The role of PET in the management of diffuse large B-cell lymphoma

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A B S T R A C T

The introduction of fluorodeoxyglucose positron emission tomography (PET) at the beginning of this century and its widespread diffusion has overtaken the standard computed tomography (CT) as routine practice for staging and evaluating the response at the end of treatment in patients with diffuse large B-cell lymphoma (DLBCL). This functional imaging modality measures the glucose metabolism of lymphoma cells and new uses of PET based on overall tumor activity and its evolution under treatment have emerged. Total metabolic tumor volume, targeting the more active part of the tumor, gives prognostic indications independent from the stage and bulk, but still require computation standardization and to be analyzed in prospective studies. The role of interim PET scan in guiding therapy also remains investigational. So far, PET guided de-escalating strategies have been more successful than those proposing an alternative chemotherapy regimen for patients with a positive interim PET, firstly because the negative predictive value (NPV) of interim PET is better than its positive predictive value (PPV), and secondly because among patients with a true positive PET related to a chemoresistant disease, the alternative conventional chemotherapy approaches currently available have a limited efficiency. The use of semi-quantitative assessment may increase the interim PPV and better identify patients eligible for new drugs.

Learning goals

At the conclusion of this activity, participants should:
- be able to identify the role for PET in the course of the disease;
- recognize the Interest in assessing the base-line metabolic tumor volume;
- know what to expect from a PET-guided treatment strategy;
- know which criteria to adopt in order to interpret interim PET in DLBCL patients.

Introduction

Fluor-18 radiolabeled glucose analog positron emission tomography (FDG-PET) is a metabolic imaging technique using a Fluor-18 radiolabeled glucose analog (FDG) to target the glucose metabolism *in vivo*. The FDG is transported into cells and phosphorylated in a similar manner to glucose but remains trapped in the cells, because FDG-6-phosphate cannot be further metabolized. Thus FDG-6-phosphate is mainly trapped in tumor cells and related to the glycolytic activity of the tumor. Virtually all the diffuse large B-cell lymphoma (DLBCL) are FDG avid[1,2] and FDG-PET gives information on the lymphoma cell activity that is not available with conventional imaging tools, leading to a wide use of this functional imaging modality. DLBCL is probably, with Hodgkin lymphoma, the lymphoma subtype in which PET has the best adding value compared to conventional anatomical assessment because the accuracy of the staging can modify the treatment strategy and the disappearance of the tumor activity is a better end point than the reduction of the tumor mass in curable diseases.

Base-line PET in diffuse large B-cell lymphoma

PET staging

For decades, computed tomography (CT) scan was the standard imaging technique recommended for the staging of DLBCL. Several studies showed the superiority of FDG over CT scanning (with a sensitivity and specificity higher than 90%[3]) to assess the extent of the disease, leading to modifying the staging in 15%-40% of cases with an impact on the therapeutic strategy in approximately 15%-20% of cases.[1,2]

The superiority of PET over CT scanning is related to a better assessment of the node involvement, because normal-sized nodes may have abnormal FDG uptake. PET can also better identify extranodal lesions, specifically in the liver, the spleen, the bone and the bone marrow (BM).[4] The sensitivity of PET to detect BM involvement is also better than the BM biopsy,[5,6] and patients with BM involvement identified by PET may have a poorer outcome than those without.[5] However, PET can underestimate BM involvement with small cells. So when a pre-treatment PET staging is performed BM biopsy is no longer required in

the last IWC recommendations[7] except in cases in which a small cell BM involvement would change patient management.

So compared to CT, pre-treatment PET scan assessment frequently results in an up-staging rather than a down-staging of the disease.[8] Disease up-staging can have clinical consequences when a localized disease Ann Arbor (stage I or II) turns into a disseminated disease (Ann Arbor stage III or IV) thus modifying the resulting IPI, specifically in young patients who can benefit from more aggressive regimens, which may improve outcome compared to standard CHOP in advance disease.[9-11]

In the specific situation of primary central nervous system lymphomas (PCNSL), which are mostly DLBCL, an exploratory PET at diagnosis has also been reported to be more sensitive than CT to reveal systemic disease.[12] Inversely, the brain exploration by FDG at diagnosis seems to bring limited information in addition to MRI[13] even if the intensity of FDG uptake of the brain lesion might have a prognostic impact.[14] So brain PET scanning for PCNSL cannot be recommended in routine practice outside of a clinical trial.

