RESPONSE ASSESSMENT AND OUTCOMES IN PEDIATRIC B CELL NON-HODGKIN LYMPHOMA: OUR EXPERIENCE AT SHAUKAT KHANUM MEMORIAL CANCER HOSPITAL AND RESEARCH CENTRE

Palwasha Rehman, Rabia Muhammad Wali

Shaukat Khanum Hospital Cancer Hospital and Research Centre, Peshawar Pakistan

ABSTRACT

Objective: To determine the relation of response assessment and outcome of B cell non-Hodgkinlymphoma so we can minimize utilization of our resources.

Study Design: Retrospective observational study.

Place and Duration of Study: Pediatric Oncology Department, Shaukat khanum Memorial Cancer Hospital and Research Centre, from Jan 2013 to Dec 2016.

Methodology: Patients from the age of 1 till 18 years presented at Shaukat khanum hospital were included in the study. Patients were staged as per St. Jude staging system and response assessment done as per French-American British (FAB) Lymphome Malins De Burkitt (LMB) protocol.

Results: Total 247 patients diagnosed with B cell Non-Hodgkin Lymphoma were included. When the interim scans were compared with the end of treatment assessment, 139 (82.2%) patients (n=169) had achieved complete morphological remission on the re-evaluation scans, 138 patients (86.2%) among them were in remission at end of treatment where as 01 patient had relapse disease. The interim disease re-evaluation scan is predictive of end of treatment response with sensitivity of 86.8%, specificity of 88.9% (p-value <0.005)

Conclusion: The patients who achieved rapid response on re-assessment scans have good outcomes. We recommend that in future patient's with complete response on interim scans to be followed with ultrasonography or clinical examination to minimize expenditures and radiation exposure.

Keywords: B cell Non-Hodgkin, Children, Computed tomography scan, Response evaluation.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Pediatric lymphoma is the third most common malignancy in childhood, among them 50 percent are non-Hodgkin lymphoma (NHL). Out of NHL, Burkitt lymphoma is common, present in 40-45% of the patients followed by diffuse large B cell lymphoma (DLBCL)[1]. With the introduction of the intense chemotherapy regimen the outcome of B cell NHLs have drastically improved over the years. Imaging plays key role in the diagnosis, staging, response assessment and surveillance of the B cell lymphomas. Response evaluation during the treatment is mandatory, as it navigates the treatment course[2]. Computed tomography (CT scan) is the common modality used for imaging purposes in non-Hodgkin lymphoma, it's easily available in many oncological centers and serves the purpose. However, only nodal and extranodal involvement can be evaluated whereas the extent of bone marrow involvement is poorly demonstrated[3]. Limited data is available that can indicate pediatric patients having rapid response on re-assessment scans will have good outcomes as compared to those having poor response or delayed response. With improving outcome of the NHLs and increased use of the surveillance imaging there comes the risk of radiation induced secondary malignancies in pediatric patients[4].

In country like ours with limited resources the aim of this study was to determine the relation of rapid response to the outcome of disease in B cell non-Hodgkin lymphoma, so that we can minimize radiation exposure of patients and limit expenditure.

Correspondence: Dr Palwasha Rehman, House No. 137, Street No. 11, G-11 Phase-2, Hayatabad, Peshawar Pakistan

Received: 26 Jan 2020; revised received: 07 Feb 2020; accepted: 10 Feb 2020

METHODOLOGY

Retrospective chartanalysis was done of patients diagnosed with B cell non-Hodgkin lymphoma (age 1-18 years) from January 2013 till December 2016, diagnosed at Shaukat Khanum Cancer Memorial hospital and Research Centre. The patients included in the study were followed until the last clinic date. The patients diagnosed with low risk B cell NHL (group A), who died during the cytoreductive and induction course of treatment were excluded from the study. Research ethics approval was obtained from hospital institutional board (EXEMPT-06-06-18-01-a1). Disease staging was done according to St Jude classification depending on the cross-sectional imaging, Cerebrospinal fluid (CSF) analysis, central nervous system (CNS) or intraspinal extension, bone marrow involvement as per table-I. Bone marrow involvement was considered as positive when there were more than 25% lymphoma cells, CNS involvement was also considered when there were more than 5 lymphoma cells on CSF examination or cranial nerve palsies present clinically.

