The predictive value of PET-scan in Diffuse large B-cell in optimizing the treatment decision

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Abstract: Introduction: Diffuse large B cell lymphoma (DLBCL) is the major histologic subtype of aggressive non-Hodgkin lymphomas. The role of 18F-FDG PET/CT scan is well established at the baseline and at the end of treatment for DLBCL patients. Many studies reported that patients with a negative scan after initial 2-3 cycles of chemotherapy showed both a better progression-free (PFS) and a better overall survival (OS). Therefore it is important to determine an accurate predictive tool to stratify patients who are more likely to relapse, to allow clinicians to modify their treatment accordingly. **Aim of the work:** In our study we are concentrating on the predictive value of interim 18F-FDG PET/CT in patients with recently diagnosed pathologically proven DLBCL treated with chemotherapy as first line. **Patients and Methods:** This prospective study was performed in Kasr alainy Center of Clinical Oncology and nuclear medicine after being approved by the ethical committee. The study included thirty-nine patients, with newly diagnosed pathologically proven DLBCL. Patients were subjected to whole body 18F-FDG PET/CT as a baseline and after 3 cycles of their 1st line chemotherapy (interim PET). **RESULTS:** Between June 2015 and July 2017, The study included 39 patients. Thirty-one patients received R-CHOP-21 and 8 patients received R-EPOCH-21). All patients underwent a complete evaluation with a baseline scan, interim PET-I scan (PET-I), and an end-of -treatment scan (PET-E). According to PET-I (interim PET) results, patients were subdivided into metabolic responders (PET-negative patients) including patients with complete and partial response and metabolic non-responders (PET-positive patients) with progressive and stable disease using Deauville criteria. PET-negative patients 92.3% (36 patients) received three additional courses, whereas in PET-positive patients (3 patients) 2nd line chemotherapy was prescribed (two patients received GEMOX and the other one received ESHAP). Two of them were still non-responder at the end-of-treatment study while the other one became responder. At the end-of-treatment PET/CT scan, 89.7% of patients (n=35) were metabolic responders and 10.3% (n = 4) were metabolic non-responders. Two patients of the end treatment non-responders were also non-responder at the interim study while the other two patients were responders at the interim study. **Conclusion**: In DLBCL, optimization of the management of patients has been considered of great importance as conventional chemotherapy has been shown to be effective only in 60% of patients. Using PET-CT is of value in treatment decision and early shift for non-responding patients.

Key words: PET-CT, Predictive value, DLBCL.

Introduction

Management of lymphomas follows well-established guidelines based on the initial staging assessment. Therefore accurate staging is the basis for selection of appropriate therapeutic approach in order to prevent over or under treatment as well as to minimize morbidity related to the radio-chemotherapy regimens given.[1] Diffuse large B cell lymphoma (DLBCL) is the major histologic subtype of aggressive non-Hodgkin lymphomas (NHL) and comprises about 30% of cases. Many studies reported that patients with a negative scan after initial 2-3 cycles of chemotherapy showed both a better progression-free

(PFS) and a better overall survival (OS).[2] Therefore it is important to determine an accurate predictive tool to stratify patients who are more likely to relapse, to allow clinicians to modify their treatment accordingly.[3] The role of 18F-FDG PET/CT scan is well established at the baseline and end of treatment for DLBCL patients.[4] However, the role of interim PET/CT in therapeutic decision making in those patients is yet to be confirmed.[5]

Metabolic tumor burden can express not only intensity of FDG accumulation but extent in volumetry. Some investigators have reported the greater usefulness of metabolic tumor volume or total

lesion glycolysis for response assessment, because these volumetric parameters reflect metabolic tumor burdens.[6] In our study we are concentrating on the predictive value of interim 18F-FDG PET/CT in patients with recently diagnosed pathologically proven DLBCL treated with chemotherapy as first line.

Aim of work

We aimed at evaluating the predictive value of the interim 18F-FDG PET/CT in patients with pathologically proven DLBCL to be provide basis for treatment.

