cytometry, cytogenetics and FISH analysis, and molecular PCR methods have led to further improvement in the detection of minimal disseminated disease (MDD) at diagnosis or minimal residual disease (MRD) during response assessment.

The ability to detect MRD in acute lymphoblastic leukemia (ALL) has greatly informed the risk stratification, prognostication, and treatment for this disease [3, 15]. In NHL, MRD detection has been applied most commonly in lymphoblastic lymphoma using flow cytometry or molecular techniques based on clonal rearrangements of the immunoglobulin or T-cell receptor gene detected at the time of diagnosis [8]. Molecular methods have increased the sensitivity of disease detection with the use of PCR for immunoglobulin gene rearrangements for mature B-NHL (BL and DLBCL) [1]. In the AIEOP LNH-97 study, the Italian group used long-distance PCR for the t(8;14) for MDD detection in patients with Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) [18].

In pediatric ALCL, over 90% of patients will have rearrangement of the *NPM* gene on 5q35 to the anaplastic lymphoma kinase gene *ALK* on 2p23, forming the translocation t(2;5) and the resulting fusion protein *NPM-ALK* [9]. When combined with the detection of antibodies to ALK protein, the BFM and Italian study groups showed that detection of *NPM-ALK* by PCR at diagnosis in blood and/or BM was highly predictive of outcome. High-risk patients with positive MDD and low ALK antibody titer had the lowest progression-free survival (PFS) of 28% compared to the low-risk group (MDD negative and high ALK titer) who had a PFS of 93% [14]. Moreover, detection of persistent *NPM-ALK* by PCR at the end of the first course of chemotherapy (MRD) was highly prognostic and associated with a high risk of relapse [10].

Novel methods such as next-generation sequencing using cell-free circulating tumor DNA are now being developed by many groups with potential future applications to various tissue types including the primary tumor mass, bone marrow, CSF, and/or blood at the time of follow-up [22]. To date, the role of MRD and MDD assessment in response evaluation and risk stratification remains investigational. A thorough review of minimal disseminated disease is presented in the following chapter.

Response Assessment by Imaging

The use of imaging modalities to detect response to treatment remains standard practice in pediatric NHL. The most commonly used modalities are computerized tomography (CT) and magnetic resonance imaging (MRI), each having their unique advantages and applications. CT is the most readily available modality at almost every center, is inexpensive, is fast to perform, and often does not require a general anesthetic in young children. However, exposure to radiation is major concern, especially in patients with predispositions that increase sensitivity to ionizing radiation. For detection and follow-up of pulmonary lesions, CT remains the best modality. For lymphoma patients, MRI is best used for the evaluation of CNS disease in the case of neurologic symptoms or parameningeal mass but is a lengthier procedure which often requires a general anesthetic in young children.

The definitions of imaging-defined response categories, CR, PR, PD, etc., were historically based on the measurement of tumors on cross-sectional imaging. Many measurement methods have been used to assess disease burden and calculate response, leading to variability in practices and difficulty in comparing responses across clinical trials. Currently, the general practice is to identify the most representative lesion and measure it using the longest diameter (LDi) and the

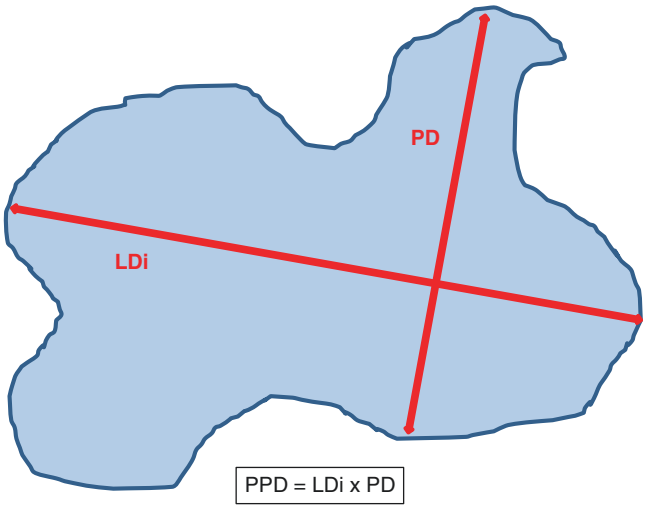

Fig. 9.1 Drawing of cross-sectional image and calculation of the sum of the product of the greatest perpendicular dimensions (SPD)