Patients were treated on United Kingdom Children Cancer Group- UKCCSG NHL group adapted from FABLMB protocol[5]. Stage I and completely resected stage II tumors were included in group A. Group B included unresected stage I, stage II, stage III and stage IV with bone marrow involvement <25%. Table-I group C included stage IV (bone marrow >25%) patients. Initially imaging for diagnosis and staging was done in all patients and CT scan (neck, chest, abdomen, and pelvis) was used. Group A patients received low risk chemotherapy (2 cycles) followed by end of treatment scan. Group B and C patients with bulky disease received initial cytoreductive chemotherapy followed by re-evaluation scan for response, followed by induction and consolidation chemotherapy. In group C patient consolidation phase was followed by maintenance cycle. After the cytoreduction chemotherapy, in group B and C patients, complete response (CR) was defined as complete disappearance of all measurable lesions (except bone lesions), no blast cells in the bone marrow and CSF. Incomplete response was defined as 20-99% reduction in the product of the two largest diameters of measurable lesion and or 20-99% reduction in number of blasts cells in marrow and/or in the CSF. Non-responders were labelled as having <20% tumor reduction of the product of the two largest diameters of measurable lesions <20% reduction in the number of blasts in bone marrow or CSF. Tumor progression was defined as, Any progression of more than 25% in the product of the two largest diameters of measurable lesions.[5]

Table-I: Staging system Non-Hodgkin lymphoma.

Stage	Criteria
Stage I	A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
Stage II	A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tumour, usually in the ileocaecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected
Stage III	Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intra-thoracic tumours (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease. All paraspinal or epidural tumours, regardless of other tumour site (s).
Stage IV	Any of the above with initial CNS and/or bone marrow involvement.

Group B non-responders after the initial cytoreductive chemotherapy were escalated to

group C chemotherapy. Group B patients having residual disease on re-evaluation scans undergoes biopsy or resection of the remaining disease where possible. In patients where having difficulty to do a biopsy and or where resection not possible in residual disease a Positron Emission Topography (PET) scan was used to assess response in form of avidity. Patients who had viable tumor on biopsy or avid disease on PET scan where escalated to group C chemotherapy. At the end of treatment disease response was assessed by cross sectional imaging. Patients were followed two years post treatment clinically, abdominal ultrasound and xray chest were done depending upon the site of disease as surveillance tools.

Statistical analysis: Statistical analysis was performed using the SPSS software (version 22.0; SPSS, Chicago, IL). Descriptive statistics were reported as frequencies and percentages for quantitative data. The interim disease re-evaluation scans predictive of treatment response in terms of sensitivity, specificity and positive predictive value (PPV) was calculated. A *p*-value ≤0.05 was considered significant.

RESULTS

Total 284 patients were diagnosed with B cell NHLs. Eleven patients belonged to group A whereas 26 patients presented with high disease burden died during the start of treatment, so they were excluded from the study.

Patients included in the study were 247, mean age of presentation 7 years (range 1-18 years) out of which 191 (76.9%) were males and 56 (22.7%) were females. With the common site of presentation abdominal disease in 173 patients (70.0%) followed by cervical lymph nodes in 32 patients (13%) (fig-1).

Burkitt lymphoma (BL) was present in 169 (68.4%) patients followed by diffuse large B cell lymphoma (DLBCL) in 72 (29.1%) patients and B cell nonspecific (B-Nos) in 6 (2.4%) patients.

One patient had stage I (0.4%), 35 stage II (12.8%), 148 (59.9%) stage III whereas 63 (25.5%) had stage IV involvement. In 247 patient's re-evaluation scans after cytoreductive chemotherapy were done on day 7, among them 182 (73.7%) belonged to group B and 65 (26.3%) to group C. In group B, 173 patients had >20% response after cytoreductive chemotherapy whereas 09 patients had <20% response and therefore escalated to group C.

