EXPERT REVIEWS

The utility of newer imaging techniques as predictors of clinical outcomes in multiple myeloma

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The International Myeloma Workshop (IMW) is a biannual meeting that gathers experts in multiple myeloma (MM) from all over the world and scientists interested in clinical and biological aspects of myeloma. The 2013 IMW was held in Kyoto, Japan and presented an interesting program with an appealing section on newer imaging techniques as predictor of outcome in asymptomatic and symptomatic MM. During the meeting, the importance of newer functional imaging techniques as new ways of assessing bone disease and the extent of marrow infiltration by myeloma cells was highlighted. This short meeting report will provide a review of new and/or functional imaging techniques, such as magnetic resonance imaging (MRI), both axial and whole body (WB-MRI), dynamic contrast enhanced (DCE) MRI, diffusion weighted imaging (DWI) and PET integrated with computed tomography.

This year's International Myeloma Workshop (IMW) was held from 3–7 April in Kyoto, Japan. The meeting, which is held every 2 years, gathers experts on multiple myeloma (MM) from all over the world and is focused on both clinical topics and basic research. New developments and future perspectives are also presented. The aim of the conference is to advance knowledge in MM biology and treatment. One well-attended session was the one on newer imaging techniques as predictors of outcome in asymptomatic and symptomatic MM. This report will focus on data on imaging presented at the meeting and will discuss recently published research and new insights on bone disease localization in MM.

Novel imaging techniques in different settings

Elena Zamagni discussed the usefulness of newer imaging techniques as predictors of outcomes in different settings. Bone disease is one of the most frequent features of MM, and significantly impairs patients' quality of life [1,2]. Functional imaging techniques can assess bone marrow infiltration and evaluate disease response and metabolism. In particular, important new ways of assessing bone disease and the extent of marrow infiltration by myeloma cells are provided by imaging techniques such as MRI, both axial and whole body (WB-MRI), dynamic contrast-enhanced (DCE) MRI, diffusion weighted imaging (DWI) and PET with ^{18}fluorine-fluoro-deoxyglucose (FDG) integrated with computed tomography (PET/CT). These newer and more sensitive imaging methods can upstage approximately one-third of newly diagnosed patients in comparison with standard x-ray [3,4]. MRI is the most sensitive technique for assessing bone involvement of the spine and is the mandatory diagnostic procedure to perform when there is suspicion of cord compression. PET/CT or WB-MRI is the best approach for the identification of unsuspected disease sites involving the bones and/or extramedullary sites. For assessing and monitoring response to therapy, both MRI and PET/CT can be used. Moreover, PET/CT and MRI proved to be reliable predictors of outcome.

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The importance of these new functional techniques, in particular, regarding the prognostic role, was highlighted in the context of different clinical settings.

Smoldering myeloma

The percentage of bone marrow plasma cells, the presence of chromosomal aberration, the level of paraprotein, abnormalities in serum free light chain [5,6] and the presence of aberrant plasma cells at multiparametric flow cytometry [7] identify a subset of patients with asymptomatic myeloma (smoldering MM, SMM) that are at a higher risk of progression. The presence of an abnormal MRI has been shown to be able to stratify patients at a higher risk of progression to symptomatic MM [8]. This observation was confirmed in a recent study using WB-MRI, in which the presence of focal lesions (FLs) was identified as the strongest prognostic factor associated with SMM progression [9]. The MRI of spine and pelvis has been recommended by the International Myeloma Working Group for the staging of SMM, because of its ability to detect occult lesions that, if present, are a prognostic factor associated with a more rapid progression to symptomatic MM [10]. The role of other functional imaging techniques in this setting, such as PET/CT, is still a matter of debate, and it is an open issue whether the availability of these new and more sensitive methods to screen for extramedullary disease should change our approach and lead to an earlier start of treatment [11].

Symptomatic myeloma at presentation

The presence of a PET/CT positivity is an independent prognostic factor for both progression-free survival (PFS) and overall survival (OS) in newly diagnosed transplant-eligible MM patients. This evaluation is based on detection of the number of FLs (> or ≤3) [12–14] and of the intensity of FDG uptake (estimated by the standardized uptake value > or ≤4.2) [12,15]. There are however a number of open issues. One of the main limitations of PET/CT is the definition of PET positivity: a PET/CT-positive lesion is defined by visual criteria and is affected by inter-observer error [11,16]. Similarly to PET/CT, the presence of FLs or a diffuse pattern of involvement on axial MRI correlates with a reduced OS in newly diagnosed MM patients [17–19]. The implementation of MRI with risk groups defined by cytogenetic abnormalities has allowed the identification of a group of patients with a particularly poor outcome, such as those patients carrying more than seven FLs and cytogenetic abnormalities [19].

