Response Assessment by PET CT as compared to CECT in childhood Hodgkin Lymphoma can reduce the need for radiotherapy in low and middle income countries

Manas Kalra[1], Sameer Bakhshi[2], M. Singh[3], Rachna Seth[4], Nishant Verma[5], Sandeep Jain[6], V. Radhakrishnan[7], Piali Mandal[8], Amita Mahajan[9], Ramandeep Arora[10], Veronique Dinand[11], Gauri Kapoor[6], M. Sajid[3], Rakesh Kumar[4], * Taluja[12], Saumyaranjan mallick[4], and Jagdish Chandra[8]

[1]Sir Ganga Ram Hospital
[2]All India Institute of Medical Sciences Department of Medical Oncology
[3]Mahavir Cancer Sansthan and Research Centre
[4]All India Institute of Medical Sciences
[5]King George's Medical University Department of Pediatrics
[6]Rajiv Gandhi Cancer Institute Pediatric Oncology New Delhi India
[7]Cancer Institute Women's India Association
[8]Kalawati Saran Children's Hospital
[9]Indraprastha Apollo Hospital
[10]Max Super Speciality Hospital Saket
[11]Bai Jerbai Wadia Hospital for Children
[12]Cankids Kidscan New Delhi India

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Abstract

Introduction: The InPOG-HL-15-01, a multi-centric prospective study used a risk-stratified and response-based approach with a doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) backbone to treat children with newly diagnosed Hodgkin Lymphoma (HL) and reduce the use of radiation therapy (RT). Children/adolescents with bulky disease or inadequate response at early response assessment (ERA) after 2 cycles of chemotherapy were assigned to receive RT. For ERA, positron emission tomography computed tomography (PET-CT) was recommended but not mandatory in view of limited access. This study aimed to compare the impact of using contrast enhanced computed tomography (CECT) vs PET-CT on treatment decisions and outcomes. Methodology: 396 patients were enrolled and 382 had an ERA at the assigned time point. Results: At ERA, satisfactory response was documented in 277/382 (72.5%) participants and this was significantly higher in PET-CT (151/186, 81.2%) as compared to CECT (126/196, 64.3%) respectively (p value<0.001). Amongst the 203 patients with non-bulky disease (wherein the indication for RT was entirely dependent on ERA), 96/114 (84.2%) and 61/89 (68.5%) patients achieved a satisfactory response according to the PET-CT and CECT (p value=0.008) respectively and hence a lesser proportion of patients in the PET-CT arm received RT. Despite a lower usage of RT the 5 year overall survival (OS) of both groups- ERA based on CECT (91.8%) vs PET-CT (94.1%) was comparable (p value=0.391) and so was the 5 year event free survival (EFS) (86.7 vs 85.5%, p value=0.724). Conclusion: Use of PET-CT as the modality for ERA is more likely to indicate a satisfactory response as compared to CECT and thereby decreases the need for RT in response-based treatment algorithm for HL afflicted children. The reduction in the application of RT did not impact the overall outcome and plausibly would lower the risk of delayed toxic effects.

Introduction

Most children with Hodgkin lymphoma (HL) can be cured with modern day chemotherapy with or without radiation therapy (RT). As the cure rates have ameliorated, the delayed effects of therapy have become an important concern. RT is one of the important causes of serious delayed effects in these young patients. Every attempt should be made to limit usage of RT to preclude secondary malignancy, endocrine impairment and cardiovascular damage. Risk and response based adaptation of protocols have led to better decision-making, reduced treatment burden and improved outcomes. Fluorodeoxyglucose based positron emission tomography-computed tomography (PET-CT) for initial disease assessment and response evaluation has now become the standard of care for HL. However, its use for treatment attenuation is debatable[1,2]. Moreover, dearth of availability of PET-CT facility and higher expenses still pose an obstacle in usage of this modality in low-to-middle- income countries (LMIC).

Indian pediatric oncology group (InPOG), a research/clinical trial division of Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics established disease specific research groups in 2015[3]. With the specific mandate of promoting collaborative clinical research, InPOG-HL-15-01 was the first multicenter study that recruited patients from 27 hospitals across India for a uniform risk adapted and response based management of childhood HL[4]. The study utilised ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) and stratified patients into early and advanced stage disease. RT was delivered to children with suboptimal response at early response assessment (ERA) or those with bulky disease. Initial disease assessment and response evaluation were done by CECT or PET-CT as per centre practice and availability of resources. We tried to evaluate the impact imaging modality used on staging, response assessment, therapy decisions especially usage of RT and outcomes of children with HL.

