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The role of positron emission tomography in T-cell lymphoma and T-cell specific response criteria

Introduction

An increasing number of effective treatments are becoming available for lymphomas in general, and T-cell NHL specifically. Thus, standardized measures of evaluation of response become of greater importance to permit comparison amongst studies and to facilitate evaluation by regulatory agencies. Prior to 1999, a lack of standardized of response assessment led to variability among clinical trials groups and cancer centers impairing comparisons of various studies. In 1999, an International Working Group (IWG) composed of clinicians, radiologists and pathologists with expertise in the evaluation and management of patients with lymphoma convened to develop guidelines that standardized response assessment, and defined response categories and study endpoints.[1] These recommendations were widely adopted by clinical trials groups and were used by regulatory agencies for the assessment of new agents.

However, as these criteria were used over time, the need for revisions became apparent. For example, the IWG criteria relied on physical examination, which is subject to marked inter- and intra-observer variability; CT scans, and SPECT gallium scans, the latter no longer being used.

Another major problem with the original IWG criteria was the misinterpretation of the term complete remission/unconfirmed (CRu). CRu was originally proposed to designate two types of responses: the first were in patients with curable histologies, such as Hodgkin's lymphoma or diffuse large B-cell lymphoma (DLBCL), with a large mass prior to therapy and for whom treatment resulted in a disappearance of all detectable tumor except for persistence of the mass, but which decreased by at least 75% on CT scan from its pretreatment size. In as many as 90% of cases, these lesions represent scar tissue or fibrosis rather than active tumor.[2,3] Instead, CRu was often applied to situations in which the sum of the product of the diameters (SPD) of multiple nodes decreased by at least 75%, even in patients with incurable histologies, which would more appropriately be considered partial responses. One consequence was an artificial inflation of CR rates. The second type of CRu included patients with bone marrow involvement prior to treatment who fulfilled all of the criteria for a CR following therapy except that the bone marrow was considered by the pathologist as morphologically indeterminate. Instead, the term was also assigned to patients who did not undergo a repeat biopsy to confirm a complete response.

Positron emission tomography in the management of lymphoma

Over the past decade, thousands of papers have been published describing the role of FDG-PET in the management of patients with NHL resulting in a major change in lymphoma patient management.[4-6] However, the clinical use of FDG-PET has far exceeded the demonstrated beneficial effect of this technology.[7]

The role of positron emission tomography in staging

For decades, the Ann Arbor system has been used to stage the extent of B-NHL and peripheral T-cell NHL based primarily on physical examination and bone marrow evaluation with CT scans subsequently incorporated.[8]

Numerous papers have shown that PET is more sensitive and specific than CT, and identifies more lesions. Nevertheless, PET is currently not part of standard lymphoma staging primarily because of its expense and the generally small percentage of patients (~15-20%) in whom PET detects additional disease sites that modify clinical stage, and even fewer patients (~10-15%) for whom this modification alters management or outcome.[9-12] PET and CT are 80-90% concordant in staging of patients with diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma.[10,13] In those patients with discordant results, PET typically results in upstaging due to the additional presumed sites of nodal, hepatic or splenic disease. Although PET identifies more lesions than CT, PET alone does not currently replace CT for pretreatment staging.[6,14-17]

FDG-avidity and histology

Importantly, the various lymphoma histologies vary in their FDG-avidity. The more common lymphoma subtypes in the US and Europe (e.g., diffuse large B-cell NHL, follicular NHL, mantle cell NHL, HL) are routinely FDG-avid.[10,18,19]

The data for PET in T-NHL are more limited and suggest that FDG-avidity is less predictable in T-NHL than in other lymphomas. Elstrom *et al.*[20] reported a retrospective analysis of FG-PET scans in 172 patients with a variety of histologies of NHL. The diagnosis was histologically confirmed and the imaging studies were performed either at diagnosis or at relapse prior to further treatment. Whereas DLBCL, MCL, HL and FL were almost uniformly FDG-avid, the scan was positive in only 2 of 5 patients with peripheral T-cell lymphoma (PTCL).