Patients and Methods

This prospective study was a co-operative work between nuclear medicine unit and clinical oncology unit in Kasr El Ainy Center of Clinical Oncology and nuclear medicine after being approved by the ethical committee. This study included thirty-nine patients, with newly diagnosed pathologically proven DLBCL presented to us between June 2015 and July 2017. Patients were subjected to whole body 18F-FDG PET/CT as a baseline and after 3 cycles of their 1st line chemotherapy (interim PET). According to interim PET results the patients were subdivided into 2 categories; the 1st category is metabolic responders (PET-negative patients) including patients with complete and partial response. The 2nd category is metabolic non-responders (PET-positive patients) with progressive and stable disease according to Deauville criteria (5-point scale), and interpretation of the results was done using EORTEC and RECIST scales. PET-negative patients (36 patients) completed their preplanned treatment protocols, whereas PET-positive patients group (3 patients) received 2nd line chemotherapy.

At the end of treatment (6 cycles of chemotherapy), further follow-up was done by PET-CT scan (PET-E). Metabolic response assessment was done by using Deauville criteria and also interpretation was done using EORTEC and RECIST scales.

PET/CT protocol:

o Patients were asked to fast for 6 hours before the 18 F FDG PET/CT scan. Each patient was injected with 0.14 mCi/kg body weight (5.5 MBq/Kg) with 18F FDG. During the uptake phase of the FDG, patients were laid in a quiet warm room, in order to minimize non-desired FDG uptake. After IV injection of 18F FDG by 45 – 60 minutes, PET/CT images were acquired using a combined PET/CT scanner (Philips Gemini Time-of-flight PET/CT machine equipped with LYSO (lutetium–yttrium oxyorthosilicate) crystals). and a 512 x 512 matrix size, acquiring a field of view (FOV) of 700 mm in 22.5 seconds. For each patient, maximum and mean SUV (SUVmax and SUVmean) of the lesions were measured. The tumor boundaries were identified using ellipsoid isocontours and drawn large enough to include all the tumor

volume but careful enough to exclude any background activity. The selected volumes were based on the automatically fixed threshold method, This method applies a threshold based on a percentage (typically, 41%) of SUV max within the tumor.[7]

Analysis of the interim scan:

Assessment of metabolic response was done using Deauville criteria. 5-PS scores the most intense uptake in the site of initial disease, if present, in relation to normal uptake in mediastinum and liver.

Analysis of the follow up scan:

Assessment of response to the given treatment was done using Deauville criteria as well as EORTEC and RECIST criteria. Determination of true or false positive and/or negative lesions was based on clinical and radiological follow up as well as histo-pathological examination.

Statistical analysis

SPSS version 21 was used for data analysis. Bivariate relationship was displayed in cross tabulations and Comparison of proportions was performed using the chi-square and Fisher's exact tests where appropriate. T-independent and one-way Annova tests were used to compare normally distributed quantitative data.

Pearson correlation was used to compare normally distributed quantitative data. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for TLG and Suvmax in diagnosing cases. Kaplan-Meier survival was used to display the survival function for progression-free survival and disease-free survival cases. P-values less than 0.05 was considered statistically significant.

Results

Between June 2015 and July 2017, the accrual of patients was done. The study included 39 evaluable patients. Patients were evenly divided between males and females (20 females and 19 males). Median age was 45 years with ECOG performance status of 0 in 28.2% of the patients, 1 in 59 % and 2 in 12.8%. Ann Arbor stage I, II, III, or IV was found in 5 (12.8 %), 6 (15.4 %), 7 (17.9 %), and 21 patients (53.8 %), respectively. An IPI score of 0 to 2 was found in 20 patients (51.3 %) and a score of 3 to 5 was found in 19 patients (48.7%). According to the Tally algorithm [8], 5 patients (27.8 %) were classified as non–germinal center DLBCL, and 13 patients (72.2 %) had germinal center DLBCL (of 18 evaluable samples).

Nearly all patients had nodal disease at time of presentation (except for only one patient only who had purely extra-nodal disease). Thirteen patients (33.3 %) had no extra-nodal disease and 26 patients (66.7 %) had extra-nodal disease (12 patients with one extra-

nodal site and 14 patients with more than one extra-nodal site). LDH level was normal in 15 patients (38.5%) and was high in 24 patients (61.5%). Bone marrow biopsy was done in 12 patients and it was found positive in two patients and negative in the other 10 patients. 13 patients (33.3 %) had bulky disease and 26 patients (66.7 %) had no bulky disease. Patient's characteristics **(Table 1).**

Table 1: patient's characteristics.