Assessing the total metabolic tumor volume at baseline

The prognostic scores used in DLBCL [either the IPI established before the rituximab era[15] or the revised IPI (R-IPI)[16]] do not include tumor burden as risk factor. However, tumor bulk defined by the presence of a mass with a maximum diameter equal or higher than 10 cm[17] on base-line CT was shown to impact the outcome of young patients with low-/intermediate-risk DLBCL of the MINT and the LNH03-2B studies.[10,17,18] So far, there has been no evidence that bulky disease may have any prognostic impact in high-risk DLBCL patients,[19] but data are scarce. The metabolic volume, representing the most active part of the tumor cells, is a novel approach of tumor burden measurement which has been related to the outcome of DLBCL patients.[20-22]

In 2 series of selected DLBCL patients, Song *et al*. found an impact of TMTV0 on patient outcome. Among 169 DLBCL patients with nodal stage II and III treated with 6-8 cycles or R-CHOP,[21] those with a TMTV0 higher than 220 mL (48%) had a lower progression-free survival (PFS) (4-year PFS: 56% *vs*. 90%; $P<0.001$) and overall survival (OS) (4-year OS: 58% *vs*. 93%; $P<0.001$) than patients with a low TMTV0 independently of the Ann Arbor stage.

In 165 patients with stage IE/IIE gastrointestinal DLBCL, a TMTV0 higher than 160 mL (38% of patients) was associated with a poor outcome independently from IPI.[20]

In both studies, the volume of each individual hypermetabolic lesion was determined as the volumetric pixels (voxels) with a standard uptake value (SUV) of more than 2.5, the TMTV0 resulting as the sum of all the individual volumes of interest (VOI).

To compute TMTV0, the European guidelines[23] recommend selecting the voxel with an FDG uptake of 41% or more of the SUVmax of each individual lesion and this has been validated in DLBCL patients.[24] Given this, Sasanelli *et al*.[22] showed in a series of 114 patients with a stage I-IV DLBCL that a TMTV0 higher than 550 mL was related to a poorer outcome (3-year PFS: 60% *vs*. 77%, $P=0.04$; and 3-year OS: 60% *vs*. 87%; $P=0.0003$, respectively). TMTV0 better predicts patient outcome than the disease extent (stage I/II *vs*. III/IV), the bulk (larger mass ≥10 cm *vs*. <10cm), or the age-adjusted IPI.

So TMTV0 could bring new prognostic insights for DLBCL patients and could help clinicians to stratify patients into low- or high-risk on the basis of the base-line metabolism of the disease in addition to the standard IPI. These data still have to be confirmed in further series, preferably in prospective studies using the same methodology with strict rules to select the VOI, in order to obtain a widely accepted TMTV0 cut off predicting outcome. Moreover, the adding prognosis value of TMTV0 and its relationships with the early PET response warrant investigation.

PET restaging

Interim PET

Prognosis value of interim PET: the prognosis of DLBCL has been substantially improved since the introduction of the anti-CD20 monoclonal antibody in association to standard chemotherapy. To date, with R-CHOP or R-CHOP-like regimens the expected 5-year progression free survival (PFS) is 55% and 75% for patients older and younger than 60 years, respectively.[25] However, so far there are still no tools available to allow identification of individual patients with high-risk of treatment failure to be identified in routine clinical practice. Identification of cell of origin (COO) may help to identify such patients but molecular techniques are not yet widely available in current practice, and immunohistochemistry results obtained with few surrogate markers are related to reproducibility concerns and give an imperfect image of the COO molecular signature. In this setting, the analysis of early response to treatment using functional imaging is the more reliable and convenient approach for patient management in current practice. Early PET restaging allows the tumor metabolism to be evaluated *in vivo*, and specifically the dynamic metabolic reduction process of the tumor during the induction treatment that may reflect the treatment efficiency. In this setting the early response which reflects the changes in the glucose metabolism induced by the first cycles of chemotherapy can be considered a surrogate marker of the tumor cells' chemosensitivity.[26]

Most of the first reports testing the prognosis value of interim PET performed after 1-4 cycles of chemotherapy were encouraging[23,27-30] and showed that visual criteria to interpret PET allowed patients with high risk to be distinguished from those with low risk of treatment failure. However, other studies using also custom visual criteria for PET interpretation, showed a low PET prognostic value, some of them indicating a low PET positive predictive value.[31,32] These discrepancies on the predicting value of interim PET were partly related to the lack of interobserver reproducibility in interpreting PET images[33] or to the heterogeneity of the visual criteria used so far. In this context, the systematic biopsy of PET positive residual mass defined by an FDG uptake greater than the local background activity, performed after four cycles of dose-

dense R-CHOP, was related to a biopsy proven active lymphoma in only 23% of cases.[11] The 87% PET false positive rate observed in this series did not deny any clinically relevant prognostic value to early PET, but rather indicates that the key challenge is to set up reproducible interpretation criteria able to both identify FDG uptake associated with active disease and minimize the risk of interpreting overlapping FDG uptake related to non-specific post-therapy inflammatory changes as active lymphoma.