In group C, 55 patients had >20% response whereas 06 patients had <20% response, but

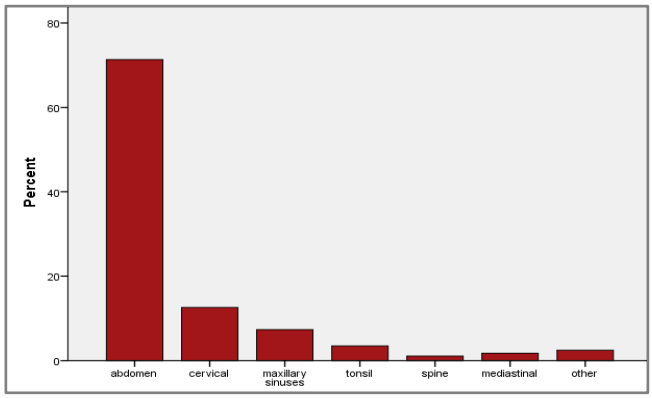

Figure-1: Sites involved at the time of disease presentation.

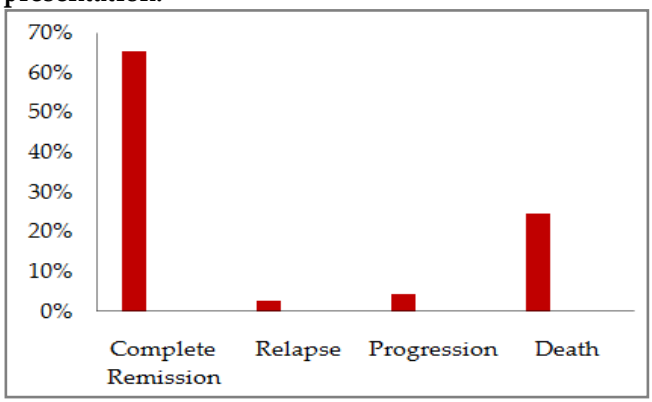

Figure-2: End of treatment outcomes.

they were treated on the same treatment group. In 4 patients' day 7 scans were not done and were assessed clinically for response.

On interim evaluation, scans were on done in 188 patients (n=247 patients) after induction chemotherapy. In group B complete response seen in 125 patients, partial response in 28 whereas disease progression in 6. Chemotherapy regimen was escalated in patients who had disease progression on interim scans. Fifteen patients in group B had an additional PET

scan done on interim due suspicious of residual disease which was so minimal that either a biopsy couldn't be done or the residual disease was in such place that surgical resection was not possible. All these had metabolically non avid disease and hence considered as in complete response. In group C patients 23 patients had complete response, 06 patients had partial response (table-II).

At the end of treatment complete remission was achieved in 156 patients (63.2%). Disease relapse was seen in 7 patients (2.8%), disease progression in 11 patients (4.5%). Death as first incident was seen in 65 patients (26.3%) whereas 7 patients (2.8%) abandoned treatment (fig-2).

When the interim scans were compared with the end of treatment assessment (n=169), 139 (82.2%) patients had morphological complete response on interim scans, out of them 138 remained in remission whereas 01 had relapse disease at the end of treatment. Thirty patients (17.8%) had partial response on interim scans, 22 remained in remission whereas 08 had disease at the end of treatment. The interim disease re-evaluation scan is predictive of end of treatment response with sensitivity of 86.8%, specificity of 88.9%.

When the response assessment was analyzed in relation to treatment groups, in group B 118 patients were in morphological remission at interim scans and out of whom 117 remained in remission at end of treatment, whereas only 1 patient had relapse disease (table-III).

In group C, 21 patients who had morphological complete response on interim scan remained in complete remission till end of treatment, whereas 03 patients had partial response on interim scans, 01 had residual active disease and 02 patients achieved remission at end of therapy (table-IV).

All the patients included in the study were followed for 2 years post treatment for disease recurrence.

Table-II: Disease response after interim scans.

Treatment Group	Disease Response (n=188)		
	Complete Response	Partial Response	Disease Progression
Treatment Group B	125 (66.4%)	28 (14.8%)	6 (3.1%)
Treatment Group C	23 (12.2%)	6 (3.1%)	-

Table-III: Disease outcome treatment group B in relation to interim re-evaluation scans.

Re-evaluation Scans	End of treatment outcome, (n=145)		*p*-value
	Disease Remission	Not Remission	
Morphological complete response	117 (85.4%)	1 (12.5%)	0.000
Partial response	20 (14.6%)	7 (87.5%)	
Total	137 (100%)	8 (100%)	

Table-IV: Disease outcome treatment group C in relation to interim re-evaluation scans.

