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Review Article

To PET or Not to PET: Interim Imaging in DLBCL

Hossain NM[1] and Barta SK[2]*

[1]Department of Medical Oncology, Fox Chase Cancer Center/Temple University Hospital, USA

[2]Department of Hematologic Oncology, Fox Chase Cancer Center, USA

***Corresponding author:** Stefan K Barta, Department of Hematologic Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA, USA

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Abstract

Diffuse Large B-Cell Lymphoma (DLBCL) constitutes approximately one-third of all cases of non-Hodgkin lymphoma in the United States. With current treatment regimens, only 60% of patients are cured with frontline therapy. This has fueled efforts to better predict who may benefit from further escalation of treatment within the first line setting. [^{18}F] fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) has emerged as an excellent method of detecting overall disease burden at time of diagnosis. Given its high sensitivity in detecting lymphoma involvement much interest has been raised regarding its potential role in helping to predict early which patients will fail frontline standard therapy. Here, we survey the available literature regarding the role of interim PET scans in the management of DLBCL. We critically review recent data on the usefulness of interim PET scans as predictive and prognostic biomarker for treatment response and briefly discuss novel ways of non-image based monitoring of disease response.

Keywords: PET scan; DLBCL; Interim PET; MRD

Abbreviations

DLBCL: Diffuse Large B-Cell Lymphoma; PET-CT: Positron Emission Tomography-Computed Tomography; R-IPI: Revised International Prognostic Index; iPET: Interim PET-CT; MRD: Minimal Residual Disease; PFS: Progression Free Survival; OS: Overall Survival; R-CHOP: Rituximab + Cyclophosphamide + Hydroxydaunorubicin + Vincristine + Prednisone/Prednisolone; NHL: Non-Hodgkin Lymphoma; ESHAP: Etoposide + Methylprednisolone + High-dose Cytarabine + Cisplatin; ICE: Ifosfamide + Carboplatin + Etoposide; EFS: Even Free Survival; R-IFE: Rituximab + Ifosfamide + Etoposide; BEAM: BCNU + Etoposide + Cytarabine + Melphalan; ASCT: Autologous Stem Cell Transplant; CR: Complete Response; ECOG: Eastern Cooperative Oncology Group; GELA: Groupe d'Etude Des Lymphomes De l'Adulte; IHP: International Harmonization Project; NPV: Negative Predictive Value; PPV: Positive Predictive Value; SAKK: Swiss Group for Clinical Cancer Research; ACVBP: Doxorubicin + Cyclophosphamide + Vindesine + Bleomycin + Prednisone + Intrathecal Methotrexate

Introduction

Diffuse Large B-Cell Lymphoma (DLBCL) constitutes the most common lymphoid malignancy in adults in the western hemisphere [1]. In the past decade a variety of advances in our understanding of morphology, biology and clinical characteristics of this heterogeneous entity have led to the subdivision of DLBCL into a number of subtypes [2]. In addition to morphology and location, these include subtypes defined by differential gene expression profiles (i.e. activated B-like DLBCL (ABC) and germinal center B-like DLBCL (GCB) subtypes) [3] or based upon specific cytogenetic alterations, such as concurrent translocations of BCL2 and MYC in "double-hit lymphoma" [4]. Anthracycline-based combination regimens, most commonly cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), have been established as the most active upfront chemotherapy regimens resulting in cure for more than 50% of patients [5]. Additionally, incorporation of the anti-CD20 monoclonal antibody rituximab into standard treatment regimens has further increased cure rates in DLBCL patients [6].

Currently, prognostication is based upon the Revised International Prognostic Index (R-IPI) which categorizes newly diagnosed patients into one of 3 risk groups: very good, good and poor [7]. However, despite improved response rates with rituximab-based chemoimmunotherapy, approximately 15% of patients have refractory disease (nonresponse or relapse within 3 months of first therapy) and an additional 25% relapse later, usually within the 2 years after front-line therapy [8]. These sobering observations have driven the effort to find more effective early predictors of treatment response and outcome, which might allow early intervention and treatment modification. Interim PET-CT (iPET) has been identified in Hodgkin lymphoma as an effective test to assess tumor chemosensitivity. Its sensitivity and specificity to predict treatment failure in HL ranges between 43-100% and 67%-100%, respectively [9]. Given these promising findings in HL, the role of iPET in DLBCL has been explored similarly as a means to effectively identify poor responders to first-line therapy and potentially adapt treatment in an expedient manner to improve outcomes.

