



## Report of the 6th International Workshop on PET in lymphoma

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## Report of the 6th International Workshop on PET in lymphoma

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### ABSTRACT

Two hundred and ten nuclear medicine physicians, radiologists, and hematologists from 26 countries attended the 6th International Workshop on Positron Emission Tomography (PET) in Lymphoma and Myeloma held in Menton, France, in September 2016. The meeting was under the auspices of the European Lymphoma Institute (ELI), the European Association of Nuclear Medicine (EANM) the Lymphoma Study Association (LYSA), the Italian Foundation on Lymphoma (FIL) and the Carnot Institute for Lymphoma (CALYM). Forty scientific posters were presented. For the first time, specialists in the field of multiple myeloma (MM) were involved in the expert session. The aim was to establish from the experience of Italian and French studies new guidelines of FDG-PET/CT reporting for myeloma staging and restaging. The meeting dedicated an entire session to MM imaging followed by a session on the role of PET in Peripheral T cell Lymphoma. An entire session addressed the issues of Deauville scale particularly for end treatment assessment and the challenging consequences of immunomodulatory treatments on PET reporting. A specific session presented the potential role of baseline metabolic tumor measurement to predict outcome and identify different risk categories and the main results obtained in different lymphoma entities were described. Whether it could replace clinical staging has been extensively discussed. The more recent results obtained in the H10 trial have been presented and compared to the published data in early stage Hodgkin lymphoma. Finally, the ongoing studies using PET for guiding therapeutic strategies have been reported by the various lymphoma cooperative groups that participated to the meeting.

### ARTICLE HISTORY

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The 6th edition of the international workshop on Positron Emission Tomography (PET) in lymphoma was held in Menton on 19–21 September 2016 and was attended by 210 hematologists and imaging physicians from 26 countries. The sessions encompassed all the main research projects and ongoing studies in lymphoma based on quantitative imaging as well as

the new fields of application of PET such as T cell lymphomas. Limitations of Lugano criteria in the era of immunomodulatory agents were also debated. For the first time, a session of the meeting was dedicated to multiple myeloma (MM) imaging aimed at establishing new imaging criteria for diagnosis and response assessment.

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All the presentations and abstracts from the meeting are available in PDF format on the website: <http://lymphomapet.com> and this brief report will summarize the main points addressed during presentations and discussions.

### **Imaging in multiple myeloma**

The first session of the meeting was dedicated to imaging of MM.

#### **Staging**

Rahmouni presented the different magnetic resonance imaging (MRI) techniques that have been used for MM staging. First of all the standard (MRI), with T1 and T2 images which was integrated in the 1986 Durie & Salmon PLUS classification and giving good visualization of bone marrow (BM) involvement. Second, the whole-body dynamic contrast enhanced-MR (DCE-MR) imaging, thanks to its ability to image the increased angiogenesis in BM induced by the MM clone proved useful to evaluate the treatment response. Messiou emphasized the potential role of diffusion weighted (DW) MRI: its advantage over standard MRI is a higher sensitivity in detecting low-tumor burden plasma cell disorders, like smoldering MM, diffuse involvement of BM in MM, and minimal residual disease (MRD) after treatment. However, standardization of image acquisition and reproducibility across MR centers still represent an issue. Zamagni, on behalf of the Italian MM-GIMEMA group, addressed the emerging role of PET/CT as a cutting edge new imaging technique in MM. The latter has been included in the most recent recommendations and consensus for tumor staging, due to its high sensitivity and specificity in detecting spinal and extra-spinal disease. In particular, PET/CT was able to detect lesions not accompanied by visible osteolysis, extramedullary lesions, other lesions in apparently 'solitary' bone plasmacytoma and to stage smoldering MM. Its prognostic role is also relevant: the presence of multiple focal lesions (>3) and/or a SUV max >4.5 at baseline have been associated with a poor prognosis.

#### **Response assessment**

The role of FDG-PET/CT for treatment response evaluation at the moment is under study. Complete suppression of FDG uptake in MM lesion proved an independent prognosticator of progression free survival (PFS) and overall survival (OS) before autologous stem cell transplantation (ASCT), while 25–30% of