Methodology

The study was registered with Clinical Trial Registry of India (CTRI/2016/03/010916). Ethics approval from local institutional review board was obtained by all the 27 participating centres. Consent from the parents and assents from participants as applicable were taken prior to the commencement of treatment.

InPOG-HL-15-01 utilized ABVD chemotherapy regimen as most of the centres in India were familiar with this regimen. It can be easily administered as day care chemotherapy and the need for supportive care is very minimal. RT was reserved for children with bulky disease at diagnosis and those with suboptimal response to chemotherapy. A conservative estimate of event free survival (EFS) of 70% was targeted as this was the maiden attempt of Indian pediatric oncologists to work together on such a large scale. Most of the centres were remotely located and did not even have a long track record of a fully functional pediatric oncology unit.

Primary objective of this study was to prospectively collect epidemiological and outcome data in children and adolescents with early and advanced stage HL which has been reported previously[5,6].

Study Population

The patient population comprised of children and adolescents up to 18 years of age with a confirmed diagnosis of HL. For the purpose of this study, patients with stage I and II A were classified as early and those with II B, III and IV were classified as advanced disease. 27 centres across the country participated in the study from August 2015 till February 2018. Children with prior treatment (RT or chemotherapy) or those with a relapse were excluded from the study.

Diagnosis, Staging and Baseline data

Details of data collected and investigations done have been reported elsewhere[5,6]. Staging was done as per Ann Arbor classification by either contrast enhanced computed tomography (CECT) neck, chest, abdomen and pelvis or PET-CT scan. Choice of staging modality was at the discretion of local treating team based on the availability of PET-CT facility. Financial support was available through partnership with a Non-governmental Organization (NGO) for facilitation of scans, chemotherapy drugs and RT. Bone marrow aspiration and biopsy were done for all patients. Bulky disease was defined as a single node or conglomerate

nodal tissue measuring more than 6 cm in the longest diameter or a mediastinal mass with a diameter exceeding one third of the maximum mediastinal width at the level of the dome of the diaphragm or hilum in an upright postero-anterior chest radiograph. Spleen and liver involvement was defined as presence of one or more hypodense lesion on CECT or PET-CT imaging.

Treatment

Treatment for early disease included 4 cycles of ABVD and for advanced disease incorporates 6 cycles of same chemotherapy (doxorubicin-25mg/m^2, bleomyicn-10 Units/m^2, vinblastine-6mg/m^2 and dacarbazine-375 mg/m^2 given on days 1 and 15 of a 4-weekly cycle) with interim assessment after two cycles. For patients who did not achieve complete response (CR) or very good partial response (VGPR) after 2 cycles, second interim assessment was done after completion of 4 cycles. Response evaluation was recorded as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) for patients undergoing PET-CT and CR, VGPR, PR, SD or PD was recorded for patients undergoing CECT scan. CR was defined as complete metabolic resolution (Deauville criteria 1-3) of initial demonstrable disease on PET-CT scan or more than 80% reduction in the product of perpendicular diameter (PPD) of each of the nodal masses on CECT scan. VGPR was defined as reduction of at least 60% in nodal masses on conventional imaging. PR was defined as at least 50% reduction in the PPD of each of the areas of measurable disease or presence of metabolically active disease (Deauville criteria 4-5) in one or more of the previously involved sites without evidence of any new lesion. The response of SD was less than PR in the absence of PD. PD was defined as a disease with at least 50% increase in the PPD of any of the involved sites or eruptions of new lesions. For patients, who did not have a complete response after 4 cycles, were offered an option of alternative salvage therapy. Radiological disease assessment at the end of treatment was not necessary but it was recommended for patients not in CR after first and second interim evaluation. RT was reserved for those with initial bulky disease or less than satisfactory response at ERA. Satisfactory response to decide avoidance of RT after ERA (post 2 cycles of ABVD) was defined as CR for patients undergoing PET-CT and CR or VGPR for patients undergoing conventional scanning. RT was administered in once-daily fractions of 1.5 Gy to the afflicted nodal region (site of bulky disease or the sites with residual disease) using anteroposterior/posteroanterior techniques, usually 2-4 weeks following completion of last dose of chemotherapy to a total dose of 21 Gy.

Follow up

After completion of treatment, patients were followed up clinically every three months for the first year, every four months in the second year, every six months from third to fifth year and yearly thereafter. Radiological investigations were done only for clinically suspected cases.

