Original Article

The role of fluorodeoxyglucose positron emission tomography-computerized tomography in resolving therapeutic dilemmas in pediatric Hodgkin lymphoma

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ABSTRACT

Introduction: Hodgkin lymphoma (HL) is a highly curable lymphoma with cure rates of over 80% and even higher with limited stage disease. Computerized tomography (CT) scan is currently the recommended modality in staging and assessment of response to therapy in patients with HL. However, CT has its limitations. This study describes our experience with patients of HL where fluorodeoxyglucose positron emission tomography (FDG-PET)-CT scan helped decide further management, after completion of chemotherapy. **Methodology:** This is a retrospective review of the records of children diagnosed with HL at our center. Patients with post-treatment CT scan showing evidence of residual disease, who underwent FDG-PET-CT for deciding further management, were included in the study. **Results:** Thirty one patients were diagnosed with HL during this period. Nine patients were eligible and underwent PET-CT. In 8 out of 9 patients, PET-CT showed no scan evidence of active disease. In one patient, FDG-PET-CT carried out after completion of chemotherapy showed evidence of active disease and was given radiotherapy. **Conclusion:** FDG-PET-CT is a promising modality in deciding further management when there is discordance between the post-treatment CT scan and clinical condition of the patient with HL thus avoiding unnecessary chemotherapy/radiotherapy.

Keywords: Children, hodgkin lymphoma, positron emission tomography-computerized tomography

INTRODUCTION

Hodgkin lymphoma (HL) is a highly curable lymphoma with overall cure rates exceeding 80% and over 90% with limited stage disease.[1] The improved survival has led to the concern about long-term effects of cancer therapy adversely affecting the quality of life of these children.[2-4] Computerized tomography (CT) scan is currently the recommended modality in the staging and assessment of response at the end of therapy in patients with HL.[5] The drawbacks of CT scan include its failure to differentiate areas of necrosis and fibrosis in residual masses from viable tumor thus, creating a therapeutic dilemma whether the patient requires further treatment or not.[6] It also fails to identify tumor deposits in unenlarged nodes thus, underestimating the stage of the disease before starting therapy.

Fluorine-18 fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) has been widely established in the treatment protocol of non-Hodgkin lymphoma (NHL).[6-9] In recent times it is being used with in HL, for staging at the time of diagnosis, to differentiate persistent, active disease from residual, but inactive masses at the completion of therapy as well as for monitoring for relapse.[6-11] However, PET alone has lower specificity because of poor localization details. Introduction of combined PET and CT (18F-FDG-PET/CT) technology has revolutionized imaging by fusing functional and anatomical data. It is being routinely used for staging, response monitoring and prognostication of a wide array of tumors. This study describes our experience with nine patients of HL where FDG-PET-CT scan helped us to decide further management after completion of planned chemotherapy.

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METHODS

This is a retrospective review of the records of all children aged less than 12 years, diagnosed with HL on biopsy enrolled

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in pediatric oncology clinic at the All India Institute of Medical Sciences between October 2005 and May 2010. Patients with post-treatment CT scan showing evidence of residual disease, who underwent FDG-PET-CT for deciding further management, were included for the study. Those with concurrent HIV infection, any pre-existing severe organ (kidney, liver, cardiac, and cerebral) dysfunction were excluded.

The pre-treatment evaluation included a detailed history and physical examination. A baseline hemogram and serum biochemistry including lactate dehydrogenase (LDH) was obtained. A chest X-ray and contrast enhanced computerized tomographic scan (CECT) of chest, abdomen and pelvis were carried out in all patients. A biopsy was carried out from the most appropriate site. A bone marrow aspiration/biopsy was carried out in all except in stage IA-IIA patients. A technetium-99 bone scan was carried out if indicated. Clinical staging was carried out according to the Ann-Arbor classification.[12] Splenic involvement was defined as clinically detectable splenomegaly or presence of hypodense lesions on abdominal CECT in patients without clinically detected splenomegaly bulky disease was defined as presence of lymph nodal mass of at least 6 cm diameter or a mediastinal mass with a diameter exceeding one-third of the maximum intra-thoracic cavity width on an upright postero-anterior chest radiograph. Patients were histologically classified according to the Ryes modification of Lukes and Butler scheme.[13]

Patients treated at our center received either 4 alternate cycles of adriamycin, bleomycin, vinblastine, dacarbazine/cyclophosphamide, oncovin, procarbazine, prednisone (ABVD/COPP) or 4-6 cycles of ABVD as initial therapy. Patients were reassessed for residual disease and need for radiotherapy/escalated chemotherapy at end of chemotherapy with CT scan of the site of disease. FDG-PET scan was carried out whenever there was a discordance of clinical evaluation and CT findings.