Tsukamoto *et al.*[21] staged disease in 255 patients with lymphoma. FDG-PET was routinely avid in patients with non-cutaneous anaplastic large cell lymphoma (ALCL) (100%), angioimmunoblastic T-cell NHL (AITCL) (100%), PTCL (98%) and natural killer (NK)-T-cell lymphoma (100%); however the likelihood was lower in subcutaneous panniculitis-like T-cell lymphoma (SCPLTCL) (71%). Khong *et al.*[22] evaluated pretreatment FDG-PET in 30 patients with T-NHL or NK-T-NHL. In 12 NKT all nasal and extranodal lesions were positive. Nasal maxillary lesions were more localized than on CT suggesting an effect of inflammation. PET failed to identify marrow involvement in several patients. Whereas they found AITCL (n=7), PTCL-not otherwise specified (NOS) (n=7) and ALCL (n=3) were concordant with CT scans, cutaneous ALCL (n=1) and mycosis fungoides (MF) (n=2) had minimal FDG uptake. They were unable to identify a correlation between SUV and prognosis.

Other studies have confirmed FDG-avidity in patients with NK/T-cell lymphoma.[23] Kako *et al.*[24] retrospectively evaluated FDG-PET scans from 41 patients with NK-T-cell lymphoma. FDG-PET identified at least one lesion

in 36 patients; however, the likelihood of detecting a lesion was lower for cutaneous disease. Overall, the likelihood of FDG-avidity for PTCL-NOS was 91%, extranodal NK-cell lymphoma (ENKL) 100%, ALCL 60%, AILT 100%, MF/Sézary syndrome (SS) 33%. However, the results were disappointing for patients with cutaneous lesions with an overall positive rate of 50%, including 0% for MF/SS and 40% for cutaneous ALCL. They noted discordance between cutaneous and other lesions. They also concluded that FDG-PET was poor for identifying bone marrow disease.

Suh *et al.*[25] included PET scans in the initial evaluation of 21 patients with previously untreated ENKTCL of the head and neck. All pretreatment lesions were considered positive by PET scan with a median SUV of 5.3. They identified a correlation between the intensity of the FDG uptake and tumor aggressiveness and failure to respond to therapy. Since PET scans were not performed following treatment they were unable to predict outcome.

Horwitz *et al.*[26] evaluated PET scans as part of initial staging for patients with T-NHL, including CTCL with suspected extracutaneous disease. Of the 107, PET was considered positive in 89% with SUVs from 1.1-20.5. Of 12 patients with a negative scan, 58% had no disease on CT. PET detected additional sites in 32% of patients, including 3 new malignancies. However, stage was altered in less than 10%. Thus, while additional sites of extranodal disease were identified, stage was not changed because patients were already known to have advanced disease.

Karantanis *et al.*[27] evaluated 21 FDG-PET/CT scans performed on 10 patients with NK-T-cell NHL. Four studies were performed for initial staging, 9 during therapy, and 8 after completion of therapy. For those patients with nasal involvement, 5 scans were true positive, whereas 15 were true negative, with one case considered positive but unconfirmed. For those patients with extranodal disease, the scan was true positive in 3, true negative in 16, and false negative in 2.

The mean SUV_{max} for nasal lesions was 16, and 10.9 for extranasal lesions.

Other histologies of peripheral T-cell lymphoma

Anecdotal case reports suggest avidity in ATLL.[28] PET scans may also be positive in patients with subcutaneous panniculitis-like T-cell lymphoma,[29] although the likelihood of FDG-avidity may be less than with other PTCLs.[21] Hoffmann *et al.*[30] reported that FDG-PET was useful in assessing 5 patients with ETCL.

Cutaneous T-non-Hodgkin's lymphoma

The likelihood of FDG-avidity in CTCL appears to depend on whether the tumor is cutaneous or extracutaneous. Kuo *et al.*[31] reported that PET was superior to physical examination for identifying subcutaneous lesions in patients with CTCL. PET was useful in Identifying advanced visceral disease. Of interest was the variability in FDG-avidity among lymph nodes in individual patients. Tsai *et al.*[32] evaluated the role of FDG-PET in staging of patients with CTCL at risk for lymph node involvement. Whereas by CT criteria, only 5 of 13 patients had lymphadenopathy, tumors from all patients were FDG-avid. Those with aggressive transformation had the highest SUV values. However, the PET scan did not routinely identify cutaneous involvement. They concluded that FDG-PET was more sensitive than CT scan for nodal disease.