What constitutes a "positive" PET?

An important issue encountered early on during efforts to evaluate iPET has been defining what constitutes a "positive" PET scan as opposed to a "negative" PET scan as well as identifying a method which allows reliable interpretation that can be easily reproduced across different sites and practices. The lack of standardized methods of assessing PET scans led to the development of the International Harmonization Project (IHP) criteria. These criteria asserted that visual assessment of areas of interest as compared to reference activity in the mediastinal blood pool should be utilized to determine if a PET is positive or negative. Of note, this recommendation applied specifically for end of treatment scans [10]. An alternative visual assessment approach are the Deauville Criteria, which employ a

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5-point scale to score PETs based on uptake in areas of interest as compared to reference levels of uptake in the liver and the mediastinum [11]. Another approach is the semiquantitative assessment method, which has been primarily utilized by the GELA group, and focuses on determining differences in SUV (δSUV) between initial and interim scans. However, this approach is hindered by the differences in timing of the imaging and difficulties in calculations for patients with low baseline metabolic activity [12]. Currently, there is no universally accepted method or set of criteria for determining positive and negative iPETs and therefore clinical trials have adopted different approaches when interpreting iPETs to assess their utility in DLBCL.

What is the prognostic impact of interim-PET?

Early work with iPET focused on the prognostic impact of iPET on patient outcomes. However, these studies had mixed results in terms of the specificity and sensitivity of iPET. Many highlight a high false positive rate for positive iPET, which ultimately requires a biopsy to confirm persistent lymphomatous involvement in contrast to inflammatory changes. Jerusalem et al. prospectively looked at the value of iPET in 28 patients with a variety of different lymphomas including 16 patients with DLBCL after 3 cycles of polychemotherapy (anthracycline, mitoxantrone or platinum-based regimens). Five of 28 patients had a positive iPET after 3 cycles of therapy (defined as having ≥1 focus of increased uptake over background levels that was not located in areas of normal uptake). On follow-up all five had relapsed/refractory disease (positive predictive value=100%), while only 7 of the 21 patients with a negative iPET were treatment refractory or relapsed later (Negative Predictive Value [NPV] =67%). Furthermore, those with a negative interim scan had better 1 and 2-year Progression-Free Survival [PFS] (81% and 62% versus 20% and 0%) and Overall Survival [OS] (87% and 68% versus 20% and 0%) [13].

Jerusalem's et al. observations were supported by the results of a prospective trial by Haioun et al. on behalf of the Groupe D 'Etude Des Lymphomes De l'Adulte [GELA]. In this trial investigators evaluated the efficacy of iPET in 90 DLBCL patients treated with 4 cycles of doxorubicin-based induction chemotherapy with (41%) or without rituximab (59%). Patients had PET-CT scans prior to therapy, after two cycles of chemotherapy (iPET) and a final PET after four cycles of anthracycline-containing induction therapy. All scans were scored for uptake and intensity on a 3-point scale and a "negative scan" was defined as having no residual abnormal uptake or as having a unique residual site (score of 1) and an intensity score of 1 with all other previously hypermetabolic sites having no uptake. Furthermore, all patients ≤60 years of age a score of with at least 2 in the age adjusted IPI (n=36) had post-induction high dose therapy followed by autologous stem cell rescue. In addition, those patients who underwent induction with ACVBP underwent consolidation with 2 courses of intravenous methotrexate with leucovorin rescue, 4 courses of etoposide and ifosfamide with mesna protection, and 2 courses of cytosine-arabinoside. At the time of the first iPET, 54 patients were determined to have negative scans and 36 to have positive scans. After the fourth cycle, 83% of iPET-negative patients achieved complete remission compared with only 58% of iPET-positive patients, based upon end-of treatment assessment which included clinical examination, final PET scan, laboratory screening, and bone marrow biopsy as indicated. After a median follow up of 24 months, 38 of the 54 iPET negative patients remained disease free (NPV=70%) while 16 of the 36 with a positive iPET had relapsed/refractory disease (PPV=40%). The 2-year estimates for event-free survival (EFS) were 82% and 43% for iPET negative and iPET positive patients, respectively (P <.001). Additionally, the 2-year OS estimates were 90% and 61% for iPET negative and iPET positive patients, respectively (P= .006). While this trial supported the significant prognostic impact of iPET as noted in the Jerusalem et al study, the investigators were unable to produce a similarly high degree of sensitivity and specificity [14].