After fasting for at least 4 h and with patients in a resting state, in a quiet room, a dose of 5.3 MBq/kg (0.14 mCi/kg) of FDG was injected intravenously. Older children were instructed to lie still whereas smaller children were encouraged to sleep. Sedation was carried out when needed using 0.1 mg/kg midazolam to avoid motion artifacts. PET-CT scan was acquired on a dedicated PET-CT scanner approximately 60 min after intravenous injection of radiotracer on a Biograph scanner (Siemens, Germany). After the acquisition, data was transferred to a workstation for processing and interpretation. After reconstruction of the images were displayed in axial, sagittal and coronal planes. The image interpretation and analysis was performed qualitatively (visually).

RESULTS

Thirty one patients were diagnosed with HL at our center during the study period. Nine of these patients underwent PET scans at the end of treatment and were found to be eligible. The patient profiles are summarized in Table 1.

In all nine patients, CT scan evaluation after completion of chemotherapy revealed residual disease. As there was discrepancy between clinical and radiological findings, the patients underwent a FDG-PET scan. The findings are described in Table 2.

In 8 out of 9 patients, FDG-PET showed no scan evidence of active disease. No further treatment was given to these patients. In one patient, FDG-PET carried out after completion of chemotherapy showed evidence of active disease in spleen and retroperitoneal lymphnodes. This patient was given escalated chemotherapy for HL. Follow-up FDG-PET performed. After completion the chemotherapy, showed no scan evidence of active disease. The patient continues to be in remission at a follow-up of 20 months.

DISCUSSION

Recent changes in the treatment protocols for over the past two decades have resulted in improved survival among patients of HL.[1,2] CT scan is the recommended imaging modality at the end of therapy and often detects residual disease based on persistence of sizeable lymphadenopathy/organ enlargement/hypoechoic lesions in patients who are clinically well.[5] Treating all these residual masses with chemotherapy or radiotherapy may result in unwanted morbidity. There is thus, a need for an imaging modality to differentiate residual but inactive/inert masses from active lesions that require further treatment. The use of PET in detection of cancer cells employing FDG as the tracer molecule is based on Warburg's demonstration that malignant cells show accelerated glucose metabolism.[10] As early as 7 days after first administration of chemotherapy and in most patients after 2 cycles of chemotherapy, there is shutdown of cellular metabolic and chemokine-synthetic machinery.[10]

Table 1: Clinical profile of patients

Number of patients	9
Mean age (years)	9 (3-12)
Sex	
Male	9
Female	0
Disease status	
Initial diagnosis	7
Relapse	2
Ann-Arbor clinical stage	
IA	1
IB	3
IIB	2
IIIB	3
Histological diagnosis	
Nodular sclerosis	6
Mixed cellularity	3
Protocol	
ABVD	4
ABVD/COPP	4
ABVD followed by BEACOPP	1
Mean follow-up duration (months)	24 (6-48)

ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine, COPP: Cyclophosphamide, Oncovin, Procarbazine, Prednisone, BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine, Prednisone

Table 2: Computerized tomography and fluorodeoxyglucose-positron emission tomography-computerized tomography findings