Which criteria for interim PET interpretation in DLBCL?

Visual criteria

The main attempt to provide standardized criteria to interpret PET was based on a consensus of experts and designed to analyze response at the end of treatment.[34] The international harmonizing project (IHP) criteria were purely visual and used either the mediastinal blood pool as background reference for residual mass equal or greater than 2 cm or the surrounding background for mass less than 2 cm. However, when IHP criteria were strictly applied to evaluate interim PET after two or four cycles of immunochemotherapy, they were unable to clearly identify patients with different outcome[35-37] mainly due to a low (approx. 30%) positive predictive value (PPV). The Deauville criteria,[38] designed as a semi-quantitative visual analysis using a 5-point scale (5PS), were found to improve the accuracy of the interpretation compared to IHP criteria: the residual mass uptake is then compared to the liver uptake, a 5PS score of 4 or 5 being required to consider a positive PET.[34,35,38] Thus a residual mass with a FDG uptake higher than the liver background better differentiates from the background noise and has a lesser risk of being attributed to a non-specific uptake.[37]

Based on these findings, the IHP criteria can no longer be recommended for early or mid-treatment response assessment[39] and the 5PS has to be preferred.[38] An international validation study (IVS) of 5PS score has been performed enrolling 120 patients from 5 institutions in Europe and the US, treated with an R-CHOP regimen with an available PET2 and no treatment change on the basis of PET results. This study showed that PET2 negative patients have a significantly better 2-year EFS that PET2 positive patients on the basis of 5PS criteria (83% *vs*. 56%; $P<0.001$).[40] Thus the Deauville score has to be used to visually interpret interim PET, and has been implemented in the recently published Lugano classification.[7,41]

Quantitative criteria for the interpretation of interim PET

The metabolism reduction of lymphoma cells during treatment is a continuous process that can be quantitatively measured using FDG avidity assessment.[26] Semiquantification of FDG uptake using standardized uptake values (SUV) at baseline and interim PET allows the lymphoma metabolism changes during induction treatment to be evaluated, and was shown to reduce false-positive interim PET interpretations and better predicts outcome than visual analysis.[42,43] This was confirmed in the LYSA/GELA LNH2007-3B prospective phase II randomized trial (*clinicaltrials.gov identifier: 00498043*): 78% and 80% of PET positive patients according to IHP criteria after two and four cycles of induction treatment, respectively, could be reclassified as good responders when using ΔSUVmax, and have a similar outcome when compared to patients with a visually negative PET2 or PET4, respectively.[36] The prognostic discrimination of the ΔSUVmax approach was also superior to that of the 5PS assessment.[35,36] Moreover, the review by 3 independent experts of the scans performed at baseline and after two cycles of induction treatment in the IVS showed a significantly better interobserver reproducibility for the ΔSUVmax approach (Kappa=0.81) than for the 5PS visual analysis (Kappa=0.65).[40]

A challenge in metabolic response assessment is to turn the FDG uptake, a continuous variable, into a binary response which allows identifying subsets of patients with different risk of treatment failure to be identified, which could then be used to help guide therapy. The ΔSUVmax cut-off value estimated by ROC analysis in several independent series,[35,36,42,43] and used to distinguish good and bad responders, increases with time and is higher after four cycles than after two cycles of induction treatment. This indicates that the closer the patient is to the end of treatment the more the criteria become stringent. Therefore, studies mixing interim PET results performed after different cycles of treatment may lead to inconsistent PET prognosis results since the cut-off values move along the treatment.[44] It also implies that a cut-off value has to be determined according to the time the PET scan has to be achieved. After two cycles all studies were consistent with a 66% threshold,[35,36,42] while after four cycles the threshold range rose from 70% to 73%.[36,43] These thresholds appear to be robust and reproducible regardless of age and IPI in patients treated with CHOP regimen administrated every 14 or 21 days, combined or without rituximab[45] and are able to identify patients with different outcome.

In some cases, ΔSUVmax analysis can generate false positive results when the base-line SUVmax is low (<10).[46] A base-line SUVmax less than 10 with a ΔSUVmax less than 66% was a rare event in the Lin[42] and the IVS series[47] identified in 3% and 4% of patients, respectively. In this situation, the response has to be assessed according to 5PS criteria.