Statistical Analysis

Continuous variables were described using mean with standard deviation or median with range and categorical variables were represented by frequencies with corresponding percentages. Differences in the distribution of individual parameters were analyzed using Fisher's exact test or chi-square test for categorical variables and t-test for continuous variables. Primary outcome was assessed by EFS which was defined as time from date of start of chemotherapy to relapse, progressive disease during treatment, failure to attain CR or VGPR at the end of treatment or death from any cause. Secondary outcome was assessed by event free survival including abandonment (EFSa) in which abandonment of treatment was also considered as an event and overall survival (OS) which was defined as time from start of chemotherapy to death from any cause. Treatment abandonment was defined as the termination of care by the caregiver or not presenting for scheduled treatment for four weeks or more from the scheduled date of treatment. Various risk factors likely to affect EFS, EFSa and OS were evaluated in the univariate analysis. Kaplan Meier method and log rank test were used for survival analysis. The data was analyzed using IBM SPSS statistics for windows version 21.0 (Armonk, NY, USA). The timeline cut off for data analysis was December 2020.

For the analysis in this paper, the main outcomes of interest were percentage of patients who achieved satisfactory response on

ERA via CECT vs PET-CT. The outcome variable was categorical and Chi-square test was used to test for significance.

Results

Baseline

A total of 396 were enrolled onto the study and 382 underwent ERA (186 PET-CT and 196 CECT). Based on the modality used at ERA, patients were divided into two groups (CECT and PET-CT). As shown in table 1, patients in CECT group had a lower mean age, lower hemoglobin value, more bulky disease and more B symptoms. Distribution in terms of early and advanced disease was similar in both groups. Of all the CECTs done, 75.5% of ERA were done at government hospitals, 5.1% at private and 19.4% at trust hospitals. PET-CT was the preferred modality at private and trust (36% + 37.6%=73.6%) hospitals as compared to the government hospitals (26.4%) (p<0.00001). This reflects that financial disparity, availability of scanning modality and institutional preference plays an imperative role in response evaluation.

Early response assessment

At ERA, more satisfactory response was observed in the PET-CT based assessment (151/186, 81.2%) as compared to CECT (126/196, 64.3%) (p value<0.001).

While analysing the significance of modality of scans at ERA, we also looked at its impact on patients with non-bulky disease. These were the patients who by the virtue of their disease did not merit RT unless their response was suboptimal. For the PET-CT arm 96/114 non-bulky patients achieved a satisfactory response (84.2%) as compared to 61/89 patients in the CECT arm (68.5%) with a p value=0.008. This showed that, by intention to treat analysis, children who undergo PET-CT at reassessment are significantly less likely to receive RT as compared to those who undergo CECT. RT was given (significantly) more in CECT arm, 98/196 (50%) as compared to 72/186 (38.7%) PET-CT patients (p value=0.017).

TABLE 1 Comparison of baseline variables in cohort of patients who had PET-CT vs CECT at ERA

	PET-CT (n=186)	CECT (n=196)	p-value
Demographic Variables			
Age (Mean (SD))	9.96 (4.3)	8.79 (3.7)	0.005
Gender (M:F)	5.4: 1	5.3: 1	0.532
Proportion from private Hospitals	36%	5%	<0.001
Disease related-Variables			
B-Symptoms	41.5%	58.5%	0.004
Bulky Disease	38.7%	54.6%	0.001
Advance Stage Disease	64.5%	68.4%	0.246
Laboratory Variables			
Hemoglobin (Mean (SD))	10.4 (2.2)	9.47 (2.5)	<0.001
ESR (Mean (SD))	46.49 (37.36)	43.80 (30.21)	0.472
LDH (Mean (SD))	496.7 (560.6)	470.9 (253.3)	0.293
Albumin (Mean (SD))	3.75 (0.76)	3.83 (0.95)	0.378

SD-Standard Deviation

M-Male

F-Female

Late response assessment

While analysing the outcomes at the second interim assessment, we found that those who underwent PET-

CT, satisfactory response (CR) was found in 64% patients whereas those who underwent CECT, satisfactory response (CR + VGPR- 38.18% + 23.64%) was found in 61.82% patients. Therefore, there was not much difference in the treatment recommendations (alternate chemotherapy) based on the modality of scan at second interim assessment.

Survival based on imaging modality

The 5 year OS of both groups- ERA based on CECT (91.8%) vs PET-CT (94.1%) was comparable (p value=0.391) and so was the 5 year EFS (86.7 vs 85.5%, p value=0.724).