Symptomatic myeloma after treatment

The persistence of a positive PET/CT after treatment (both number of FLs and high standardized uptake value) has been associated with a reduced PFS and OS, both at the end of induction [12] and very early in the course of treatment [13]. In addition, PET/CT negativity after autologous stem cell transplantation was associated with a better outcome [12]. PET/CT retained prognostic relevance for the risk of progression also in the sub-group of patients achieving complete remission (CR) [12]. The resolution of FLs on the MRI scan, evaluated at different time points, both pre- and post-transplant, has also been associated with an improved outcome [13,19]. It is important to consider how these new imaging techniques can be used to evaluate the depth of response. Interest has progressively grown, and PET/CT and/or WB-MRI could become investigation tools for the detection of residual disease outside the bone marrow due to their ability to identify the persistence of FL(s). PET/CT and MRI, that when combined show a sensitivity of 92% [20], could become complementary to other techniques already used to detect minimal residual disease within the bone marrow, such as PCR and flow cytometry [11]. Despite the proven advantages, open issues still exist, such as the timing of imaging (i.e., early on treatment, pre-transplant, post-transplant) or the significance that has to be given to positive findings. Does the persistence of a highly positive spot on imaging early on therapy allow a change in treatment similar to lymphoma patients? In patients achieving a serological CR, should an attempt to eradicate residual lesions be made with localized or systemic treatment? Specifically powered prospective trials need to be designed to assess these questions.

Newer approaches to MRI: WB-MRI & DWI

MRI can be implemented with DCE images, which evaluate changes in bone marrow microcirculation with the intravenous infusion of gadolinium-containing contrast agent [21]. In patients with progressive or relapsed MM, an increased signal of DCE-MRI was associated with a shorter PFS, possibly in relation with higher angiogenesis and bone marrow microcirculation [21]; nevertheless, gadolinium-based contrast agents are associated with a risk of nephrogenic systemic fibrosis. Both axial MRI and PET/CT have some major limitations, such as the exposure of patients to radiation (PET/CT) or the long time of acquisition (MRI), which can be cumbersome for patients [22]. WB-MRI partially overcomes these disadvantages, having a total scan time of less than 20 min and avoiding the use of radiation or contrast media. Furthermore, in a study of 62 patients, the presence of diffuse involvement and FLs on WB-MRI was found to be associated with an increased mortality risk due to progression [23]. Newer functional MRI protocols, such as whole body DWI are also undergoing investigation. This technique is able to quantify structural and functional changes of tissues, related to cellular density and perfusion. DWI has been evaluated for response monitoring in MM; however, timing of imaging and data acquisition still need to be standardized [24,25]. Despite this, it seems that changes in the level of bone marrow infiltration can be monitored, which can provide additional important clinically useful information. Important information will also come from comparing DWI with PET/CT in prospective clinical trials.

Newer approaches to PET/CT: ^{11}C-labeled methionine PET & thio-tymidine PET

Yuji Nakamoto and Akiyoishi Miwa both presented on the potential applications of newer PET techniques using alternative

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markers to FDG. ^{11}C-labeled methionine (MET) is a radiolabeled PET tracer, which can image hyper-metabolism of amino acid. In a preliminary study on 20 patients, MET/PET compared favorably with FDG-PET [26]. Thio-thymidine PET can detect foci of DNA-synthesizing cells and, in conjunction with MET-PET, might have the potential to evaluate DNA synthesis in various FLs [27]. Although data presented at the meeting were extremely interesting, both techniques are at present inapplicable; thio-PET is still at an experimental level, and the extreme difficulty in the production of MET makes this technique inapplicable in most centers.

Summary & future directions

Novel imaging techniques have proved to be reliable tools for predicting the outcome in both SMM and MM patients. PET/CT and MRI are the favorite techniques for assessing and monitoring response to therapy and are becoming complementary investigation tools for detecting MRD, going beyond the conventionally defined CR level. It has recently been noted that MM is a heterogeneous disease, characterized by the co-existence of multiple clones in the same patients [28–30]. Different clones might have distinct biological properties and it is possible that different clones are present in different areas of the body. It has been postulated during the meeting, in an interesting talk by Gareth Morgan, that intra-clonal heterogeneity might ultimately translate into a different sensitivity to treatment. Pairing functional imaging studies with targeted biopsies and biological studies of specific hot spot lesions might be the way forward to understand the underlying biology of MM, and tailor therapy accordingly. The use of novel imaging techniques has to be consolidated as a prognostic tool, and has to be implemented in prospective clinical trials, with the attempt to standardize the interpretation of the results. It is the author's opinion that both PET/CT and MRI should be implemented in the workup of MM patients, both at diagnosis and when assessing response. The combination of PET/CT and MRI is highly sensitive and integrating these techniques into the algorithm of MM follow-up may improve disease management. This will help address several issues and may eventually improve myeloma treatment going toward a personalized medicine approach.

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