In contrast to the GELA group, a trial by Spaepen et al. found iPET to be more reliable in prognostication. Seventy newly diagnosed patients with aggressive NHL (47 with DLBCL) were treated with 8 cycles of doxorubicin-based chemotherapy and underwent an iPET after 3 or 4 cycles. Thirty-three patients had a positive iPET and none were able to maintain a durable complete response after finishing first-line chemotherapy. Out of those 33 patients, eight progressed during the initial regimen; fifteen had a partial response and ten had a complete response. Of those 25 , with a response all relapsed after a median of 175 days (PPV=100%). On the other hand, of the 37 who had a negative iPET, 31 remain disease free at last follow up (NPV=84%). In their analysis, a positive iPET was associated with a shorter PFS (median 45 days) compared with a negative iPET (median PFS 1059 days). Furthermore, a positive iPET was strongly predictive of PFS and OS on multivariate analysis. Thus, this study supported the hypothesis that iPET not only has a prognostic impact but also acceptable positive and negative predictive values [15].

In a more recent trial an Italian group led by Pregano et al. conducted a prospective study with the primary intent to determine the predictive value of iPET [16]. Eighty-eight DLBCL patients treated with R-CHOP (6-8 cycles) were enrolled and had an iPET after 2-4 cycles of therapy. PET scans were assessed based on the Deauville scoring system (score ≥4 considered positive). Interim PET was negative in 63 (72%) patients and positive in 25 (28%) patients; 77 (88%) patients had a negative final PET and 11 (12%) had a positive final PET. At the end of initial therapy, 79 (90%) patients achieved a clinical CR while 9 (10%) failed to achieve a clinical CR. Furthermore, fifteen of the 25 (60%) patients with a positive iPET had a negative final PET and only 1 of 63 (2%) with a negative iPET had a positive final PET. With median follow-up of 26.2 months the 2-year OS was 91% and 2-year PFS was 77% for all patients. Analysis revealed that a negative iPET was associated with improved PFS (HR 2.45, p=0.047). However, after a median follow up of 26.2 months, 11 of 63 (17%) patients with a negative iPET relapsed (NPV 83%) compared to 9 of 25 with a positive iPET (PPV 36%). These results lead the authors to conclude that iPET was unable to effectively identify patients who will experience treatment failure.

Based on the above findings, Cashen et al. conducted a prospective study with 50 patients with advanced-stage DLBCL treated with R-CHOP. Patients had iPET performed after cycle 2 or 3 and another PET-CT at the end of therapy. PET scans were evaluated based on IHP criteria. After a median follow-up of 3 years, the positive predictive value (PPV) of iPET for relapse or progression of disease was 42% and the NPV was 77%. EFS based on iPET was 63% at 2 years for patients with a positive iPET compared to 85% for those with a negative scan (p = 0.017), however there was no significant difference in OS (p=0.08). The authors concluded therefore that, although the

results were statistically significant, the high false-positive rate of iPETs would make utilization for risk-adapted therapy difficult [17].

With ongoing uncertainty about the merits of iPET in DLBCL, Carr et al., under the auspices of the International Atomic Energy Agency, conducted a multinational prospective study aimed at elucidating whether differences in healthcare systems and facilities could influence the reliability of risk prediction by iPET. Patients received 6-8 cycles of R-CHOP with an iPET after 2-3 cycles of therapy but no change in therapy was allowed based on the iPET results. The scans were evaluated based on modified Deauville criteria. Three-hundred and eighty-three patients with DLBCL were initially enrolled though only 361 proceeded through the entirety of the study. During the course of the study 210 (64%) patients had a negative interim PET-CT and 117 (36%) patients had a positive scan. At median follow up of 35 months, the entire group 2-year EFS and OS were 79% and 86% respectively. In patients with a positive iPET the 2-year EFS and OS were 58% and 72% respectively compared to 90% and 93% for iPET negative patients. However, the authors reported that more than half (54%) of patients with a positive iPET became PET-CT negative by the end of their chemotherapy course and achieved a durable remission (PPV=46%). This provided further evidence that a positive iPET does not accurately identify chemo resistant residual tumor in mid-therapy or inform early escalation of therapy in patients with DLBCL [18].

Given the mixed results from previous trials, Huntington et al. carried out a retrospective analysis of the experience within the University of Pennsylvania health system, and reached slightly different conclusions. Their retrospective analysis included 94 DLBCL patients, who underwent frontline therapy with one of a variety of doxorubicin-based regimens and had at least one iPET (interpreted based on IHP criteria). They reported an end-of-treatment CR rate of 79% with excellent concordance between a negative iPET and end-of-therapy response; all patients with a negative iPET were in CR at time of analysis. This resulted in a PPV and NPV for iPET to predict primary refractory disease of 40.5% and 100% respectively. Furthermore, 61% of the patients with a partial response (defined as >25% reduction of maximum SUV in lesions of interest) on iPET had achieved a CR by the end of treatment. The calculated PPV and NPV for iPET to predict primary refractory or relapsed disease were 51.4% and 86.8% respectively. On statistical analysis, improved OS (p= 0.046) and PFS (HR 2.7; p <0.001) correlated with a negative iPET. Based on the high NPV, the study authors concluded that a negative iPET might negate the need for an end of treatment scan [19].

The Swiss Group for Clinical Cancer Research (SAKK) performed a prospective study to evaluate the prognostic value of iPET. They enrolled 138 patients with any stage newly diagnosed DLBCL who were treated with 6 cycles of R-CHOP-14. All patients underwent an iPET after 2 cycles (iPET2), which were interpreted based on Deauville criteria. Patients with a positive first iPET had an additional iPET after cycle 4 (iPET4). Eighty-three (60%) patients had a positive iPET2 and 55 (40%) had a negative scan. Of those with an initial positive scan, 44 (64%) had a positive iPET4 after four cycles of R-CHOP. After a follow-up of at least 24 months, there was a significant difference in 2-year EFS between patients with a positive iPET2 compared to those with a negative iPET2 (48.2% versus 74.2% respectively, p= 0.004). For patients with a positive iPET2 who had an iPET4, there was no difference in 2-year EFS appreciated (p= 0.9) between patients with a negative versus a positive iPET4 scan. Furthermore, the study reported no OS difference at two years between the iPET2 groups (87.7% for iPET2 positive versus 90.6% for iPET2 negative groups, p=0.6). The study authors concluded that their findings illustrated worse 2-year EFS in patients with a positive iPET after 2 cycles of R-CHOP with a NPV of 70.9% and a PPV of 51.8%. However, within this trial, any disease progression, death or initiation of non-protocol therapy was deemed an "event" for purposes of statistical analysis and the study categorized 25 patients (24 received involved field radiotherapy for bulky disease and 1 received high-dose methotrexate for CNS prophylaxis) as having had an event based on the above criteria which significantly impacts interpretation of the results.

Taken together, the mixed conclusions from these studies highlight that though a positive iPET can be associated with worse outcomes and therefore may have prognostic significance, its variable specificity however renders it unreliable as early biomarker for treatment response.

Changing tides: does changing treatment based on iPET change outcomes?