patients otherwise considered to be in CR by conventional imaging were still PET-positive and had an inferior prognosis. Three independent prospective studies (US, Italy, France) conducted to assess MRD in pre and post ASCT and before maintenance have confirmed that FDG PET is a good tool for response evaluation and MRD detection in BM correlated with the results of multiple flow cytometry. Moreau, on behalf of the French intergroup on Myeloma (IFM), reported the preliminary results of the IFM2009 trial (IMAJEM study). In 134 patients scanned with MRI (T1 and T2 images) and PET/CT at baseline, after three cycles of treatment and before maintenance, the 'classic' MRI of the spine and pelvis and whole-body PET-CT are equally effective in detecting bone involvement in symptomatic patients at diagnosis. Nonetheless, MRI proved to be an inadequate imaging technique during follow-up, whereas PET-CT after three cycles of lenalidomide and pre-maintenance was a powerful predictor of PFS and OS. Moreover, FDG/PET-CT and bone marrow flow cytometry (BMFC) are complementary tools to evaluate MRD. Among the 134 patients assessed by PET at various stages of therapy, the results of BMFC-detected MRD were available in 86 patients. PFS was superior in the 41 patients without evidence of BM invasion on PET/CT compared to patients with a positive result with either or both methods. The Italian and the French groups proposed different PET/CT reporting criteria for MM, but, similar to PET reporting in lymphoma, simple and agreed criteria also appeared feasible for application in MM (see below). FDG proved to be an accurate tracer to image MM lesions, but other radiopharmaceutical agents showed similar tumor affinity. Garderet and Montravers presented preliminary results from a study comparing F18 choline and F18 FDG PET in MM staging. F-18 Choline showed a slightly superior overall sensitivity in tumor detection compared to FDG, probably due to an increased serum lysophospholipid level in MM patients. These results await confirmation in a prospective study.

#### **Bruce Cheson lecture**

Cheson gave a lecture entitled: 'Imaging in Lymphoma from 1999 to Lugano: What is Next?'. He provided an extensive overview of the evolution of PET reporting criteria and explained how the new Lugano criteria were developed. He alluded to quantitative PET for treatment response assessment but also to the prognostic role of baseline metabolic tumor volume (MTV), and showed the advantages of a combined approach with clinical, molecular, and imaging markers to refine the predictive value of PET for treatment outcome.

Finally, he stressed the limitation of PET reporting in the era of immunomodulatory agents and described the new LYRIC criteria as a complementary tool to the Lugano classification in order to avoid premature treatment withdrawal based on false positive results, which often occur during treatment with immune checkpoint inhibitors [1].

### **Role of FDG-PET/CT in peripheral T cell lymphoma and NK/T cell lymphoma**

Recently, several retrospective studies arose increasing interest in the use of PET/CT in peripheral T-cell lymphoma (PTCL) management, but prospective studies are still lacking addressing its use in specific PTC subsets, due to the large variety of histological subtypes and the constant progress of the taxonomy of this broad category of neoplastic disorders. Several presentations focused on the prognostic and predictive value of baseline, interim and end of treatment PET (EoTPET) in PTCL.

#### ***Clinical presentation, prognosis, and new treatments***

Pro described the clinical presentation and new treatment issues in PTCL. The latter are more frequent of nodal nature (56%), respond poorly to conventional anthracycline-based chemotherapy, and most treatment failures are observed in the first two years, with less than 20% of patients experiencing long-term disease control. CHOP gives an overall response rate (ORR) of 60–80% and 39–60% of patients achieved complete response, which is not durable in most cases. Two different approaches proved superior to standard CHOP: adding etoposide to CHOP (CHOEP) or up-front ASCT to consolidate CHOEP response. The latter was tested in a prospective multicenter trial by the Nordic group, with a 5-y-OS and 5-y-PFS of 51% and 44%, respectively. Outcome after the first relapse is extremely poor, and several agents have been investigated targeting the surface antigen receptors (CD30, CCR4), the cell immortalization mechanism, the microenvironment, or specific genetic alterations. Romidepsin induced complete and durable responses with manageable toxicity in patients with relapsed or refractory PTCL across all major PTCL subtypes, regardless the number or type of prior therapies. Brentuximab in relapsed anaplastic large cell lymphoma (ALCL) patients has improved outcome with a 63% 4-y PFS and an 86% 4-y OS in PET negative patients after four cycles. Interesting results have been obtained with other agents such as PI3K inhibitors in