Re-evaluation Scans	End of Treatment, (n=24)		*p*-value
	Disease Remission	Active Disease	
Morphological complete response	21 (91.3%)	O	-0.125
Partial Response	2 (8.7%)	1	

DISCUSSION

Around fifty types of lymphoma based on histopathology, immunohistochemistry, molecular biology and radiological finding been classified by the World health organization (WHO)[6]. With the introduction of the intensive chemotherapy regimen and auto-transplant, the over-all survival of lymphomas has drastically improved over the years. The presentation of lymphoma is variable, Hodgkin lymphoma most commonly involves the nodal areas whereas non-Hodgkin lymphoma most commonly in pediatric age group presents in extra-nodal areas with abdominal symptoms[7]. Faizan, (2018) reported male predominance among the NHL patients and the same was observed among our patients[8]. The

commonest site of presentation was abdominal disease. On initial presentation majority of the patients had extensive disease, stage III and stage IV hence they were either stratified in group B or C. Significant number of patients (n=27) were excluded from the study as they died during the initial cyto-reductive phase of the chemotherapy due to high tumor burden related complications which is the same as reported in low income countries[9].

For assessing the disease response in adult population there has been established the Lugano classification system[10], it's specific for adult but limited data is available for pediatric patients. Similarly, definitive role of Positron emission topography (Pet-scan) is not established in pediatric age group, though in residual disease or relapse it can be helpful. Barrington, Mikhaeel *et al* proposed response criteria for the pediatric NHL patient[11]. Clinically to assess the prognosis of NHL patients the initial response to therapy can be one of modality to assess, though the risk of disease relapse or mortality is often linked to the initial tumor burden and treatment related complications[12]. In our study we emphasized on the outcome of group B patients based on the interim scans, significant outcome was observed at the end of treatment in patients achieving complete morphological remission on interim scans (*p*-value less than 0.005), no documented evidence available in literature. One patient in our study who had complete response on re-evaluation scans, had relapse disease. The relapse disease was diagnosed almost 6 months after end of treatment on clinical examination. Fifteen patients in the study had suspicion of residual disease on interim scans so PET-CT was performed and revealed metabolically non avid disease. The use of Pet scan- especially Pet/MRI is gaining popularity in the disease staging and assessment in pediatric NHL patients, as it accurately measures the response to treatment and exposes patients to low doses of radiation[13].

Eissa & Allen *et al* reported the low risk of relapse in pediatric B cell NHL patient who achieved complete remission at end of treatment, as out of 44 patients, 3 patients had relapse disease. It was noted that 44 patients were exposed to 480 radiological (including chest radiograph, CT, PET/ CT) scans, with median effective dose of 40mSv[14]. No consensus has been proposed of the use of surveillance scans in pediatric patients, in order to minimize radiation exposure magnetic resonance imaging (MRI) for assessment and surveillance been suggested[15]. MRI is considered superior to CT scan specially in patients who are sensitive to radiation exposure like ataxia telangiectasia, Nijmegen breakage syndrome[16].

We cannot adapt these recommendations at our institute due to limited resources. The common modality used in our patients for disease staging and re-assessment was CT scan depending on the anatomical location, for the CNS/ Spine involvement MRI scan was used for better resolution. As the development of newer agents and targeted therapy (rituximab -anti CD 20) the outcome of pediatric B cell NHLs has drastically improved[17], though now considered as the standard of care none of our patients received rituximab as part of treatment protocol cause of financial constraints. With the introduction of minimal residual disease (MRD) in non-Hodgkin lymphoma (NHL) response assessment, further understanding of the disease course, treatment response and modification of the maintenance therapy can be achieved which can even guide therapy after stem cell rescue[18,19].

ACKNOWLEDGMENT

We are grateful to our patients and their families.

