Interim PET/CT Result Is The Sole Prognostic Factor Of Survival In Patients With Advanced-Stage Diffuse Large B-cell Lymphoma A Prospective Trial

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Abstract

Background We assessed whether interim positron emission tomography (iPET) had a prognostic value for diffuse large B-cell lymphoma (DLBCL) and whether PET-driven intensified therapy was needed.

Methods: A prospective analysis of newly diagnosed stage III-IV DLBCL patients treated was conducted. The iPET scan was performed after 4 cycles of RCHOP (rituximab 375 mg/m² d1; cyclophosphamide 750 mg/m² d2; doxorubicin 50 mg/m² d2; vincristine 1.4 mg/m² [maximum 2 mg] d2; prednisone 100 mg orally daily d2-6) in all cases. Patients received 2 additional cycles when they achieved complete response. If they achieved partial response (PR), they received 4 additional cycles, and a final PET scan (fPET) was performed. If they had stable disease or progressive disease (PD), they were managed by salvage chemotherapy. The primary endpoint was 3-year progression-free survival (PFS), and secondary endpoints included 3-year overall survival (OS) and objective response rate (ORR). The trial is registered with ClinicalTrials.gov, number NCT 01804127.

Results: From 2013 to 2015, a total of 55 patients were enrolled and 53 with both baseline and iPET scans were analyzed for efficacy. Thirty-nine patients had iPET-negative (iPET-) and 14 patients had iPET-positive (iPET+) scans (11 had PR and 3 had PD). The ORR was 94.3%. With a median follow-up time of 36.4 months, 3-year PFS was 65.7% and 3-year OS was 79.9% for the entire cohort (n=53), and the median PFS and OS were not yet reached. iPET- patients had a higher 3-year PFS rate (78.1%) than iPET+ patients (34.3%) with a P value lower than 0.01. A trend for improved OS was also observed, with 3-year OS of 87.1% versus 62.3% (P=0.03). All 11 patients who had iPET PR received another 4 cycles of RCHOP, and 10 underwent fPET. Six patients had fPET-negative (fPET-) and 4 had fPET-positive (fPET+) scans. The 3-year PFS did not differ significantly between the iPET- and fPET- patients. In the univariate analysis, iPET- was the sole independent prognostic factor for PFS.

Conclusions: PET/CT has a good prognostic value in patients with advanced-stage DLBCL. There was little significant benefit to intensifying chemotherapy if the iPET scan was positive.

Background

Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of adult non-Hodgkin's lymphoma (NHL), and is associated with an aggressive clinical course. However, treatment failure is still an important problem as the 3-year progression-free survival (PFS) of DLBCL patients is approximately 60-70% after RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)-like treatments as first-line strategies[1, 2].

The interim ¹⁸F-fluoro-2-deoxy-D-glucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) scan (iPET) during first-line therapy has been validated as a strongest prognostic tool in advanced Hodgkin's lymphoma (HL), even offsetting the role of traditional International Prognostic Index (IPI) Score[3]. In advanced HL patients, better survival and life quality can be achieved, if using iPET-driven strategy. When iPET-negative (iPET-) indicates a good prognosis, doctors may downgrade the treatment such as removing Bleomycin, avoiding toxicity and second primary tumor[3]. And iPET-positive (iPET+) shows a poor outcome, early therapy intensification in response to positive iPET findings could

improve the survival. However, compared to the conventional ABVD regimen, intensified treatments such as BEACOPP and high-dose chemotherapy with autologous stem cell transplantation could result great toxicities[4]. The role of cytotoxic drugs is limited, so not all iPET+ patients can achieve complete response (CR) after intensified chemotherapy[5, 6]. To further improve the outcome, such new therapies as brentuximab vedotin are needed.

In DLBCL, it is common to perform an iPET after 2 to 4 cycles of first-line chemotherapy. Whether or not patients with a positive iPET should receive a more intensive regimen as an immediate salvage treatment is still a topic of debate. We conducted an open-label, non-randomized, single arm, phase 2 study of a cohort of DLBCL patients treated at a single academic medical center to examine the prognostic value of iPET for DLBCL. This study adhered to CONSORT guidelines.

Methods

Inclusion and exclusion criteria

Newly diagnosed stage I-IV DLBCL patients (Ann Arbor staging system), age 18-80 years, were eligible for this study. All patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 and adequate hepatic, renal, and hematologic functions. Patients had at least one measurable target lesion. Patients with left ventricular ejection fraction less than 50%, which was evaluated by echocardiogram at baseline, were excluded. Patients with a history of severe heart disease, uncontrolled hemorrhage, or infection were also excluded. All patients provided written informed consent.

