Standardization of 18F-FDG PET/CT According to Deauville Criteria for MRD Evaluation in Newly Diagnosed Transplant Eligible Multiple Myeloma Patients: Joined Analysis of Two Prospective Randomized Phase III Trials

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Blood 2018 132:257; doi: https://doi.org/10.1182/blood-2018-99-111321

Published By American Society of Hematology
Print ISSN 0006-4971
Online ISSN 1528-0020
Published online November 21, 2018.

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Abstract

F-18-fluorodeoxyglucose positron emission tomography integrated with computed tomography (FDG-PET/CT) is actually considered as the standard technique to assess and monitor the metabolic response to therapy and to define minimal residual disease (MRD) status outside the bone marrow (BM) in multiple myeloma (MM) patients. In this regard, standardization of image criteria and definition of cut-offs for positivity/negativity is of highly importance.

Aim of the present study was to prospectively evaluate FDG-PET/CT at diagnosis and prior to maintenance therapy in a joined analysis of a sub-group of patients with newly diagnosed transplant-eligible MM, enrolled in 2 independent European randomized phase III trials (EMN02/HO95 and IFM2009) (Cavo M et al, Blood 2017 abs; Attal M et al, NEJM 2017). The primary end-point was to standardize PET/CT evaluation by centralized imaging and revision and to define criteria for PET negativity after therapy (MRD definition).

236 patients (102 and 134 from the EMN02 and IFM2009 trial, respectively) were enrolled in the PET/CT imaging sub-studies and followed for a median of 62.9 (IQR: 44.9-67.9) months. By study design, PET/CT scans were performed locally at baseline (B) and prior to the start of maintenance (PM), uploaded in a central website and re-interpreted a-posteriori in a blinded independent central review process, by a panel of expert nuclear medicine physicians. According to the IMPeTUs criteria (Nanni C et al, EJNM 2017), the five-point Deauville scores (between 1 and 5) were applied to the following parameters: bone marrow (BM), focal lesions (FLs), extramedullary disease (EMD). The impact of each parameter on outcomes was evaluated by landmark analyses at PM; the univariate and multivariate analyses were stratified by trial to smooth out differences between the 2 studies.

Baseline characteristics of the patients were generally homogeneous between the 2 trials and as follows: median age 59 years, ISS and R-ISS stage III 15.8% and 11.5%, respectively, high-risk cytogenetics (t(4;14) ± del(17p) ± t(14;16) detected by FISH) 14%. Fifty seven percent of the patients were randomized in the transplant arm, and 43% in the bortezomib-intensification arm, with a higher percentage in the IFM2009 vs EMN02 trial (54% vs 24%, respectively).

At baseline, 80% of the patients had FLs, with a median maximum standardized uptake value (SUVmax) of 5. Median BM SUVmax was 3. Both median FLs and BM SUVmax were slightly higher in the IFM2009 vs the EMN02 trial (5.7 vs 4.2 and 3.7 vs 2.68, respectively), while reference SUVmean (mediastinal blood pool and liver) did not differ between the 2 studies. FLs Deauville score (FS) and BM Deauville score (BMS) > 3 (higher than the liver) were present in 79.8% and 35.5% of the patients, respectively, with no difference between the 2 trials. EMD was present in 11% of the patients.

Prior to maintenance therapy, median FLs and BM SUVmax were 3.6 and 2.3, respectively, with 53.5% and 71.2% of the patients obtaining a FS and BMS ≤ 2 and 79% and 91.4% ≤ 3, respectively. In univariate analysis, at Landmark time prior to maintenance, attaining a FS and BMS ≤ 3 was the strongest predictor for prolonged PFS (FS≤ 3 vs >3: median 40 vs 26.6 months, HR 0.6, CI 0.39-0.98, P= 0.0019; BMS≤ 3 vs >3: median 39.8 vs 26.6 months, HR 0.47, CI 0.24-

0.91, P= 0.024, respectively) and OS (FS≤ 3 vs >3: estimate at 63 months 73% vs 63.6% months, HR 0.51, CI 0.26-0.98, P= 0.028; BMS≤ 3 vs >3: estimate at 75.5% vs 49.7%, HR 0.28, CI 0.12-0.64, P= 0.002, respectively) and could be identified as the most representative cut-off values for PET negativity after therapy. Of the two PM scores, only FS ≤ 3 retained prognostic relevance in the subgroup of patients not receiving transplant, in terms of PFS. In Cox multivariable analysis, FS and BMS ≤ 3 at PM were independent predictors of prolonged PFS (FS: HR 0.58, CI 0.35-0.96, P= 0.036; BMS HR 0.41, CI 0.20-0.84, P= 0.014) and OS (FS: HR 0.36, CI 0.17-0.74, P= 0.005; BMS HR 0.24, CI 0.09-0.63, P= 0.004).

In conclusion, FDG PET/CT was confirmed to be a reliable predictor of outcomes in newly diagnosed MM, regardless of treatment. Reduction of FDG uptake lower than the liver after therapy, both in the FLs and in the BM (FS and BMS), was an independent predictor for improved PFS and OS. Findings from this analysis could be proposed as standardized criteria to define PET negativity after therapy, confirming the value of Deauville scores in MM.

Disclosures Zamagni: Celgene: Honoraria, Membership on an entity's Board of Directors or advisory committees; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees; Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees; BMS: Honoraria, Membership on an entity's Board of Directors or advisory committees. Tacchetti: Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees; Celgene: Honoraria; Janssen: Honoraria; Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; BMS: Honoraria. Gallamini: Takeda: Consultancy, Speakers Bureau. Patriarca: Jazz: Other: Travel, accommodations, expenses; Medac: Other: Travel, accommodations, expenses; Celgene: Other: Advisory Role; Travel, accommodations, expenses; Janssen: Other: Advisory role; MSD Italy: Other: Advisory Role. Macro: Celgene: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Financial support for congress; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Financial support for congress; Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Financial support for congress; Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Financial support for congress. Boccadoro: Bristol-Myers Squibb: Honoraria, Research Funding; AbbVie: Honoraria; Novartis: Honoraria, Research Funding; Janssen: Honoraria, Research Funding; Amgen: Honoraria, Research Funding; Celgene: Honoraria, Research Funding; Sanofi: Honoraria, Research Funding; Mundipharma: Research Funding. Garderet: Takeda: Consultancy; Amgen: Consultancy; Celgene: Consultancy. Perrot: Takeda: Honoraria; Sanofi: Honoraria; Amgen: Honoraria; Janssen: Honoraria; Celgene: Honoraria. Sonneveld: Amgen: Honoraria, Research Funding; BMS: Honoraria, Research Funding; Karyopharm: Honoraria, Research Funding; Janssen: Honoraria, Research Funding; Celgene: Honoraria, Research Funding. Karlin: Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; Celgene: Honoraria, Membership on an entity's Board of Directors or advisory committees; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support. Cavo: Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees; Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; AbbVie: Honoraria, Membership on an entity's Board of Directors or advisory committees; GlaxoSmithKline: Honoraria, Membership on an entity's Board of Directors or advisory committees; Bristol-Myers Squibb: Honoraria, Membership on an entity's Board of Directors or advisory committees; Celgene: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; Adaptive Biotechnologies: Honoraria, Membership on an entity's Board of Directors or advisory committees. Moreau: Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees; Celgene: Honoraria, Membership on an entity's Board of Directors or advisory committees; Abbvie: Honoraria, Membership on an entity's Board of Directors or advisory committees; Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees.