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Br J Haematol. Author manuscript; available in PMC 2013 March 1.

Published in final edited form as:
Br J Haematol. 2012 March ; 156(6): 761–765. doi:10.1111/j.1365-2141.2012.09026.x.

Burkitt Lymphoma: Staging and Response Evaluation

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Summary

The refinements in both the staging and response evaluation of children with Burkitt lymphoma (BL) have contributed to the improvements in treatment outcome observed over the past 40 years. Ziegler and Magrath designed a staging system in the 1970s for children with BL in equatorial Africa. Currently, the most widely used staging system around the world is that described by Murphy in 1980, which was developed for children with non-Hodgkin lymphoma (NHL) of any histology. There are opportunities for refinement in this system, particularly with respect to certain extra-nodal sites, such as skin and bone. The findings obtained at diagnosis with novel technologies [functional imaging (eg., positron emission tomography [PET]) and minimal residual disease (MRD) technology], which are more sensitive with respect to disease detection than historic modalities, also need to be considered. Technological advances have also had impact on the assessment of response evaluation. Standard x-rays were routinely used in the 1960s; nuclear imaging became widely used in the 1970s; computerized axial tomography was incorporated in the 1980s; PET imaging was incorporated and, in many cases, has replaced gallium/bone scans since 2000; and MRD technology has been explored in some of the most recent clinical trials.

There is clearly a need for more clinical data on the use of PET and MRD technology in the determination of response evaluation of children with BL as well as other histological subtypes of NHL. An international working group is currently addressing the refinement of both disease staging and response evaluation in children with NHL.

Keywords

Burkitt lymphoma; staging; response evaluation

Introduction

Accurate staging and response evaluation for children with Burkitt lymphoma (BL) have provided a critical foundation for optimal treatment planning over the past 4 decades (Murphy 1980). The refinements in both diagnostic imaging technology and pathological tools for disease detection have significantly influenced the ability to identify sites of disease and to determine response to therapy. This article will review the history of both staging and response evaluation for BL, and highlight some of the opportunities and challenges for the future.

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Presented at the Burkitt Lymphoma Symposium, School of Medicine, Trinity College Dublin.

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Staging

The purpose of disease staging is to determine and describe the extent of disease spread and to permit a uniform treatment approach based on this information. A clearly defined staging system also permits comparisons among treatment approaches with respect to stage and to determine the prognostic significance of specific disease locations and stage.

The earliest staging system for BL was described by Zeigler & Magrath (1974). In this system, Group A comprised a single solitary extra-abdominal site and Group AR indicated an intra-abdominal tumour for which greater than 90% was surgically resected. Groups B, C and D (multiple extra-abdominal sites, intra-abdominal tumour, and intra-abdominal tumour with involvement of greater than or equal to one extra-abdominal site, respectively) indicated more disseminated disease. Wollner *et al* (1976) described a system for non-Hodgkin lymphoma (NHL) of all histologies comprising limited stage (stage I and II: one single site, two or more sites on the same side of the diaphragm, respectively) and advanced stage (stage III and IV: disseminated disease without bone marrow or central nervous system involvement, and bone marrow and/or central nervous system involvement, respectively). The St. Jude staging system, which was intended for all histological subtypes and also included stages I to IV (stages I and II, limited stage; stages III and IV, advanced stage), was described by Murphy (1980). In this system, primary intra-thoracic and primary intra-abdominal sites were defined as criteria for stage III, and usually corresponded to lymphoblastic lymphoma and BL respectively. As in the Zeigler system, those with BL who had completely resected intra-abdominal disease, were classified as a lower disease stage (i.e., II - associated with a better prognosis), whereas more disseminated disease was associated with a poorer outcome.

The modalities available for staging have changed significantly over the decades. (Murphy, *et al* 1989) During the 1960s, staging was largely based on physical examination, complete blood count, chemistry screen, chest x-ray, intravenous pyelogram, gastro-intestinal contrast studies, bone marrow aspirations and cerebrospinal fluid examinations. During the 1970s, bone marrow biopsies were performed in cases where the bone marrow aspirations were inconclusive, and nuclear imaging studies were introduced (i.e., bone scan, gallium scan). Computerized axial tomography (CT scan) was incorporated into the staging workup in the 1980s. Since 2000, positron emission tomography (PET) imaging has been incorporated and, in many centres, replaced the use of bone scans and gallium scans. In the current decade, minimal residual disease (MRD) technology (flow cytometry and polymerase chain reaction [PCR] for immunoglobulin gene rearrangements) has also been studied and now introduced into current protocols of further investigation.

Although the current St. Jude System is still widely used 30 years after its initial description, there are some areas where further clarification and refinement are possible and needed. For example, there are disease locations for which the system is somewhat vague, such as in the cases of bone and skin involvement. The significance of PET activity in lymph nodes that are not enlarged on CT will have to be clarified. Moreover, the development of more advanced technology for pathological detection of minimal disease will require more specific definitions than simply bone marrow involvement. An international group of paediatric oncologists is working toward addressing these issues in an updated staging system.