S.No.	Baseline CT	CT (at point of dilemma)	FDG-PET-CT at point of dilemma	Plan after PET-CT	Duration of follow-up (months)
1	Mediastinal, bilateral hilar, mesenteric lymphnode and few retroperitoneal lymphnodes	Few lymph nodes in mediastinum	No evidence of active disease	Follow up	48
2	Bilateral cervical and mediastinal lymphadenopathy	Bilateral deep cervical lymphnode enlargement	No evidence of active disease	Follow up	40
3	Large mass lesion on right side of neck with compression effects	Small lymph node in posterior triangle of neck and parotid region	Residual disease in bilateral cervical region	Radiation therapy	39
4	Mediastinal lymphnode enlargement; bilateral kidney enlargement with hypodense lesions	Mediastinal lymphnode enlargement	No evidence of active disease	Follow up	26
5	Mediastinal and retroperitoneal lymphnode enlargement, splenomegaly with multiple small hypodense lesions,small bowel thickening	Mediastinal lymphnode enlargement, hepatosplenomegaly with splenic deposits	Active disease in spleen, retroperitoneal, splenic hilar, perigastric lymphnodes	The child was labeled as having progressive disease and was treated with the escalated BEACOPP regime after review of biopsy	
	After completion of escalated BEACOPP regime	Persistent pretracheal lymphadenopathy, hepatosplenomegaly,	No evidence of active disease	Follow up	20
6	Bulky mediastinal lymphnodes, enlarged retroperitoneal nodes,	Retroperitoneal lymphnode enlargement	No evidence of active disease	Follow up	14
7	Splenomegaly with multiple hypoechoic lesions, right paratracheal lymphnode enlargement	Hypodense lesion in spleen, few mesenteric lymphnodes	No evidence of active disease	Follow up	14
8	Bulky cervical and superior mediastinal lymphnode enlargement	Decreased size cervical lymphnodes	No evidence of active disease	Follow up	12
9	Linear opacity in right lung middle lobe The child had a single significant cervical lymph node which was biopsied.	Hepato splenomegaly with no lymphadenopathy	No evidence of active disease	Follow up	6

However, tumor shrinkage takes a longer. In contrast, in patients not responding to chemotherapy, the cellular metabolic activity persists and is evidenced by increased uptake.[10] This sensitivity of PET holds promise for extensive use in both response assessments during chemotherapy, as well as in cases with discordant clinical and CT findings after therapy completion.

PET scan has widespread use among NHL patients in staging, post-therapy assessments and evaluation of residual masses.[6-9] Teresawa, *et al.* in a systemic review found varying sensitivities from 0.33 to 0.77 and specificity from 0.82 to 1.00 in post-therapy evaluation of NHL patients.[8] It is a recommended modality in the response assessment of NHL.[6] As in NHL, PET has been evaluated in the context of staging, response assessment and end-therapy assessment in HL but pediatric data is scarce. Though, PET scan detects smaller lymph node involvement and elucidates bone marrow, splenic and liver involvement, it is not the standard in HL staging due to high sensitivity and false positivity rates.[9]

The main utility of FDG-PET in HL is post-treatment assessment. But studies in this regard have produced conflicting results. Terasawa, *et al.* in a systemic review reported sensitivity between 0.50 and 1.00 and specificity between 0.67 and 1.00 for post-treatment evaluations.[8] Juweid reported a consistently high negative predictive value averaging about 90% and exceeding 80%, which is similar to that of CT.[11] The positive predictive value while being more variable (averaging approximately 65% with most studies reporting values exceeding 50%), was higher than that of CT (about 20%).[12,14-17] However, these data primarily reflects that of adult patients of HL. Pediatric data is scarce and inconclusive.[18-20]

FDG-PET has also been studied as a predictor of outcome in HL. A negative interim PET after 2 cycles of chemotherapy was associated with an increased 2 year progression free survival rate compared to the PET positive group.[21-23] Furth *et al.* in a prospective study demonstrated that pediatric HL patients with a negative PET during early response assessment (after 2 cycles of chemotherapy) have an excellent prognosis while PET-positive patients have an increased risk for relapse. They also demonstrated that a standardized uptake value $(SUV)_{max}$ reduction of < 58% was associated with an increase in risk of relapse.[19]

The present studied demonstrated the role of PET-CT in resolving therapeutic dilemmas in 29% of patients which are common after therapy for HL. The limitations of the present study are small sample size and retrospective nature.

Though, doing a PET-CT in all such patients involves lot of cost, the cost of further chemo/radiotherapy and its side-effects outweigh the monetary burden. However, this modality of investigation has the potential as a baseline evaluation to detect small areas of disease involvement not detected by CT and as a prognostic marker for predicting disease free interval.

CONCLUSION

PET-CT scan is a promising modality in deciding further management when faced with situations where there is discordance between the post-treatment CT scan and the clinicalcondition of patient with Hodgkin lymphoma, thus, avoiding unnecessary chemotherapy/radiotherapy.

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