PTCL not otherwise specified, angioimmunoblastic T cell lymphoma and ALCL ALK-ve and by the ALK inhibitor Crizotinib in ALCL ALK+ve patients. New treatment strategies are moving to investigate the possibility to dedicate a specific drug to a specific molecular abnormality. Gallamini described the old and new prognostic factors in PTCL and pointed out that at least seven different prognostic models have been proposed in PTCL, stressing the concept that the need of prognostic models in a given neoplastic disorder is inversely related to its curability. In PTCL, the clinical utility of prognosticators appears limited, due to the fact that PTCL has a very poor disease outcome with survival ranging from 0 to 32% at 3 years. Functional imaging could be helpful in this setting to identify patients with a very poor outcome, awaiting a more aggressive treatment: interim PET (iPET) performed after two cycles of treatment proved able to identify patients with a treatment outcome that was inferior to the whole PTCL population; however, a similar course is observed with respect to PFS during the two first years, irrespective of the PET-2 status. Total metabolic tumor volume (TMTV) appears predictive of outcome with a significantly inferior PFS and OS in patients with high TMTV values. Among the molecular prognosticators, the GATA3 expression correlated with poor prognosis and macrophage-associated infiltration in nodal PTCL. In ALCL cytogenetics and molecular profiling could separate different risk categories such as the presence of a recurrent translocation involving TP63 in ALK-ve patients with bad prognosis. In the future, combining clinical genetic and imaging biomarkers may aid in risk stratification and help guide initial patient management.

#### ***PET/CT imaging***

Cottreau reviewed the role of FDG-PET/CT performed for PTCL staging and restaging purpose from the literature and presented the results of a retrospective Lymphoma Study Association (LYSA)/Danish group study. Baseline PET/CT detected more extranodal sites than CT, with the notable exception of BM invasion, which could not be detected by either method, thus concluding that, different from HL or DLBCL, PET/CT cannot replace BM biopsy in PTCL staging. PET/CT-detected spleen involvement is not more predictive than splenomegaly measured on CT. In contrast, TMTV is predictive of PFS (2y-PFS 71% versus 26% and OS 80% versus 50% for low and high volume, respectively). Combined with the Prognostic Index for PTCL (PIT), TMTV stratifies the population into three different risk categories, the highest in patients with both high PIT

and high TMTV, with a 19% 2-y PFS and 41% 2-y OS. Although reports about the prognostic value of iPET and EoTPET are controversial, the results from the LYSA/Danish retrospective series of 142 patients have shown that iPET and EoTPET reported using the Deauville scale (DS) with a positivity cutoff using the liver threshold were predictive of outcome and independent from International Prognostic Index (IPI) and PIT. In NK/T cell lymphoma, PET/CT plays an important role in tumor staging as it proved significantly more sensitive and accurate than conventional imaging methods, especially in detecting extranodal sites involvement and in radiation planning. Kim gave relevant clinical examples and also emphasized the predictive role of end treatment PET reported with Deauville criteria. From the results of circulating Epstein-Barr virus (EBV) DNA combined with Deauville score at end treatment, Kim and coworkers could stratify patients in different risk group according to the number of adverse factors (PET positivity and circulating EBV-DNA or both).

### **Use and limitations of the Lugano classification**

In the following session dedicated to Lugano classification [2], Kobe presented results from the German Hodgkin Study Group (GHSG), demonstrating that a negative iPET cannot circumvent the need for an end of treatment evaluation and that score 3 of the DS has only a moderate reproducibility. In pediatric Hodgkin lymphoma Kluge found a low reproducibility between observers in iPET reporting upon settling the cutoff value  $\geq 4$  for a positive scan. She proposed a quantitative scoring obtained by the ratio of SUV<sub>peak</sub> of the lesion to SUV<sub>mean</sub> of the liver, with a value of 1.3 as cutoff value to differentiate score 3 from score 4. Barrington reported the experience of using Deauville criteria in the large clinical trials conducted in HL by the NCRI (RAPID and RATHL) and the good agreement between central and local reporting for iPET scan, with the best agreement adopting a cutoff value between scores 1, 2, 3 versus 4, 5, which was also shown to have the highest positive and negative PV. However a higher NPV was obtained in the RAPID trial using score 1–2 for treatment de-escalation. Further data presented from these trials and Italian trials (HD0801, HD0607) demonstrated that score 5 was associated with the worst prognosis. In HL and DLBCL a negative iPET predicts a negative EoTPET in 90–100% of the cases, depending on the stage and risk factors, as stressed by Casasnovas in his presentation. In the AHL2011 trial, conducted in a large cohort of 811 advanced-stage HL, a treatment de-escalation from

eBEACOPP to ABVD for PET2 negative patients in the experimental arm did not compromise overall treatment efficacy. In an interim analysis performed after a median 18 months follow-up the treatment outcome of patients receiving this de-escalated treatment was not statistically different from that in the conventional, full-dose eBEACOPP arm. Zucca stressed the different meanings of DS for interim (quality of response) and end treatment (remission assessment in DLBCL). Trotman gave a panorama of the current world practices on PET use in follicular lymphoma (FL). Except in US, France, Italy, and Korea. PET, which is the most accurate imaging modality for lymphoma staging and restaging in this lymphoma subset, is not routinely reimbursed by health insurance. In EoT setting, PET is not always reported using DS, although it has been shown that a score  $\geq 4$  is one of the most powerful predictors of inferior PFS and OS in FL. iPET does not seem useful as it is less predictive than an EoT scan and the clinical need to detect earlier poor prognosis patients is not that relevant in this indolent lymphoma. Treatment response adapted strategy based on EoT PET to guide rituximab maintenance therapy as in the Italian Foundation of Lymphoma (FIL) FOLL 12 trial will assist us to determine if this prolonged (and expensive) treatment is indicated in all FL patients.