Risk-adapted therapy according to interim PET results

Based on its prognosis value, functional imaging could address the need for tailored therapy in DLBCL in order to reduce toxicity in patients with a favorable outcome and improve treatment in those with high risk of failure to standard treatment.

The transition from the prognostic predictive value of interim PET to its use to adapt and guide treatment strategy has already been made by several groups worldwide. Most are based on PET visual criteria analysis, but few data analyzing the relevance and the efficiency of such strategies have been published so far. Two types of approach are possible: either using interim PET assessment for de-escalating the consolidation treatment of interim PET negative patients, or intensifying the treat-

ment of interim PET-positive patients.

The quite good negative predictive value (NPV) of interim PET interpreted according to either visual or semi-quantitative analysis allows therapeutic strategies for de-escalating consolidation treatment to be designed.

Thus in the LNH2007-3B LYSA/GELA trial, high-dose therapy followed by an autologous stem cell transplantation (ASCT) was safely avoided in approximately 30% of age-adjusted (aa)IPI 2-3 patients who reached a fast complete response with a negative PET according to IHP criteria after two cycles of chemotherapy and remained in first complete response after four cycles of R-chemo14.[48] The outcome of these patients appears quite similar to that observed in a previous LYSA/GELA trial in which all aaIPI 2-3 patients in first response after four cycles of R-chemo14 underwent a high-dose therapy followed by ASCT.[9] Based on the PET quantitative assessment in the LNH2007-3B series, one can expect that patients who reach a ΔSUVmaxPET0-2 >66% and a ΔSUVmaxPET0-4 over 70% (who represent 80% of the whole population of these high-risk patients) might avoid high-dose therapy. This approach assessing the allocation of the post-induction treatment according to the ΔSUVmax reduction on PET2 and PET4 will be validated in the ongoing GAINED trial (*clinicaltrials.gov identifier: 01659099*).

In the LNH 02-03 LYSA/GOELAMS[49] phase III trial which enrolled patients with non-bulky limited stage DLBCL, a negative interim PET after four cycles of R-CHOP allows radiotherapy to be avoided without impairing patient outcome. Inversely, the 14% of patients with a positive PET4 who received 2 additional R-CHOP followed by radiotherapy have a similar outcome compared to PET4-negative patients suggesting that radiotherapy could bring a clinical benefit in this setting.

A PET-guided escalated therapy strategy is more risky since the positive predictive value of interim PET assessment is always inferior to its negative predictive value. In addition, this kind of strategy requires a very efficient alternative treatment to overcome the poor prognosis of patients with a true positive PET.

A phase II study of PET adapted therapy was previously reported in 56 newly diagnosed DLBCL.[50] PET was performed after two or three cycles of R-CHOP and interpreted according to IHP criteria. Fifty-six percent of patients had a positive interim PET and were programmed to receive an intensified treatment consisting of two cycles of platinum-based chemotherapy plus a high-dose therapy followed by an ASCT: 27% of them relapsed at two years. Most PET-positive patients in this study were probably over-treated if we consider that previously reported PPV of IHP visual criteria is approximately 30% in series with a non-PET-guided treatment,[35-37] and that only 12% of the LNH2007-3B trial patients were bad responders according to the ΔSUVmax results after two cycles of treatment. In addition, despite an intensified treatment, PET-positive patients had a higher risk of relapse compared to PET negative patients (2-year relapse rate 8%), suggesting that the high-dose therapy was insufficient to completely overcome the poor prognosis related to the interim PET positivity.

Another phase II study presented at the last ASH meeting[51] showed that 50 of 150 (33%) patients who had a positive PET according to IHP criteria after four cycles (PET4) of R-CHOP and received an intensified R-ICE treatment have a less favorable outcome (4-year PFS 59%; 4-year OS 73%) compared to patients who achieved a negative PET4 (4-year PFS 91%; 4-year OS 96%). So in this study also the intensified treatment based on an R-ICE regimen did not completely overcome the poor prognosis related to the PET4 positivity, even if these patients may do better than historical reports of patients pursuing R-CHOP treatment.[51]