Based on the initial encouraging results highlighting the prognostic impact of iPET, Kasamon, et al. conducted a single center phase II study of risk-adaptive therapy base using iPET in patients with newly diagnosed aggressive lymphoma at Johns Hopkins. The trial enrolled a total of 59 patients (56 DLBCL, 2 FL-grade 3, 1 peripheral T cell) all of whom started initial therapy with R-CHOP or CHOP and had an iPET after 2-3 cycles with assessment based upon criteria similar to the IHP guidelines. Patients with a positive scan were then switched to high-dose therapy with Rituximab + etoposide + methylprednisolone + high-dose cytarabine + cisplatin (R-ESHAP) or Rituximab + ifosfamide + carboplatin + etoposide (R-ICE)followed by an autologous stem cell transplant. Those patients with a negative iPET continued with their remaining cycles of R-CHOP. At the time of their iPET, 26 patients (44%) had negative scan and 33 (56%) had a positive scan. Of the patients with positive iPET, 28 (85%) received an autologous stem cell transplant (two withdrew from the trial and 3 progressed prior to transplant). In this group, EFS was 75% at 2-years and 65% at 3-years.After a median follow-up of 33.6 months 19 of 28 (68%) were disease free. In the negative iPET group, the EFS was 89% at 2-years and 82% at 3-years with 4 of the 26 (15%) having relapsed disease at the time of last follow up. The authors concluded that the results were encouraging and suggested that iPET may be useful in helping to guide treatment decisions [21].

In a larger, multi-center, phase II study, Pardal, et al. enrolled 71 patients with DLBCL or grade 3 FL. Sixty-six patients were initially treated with Mega-CHOP for three cycles (5 patients dropped out of the study: 3 due to early death, 1 due to protocol violation, and 1 due to toxicity). Afterwards, they underwent an iPET, which was evaluated based upon the Deauville criteria. Patients with a negative scan (Deauville score <4) received three additional cycles of Mega-CHOP, while those with a positive scan (Deauville score ≥4) switched to two course of R-IFE (rituximab + ifosfamide + etoposide) followed by a BEAM-conditioned ASCT (BEAM- BCNU + etoposide + cytarabine + melphalan). After a median 42.8 months of follow-up, the 4-year OS and PFS were 78% and 67% respectively for the entire study group. The 36 patients (51%) with a negative iPET had

a statistically better 3-year PFS (81% *vs.* 57%; p= 0.023) but non-significantly longer OS (89% *vs.* 73%; p= 0.11). The authors concluded that in this era of rituximab-based therapies for DLBCL, patients with a positive iPET are not rescued by a switch from standard therapy to salvage regimens. However, as noted in some of the earlier trials, a positive iPET was the strongest prognostic factor of PFS, supporting the view that iPET can serve as a potential early predictive marker for treatment outcome in DLBCL patients [22].

In a further effort to clarify the role of iPET to guide treatment intensification in DLBCL, the Eastern Cooperative Oncology Group (ECOG) carried out a prospective phase II clinical trial evaluating a response-adapted treatment strategy based on iPET (ECOG 3404). In this trial, newly diagnosed patients with Stage III, IV or bulky stage II DLBCL were initially treated with 3-cycles of R-CHOP followed by an iPET, which was interpreted based on modified IHP criteria. Patients with a negative iPET received two additional cycles of R-CHOP while patients with a positive scan switched to therapy with four cycles of R-ICE. Out of 100 enrolled patients, 80 (19 were found to be ineligible; 1 never started therapy) patients started treatment with R-CHOP. Seventy-six completed three cycles and underwent iPET. Sixty-three (79%) had a negative scan and 13 (16%) patients had a positive iPET, out of which 10 patients went on to complete 4 cycles of R-ICE. By the end of treatment, of the 70 patients who had an end-of-treatment PET, 4 patients out of 13 with a positive iPET remained PET positive, while 6 patients out of 61 with a negative iPET had a positive end-of treatment scan. The two-year PFS for the overall group was 70%; 42% for the iPET positive group and 76% for the iPET negative group. The two-year OS was 90% for the study group; it was 77% in the iPET positive group and 93% in the iPET negative group. The NPV for relapse was 75% (43 of 57 evaluable patients) for iPET and 79% (45 of evaluable 57 patients) for final PET. The authors concluded that their findings suggest that patients with a positive iPET have a less favorable outcome than those with a negative scan, as had been previously reported; however, even with treatment intensification outcomes were unchanged [23].