Treatment and response evaluation

All newly diagnosed DLBCL patients were initially treated with 4 cycles of RCHOP (rituximab 375mg/m² d1; cyclophosphamide 750 mg/m² d2; doxorubicin 50 mg/m² d2; vincristine 1.4 mg/m² [maximum 2 mg] d2; prednisone 100 mg orally daily d2-6). RCHOP was administered every 3 weeks.

All patients conducted a baseline PET within two weeks before commencement of therapy and had positive and measurable lesions on PET. The iPET scan was performed after 4 cycles of RCHOP in all cases on cycle 4 day 18 to day 20. The Lugano criteria (Cheson 2014) was used for the evaluation of the therapy response. Response criteria were based on Deauville 5-point scale, with scores of 1-2 considered negative, and scores of 3-5 considered positive.

iPET- patients with low risk (IPI scores 0-2), limited stage (I-II) DLBCL received 2 cycles of rituximab monotherapy, unless they had any risk factors (primary mediastinal large-B cell lymphoma, extra-nodal primary or bulky disease). Patients with abovementioned risk factors received another 2 cycles of R-CHOP as routine practice (6 in total). iPET+ patients with limited stage DLBCL, but achieving partial response (PR) received another 4 cycles of R-CHOP, and a final PET scan (fPET) was performed on cycle 8 day 18 to day 20.

iPET- patients with advanced stage (III-IV) DLBCL received 2 additional cycles of RCHOP (6 in total). iPET+ patients with advanced stage (III-IV) DLBCL, but achieving PR received 4 additional cycles of RCHOP (8 in total), and a fPET was performed.

If patients (stage I-IV) had stable disease or progressive disease (PD) on iPET, they were managed by salvage chemotherapy and discontinued the clinical trial but included in efficacy analysis.

After completion of therapy, patients were followed up every 3 months for the first 2 years, then every 6 months for 3 years.

Statistical analysis

The primary endpoint was 3-year PFS, and secondary endpoints included 3-year overall survival (OS) and objective response rate (ORR). PFS was defined as the interval between initiation of RCHOP treatment and disease progression or the last follow-up visit in remission. OS was calculated from the date of initiation of RCHOP treatment to the date of death from any cause or last follow-up.

Reported data showed that 3-year PFS of DLBCL patients is approximately 60-70% after 6-8 cycles of RCHOP-like treatments as first-line strategies[1,2]. We conducted a phase II study to adapt the therapy based on the response assessed by iPET. The hypothesis was that personalized treatment cycles according to iPET could get similar efficacy with the previous studies. We expected the 3-year-PFS of patients (stage I-IV) to be 70% and 80%. At least 164 patients (stage I-IV) were needed to be enrolled when significance was set at a one-sided 5% type I error and at least 90% power. Accounting for a 20% dropout rate, the final number of patients needed was 196.

Categorical variables are expressed as frequencies. Chi-square test or Fisher's exact test were applied to detect differences between groups. PFS and OS were calculated using Kaplan-Meier analysis, with differences between groups compared using a log-rank test and a difference of $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

The study was approved by the institutional review board of Fudan University Shanghai Cancer Center. The trial is registered with ClinicalTrials.gov, number NCT 01804127.

Results

From 1 April 2013 to 30 September 2015, a total of 198 patients (stage I-IV) were enrolled. In those 198 patients, 143 patients were diagnosed with limited stage (I-II) DLBCL and 55 patients with advanced stage (III-IV) DLBCL.

Here, we reported the subgroup analysis of patients with advanced stage (III-IV) DLBCL (n=55). And finally 53 patients with baseline and interim PET/CT scans were analyzed for efficacy. The reasons for

exclusion were disease progression (n=1) and serious adverse event (n=1) before the interim response assessment.

A total of 24 women (45.3%) and 29 men (54.7%) were included. The mean age was 50 years (range, 23-76 years). In total, 32 patients (60.4%) had stage IV disease, and 14 patients (26.4%) exhibited B symptoms. Based on the IPI scores, 62.3% of patients were within intermediate-high or high risk of relapse parameters. The baseline clinical characteristics of the patients are summarized in Table 1.

Thirty-nine patients had iPET-negative and 14 patients had iPET-positive scans. Among the 14 iPET+ patients, 11 had PR and 3 had PD. The ORR was 94.3%. All 53 patients were included in efficacy analysis. At a median follow-up time of 36.4 months (range, 3.8-63.6 months), 3-year PFS was 65.7% and 3-year OS was 79.9% for the entire cohort (n=53), and the median PFS and OS were not yet reached.