Response evaluation

A standardized system to describe response evaluation is clinically important for a number of different reasons. It is used to determine and accurately describe the activity of specific treatment regimens. In some treatment protocols, treatment modifications are based on early

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and late response to therapy. Lastly, a standardized system to describe response evaluation permits comparisons between differing treatment approaches.

Historically, the designations of CR (complete response), PR (partial response) and NR (no response) have been used to describe response to therapy. CR generally referred to disappearance of all disease. Some have included an unconfirmed CR sub-designation (CRu) for cases in which subtle residual abnormalities preclude absolute confidence of the CR designation. PR has generally been used to designate a ≥50% reduction in tumour size. Some have actually included a minor response (MR) to designate a ≥25% but <50% tumour size reduction. NR has generally been used to designate no change in tumour size. Although these designations initially appear relatively straightforward, there remains the need for further clarification as to how these size changes should be measured. For example, what are the specific measurement criteria used to indicate change? These are actually quite variable and have included change in the transverse diameter, change in longitudinal diameter, change in the sum of the product of the largest diameters, change in the sum of the product of the largest "perpendicular" diameters, and/or change in volumetric measurement (3 dimensions). Of note, comparable size-based response definitions cannot be applied uniformly across varied measurement methods. For example, a 50% decrease in the sum of the products of the perpendicular diameters is equivalent to a 65% decrease in tumour volume. (Therasse, *et al* 2000) Moreover, questions persist as to how many lesions should be measured. Questions also remain as to how response measurements in nodal disease sites are to be compared to extra-nodal disease sites. Finally, questions remain as to how to document response in certain problematic disease sites, such as skin and bone.

In an effort to address these issues, a multi-disciplinary group of experts in the management of adults with lymphomas convened to develop a uniform approach to describing treatment response for malignant lymphomas. This initiative was referred to as the International Harmonization Project (Cheson, *et al* 1999). This system was widely adopted, with an updated set of guidelines published in 2007 (Cheson, *et al* 2007). In this system, CR indicated disappearance of disease; PR indicated regression, SD (stable disease) indicated non-CR, non-PR and non-PD (progressive disease); PD indicated >50% increase in size of old lesions or the development of new lesions. One of the key differences between the initial set of guidelines and the updated version was the significance of a positive PET scan. In the 2007 guidelines, patients with a residual mass that was PET-negative were considered in CR (Cheson, *et al* 2007), whereas in the earlier document (Cheson, *et al* 1999), this entity was referred to as CRu (CR unconfirmed).

The significance of a residual mass among children with NHL has yet to be determined. Many paediatric NHL protocols call for resection or biopsy of residual masses. A biopsy that is positive for residual NHL would indicate induction failure, whereas a negative biopsy result would result in a CR designation; however, in the case of a negative core biopsy, there remains the potential concern of a sampling problem. In the case of paediatric lymphoblastic lymphoma, end of induction biopsies are often negative, which indicates to the limitations of conventional diagnostic imaging. (Reiter, *et al* 2000) Functional imaging with PET scanning may help resolve this dilemma in the management of paediatric NHL patients. A subcommittee of the International Harmonization Project, which examined the use of fludeoxyglucose (FDG)-PET in response evaluation of adult NHL patients, made the following conclusions: visual assessment alone is adequate for determining PET positivity versus negativity at the time of the completion of therapy response evaluation; mediastinal blood pool activity may be used as the reference background for lesions ≥ 2 cm; smaller lesions may be considered positive if uptake is greater than surrounding background; use of attenuated-corrected PET is strongly recommended; and, use of PET for treatment monitoring during a course of therapy should be used only in a clinical trial or prospective

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registry.(Juweid, *et al* 2007) In a more recent review of the value of PET in the management of NHL in adults, Dunleavy, *et al* (2010) made the following observations and recommendations: the role of PET in determining prognosis and early response is still being defined; reports from studies that incorporate PET imaging in the management of diffuse large B-cell lymphoma have demonstrated that PET can be successfully used to identify early response to chemotherapy and interim PET results can predict outcome; using PET to guide therapeutic decision making is currently under investigation; limitations of interim PET include the lack of standardized imaging protocols and reporting criteria as well as unproven reproducibility of interpretation; the final recommendation was that interim PET should be considered investigational and applied only within the confines of clinical trials. Moreover, there have been studies that indicate that PET results may not always be indicative of treatment outcome (Cahu, *et al* 2011, Palmer, *et al* 2011). False positive PET studies were described in a small series of children with BL(Riad, *et al* 2010). In children with a residual mass following treatment for NHL, a false positive PET may be the result of a benign inflammatory process, xanthomatous pseudotumour, brown fat, rebound thymic hyperplasia, infection or an effect of granulocyte colony-stimulating factor.