Characteristics	No	%
Age, years		
Median	45	
Range	22-69	
Sex		51.3%
Female	20	48.7%
Male	19	
Ann Arbor stage		12.8%
I	5	15.4%
II	6	17.9%
III	7	53.8%
IV	21	
Performance status		28.2%
0	11	59%
1	23	
2		
LDH, IU/L		38.5%
Normal	15	61.5%
High	24	
No. of extranodal lymphoma sites		33.3%
0	13	30.8%
One site	12	35.9%
More than one site	14	12.8%
5		
IPI score		30.8%
0,1 (low)	12	20.5%
2 (low intermediate)	8	28.2%
3 (high intermediate)	11	20.5% DLBCL
4,5 (high)	8	72.2%
GC (Tally algorithm)	13	27.8%
Non-GC	5	
Interim PET-I (Deauville)		38.5%
Complete response	15	53.8%
Partial response	21	0.0%
Stable disease	0	7.7%
Progressive disease	3	
End-of-treatment PET-E (Deauville)		56.4%
Complete response	22	33.3%
Partial response	13	0.0%
Stable disease	0	10.3%
Progressive disease	4	
End-of-treatment PET-E (EORTEC)		38.5%
Complete response	15	38.5%
Partial response	15	10.3%
Stable disease	4	12.8%
Progressive disease	5	
End-of-treatment PET-E (RECIST)		30.8%
Complete response	12	48.7%
Partial response	19	10.3%
Stable disease	4	10.3%
Progressive disease	4	
Abbreviations: DLBCL, diffuse large B-cell lymphoma; GC, germinal center; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PET, positron emission tomography; PET-I, PET scan after two cycles of therapy; PET-E, PET scan after end of therapy (6 cycles). EORTEC, European Organization for Research and treatment of cancer; RECIST, Response Evaluation Criteria in Solid Tumors.		

PET/CT Results:

All 39 patients underwent initial pretreatment PET/CT and interim PET/CT after three cycles of 1st line chemotherapy. Thirty-one patients received R-CHOP-21 and 8 patients received R-EPOCH-21). All thirty-nine patients underwent a complete evaluation with a baseline scan, interim PET-I scan (PET-I), and an end-of-treatment scan (PET-E). Involved field radiotherapy to bulky disease to 9 patients was delivered regardless of PET/CT results. According to PET-I (interim PET) results, patients were subdivided into metabolic responders (PET-negative patients) including patients with complete and partial response and metabolic non-responders (PET-positive patients) with progressive and stable disease using Deauville criteria. PET-negative patients 92.3% (36 patients) received three additional courses, whereas in PET-positive patients (3 patients) 2nd line chemotherapy was prescribed (two patients received GEMOX and the other one received ESHAP). Two of them were still non-responder at the end-of-treatment study while the other one became responder. At the end-of-treatment PET/CT scan, 89.7% of patients (n=35)

were metabolic responders and 10.3% (n = 4) were metabolic non-responders. Two patients of the end treatment non-responders were also non-responder at the interim study while the other two patients were responders at the interim study.

Using the EORTEC criteria; 38.5% of the studied population had complete response, 38.5% had partial response, 10.3% had stable disease and 12.8% had metabolic progression. Morphologic response according to the modified RECIST response criteria showed that 30.8% of the studied population had complete response, 48.7% had partial response, 10.3% had stable disease and 10.3% had morphologic progression. Again, patients with stable and those with progressive disease were grouped together as non-responders and those with complete or partial response were labeled responders.

3- Measurements of the baseline scans:

Mean baseline SUVmax was 31.8 (range=4.3-46.2) while mean baseline TLG was 4099.9(range-=25-87862.7) **(Table 2)**

Table 2: Measurements of the baseline scans.

Parameter	Mean	Median	Range	Minimum	Maximum
Baseline SUVmax	31.8	19.1	41.9	4.3	46.2
Baseline TLG	4099.91	517.30	87837.70	25.00	87862.70

Correlation between baseline measurements and response at the end of treatment: ROC analysis of SUV max and TLG showed no statistical correlation between baseline measurements and response at the end of treatment. The identified

SUVmax value of 19.1 and TLG value of 532.90 gave only modest sensitivity (52% and 48.6% respectively) and specificity of 49% and 50% respectively.

Correlation between interim PET-CT and response of treatment:

Table 3: Relationship between different studied clinical parameters and metabolic response to treatment.