EFS and OS for early-stage disease patients who underwent CECT vs PET-CT at ERA were similar (EFS-96.8 vs 92.4%, p value=0.288, OS-98.4 vs 97%, p value=0.563). Similarly, there was also no significant difference in the EFS and OS for advanced stage children who underwent CECT vs PET-CT at ERA (EFS-82.1 vs 81.7%, p value=0.926, OS-88.8 vs 92.5%, p value=0.316). Even the survival outcomes for bulky and non-bulky disease based on imaging modality did not differ statistically (EFS of bulky disease- CECT vs PET-CT-83.2 vs 84.7%, p value=0.77; OS of bulky disease- CECT vs PET-CT-90.7 vs 94.4%, p value=0.355. EFS of non- bulky disease; CECT vs PET-CT-91 vs 86%, p value=0.268, OS of non-bulky disease, CECT vs PET-CT-93.3 vs 93.9%, p value=0.869)

Discussion

The success story of Hodgkin lymphoma is attributed to collaborative efforts of research groups and sets an example for improving outcomes of childhood cancer by participation in national and international co-operative clinical trials. LMICs are largely dependent on outcomes demonstrated by trials conducted in developed countries and that poses unique challenges in implementation of such protocols. We successfully demonstrated the execution of a multicentric, prospective clinical trial in Indian setting where lack of resources and trained manpower (data managers/clinical trial coordinators), adept pathologists, PET scan machines etc was substantial and these facilities were available only at a few centres. We reported excellent outcomes in early-stage HL and suboptimal outcomes in advanced disease as compared to those reported from the developed world with a risk stratified and response based algorithm using ABVD as the backbone of treatment. Although most high-income countries have moved to a PET based treatment protocol for management of adult and pediatric HL, it is still not a norm in many LMICs. Our prospective multicentre trial with 27 centres provided an opportunity to examine the impact of the modality used assess response in childhood Hodgkin disease. We attempted to compare the differences in staging, response assessment, treatment and outcomes in the cohorts that underwent CECT or PET-CT. Equitable distribution of early and advanced disease patients made the comparison feasible with minimal bias.

Our study detected more stage IV patients in PET-CT arm as compared to CECT arm. Notwithstanding the similar baseline characteristics of the two groups, this discrepancy indicates the ability of PET-CT to identify more nodal and extra-nodal sites and upstage the disease. The CECT arm of our study did pick more bulky disease patients as compared to PET-CT. Nonetheless, we do not anticipate this denotes superiority of one modality over the other as both CECT and PET-CT have the accurate ability to obtain two dimensional measurements[7]. This difference though significant may be due to the late presentation of patients in government hospitals where CECT was more often used as compared to the trust hospitals or private sector where PET-CT was the preferred modality. Despite a misconstrued perception that PET-CT will detect more FDG avid lesions in a tropical country like ours where infectious diseases like tuberculosis are rampant, we did not find any reports of an inadvertent or missed diagnosis of infection amongst the trial participants on a reasonably long follow up.

PET upstaged 14% of the patients (159) and down staged 6% (74) in the Response-Adapted Therapy in HL study (RATHL). Extranodal disease in bone marrow (92 patients), lungs (11 patients), or multiple sites (12 patients) were left undetected in patients undergoing a conventional CECT scan[8]. Another study highlighted better detection of nodal disease in 62 patients with HL and superiority of PET-CT in identifying bone and bone marrow disease. Detection of other extra-nodal sites however did not vary significantly between the two modalities[9]. A Spanish randomised multicentric study, in contrast, showed similar staging outcomes

when comparing a PET-CT with a 64 slice multi-detector row CT among 181 patients with HL, diffuse large B-cell lymphoma and follicular lymphoma[10].

A satisfactory response in PET-CT was defined as Deauville score 1-3 and for CECT arm was defined as patients with VGPR/CR based on the published consensus of the international conference on malignant lymphoma classification imaging group recommendations[11,12]. Two major single centre Indian studies have also used similar criteria to consider optimum metabolic response in children assessed with PET scan[13,14] while one Indian study has used Deauville 1-2 for early stage and 1-3 for advanced stage HL[15]. Some studies from western world also use a more stringent criteria of Deauville score 1-2 to determine good response post 2 cycles of chemotherapy especially those contemplating therapy de-escalation. EURONET-PHL-C1 study defined adequate response as a combination of partial remission ($>$ 50% volume reduction in any involved site) and visual category-based PET response (no FDG uptake/activity or only slight FDG uptake/activity corresponding to Deauville score 1-2)[2]. Even the AHOD0831 study used Deauville score 1-2 at interim PET to consider omission of radiotherapy. This has important implication when we compare results and may account for more relapses in protocols using relatively liberal Deauville criteria for de-escalation. We performed the response assessment scan after 2 cycles of chemotherapy in line with the most contemporary protocols. Some of the older trials have implemented the response scan after 4 cycles of chemotherapy and it has been ascertained to have an inferior predictive value [16,17].