### **PET and immunotherapy**

Lopci addressed the problems of reporting PET performed after immunotherapy, which activates and restores the T-cell response against tumor cells and may induce inflammatory unspecific FDG uptake during or after the course of therapy. Immunoreactive (IR) cells such as macrophages and granulocytes are critically dependent on HIF-1 $\alpha$ -mediated induction of glycolytic genes to infiltrate inflamed tissue and adaptive IR cells upregulate the expression of GLUTs and hexokinase in response to mitogenic signals. This metabolic activation of IR cells could simulate tumor progression and the LYRIC (Lymphoma Response Indeterminate Criteria) criteria were proposed to overcome the limitations of the Lugano classification in this setting. The patient clinical status plays a central role in managing the false positive PET results and repeated follow up scans with an interval of 12 weeks are mandatory to decide the appropriateness of treatment withdrawal.

### **Total metabolic tumor volume and clinical staging**

The first session of the second day was dedicated to quantitative PET with a special emphasis on TMTV.

Trotman presented the historical evolution of tumor burden assessment from Ann Arbor classification to TMTV, the different methods for TMTV computing (fixed, relative threshold for SUVmax, or adaptive threshold) and the clinical impact of TMTV in retrospective series of HL, DLBCL, PMBCL, FL, PTCL, and ENNK/TCL patients. TMTV assessment by functional imaging unveiled the limits of the existing prognostic indices as surrogates of TMTV; however, there are concerns regarding the lack of standardization and reproducibility of the results obtained in retrospective studies. Buvat stated that no single method was superior to others in terms of accuracy of volume measurement, and that performance varies as a function of the activity distribution, noise, spatial resolution, and contrast. Each method has some intrinsic bias but a given cutoff value should ideally be determined for prognostic purpose. Buvat proposed an innovative method for measuring MTV, to be validated in well-designed prospective multicentre trials. Casanovas reported preliminary results on the prognostic role of baseline TMTV in advanced stage HL patients enrolled in the AHL 2011 LYSA trial. A  $350\text{cm}^3$  threshold obtained in a training set, was validated in an independent, prognostically well-matched validation cohort, which was predictive of PFS in the whole population of 387 patients valuable for TMTV assessment. Hoekstra and Chauvie presented at the end of the session two programs for quality control and scanner normalization for PET sites participating in prospective trials, developed by EARL and by FIL, respectively.

### Final results of the H10 trial

André presented the main results of the PET response-adapted large clinical trial H10 conducted by EORTC/LYSA/FIL in early stage HL. Early iPET performed after two ABVD cycles (PET-2) helped to define a poor risk PET-2 positive group in whom treatment intensification after PET-2 improved disease control; and a standard risk group in whom the omission of radiotherapy failed to show non-inferiority of chemotherapy alone compared with combined modality treatment (CMT).

As in previous workshops, abstracts selected for posters and oral presentations were presented by Van der Borgh and Duhren and are summarized on the website where the abstracts are also available.

### Ongoing studies using PET (GELTAMO, FIL, LYSA, ALLG, GHSG, IELSG)

As in previous meetings, the different cooperative groups in lymphoma presented their ongoing PET-guided studies.

### GELTAMO

Caballero and Coronado from the Spanish GELTAMO group presented the results of two trials conducted in DLBCL with drugs active against the nuclear transcription activating factor NFkB. In a randomized trial performed in young, poor-prognosis DLBCL patients comparing standard R-CHOP to six cycles of bortezomib plus R-CHOP. Interim PET after two or four courses was performed to assess prognosis with these treatment regimen. The second trial was a phase II study in refractory/relapsed non-germinal center DLBCL, designed to assess the efficacy of rituximab gemcitabine oxaliplatin dexamethasone and ibrutinib followed by ibrutinib maintenance in which the value of PET/CT to assess BM infiltration by lymphoma was compared to multi-parametric flow cytometry and histology.