		PET-E (Deauville)				
		Non-responding		Responding		
		Number	percent	Number	percent	P value
Age category	≤60 years	3	75.0%	27	77.1%	0.923
	>60 years	1	25.0%	8	22.9%	
Gender	Male	3	75.0%	16	45.7%	0.267
	Female	1	25.0%	19	54.3%	
Bulky disease	No	0	0.0%	26	74.3%	*0.003* (*significant*)
	Yes	4	100.0%	9	25.7%	
IPI score	Low	0	0.0%	12	34.3%	0.196
	Intermediate	2	50.0%	17	48.6%	
	High	2	50.0%	6	17.1%	
Stage	Early (I,II)	0	0.0%	11	31.4%	0.186
	Late (III,VI)	4	100.0%	24	68.6%	

Using Deauville criteria, results of the interim PET-CT were directly correlate with treatment outcome *(P value= 0.002)*. ROC analysis of the interim results by the quantitative approach using the ΔSUVmax between baseline and interim PET-CT was also statistically significant *(P value = 0.05)*. The ROC analysis identified ΔSUVmax value of 80.85 % as the best predictive cut-off value for the presence of response with 74.3% sensitivity, 75% specificity and 74.3% accuracy. It had higher negative predictive value of 96.3% with lower positive predictive value of 25%. The relationship between different clinical factors of the studied population, such as age, gender, stage, IPI score, bulky disease as well as nodal and extra-nodal disease were examined for possible associations with the treatment outcome. However, the fore-mentioned studied parameters showed *no statistical significance* in identifying the future metabolic response to treatment except for presence of bulky disease (>7.5) cm that shows strong significant difference (*P value 0.003) (*Table 3).

5. Further follow-up

Patients were subjected to regular follow up after end of treatment with mean period of 14.8 months and median of 14 months.

Correlation of interim PET-CT with PFS and OS showed no significant difference between PET-positive and PET-negative patients (P=0.25 and P=0.596 significantly).

Discussion

We believed that a standardized method for evaluating PET results should be defined before planning an intervention study that compared different therapy strategies which depended on interim 18F-FDG PET/CT results. In our study, we included 39 patients prospectively to specifically define the prognostic role of interim PET/CT scanning in patients with DLBCL under standardized treatment and evaluation conditions. In addition, we were looking for evaluating the use of interim 18F-FDG PET/CT for risk-adapted strategy for newly diagnosed patients with DLBCL. The prognostic value of interim 18F-FDG PET/CT performed during first-line therapy of patients with DLBCL is still unclear. Previous studies showed poor reproducibility and inconsistent accuracy and sensitivity of interim 18F-FDG-PET/CT due to different treatment modalities and response criteria. In an attempt to standardize interim 18F-FDG PET/CT reporting criteria, the "First International Workshop on Interim 18F-FDG PET in Lymphoma," created in 2009, developed a consensus of response criteria for the interim PET. The response criteria were mainly based on visual and semi-quantitative analysis. The

visual response criteria used the Deauville five-point scale (5-PS): 1, no uptake; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤liver; 4, uptake moderately increased compared to the liver uptake at any site; and 5, markedly increased uptake compared to the liver at any site and new sites and/or new sites of disease. For semi-quantitative analysis and since maximal standardized uptake value (SUVmax) is the most commonly used semi-quantitative method of PET analysis in oncology, assessment of the decrease in SUVmax after a few cycles of chemotherapy compared with basal or pretreatment SUV expressed as a percentage (ΔSUVmax) can be useful in interim PET evaluation.[9] Several studies have been conducted to improve the NPV and PPV in patients with DLBCL by using a more quantitative approach based on ΔSUVmax between baseline and interim 18F-FDG-PET/CT. [10-11]

Spaepen et al.reported the value of interim PET in predicting the outcome of DLBCL patients who had been treated with different chemotherapy regimens using delta-SUV-based criteria.[12] In this study, our results confirmed that results of the interim 18F-FDG-PET-CT by visual assessment using Deauville criteria were directly correlated with treatment outcome *(P value= 0.002)*. ROC analysis of the interim results by the quantitative approach using the ΔSUVmax between baseline and interim PET-CT was also statistically significant *(P value = 0.05)*. The ROC analysis identified ΔSUVmax value of 80.85 % as the best predictive cut-off value for the presence of response with 74.3% sensitivity, 75% specificity and 74.3% accuracy. It had higher negative predictive value of 96.3% with lower positive predictive value of 25%.