CONCLUSION

The patients who achieved complete morphological response on interim scans have better outcome. We cannot apply this for treatment group C, as they have high number of treatment/ disease related mortality. We recommend that for our institution and elsewhere in country patients stratified on group B who achieve complete morphological remissionon interim scans can be followed with ultrasonography or clinical examination (depending on the primary location) at

the end of treatment and on surveillance in order to minimize expenditures, resources and radiation exposure.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, et al. The impact of age and gender on biology, clinical features and treatment outcome of non Hodgkin lymphoma in childhood and adolescence. Br J Haematol 2005; 131(1): 39-49.
2. Kulkarni NM, Pinho DF, Narayanan S, Kambadakone AR, Abramson JS, Sahani DV. Imaging for oncologic response assessment in lymphoma. Am J Roentgenol 2017; 208(1): 18-31.
3. Cheson BD. Role of functional imaging in the management of lymphoma. J Clin Oncol 2011; 29(14): 1844-54.
4. Baysson H, Etard C, Brisse HJ, Bernier MO. Diagnostic radiation exposure in children and cancer risk: current knowledge and perspectives. Arch Pediatr 2012; 19(1): 64-73.
5. Patte C, Auperin A, Michon J, Behrendt H, Leverger G, Frappaz D, et al. The societe francaised' 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. J Am Soc Hematol 2001; 97(11): 3370-79.
6. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. J Am Soc Hematol 2011; 117(19): 5019-32.
7. Meena JP, Gupta AK, Parihar M, Seth R. Clinical profile and outcomes of Non-Hodgkin's lymphoma in children: A report from a tertiary care hospital from India. Indian J Med Paediatr Oncol 2019; 40(1): 41-49.
8. Faizan M, Anwar S, Khan S. Demographics and outome in paediatric non-hodgkin lymphoma: single centre experience at the children hospital lahore, Pakistan. J Coll Physician Surg Pak 2018; 28(1): 48-51.
9. Mansoor R, Saeed H, Wali RM, Rehman P, Abubakar M. Malnutrition, sepsis, and tumor lysis syndrome are associated with increased rate of acute mortality in mature B cell non-hodgkin lymphoma in a pediatric population-study from Tertiary Care Hospital in Pakistan. Mediterranean J Hematol Infec Dis 2019; 11(1): 1-9.
10. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lym-phoma: the Lugano classification. J Clini Oncol 2014; 32(27): 3059-63.
11. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, 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 Clini Oncol 2014; 32(27): 3048-54.
12. Sandlund JT, Guillerman RP, Perkins SL, Pinkerton CR, Rosolen A, Patte C, et al. International pediatric non-Hodgkin lymphoma response criteria. J Clini Oncol 2015; 33(18): 2106-15.
13. Kalisz K, Alessandrino F, Beck R, Smith D, Kikano E, Ramaiya NH, et al. An update on Burkitt lymphoma: a review of pathogenesis and multimodality imaging assessment of disease presentation, treatment response, and recurrence. Insights Imaging 2019; 10(1): 56-59.
14. Eissa HM, Allen CE, Kamdar K, Simko S, Goradia P, Dreyer Z, et al. Pediatric Burkitt's lymphoma and diffuse B-cell lymphoma: are surveillance scans required?. Pediatr Hematol Oncol J 2014; 31(3): 253-57.
15. McHugh K, Roebuck DJ. Pediatric oncology surveillance imaging: Two recommendations. Abandon CT scanning, and randomize to imaging or solely clinical follow-up. Pediatr Blood Cancer 2014; 61(1): 3-6.
16. Sandlund JT, Hudson MM, Kennedy W, Onciu M, Kastan MB. Pilot study of modified LMB based therapy for children with ataxia–telangiectasia and advanced stage high grade mature B cell malignancies. Pediatr Blood Cancer 2014; 61(2): 360-62.
17. Goldman S, Smith L, Anderson JR, Perkins S, Harrison L. Rituximab and FAB/LMB 96 chemotherapy in children with Stage III/IV B-cell non-Hodgkin lymphoma: a Children's Oncology Group report. Leukemia 2013; 27(5): 1174-77.
18. Herrera AF, Kim HT, Kong KA, Faham M, Sun H, Sohani AR, et al. Next generation sequencing based detection of circulating tumour DNA After allogeneic stem cell transplantation for lymphoma. Br J Haematol 2016; 175(5): 841-50.
19. Chase ML, Armand P. Minimal residual disease in non-Hodgkin lymphoma current applications and future directions. Br J Haematol 2018; 180(2): 177-88.