Status quo and the next frontier

With encouraging results in Hodgkin's lymphoma, efforts have been underway to evaluate iPET in the management of DLBCL. Despite early results showing promise, recent studies have been disappointing, highlighting high NPV but unreliable PPV of iPET in the management of DLBCL patients. This has been further highlighted by negative results from prospective trials of altering therapy based on iPET results.

Furthermore, reviewing the literature highlights the variability surrounding the implementation and interpretation of iPET results. Between studies there is a great degree of variance of the timing of iPET ranging from after 2 cycles therapy to after 4 cycles of therapy. Furthermore, between studies a number of different criteria were utilized to assess positivity and negativity of iPET scans. These criteria included visual assessment of scans, assessing changes in maximum SUV values and utilizing the Deauville scoring system. The high degree of variance makes it difficult to assess and compare the results of different studies and highlights the limited reproducibility and inconsistencies in determining accuracy and sensitivity of iPET [24].

Although research is ongoing to study the utility of iPET, the attention has started to shift towards noninvasive monitoring for DLBCL. Roschewski, et al. conducted a retrospective study at the NIH, utilizing stored specimens from 126 patients treated for DLBCL at the NIH between 1993 and 2013. Quantitative high-throughput amplification and next-generation sequencing of immunoglobulin gene segments were used to detect circulating tumor DNA in serum at various points in a patient's clinical course and related to clinical outcomes. The investigators analyzed 36 patients with clinical progression, 25 (69%) with early progression and 11 (31%) with late progression based on imaging studies. Ninety-one percent (n=10) of late progressors developed detectable tumor DNA, and eight did so prior to clinical or radiographical evidence of lymphoma progression. For early progressors, three different dynamic patterns of circulating tumor DNA were observed. Ten never cleared their circulating tumor DNA with initial therapy, nine transiently cleared their circulating DNA followed by its reappearance prior to clinical progression, and six had clearance of circulating tumor DNA followed by clinical progression. The results of this study elegantly illustrate that circulating tumor DNA may allow for the effective monitoring of DLBCL in a non-invasive manner [25].

The findings by Roschewski, et al. were further corroborated by Kurtz, et al. who prospectively assessed the ability of immunoglobulin high-throughput sequencing to detect molecular disease from peripheral blood samples. The investigators analyzed circulating tumor cells and circulating cell-free DNA in plasma, and correlated molecular disease monitoring with clinical disease during surveillance. Of 25 patients on surveillance after first line therapy for DLBCL, five eventually relapsed. Three of the five who relapsed had detectable molecular disease prior to their clinical relapse [median lead time: 88 days] while the remaining two had detectable molecular disease at the time of relapse. When the authors compared their molecular detection method to imaging with PET-CT; sensitivity was 55% for PET-CT and 31% for molecular detection (not statistically significant), while specificity was 100% for molecular detection and 56% for PET-CT. The authors concluded that this molecular detection method may be an adjunct to imaging for patients undergoing surveillance and interim imaging while undergoing active therapy [26].

Conclusion

As the approach to personalize treatment for patients with DLBCL continues to evolve, efforts continue to more accurately and expediently identify treatment failure. PET-CT imaging has helped greatly in diagnosing and monitoring patients following therapy but has failed to produce compelling evidence for its role as an early response biomarker for patients undergoing active therapy. As the case for and against interim PET-CT has ebbed and flowed investigators have turned to alternative methods of detecting residual or re-emergent disease. Recent studies highlight the potential of novel non-invasive methods to enhance and supplement the use of radiologic studies at time of diagnosis, in the midst of therapy and during the active surveillance period. Combination of these different modalities may lead the way in better identifying treatment failures and opening the door to successful early intervention.

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