In another study, the negative predictive value (NPV) of a negative interim PET/CT, which identified a group of patients with good prognosis and a 2-year EFS of 70.9%. [13] Conversely, the positive predictive value (PPV) of a positive interim PET/CT identified a group of patients with poor prognosis, and the risk for an event within the first 2 years was 51.8%. Indeed, half the PET-2–positive patients had converted to PET negative by the end of the treatment. These numbers were confirmed in their central review and in the review that used Deauville criteria (1 to 3 *v* 4 to 5 points) with 73.1% for the NPV and 58.6% for the PPV, respectively. These numbers were clearly inferior when compared with the prognostic role of an interim PET/CT in Hodgkin lymphoma; in Hodgkin lymphoma, NPV reached 96% and PPV reached 19%**.**[14]

Our results confirmed the satisfactory prognostic value of an interim PET/CT in DLBCL treated with six cycles of R-CHOP-21 or R-EPOCH-21 in a

prospective trial. Our results failed to show satisfactory PPV of the interim 18F-FDG PET/CT that could reflect the clinical outcome for patients with DLBCL treated with standard first line chemotherapy with no sufficient data to guide therapeutic decisions such as treatment intensification/deintensification at the present stage, even when standardized treatment and evaluation procedures for PET are being used in a reasonably large cohort of patients.[15]

There are currently several ongoing trials evaluating the role of an interim PET/CT in patients with DLBCL, and first results of trials using an interim 18F-FDG-PET/CT for treatment guidance are already available. Our data suggested that interim PET assessment is the strongest prognostic factor for predicting response at the end of treatment *(P value 0.002)* compared to other clinical prognostic factors which had no significant correlation with response at the end of treatment except for presence of bulky disease (>7.5 cm) that shows strong significant difference *(P value 0.003)*. In contrast to the results, in **Adams et al** study, the NCCN-IPI (National Comprehensive Cancer Network International Prognostic Index) was shown to be the only independent prognostic factor of both PFS and OS in R-CHOP-treated DLBCL**.** However, in our trial, correlation between interim PET-CT with progression and disease-free survival showed no significant difference between PET-I positive and PET-I negative patients *(P value* 0.250 and *0.596 respectively).*[16]

The results of this study also showed that neither SUVmax in the most active lesion, nor whole-body TLG were predictive of response of treatment in R-CHOP- or R-EPOCH treated DLBCL. ROC analysis of SUV max and TLG were statistically non-significant *(P value 0.3 and 0.4 respectively)*. The identified SUVmax value of 19.1 and TLG value of 532.90 gave only modest sensitivity (52% and 48.6% respectively) and specificity of 49% and 50% respectively.

In a retrospective study that included 140 DLBCL patients who were treated with R-CHOP, **Kim et al (Kim et al, 2013)** it was reported that high whole-body TLG values were independently predictive of reduced PFS and OS, whereas Ann Arbor stage and IPI score did not predict survival.

Drawbacks of that study by were the use of two different PET/CT systems, failure to report whether 18 F-FDG PET/CT readers were blinded to outcome, and comparison with the old IPI instead of the improved NCCN-IPI**.**[17]

A retrospective study performed by **Gallicchio et al.** included 52 patients with newly diagnosed DLBCL. Remarkably, univariate Cox regression analysis indicated a low whole-body SUVmax to be associated with reduced PFS, whereas whole body MTV and whole-body TLG were not predictive of PFS at univariate analysis. Their study excluded high-risk IPI patients, did not report whether the 18 FDG PET/CT readers were blinded to outcome, and retrospectively determined optimal cut-off values for 18 F-FDG PET/CT metrics with ROC analysis which undoubtedly has overestimated the prognostic value of SUVmax at univariate analysis.[18]

The present study had several limitations in this point. First, a limited number of quantitative whole-body FDG-PET/CT metrics were investigated. Although whole-body SUVmax and whole-body TLG are currently most popular in both clinical practice and research, other, more advanced methods such as quantifying tumor heterogeneity in FDG-PET/CT by texture analysis [19] or quantitative dynamic FDG-PET studies [20] have not been investigated yet in this setting. It should be noted, however, that the latter are technically more challenging and more difficult to implement in clinical practice than the FDG-PET/CT parameters that were investigated in the present study. Second, observer agreement of whole-body SUVmax, whole body MTV, and whole-body TLG measurements was not assesse.

Conclusion
In DLBCL, optimization of the management of patients has been considered of upmost importance as conventional chemotherapy has been shown to be effective only in 60% of patients. Interim 18F-FDG PET/CT allows for prediction of response and selection of patients who can benefit from second line therapies and therefore early alteration of ineffective therapy regimens.

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