Minimal residual uptake (MRU) remains a challenge in interpreting post-treatment PET imaging studies. MRU is generally felt to represent a benign process and not likely to represent malignancy; however, there are no uniform criteria to define MRU. The various reported criteria for MRU include the following: uptake just above background in the site of previous disease; uptake equal to or slightly > or < mediastinal blood pool (standardized uptake value < 3.5); and uptake < or equal to normal liver (Barrington, *et al* 2010, Gallamini, *et al* 2007, Hutchings, *et al* 2005). The London Criteria were reviewed at the First International Workshop on Interim-PET-scan in Lymphoma (Gallamini, *et al* 2009, Meignan, *et al* 2009). According to this system, MRU is graded as 1 to 5 based on degree of uptake (1, no uptake > background; 2, uptake < or equal to mediastinum; 3, uptake between mediastinum and liver; 4, uptake moderately > liver; and 5, uptake markedly > liver). This 5-point system appeared to identify a group (Grade 5) that had a significantly poorer progression-free survival than the remaining 4 grades. This system may have some advantages with respect to prognosis over other MRU grading systems.(Le Roux, *et al* 2011)

The development of minimal residual disease (MRD) detection technology has become a valuable component of many current protocols for acute lymphoblastic leukaemia (ALL) and is currently being investigated in protocols for NHL. MRD is generally detected using either flow cytometric technology or PCR technology (looking for clonal immunoglobulin/T cell receptor gene rearrangements or molecular lesions). In a frontline ALL study at St. Jude, the level of MRD (flow cytometric) at the end of induction was shown to be significantly associated with cumulative incidence of relapse (Coustan-Smith, *et al* 2000). A study by the same group demonstrated that for patients with T-cell ALL, peripheral blood was comparable to bone marrow with respect to level of MRD, whereas for patients with B-progenitor ALL, bone marrow is superior to peripheral blood (Coustan-Smith, *et al* 2002). Based on these observations, flow cytometric MRD studies were conducted in children with lymphoblastic lymphoma enrolled on a Children's Oncology Group (COG) study, COG A5971 (Coustan-Smith, *et al* 2009). This flow cytometric approach has advantages for patients with lymphoblastic lymphoma: primary tumour is not required because TdT and T-cell markers (eg., CD3) are expressed in all cases. The COG A5971 study was amended to study MRD in T-cell lymphoblastic lymphoma patients. MRD was detected in approximately 70% of cases. The degree of minimal dissemination of disease (MDD) at diagnosis was shown to have prognostic significance. The two year event-free survival for those with MDD ≥ 1% was significantly poorer than for those with a lower level. Current frontline studies for children with lymphoblastic lymphoma are partly based on these findings. The COG MRD study also demonstrated that peripheral blood MRD levels were

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comparable to those detected in bone marrow. Among patients with MDD detected, there were some that became undetectable by day 8 induction (early responders) and some that cleared at a later time point during induction (slow responders). The prognostic significance of this difference has yet to be determined.

MRD technology has more recently been used in the study of BL. Musolin et al., (2011) reported their MDD results in children with BL treated on the Associazione Italiana di Ematologia e Oncologia Pediatrica non-Hodgkin lymphoma-97 protocol. The authors developed a long-distance PCR assay to detect t(8;14). This initiative incorporated the prospective study of both diagnostic biopsies and bone marrow examinations. The authors reported that MDD identified a poor prognosis subgroup among 51 children with high risk BL, and suggested that the incorporation of novel treatment approaches (eg., immunotherapy with anti-CD20) may be a consideration for these patients in the future. Shiramizu et al., (2011) reported their MDD results from a COG study (COG ANHL01P1, Group B plus Rituxan). B-NHL specimens were screened for *IGHV* family usage with primer pools and unique *IGHV* family primers were identified. Specimens from 32 of 45 children with B-NHL were studied. MDD was identified in either bone marrow or peripheral blood in all 32 patients. The authors concluded that this feasibility study supported further investigation.

Refinement of response evaluation criteria for children with NHL including BL will probably mirror in part the recommendations of the International Harmonization Project. Further data on the significance of a PET-negative residual mass in children with NHL is needed before a PET-negative mass that has not been biopsied could be considered a CR. In this regard, the role of PET imaging for paediatric NHL has yet to be determined and agreed upon. With respect to MRD results, additional sub-classifications will be needed for patients who have a morphologically normal bone marrow and peripheral blood at the end of induction (i.e., CR by current standards, assuming the imaging studies do not demonstrate active malignancy), but are shown to have MRD by either flow cytometry or PCR.

Conclusions

The current staging and response evaluation criteria used in the management of children with NHL, including BL, has generally worked well for many years. Nevertheless, there remains the need to clarify how certain disease sites will be staged, and how newer technology in the field of diagnostic imaging (eg., PET imaging) and haematopathology (flow cytometric and PCR-based MRD) will be used in both staging and response evaluation. An international group of paediatric oncologists, pathologists and radiologists are currently working on a set of recommendations regarding these matters, which should be forthcoming in the relatively near future.

Acknowledgments

Supported by NCI grant CA21765 and the American Lebanese and Syrian Associated Charities (ALSAC)

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