Thirty-two patients with iPET- (39 in total) did not relapse during the period of observation. iPET- patients had a higher 3-year PFS rate (78.1%) than iPET+ patients (34.3%) with a P value less than 0.01. A trend for improved OS was also observed, with 3-year OS of 87.1% versus 62.3% (P=0.03) (Fig. 1a,b).

All 11 patients who had iPET PR received another 4 cycles RCHOP, and 10 of them underwent fPET. Six patients had fPET-negative (fPET-) and 4 patients had fPET-positive (fPET+) scans. Among those 6 patients with fPET-, four patients did not relapse during the period of observation. The 3-year PFS or OS did not differ significantly between the iPET- and fPET- patients (78.1% vs 62.5%, P=0.64, 87.1% vs 83.3%, P=0.81) (Fig. 1c,d).

In addition, among the iPET4 + patients, the patients with Deauville score 3 had a significantly longer PFS and OS than those with Deauville score 4 and 5 (P<0.01, Fig. 2a and P<0.01, Fig. 2b).

In the univariate analysis, iPET- was the sole independent prognostic factor for PFS in patients with DLBCL treated with RCHOP. No other baseline clinicopathologic factors, including age, disease stage, gender, molecular subtype, B symptoms, ECOG PS, elevated lactate dehydrogenase (LDH), IPI score, or extra-nodal involvement, were predictive of PFS for the entire cohort. For this reason, multivariate analysis was not done.

In the iPET- group (n=39), seven patients relapsed during the period of observation.

For PFS using a log-rank test, patients with more than one extra-nodal involvement sites or poor ECOG status were associated with worse outcome with a boardline P value of 0.058 and 0.065, respectively. Other variables such as age, disease stage, B symptoms, IPI score, or molecular subtype did not significantly affect the risk of disease progression.

Discussion

PET/CT is currently done for staging, assessment of remission and recurrence, and evaluation of therapeutic efficacy of patients with DLBCL[7]. The focus has generally been on whether PET can guide

treatment escalation in poor responders to improve remission rates in NHL[8]. To date, in DLBCL, PET predicts response, but more intensive chemotherapy has failed to improve outcomes for patients with iPET+ scans[8, 9]. Several large prospective studies such as the PETAL and LYSA trials demonstrated that treatment intensification such as the Burkitt-type approach or autologous stem cell transplantation fail to prevent iPET+ patients from having a higher risk of relapse than iPET- patients[10]. RCHOP-like chemotherapies have been proven to be effective in DLBCL for many years. Any alternative options will be considered only after being shown to be superior to the ongoing treatment. In this study, patients who had iPET PR were treated with 4 further RCHOP cycles. If they achieved fPET CR, they had a similar good outcome to iPET- patients. Only patients with fPET+ scans had inferior PFS and OS. This study demonstrates no inferiority of continuation of the first-line regimen in patients with iPET PR. So, when aiming to maximize cure while minimizing toxicity, there is no need to escalate treatment of iPET+ patients.

Over the past decades, the IPI has become the most commonly used prognostic index in DLBCL patients[11, 12]. The IPI can differentiate DLBCL patients into distinct risk groups for survival after RCHOP. More recently, iPET has shown high predictive value in HL. It has been validated as a strongest prognostic tool in advanced HL, even offsetting the role of traditional IPS. iPET- could indicate a good prognosis, and iPET+ could indicate a poor outcome, regardless of gender, stage, age or count of hemoglobin and lymphocyte[5, 13]; however, many studies focusing on the role of iPET in PFS prediction have been done, with conflicting results[14-20]. From these studies, it can be concluded that phenotypic and genotypic heterogeneity of DLBCL, heterogeneity in patient populations, therapy regimens, PET scanners, and timing and interpretation criteria of iPET scans made it hard to clarify the accuracy of iPET to predict clinical outcome in DLBCL.

In our study, the PFS difference may be related to ECOG status and extra-nodal involvement in iPET- patients. But in statistical analysis, these two items failed to be proved to be an independent predictor of disease progression ($P>0.05$). This difference in PFS may be under estimated, given our small sample size and subsequent limited power to calculate the difference in survival.

Recently, several studies have shown that PET/CT was a more valid prognosticator of survival for patients with DLBCL than traditional clinicopathologic factors such as IPI score[21-25]. Our results confirm that only iPET was a significant independent indicator of outcome for patients with DLBCL in the rituximab era. iPET- patients had a higher PFS rate and OS rate than iPET+ patients with a statistical significance.