### FIL

Luminari presented the trials from the Italian FIL group. The DLCL-10 is a prospective, multicentre phase II study conducted in low-risk DLBCL, according to age-adjusted IPI (0 with bulky or 1) treated with R-CHOP-14 followed by PET-guided consolidation radiotherapy. End-of treatment PET scans were centrally reviewed by an expert panel and radiotherapy is given to patients with a DS score 4 to 5. The FOLL012 is a multicentre, phase III, randomized study aimed to assess feasibility and efficacy of delivering rituximab maintenance treatment after standard chemo-immunotherapy only in high-risk advanced-stage FL, showing either a positive MRD or a positive end-of treatment PET scan or both after standard R-CHOP treatment. At the time of writing, 642 patients have been included.

### ALLG

Hertzberg presented the trials from the Australasian Leukaemia Lymphoma group (ALLG). The NHL21 Phase II Trial is a trial aimed at assessing the efficacy of early treatment intensification with R-ICE chemotherapy and Zevalin-BEAM autologous SCT for high-risk DLBCL, defined by a positive iPET/CT after four cycles of R-CHOP 14. This trial used International Project Criteria for PET scan interpretation and both the primary and secondary end point were met, as improved PFS and OS were observed in iPET positive patients undergoing intensified treatment. Baseline MTV assessed on PET scan could furthermore identify patients with different treatment outcomes within the high-risk PET-4 positive and the standard risk PET-4 negative arm. The ongoing RePLY study is evaluating  $R^2$  (Lenalidomide plus Rituximab)

consolidation in patients remaining PET-positive after treatment of relapsed FL.

### **GHSg, IELSG, LYSA**

Kobe presented the results of the GHSg trials. In the ongoing HD17 trial, early unfavorable HL patients are treated with 2 BEACOPP escalated and 2 ABVD course followed by PET. PET negative patients are randomized between involved field (IFR) or no radiotherapy and PET-2 positive between IFR and involved node radiotherapy (INR). In the HD18 study conducted in advanced stage, HL patients are treated with 2 BEACOPP escalated and an iPET is performed afterwards: PET-2 negative patients are randomized to a de-intensified regimen with two more cycles of BEACOPP versus standard eBEACOPP treatment with six cycles; PET-2 positive patients are randomized to standard BEACOPP regimen versus the same regimen supplemented by Rituximab. Chauvie presented the International Extranodal Lymphoma Study Group (IELSG) 37 trial, a randomized, international phase III study assessing the role of involved mediastinal radiotherapy versus no further treatment in patients with Primary Mediastinal Large B-Cell Lymphoma (PMLBCL) with a negative PET after treatment with standard chemo-immunotherapy. The LYSA trials were presented by Casasnovas. The ongoing trial in low-risk DLBCL (aIPI = 0) patients and grade 3, transformed FL is a randomized phase III study testing the non-inferiority of an abbreviated treatment (only four instead of six RCHOP-21) in PET-2 negative patients. 566 patients are enrolled from a total of 650.

### **Summary of the expert session on PET criteria in multiple myeloma**

In the final session of the meeting, a summary of the expert session held the day before the official opening of the meeting was reported to the general audience. Nanni, from the Italian MM-GIMEMA group, presented the criteria so far reported in the literature for PET scan interpretation in MM. All the criteria so far proposed agree that in case of focal lesions >5 mm in a cold background, lytic lesions visible on the CT part of

PET/CT without increased background activity (no bone activation) and no evidence of recent vertebral fractures or collapse, could be interpreted as harbinger of MM in bone. Criteria differ in their interpretation of other findings, including BM infiltration, low focal SUV max, small areas of focal uptake, focal lesions in areas with increased background, recent fractures or vertebral collapse. A joint French-Italian consortium was formed to develop standardized criteria for PET scan interpretation at baseline and after treatment in MM. The aim of this project will be to harmonize the proposed methods for interpretation developed by these two cooperative groups, based on their clinical and research experience (the Cassio PET criteria from the French group and the IMPetUS criteria from the Italian group) to be validated retrospectively in homogeneous cohorts of MM patients.

The take-home messages from this edition of the meeting are: (1) In MM, PET outperforms MRI for treatment response assessment, (2) Moving from very preliminary studies, simple and reproducible reporting criteria could be sketched and agreed for PET performed for MM staging and restaging purpose, (3) PET quantitative parameter could be useful to stratify patients with PTCL, while interim and end-of-treatment PET is predictive of outcome and (4) iPET can be routinely used for guiding therapeutic strategy in early stage Hodgkin lymphoma.

The next meeting will be held in 2018, October 4–6.

**Potential conflict of interest:** Disclosure forms provided by the authors are available with the full text of this article online at <http://dx.doi.org/10.1080/10428194.2017.1298752>

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