The ΔSUVmax interpretation minimizes the risk of false-positive results with a PPV higher than 50% and consequently may make such an escalating approach much safer. The PETAL trial (*clinicaltrials.gov identifier: 00554164*) conducted by the Essen group in Germany was designed to randomize a standard R-CHOP14 treatment and an escalated therapy with a Burkitt-type regimen for patients with a SUVmax reduction less than 66% after two cycles of R-CHOP14. In the 853 assessable patients, 13% had a positive PET2.[52] With a median follow up of 33 months, lymphoma relapse occurred more frequently with a 2-year time to treatment failure of 47% in ΔSUVmaxPET0-2 <66% patients compared to 79% in ΔSUVmaxPET0-2 <66% (hazard ratio: 3.4; P<0.0001). So these results indicate that the bad responder rate is similar in this study to that observed in the LNH 2007-3B trial (17%), and suggest that interim PET keeps a prognosis impact despite an intensification of treatment in half of the PET2-positive randomized patients. However, this PET-guided intensified treatment did not demonstrate a better outcome for PET2-positive patients treated with a Burkitt-type regimen.

To summarize, the PET-tailored therapy data currently available show that an interim PET de-escalating approach appears to be quiet safe using a visual PET interpretation and may have still better accuracy with a ΔSUVmax PET interpretation in advanced DLBCL. Inversely, the poor prognosis of interim PET-positive patients was not overcome with the salvaged treatment used so far, and in this context there is no direct evidence that altering therapy with conventional chemotherapy on the basis of interim PET findings improves significantly patient outcome. Thus new drugs are definitively required in this setting of early chemo-resistant disease identified by interim PET.

PET at the end of treatment

The use of PET in the restaging assessment of DLBCL at the end of treatment became a standard practice and has been implemented in the IWC criteria published in 2007[53] and 2014[7] to document remission. PET after completion of treatment is highly predictive of PFS and OS in DLBCL patients and better discriminates than CT the patient's outcome[17,33] specifically because PET can identify from among patients with a residual mass those who still have an active disease from those with no residual viable lymphoma tissue. Patients with a negative PET scan have an excellent outcome, and the end of treatment NPV reach 85%-90%. The PPV is lower and varies according to authors from 45% to 65%.[41,54,55] So when PET remains positive at the end of treatment without increase in size of the residual mass, either PET scan can be repeated 2-3 months later if the patient had a low risk DLBCL, or a biopsy of the hypermetabolic residual mass has to be considered to document a high suspicion of treatment failure

in a patient with high-risk DLBCL. It has to be noted that this situation can be largely anticipated for patients who had an earlier response assessment with an interim or mid-treatment PET.

PET for follow up of DLBCL patients

The objective of early detection of disease progression in order to improve patient outcome is an attractive goal, and PET, which is more sensitive than other imaging modalities, might help improve patient monitoring. However, there is no evidence in DLBCL patients that early detection of relapse using routine imaging techniques improves patient outcome.[56-58] In addition, PET scan during follow up could be inconclusive[59] and related to a significant risk of false positive results that may lead unnecessary biopsies being perfomed.[60] So once a PET performed at completion of treatment has shown that a complete metabolic response has been achieved, even if a residual mass remains, there is no need to repeat PET scan during the patient follow up and a conventional surveillance can be proposed.[7]

PET assessment in the context of salvage therapy

The standard treatment strategy in patients with relapsed or refractory DLBCL is to obtain the best response with conventional chemotherapy before proposing a high-dose therapy and autologous stem cell transplantation (ASCT)[61] that has been demonstrated to improve patient outcome compared to standard chemotherapy alone.[62,63] The final success of this approach is largely dependent on the chemosensitivity to salvage chemotherapy. In this setting, in a meta-analysis including 313 DLBCL and 187 Hodgkin lymphoma PET was shown to outperform conventional CT and identify patients with significantly different PFS with a 69% sensitivity and 81% specificity.[64] Thus PET allows DLBCL patients with chemo-sensitive disease eligible for transplantation to be identified from those with resistant disease requiring additional treatment before ASCT.

Conclusions

Positron emission tomography scan has become the main imaging tool for the management of patients with DLBCL. It is currently a standard practice in the staging and restaging of the disease to confirm remission at the end of therapy. Base-line TMTV is a new approach targeting the more active part of the tumor, and gives prognostic indications independent from the stage and bulk. This still requires computation standardization and to be analyzed in prospective studies. Interim PET scan is commonly performed, but its role in guiding therapy remains investigational. So far, PET guided de-escalating strategies have been more successful than those proposing an alternative chemotherapy regimen for patients with a positive interim PET, firstly because the NPV of interim PET is better than its PPV, and secondly, among patients with a true interim PET positivity related to a chemo-resistant disease the alternative conventional chemotherapy approaches currently available have a limited efficiency. The use of semi-quantitative assessment may increase the interim PPV and better identify patients eligible for new drugs.

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