perpendicular diameter (PD). Multiplying these two diameters generates a product of the perpendicular diameter (PPD) (Fig. 9.1). If more than one lesion exists, as is often the case, then up to six of the most representative (often the largest) lesions are identified as "target" lesions and the sum of products of the largest diameter and the perpendicular diameter for each lesion (SPD) is calculated. The SPD is used as a measure to compare baseline disease burden to that at a later point in time [23]. Other ways to assess response have included measuring the change in transverse diameter or sum of the largest diameters and/or change in three-dimensional volume. Given the variability in response assessment, the need to establish uniform measurement criteria and standard definitions of response was well recognized.

A significant correlation has been observed between the size of the residual lesion and tumor viability. A residual mass measuring ≥5 cm in the largest diameter should be assessed by pathology while a lesion <2 cm is usually reassuring. For intermediate-sized residual lesions (i.e., 2–5 cm), pathological assessment is recommended either by biopsy or complete resection, if possible (Patte, personal communication). In clinical practice, a major challenge is also the assessment of extra-nodal residual disease, which is more frequent in children/adolescents with NHL than in adults [4, 16]. These include more frequent mediastinal residual masses, residual kidney lesions (very common), and residual hepatic and ovarian lesions. Imaging should be considered suspicious if the size of the organ is enlarged (as seen in ovarian masses) or if "stick out masses" are seen (in mediastinal masses). Cases of residual lesions detected on CT/MRI but not apparent on ultrasonography because of necrosis/fibrosis are generally more reassuring (e.g., kidney/hepatic lesions).

FDG-PET

Whole-body ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG)-PET has become an invaluable tool in staging and response assessment of non-Hodgkin lymphoma therapy in adults but its value needs to be further evaluated in pediatric NHL. FDG is a glucose analog that is taken up by cells via glucose transporter proteins. It then undergoes phosphorylation by hexokinase where it does not undergo any further metabolism and is trapped within the cell. FDG uptake is increased in certain malignancies including NHL and Hodgkin lymphoma, and its use is being actively investigated in many other cancer types.

Functional imaging with FDG-PET is often used to assess response evaluation in childhood NHL, but the data to guide such practices are lacking. Limitations to PET include the lack of standardized imaging protocols and variable reporting criteria. This creates uncertainty about the interpretation of PET for use in interim assessment and end of therapy assessment.

PET scans generally have high sensitivity and negative predictive value (NPV) for ruling out disease when negative, but more variable and modest positive predictive value when the result is positive. In a single-center study, PET/CT was compared to conventional imaging and biopsy findings in 18 children with NHL who had biopsy results for evaluation of residual disease. Patients had mature B-NHL and ALCL. A score of 4 or 5 using the London criteria defined PET-positive status. The sensitivity and NPV for PET/CT was 100% but specificity was 60% and PPV was 25%. However, conventional imaging (mostly by CT and MRI) was no better than PET/CT with a sensitivity and NPV of 100% but lower specificity of 20% and PPV of 14% [2].

In a study of 24 pediatric patients with abdominal Burkitt lymphoma, 4 were found to have PET-positive scans at the end of treatment, leading to the need for histological confirmation. Three of these patients had no evidence of malignancy while one patient did, leading to 100% NPV and 25% PPV [21]. Overall, these data indicate that false positive findings by PET/CT are common in children with NHL. A negative scan is generally reassuring as a good indicator of complete response.