There are some limitations to this study. First, this study was a single-arm, small-scale clinical trial. There is an urgent need for randomized, large-scale, prospective trials to answer the question of whether iPET+ patients should continue with the same treatment or switch to an intensified treatment. Second, the follow-up time in this study was not long enough. The 5-year PFS and 5-year OS as minor endpoints requires long-term follow-up.

Conclusion

PET/CT has a good prognostic value in patients with advanced-stage DLBCL. Univariate analysis showed that iPET- identified good outcome regardless of B symptoms, LDH, IPI score, and molecular subtypes. There was little significant benefit to intensifying chemotherapy if the iPET scan was positive. Another 4 cycles of the first-line regimen (RCHOP) was acceptable as fPET- patients could also have a good PFS.

Abbreviations

DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin's lymphoma; PFS: progression-free survival; 18F-FDG: 18F-fluoro-2-deoxy-D-glucose; PET: positron emission tomography; CT: computed tomography; iPET: interim PET; HL: Hodgkin's lymphoma; ECOG: Eastern Cooperative Oncology Group; PS: performance status; RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete response; PR: partial response; fPET: final PET; PD: progressive disease; OS: overall survival; ORR: objective response rate; IPI: International Prognostic Index; iPET-: iPET-negative; iPET+: iPET-positive; fPET-: fPET-negative; fPET+: fPET-positive; LDH: lactate dehydrogenase

Declarations

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Availability of data and materials

The dataset of the current study were available from the corresponding author on reasonable request.

Authors' contributions

JJ and YL were responsible for data collection and drafted the manuscript; XH, JC and YG participated in the design of the study. JJ, QZ, KX and ZX performed statistical analysis and data interpretation; JJ and FL designed the study and revised the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of Fudan University Shanghai Cancer Center. Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Table 1

Table 1 Patient characteristics at baseline (N=53)

Characteristics	iPET CR	iPET PR	iPET PD	P value
	n (%)	n (%)	n (%)	
No. of patients	39	11	3	
Age, years				0.103
≤60	27 (69.2)	10 (90.9)	3 (100)	
>60	12 (30.8)	1 (9.1)	0 (0)	
Age				0.734
III	16 (41.0)	4 (36.4)	1 (33.3)	
IV	23 (59.0)	7 (63.6)	2 (66.7)	
Gender				0.068
Male	19 (48.7)	7 (63.6)	3 (100)	
Female	20 (51.3)	4 (36.4)	0 (0)	
Symptoms				0.269
Yes	10 (25.6)	2 (18.2)	2 (66.7)	
No	29 (74.4)	9 (81.8)	1 (33.3)	
ECOG performance status				0.117
0	21 (53.8)	7 (63.6)	3 (100)	
1	18 (46.2)	4 (36.4)	0 (0)	
Elevated LDH				0.118
Yes	14 (35.9)	7 (63.6)	2 (66.7)	
No	25 (64.1)	4 (36.4)	1 (33.3)	
Extra-nodal site >1				0.723
Yes	7 (18.0)	3 (27.3)	0 (0)	
No	32 (82.1)	8 (72.7)	3 (100)	
I score				0.452
0 or 1	17 (43.6)	2 (18.2)	1 (33.3)	

2 or-3	21 (53.8)	9 (81.8)	2 (66.7)
4 or 5	1 (2.6)	0 (0)	0 (0)
olecular subtype			0.326
GCB	27 (69.2)	7 (63.6)	1 (33.3)
Non-GCB	11 (28.2)	4 (36.4)	2 (66.7)
Unavailable	1 (2.6)	0 (0)	0 (0)

Abbreviations: *iPET* interim positron emission tomography, *CR* complete response, *PR* partial response, *PD* progressive disease, *ECOG* Eastern Cooperative Oncology Group, *LDH* lactate dehydrogenase, *IPi* International Prognostic Index, *GCB* germinal center B-cell

Figures

Figure 1

a Progression free survival curve between iPET negative and positive patients. b Overall survival curve between iPET negative and positive patients. c Progression free survival curve between iPET CR and fPET CR patients. d Overall survival curve between iPET CR and fPET CR patients. CR; complete response.

Figure 2

a Progression free survival curve between iPET positive patients according to Deauville score (3 v 4 v 5). b Overall survival curve between iPET positive patients according to Deauville score (3 v 4 v 5).

Supplementary Files

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