We found significantly more satisfactory responses in PET-CT based ERA (81.2%) as compared to CECT (64.3%). The significance persisted while evaluating only non-bulky disease patients who would have otherwise not received radiation had their disease been considered as satisfactory responder. For the PET-CT arm 84.2% children with non-bulky disease achieved a satisfactory response as compared to 68.5% patients in the CECT arm. This led to a 50% lower allocation of patients to radiotherapy in the PET-CT arm (15.8% in PET-CT arm vs 31.5% in CECT arm). Evidently, it is exceedingly pivotal to emphasize on the usage of interim PET-CT scan which distinctly indicates the response of the tumor cells to the treatment. CECT is less helpful in deciphering the treatment response due to low specificity and therefore the clinician may misinterpret the residual node as persistence of disease leading to inaccurate treatment decisions and unnecessarily exposing the patients to RT or additional chemotherapy.

The type of imaging modality used at ERA had no impact on outcomes. This demonstrates that therapy de-escalation and omission of RT was plausible in our patients if they sustained a satisfactory response after 2 cycles of chemotherapy. This is one of the largest studies conducted in an LMIC substantiating a beneficial effect of imaging modality in therapy de-escalation in pediatric Hodgkin lymphoma patients setting a benchmark for policy makers to appraise easy and affordable access to nuclear medicine facilities. Euronet-PHL-C1 study conducted over 186 hospital sites established that a 5 year EFS of 90.1% in patients who respond adequately and confirm that omission of RT is possible if one uses an intensive vincristine, etoposide, prednisolone, doxorubicin (OEPA) induction followed by consolidation with cyclophosphamide, vincristine, prednisolone, procarbazine (COPP) or cyclophosphamide, vincristine, prednisolone and dacarbazine (COPDAC)[2]. The benefit has also been documented in other single centre studies from India[13,18]. Children's oncology group trials have also demonstrated lower usage of radiation and reduction in radiotherapy volumes as compared to historical controls for children who are deemed 'rapid early responders'[19].

The controversy of therapy de-escalation is eminent in adult studies. While the importance of outcome prediction has been shown in both international and Indian studies, the impact on EFS has been significantly different leading to a lack of consensus[8,18].

Pooled analysis from 4 randomised studies comprising 2267 early stage HL patients showed that recurrence was 11.2% in patients who did not receive RT as compared to 4.7% in RT group. The significant difference in PFS was in favour of RT group (HR= 2.08; 95% CI 1.27-3.43, p$<$0.004, RE)[1,19,20,21,22,23]. Furthermore, the more recent SWOG S0816 study also showed a poor negative predictive value of negative PET-CT after 2 courses of ABVD and suggested against therapy de-escalation[24].

Conversely, few research studies affirm that negative PET-CT allows omission of RT without leading to

a dwindled EFS. GHSG HD17 trial performed PET scan after 4 cycles of chemotherapy (BEACOPP x 2 followed by ABVD x 2) and successfully omitted RT for PET negative patients[25]. Another study on nodular lymphocyte predominant Hodgkin lymphoma (nLHPL) patients recently demonstrated the possibility of RT omission for PET negative patients after 2 cycles of ABVD. These trials have differences in timing and patient population but they provide grounds for further research in this area. In the light of above findings, we feel that more studies are needed in pediatric population, especially in centres using ABVD based chemotherapy but strongly recommend the imaging modality of choice to be PET-CT. Choosing CECT in lieu of PET-CT scan leads to gratuitous exposure of RT to the children. The relatively younger age of presentation of the pediatric HL patients in developing countries further adds to the burden of delayed side effects of radiotherapy such as secondary malignancy, endocrine impairment and cardiorespiratory damage.

Our study has some limitations. The study cohorts are not randomised. Central review of scan was not done and hence quality control of reporting could not be established. Despite being cognizant of late relapses in HL, the follow up data was collected only for 3 years[24]. Our study mainly relied on Deauville criteria for response assessment. Biomarkers such as metabolic tumor volume and total lesion glycolysis are also elicited by PET-CT which elucidate details regarding tumor burden and disease activity, however data on these newer parameters was not available for analysis[12].

To conclude, our study reinforces that PET-CT should be the preferred choice of investigation rather than CECT to preclude the needless exposure of RT/additional therapy to the patients. Moving ahead, the study team of InPOG-HL group has proposed only PET-CT based assessment in future studies with assured support from partner NGO for provision of at least 2 PET-CT scans per patient to those who are unable to access free scan at their institution or are unable to bear the costs involved.

Conflict of Interest:

The authors declare no conflicts of interest.

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