Kumar *et al.*[33] retrospectively assessed PET in 19 patients with primary cutaneous lymphoma including 15 with T-NHL. They found a sensitivity of 82% for local disease and 80% for distant metastases, which was superior to CT scans. Two patients with CTCL had no uptake at the site of disease.

Kuo *et al.*[34] assessed the role of FDG-PET in

a phase II trial of vorinostat in CTCL. Preliminary analysis of the data suggested that the results of the scan may correlate with response or lack thereof.

Where PET may be useful in CTCL is in patients for whom an aggressive transformation is suspected: a PET scan may help identify the lesion to biopsy that is most likely to support the clinical suspicion.

PET in bone marrow assessment

Bone marrow biopsies are a standard component of lymphoma staging.[5] However, the sample obtained is a small representation of the total bone marrow. PET can identify bone or bone marrow involvement in lymphoma patients with a negative iliac crest bone marrow biopsy.[35-37] However, PET is more likely to suggest the presence of disease in a bone marrow that is extensively involved, in which case, the bone marrow biopsy is typically positive as well. Diffusely increased bone marrow uptake on PET may also be due to reactive myeloid hyperplasia, which may follow the administration of myeloid growth factors or in a bone marrow that is regenerating following chemotherapy.[36] PET alone is unreliable in detecting limited bone marrow involvement where immunohistochemistry or flow cytometry may be valuable.[37] Bone/bone marrow involvement suggested by PET should be confirmed by biopsy if a change in treatment will be based on these findings. Limited data suggest that PET may not be valuable in assessing minimal bone marrow involvement in T-NHL.[24] Thus, PET cannot substitute for bone marrow biopsy in lymphoma staging.

Recommendations for the use of positron emission tomography in clinical trials

In 2005, the German Competence Network Malignant Lymphoma convened the International Harmonisation Project, including an international committee of lymphoma clinical investigators, pathologists, and nuclear medicine physicians to review the IWG and other proposed response criteria (e.g., RECIST), and to determine how best to clarify and improve them to ensure transparency among clinical trials groups.[38] Available data using PET were also evaluated to determine if it was appropriate to incorporate that technology into new response criteria. Previously Juweid *et al.* had demonstrated that integrating PET into the IWG criteria in NHL increases the number of complete remissions in patients with diffuse large B-cell NHL, eliminates CRus, and provides a better separation of the progression-free survival curves between CR and PR patients.[39] These data and others provided support for adopting FDG-PET into new guidelines.

The major outcomes of the International Harmonization Project included a standardization of performance and interpretation of PET in lymphoma clinical trials,[4] recommended indications for the use of FDG-PET in clinical trials (Table 1), and new response criteria[5] (Table 2). A positive scan was defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology. Exceptions include mild and diffusely increased FDG uptake at the site of moderate or large-size masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks following treatment. Areas of necrosis may be FDG-avid within an otherwise negative residual mass and a follow-up scan in a few months may confirm this clinical impression. Residual masses ≥2 cm in greatest transverse diameter (GTD) with FDG activity visually exceeding that of mediastinal blood pool structures are considered

Table 1. Recommended timing of PET (PET/CT) scans in lymphoma clinical trials.

Histology	*Pre-tretment*	*Mid-treatment*	*Response assesment*	*Post-tx surveillance*
Routinely FDG-Avid				
DLBCL	Yes*	Clinical trial	Yes	No
HL	Yes*	Clinical trial	Yes	No
Follicular NHL	No+	Clinical trial	No+	No
MCL	No+	Clinical trial	No+	No
Variably FDG-Avid				
Other aggressive NHLs	No+	Clinical trial	No+§	No
Other indolent NHLs	No+	Clinical trial	No+§	No

**Recommended but not required pretreatment. +Recommended only if recommended only if ORR/CR is a primary sudy endpoint. §Recommended only if PET is positive pre-treatment. Fram Cheson et al.[5]*

Table 2. Revised response criteria for assessing response in clinical trials.