The reproducibility of PET interpretation has also been called into question. To address these concerns, standard PET imaging classifications have been adopted, such as the Deauville criteria, a 5-point visual-based criteria, similar to that used in the adult Lugano classification [5, 12]. The most intense FDG site is graded, as per the following Table 9.1.

Use of PET for treatment monitoring during the course of therapy is a common practice, but there is limited evidence to support its use in clinical decision-making. Therefore, this should only be used in a clinical trial or prospective registry study.

Table 9.1 Deauville score in assessing PET response

Score	Description	Interpretation
1	No uptake above background	Complete metabolic response
2	Uptake ≤ mediastinum	
3	Uptake > mediastinum but ≤ liver	1. Probable complete response (CR) 2. May be considered inadequate response to avoid under-treatment in a de-escalation trial
4	Uptake moderately higher than liver	1. Reduced uptake compared to baseline: partial metabolic response 2. No significant change from baseline: no response 3. Increase uptake from baseline: progressive metabolic disease
5	Uptake markedly higher than liver and/or new lesions	

Adapted from: Meignan et al. [12]

The presence of residual PET uptake on an end-of-treatment PET scan, also known as minimal residual uptake (MRU), is a troubling issue and often leads to further investigations to obtain histology or increased frequency of follow-up scans. A single institution study of patients with BL and DLBCL suggests that end of therapy surveillance imaging has low yield for relapse detection but exposure to unnecessary radiation. Only 3 of 44 patients (6.8%) relapsed, none of whom were identified from CT- or PET-based surveillance imaging [11]. In addition to active residual disease, a positive PET may be due to many benign processes including brown fat, rebound thymic hyperplasia, infection, or a benign inflammatory process [24].

Standardization of Response Assessment

Given the need to standardize the measurement and assessment of PET-avid malignancies, an international collaborative effort was initiated by the adult group known as the International Harmonization Project [6] which later produced updated recommendations [7]. The latter guidelines made a formal inclusion of FDG-PET, such that patients with a PET negative residual mass were now considered CR instead of CRu (CR-unconfirmed) on the predecessor guideline. In addition, bone marrow immunohistochemistry and flow cytometry were also incorporated in the response evaluation. A further update known as the Lugano classification emphasized the importance of PET as the gold standard for routine imaging of all FDG-avid, nodal lymphomas and obviated the need for a bone marrow biopsy (BMB) at least in the case of Hodgkin lymphoma when PET-CT is used [5]. This recommendation did not directly translate to NHL as the panel recognized the importance of a BMB in DLBCL when the PET is negative and in cases where knowing BM status would change patient management.

It is well recognized that pediatric NHL differs from adult NHL in several ways: only a few subtypes form the majority of pediatric NHL, most are high-grade lymphomas, and there is a predominance of advanced disease presentations, generally involving the bone marrow and CNS. The need for separate pediatric criteria led to a multidisciplinary collaboration of experts at the third and fourth International Symposia on Childhood, Adolescent, and Young Adult NHL in 2009 and 2012, respectively, resulting in the development of the International Pediatric NHL Response Criteria [23]. The new pediatric criteria incorporate the combination of imaging, tumor histology, bone marrow, and CSF, into five major categories of response (Table 9.2). In addition, the availability of newer techniques based on immunophenotype, cytogenetics, and molecular techniques are used as supporting criteria to more accurately describe the basis for response

Table 9.2 International pediatric NHL response criteria

Criterion	Definition
CR	Disappearance of all disease (three designations) CT or MRI reveals no residual disease or new lesions Resected residual mass that is pathologically (morphologically) negative for disease[a] BM and CSF morphologically free of disease
CRb	Residual mass has no morphologic evidence of disease from limited or core biopsy, with no new lesions by imaging examination[a] BM and CSF morphologically free of disease No new and/or progressive disease elsewhere
Cru	Residual mass is negative by FDG-PET (Deauville score 1, 2, or 3); no new lesions by imaging examination BM and CSF morphologically free of disease[a] 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[a]; 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[a]; however, there should be 25–50% 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

Adapted from Sandlund et al. [23].
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
[a]Detection of disease with more sensitive techniques described as supporting data (Table 9.3)

Table 9.3 Supporting international pediatric NHL response criteria data

Supporting criterion	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[a]
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 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
Residual mass (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

Adapted from Sandlund et al. [23]
Abbreviations: *BM* bone marrow, *FISH* fluorescent in situ hybridization, *NHL* non-Hodgkin lymphoma, *PB* peripheral blood, *RM* residual mass
[a]Same approach should be used for PB involvement (i.e. PBm, PBi, PBc, PBmol)

determination (Table 9.3). The inclusion of supporting response data, though not directly incorporated into the response evaluation, is forward thinking as these measures will in no doubt be integrated in future criteria.

A standardized response evaluation schema has many benefits but requires widespread acceptance and incorporation into clinical trials. It will allow for comparison of treatment efficacy across multiple regimens while facilitating clinical decision-making for the individual patient.

References

1. Agsalda M, Kusao I, Troelstrup D, Shiramizu B. Screening for residual disease in pediatric burkitt lymphoma using consensus primer pools. Adv Hematol. 2009;2009:412163.
2. Bhojwani D, McCarville MB, Choi JK, Sawyer J, Metzger ML, Inaba H, Davidoff AM, Gold R, Shulkin BL, Sandlund JT. The role of FDG-PET/CT in the evaluation of residual disease in paediatric non-Hodgkin lymphoma. Br J Haematol. 2015;168(6):845–53.
3. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, Linda S, Martin PL, Pullen DJ, Viswanatha D, Willman CL, Winick N, Camitta BM, Children's Oncology Group. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111(12):5477–85.
4. Cairo M, 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. 2007;109(7):2736–43.
5. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA, Alliance, Australasian Leukaemia and Lymphoma Group, Eastern Cooperative Oncology Group, European Mantle Cell Lymphoma Consortium, Italian Lymphoma Foundation, European Organisation for Research, Treatment of Cancer/Dutch Hemato-Oncology Group, Grupo Espanol de Medula Osea, German High-Grade Lymphoma Study Group, German Hodgkin's Study Group, Japanese Lymphorra Study Group, Lymphoma Study Association, NCIC Clinical Trials Group, Nordic Lymphoma Study Group, Southwest Oncology Group, United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–68.
6. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999;17(4):1244–53.
7. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V, International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579–86.
8. Coustan-Smith E, Sandlund JT, Perkins SL, Chen H, Chang M, Abromowitch M, Campana D. Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: a report from the children's oncology group. J Clin Oncol. 2009;27(21):3533–9.
9. Damm-Welk C, Klapper W, Oschlies I, Gesk S, Rottgers S, Bradtke J, Siebert R, Reiter A, Woessmann W. Distribution of NPM1-ALK and X-ALK fusion transcripts in paediatric anaplastic large cell lymphoma: a molecular-histological correlation. Br J Haematol. 2009;146(3):306–9.
10. Damm-Welk C, Mussolin L, Zimmermann M, Pillon M, Klapper W, Oschlies I, d'Amore ES, Reiter A, Woessmann W, Rosolen A. Early assessment of minimal residual disease identifies patients at very high relapse risk in NPM-ALK-positive anaplastic large-cell lymphoma. Blood. 2014;123(3):334–7.
11. Eissa HM, Allen CE, Kamdar K, Simko S, Goradia P, Dreyer Z, Steuber P, McClain KL, Guillerman RP, Bollard CM. Pediatric Burkitt's lymphoma and diffuse B-cell lymphoma: are surveillance scans required? Pediatr Hematol Oncol. 2014;31(3):253–7.
12. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma. 2009;50(8):1257–60.
13. Minard-Colin V, Brugieres L, Reiter A, Cairo MS, Gross TG, Woessmann W, Burkhardt B, Sandlund JT, Williams D, Pillon M, Horibe K, Auperin A, Le Deley MC, Zimmerman M, Perkins SL, Raphael M, Lamant L, Klapper W, Mussolin L, Poirel HA,