Response	*Definition*	*Nodal masses*	*Spleen, liver*	*Bone marrow*
Complete remission (CR)	Disappearance of all evidence of disease	a. FDG-avid or PET+ prior to therapy mass of any size if PET- b. Variably FDG-avid or PET-, regress to normal size on CT scan	Not palpable, lesions disappeared	Infiltrate cleared, if indeterminate by morphology, must be negative by immunohistochemistry
Partial remission (PR)	Regression of measurable disease and no new sites	> 50% decrease in SPD of up to 6 largest dominant masses. No increase in size of other nodes. a. FDG-avid or PET+ at previously involved site b. Variably FDG-avid or PET-: regression on CT.	≥50% decrease in SPD of nodules or greatest transverse diameter of single nodule, no increase in size of liver or spleen	
Stable disease (SD)	Failure to attain CR, PR or PD	a. FDG-avid or PET+ prior to therapy, PET+ only at previously + sites of disease, no new lesions on PET or CT. b. Variably FDG-avid or PET-: No change in previous lesions on CT.		
Relapsed or progressive disease	New lesion or increase by ≥50% from nadir of previously involved sites	New lesion > 1.5 cm in any axis ≥50% increase in longest diameter of previously identified node > 1 cm in short axis or in the SPD of more than 1 node Lesions PET+ if FDG-avid lymphoma or PET+ prior to therapy, otherwise use CT	≥50% increase from nadir in SPD of previous lesions	New or recurrent involvement

From Cheson, et al[5]

PET-positive whereas residual masses 1.1-1.9 cm are considered PET-positive only if their activity exceeds surrounding background activity. However, the numerous causes of false positive scans must be ruled out including sarcoidosis, infection, or inflammation.[40]

Another major outcome of the IHP was a revision of the IWG response criteria 5. These new recommendations took into consideration the variable FDG-avidity amongst the various

lymphoma histologic subtypes, and the relevant endpoints of clinical trials (Table 1). For example, PET was recommended as standard for the initial evaluation of patients with routinely FDG-avid, potentially curable lymphomas (e.g., DLBCL, Hodgkin lymphoma) to define the extent of disease and to provide a baseline against which to compare post-treatment studies. It is also useful in confirming whether a patient has limited stage disease and, thus, who might be a candidate for local radiation only. For the FDG-avid but incurable histologies (e.g., follicular lymphoma and low-grade, and mantle cell lymphoma) PET is warranted only if complete response is a primary endpoint of the trial since time-dependent endpoints (e.g., progression-free survival) are generally of greater importance. Scans should only be performed in those FDG-variable histologies if CR is a study endpoint.

Numerous studies have demonstrated that interim PET scans predict progression-free and overall survival in DLBCL and Hodgkin lymphoma; however, no data currently exist for PTCL.[41-50] Moreover, no available data demonstrate that altering treatment on the basis of interim PET results improves patient outcome. This critically important issue is currently being addressed in a number of clinical trials.[51]

PET is essential for restaging the potentially curable lymphoma histologies (e.g., DLBCL, Hodgkin's lymphoma) following completion of therapy. When indicated, PET scans should not be performed until at least 6-8 weeks, following completion of therapy to reduce the likelihood of a false-positive result.[4] In these patients, where a complete remission is required for cure, therapeutic intervention is generally indicated if residual disease is present. However, for PTCL, PET should only be considered prior to therapy if complete response is a primary objective of a study, and repeated post-therapy if the pretreatment study was positive. For patients with PTCL and a variably avid scan, CT criteria should be used to define response.

Although widely used in clinical practice, there is no evidence to support regular surveillance CT or PET scans.[52,53]

Conclusions

FDG-PET has become an important component of the management of patients with B-NHL and Hodgkin's lymphoma. However, its role in T-NHL is still being defined. The limited data suggest that PET for initial assessment does not alter clinical stage nor treatment recommendations and, thus cannot be recommended for routine use. Since PTCL, for the most part, are not curable, PET should only be used for restaging if CR is a major study endpoint.

For patients with CTCL, PET is neither sufficiently sensitive nor specific for assessment of cutaneous disease and, therefore, more traditional criteria, such as the mSWAT score (the sum of the percentage of total body surface area multiplied by a number reflecting patch, plaque or tumor) remains a standard.

Thus, whereas there is an increasing body of data describing results with PET in T-NHL, guidance as to the use of this technology is lacking. Clinical trials should provide prospective validation of PET in T-NHL before it can be considered a standard part of patient management.

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