Macintyre E, Damm-Welk C, Rosolen A, Patte C. Non-Hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead. J Clin Oncol. 2015;33(27):2963–74.
14. Mussolin L, Damm-Welk C, Pillon M, Zimmermann M, Franceschetto G, Pulford K, Reiter A, Rosolen A, Woessmann W. Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. Leukemia. 2013;27(2):416–22.
15. Paganin M, Fabbri G, Conter V, Barisone E, Polato K, Cazzaniga G, Giraldi E, Fagioli F, Arico M, Valsecchi MG, Basso G. Postinduction minimal residual disease monitoring by polymerase chain reaction in children with acute lymphoblastic leukemia. J Clin Oncol. 2014;32(31):3553–8.
16. Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, Weston C, Raphael M, Perkins SL, McCarthy K, Cairo MS, FAB/LMB96 International Study Committee. 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. 2007;109(7):2773–80.
17. Patte C, Auperin A, Michon J, Behrendt H, Leverger G, Frappaz D, Lutz P, Coze C, Perel Y, Raphael M, Terrier-Lacombe MJ. The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood. 2001;97(11):3370–9.
18. Pillon M, Mussolin L, Carraro E, Conter V, Arico M, Vinti L, Garaventa A, Piglione M, Buffardi S, Sala A, Santoro N, Lo Nigro L, Mura R, Tondo A, Casale F, Farruggia P, Pierani P, Cesaro S, d'Amore ES, Basso G. Detection of prognostic factors in children and adolescents with Burkitt and Diffuse Large B-Cell Lymphoma treated with the AIEOP LNH-97 protocol. Br J Haematol. 2016;175(3):467–75.
19. Reiter A, Schrappe M, Parwaresch R, Henze G, Muller-Weihrich S, Sauter S, Sykora KW, Ludwig WD, Gadner H, Riehm H. Non-Hodgkin's lymphomas of childhood and adolescence: results of a treatment stratified for biologic subtypes and stage – a report of the Berlin-Frankfurt-Munster Group. J Clin Oncol. 1995;13(2):359–72.
20. Reiter A, Schrappe M, Tiemann M, Ludwig WD, Yakisan E, Zimmermann M, Mann G, Chott A, Ebell W, Klingebiel T, Graf N, Kremens B, Muller-Weihrich S, Pluss HJ, Zintl F, Henze G, Riehm H. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: a report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood. 1999;94(10):3294–306.
21. Riad R, Omar W, Sidhom I, Zamzam M, Zaky I, Hafez M, Abdel-Dayem HM. False-positive F-18 FDG uptake in PET/CT studies in pediatric patients with abdominal Burkitt's lymphoma. Nucl Med Commun. 2010;31(3):232–8.
22. Roschewski M, Dunleavy K, Pittaluga S, Moorhead M, Pepin F, Kong K, Shovlin M, Jaffe ES, Staudt LM, Lai C, Steinberg SM, Chen CC, Zheng J, Willis TD, Faham M, Wilson WH. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. Lancet Oncol. 2015;16(5):541–9.
23. Sandlund JT, Guillerman RP, Perkins SL, Pinkerton CR, Rosolen A, Patte C, Reiter A, Cairo MS. International Pediatric non-Hodgkin lymphoma response criteria. J Clin Oncol. 2015;33(18):2106–11.
24. Shammas A, Lim R, Charron M. Pediatric FDG PET/CT: physiologic uptake, normal variants, and benign conditions. Radiographics. 2009;29(5):1467–86.
25. Termuhlen AM, Smith LM, Perkins SL, Lones M, Finlay JL, Weinstein H, Gross TG, Abromowitch M. Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. Br J Haematol. 2013;162(6):792–801.