Positron Emission Tomography with Integrated Computed Tomography in Multiple Myeloma: A Silent Revolution

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From time to time, the history of multiple myeloma (MM) has been marked by an event that has changed the way we face the management of this disease. The impact of new imaging techniques in the diagnosis, prognosis and treatment of MM could be considered “a silent revolution”. For a long time, the valuation of bone disease in MM has been performed using conventional radiology. CRAB features (hypercalcemia, renal failure, anemia, and bone lesions) attributable to the clonal plasma cell proliferative disorder have been used to define active or symptomatic MM disease. MM-related bone disease, mainly in the form of osteolytic lesions, is detected in almost 80% of newly diagnosed MM patients [1]. However, the definition of positive bone disease depends on the technique used. In recent years, major advances have been made in imaging technology with the appearance of new techniques that have shown to have higher sensibility than radiographic bone survey in the detection of bone lesions [2-5]. Positron emission tomography (PET) with 18 fluorine-fluorodeoxyglucose (FDG) integrated with computed tomography (PET/CT) is a functional imaging technique that can help to assess bone marrow infiltration as well as unsuspected disease sites involving the bones and/or extra-medullary sites. The widespread use of PET/CT as well as magnetic resonance imaging has improved the understanding of the impact of bone disease in MM [6].

The International Myeloma Working Group has recently updated the criteria for the diagnosis of MM [7]. From now on, the term MM refers to MM requiring therapy. One of more sites of osteolytic bone destruction (≥ 5 mm in size) on skeletal radiography, CT or PET/CT, does fulfill the criteria for bone disease in MM and should be regarded as meeting the CRAB requirement. However, in relation to PET/CT, evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination. Although some uncertainty remains in some aspects of MM diagnosis, the boundaries between asymptomatic precursor diseases and CRAB-defined MM are now better defined. Nevertheless, the pathogenesis of MM-induced bone disease is only partially known. Mathematical models serve to better understand this process and could be applied to evaluate current therapies and even suggest new potential therapeutic targets [8].

A growing body of evidence supports the use of PET/CT in the assessment of diagnosis, prognosis and follow-up of MM patients, including concern about stem cell transplantation (SCT). The role of PET/CT in MM and related disorders has been recently reviewed [9] but little is known about the value of this technique in the assessment of monoclonal gammopathies other than active MM [10]. On the other hand, the correct diagnosis and risk of progression of precursor diseases can also be evaluated by PET/CT [11-13]. A study by the Spanish Group of Myeloma aiming to find the role of PET/CT on the risk of progression to MM is on-going. In a single institution study, we have analyzed the baseline findings of PET/CT in 158 patients with monoclonal gammopathies [10]. We were able to identify MM-related bone disease in 80% of symptomatic MM, but 100% of smoldering MM were negative. Interestingly, one of forty-six cases of monoclonal gamopathy of uncertain significance was positive. At the moment, the importance of baseline PET/CT positive findings in patients with true precursor diseases remains to be determined.

Considering the importance of bone disease in relation to the diagnosis of MM, PET/CT can highlight the baseline pattern of bone disease (diffuse or focal), the number and intensity of bone lesions, as well as the presence of extra medullary disease (EMD). The number of focal lesions and EMD give strong prognostic information [14-15]. The prognostic impact of the standardized uptake value (SUV) has been also pointed out in some studies. Serial PET/CT can add useful prognostic information [16-17]. The role of PET/CT in the assessment of response to therapy, including SCT, has been emphasized [18-21].

In our recent study analyzing 88 MM patients [10], we demonstrated a significant impact of PET/CT in overall survival curves when patients who achieved partial or complete response to induction therapy were compared with those who showed disease progression. Although patients with baseline PET/CT positive findings (EMD, more than three focal lesions or diffuse involvement) usually show worse survival curves than negative cases, the difference did not reach statistical significance, likely due to a short follow-up. PET/CT findings have even questioned the current definition of complete response in MM, [18,22], but, although an important step forward has been recently given [7], standardization of disease definitions according to PET/CT is still needed. Virtually all MM patients will suffer either biological or clinical relapse. Clinical relapse occurs frequently at bones, showing a wide range of possibilities, from a pathological fracture to an asymptomatic or mildly symptomatic bone relapse or progression. Although early diagnosis of bone relapse is still a challenge, the timely use of PET/CT can help to achieve this goal, along with a high degree of clinical suspicion and a proper valuation of biomarkers of biological relapse. Any clinician involved in the care of MM patients has to face the difficulty of some scenarios dealing with patients that may move in a short period of time from a stringent complete response to a relapse or progression. PET/CT can unravel a relapse/progression that might have passed unnoticed. Obviously, this fact has a great clinical impact, allowing early treatment and helping to plan a more definitive approach, such as...
reduced-intensity conditioning allogeneic SCT. The importance of PET/CT lies on the ability to help us to make the right decisions at the right time.

Minimal residual disease (MRD) is currently a hot topic in the global care of MM patients and it is commonly assessed in clinical trials by multiparameter flow cytometry or molecular techniques [23,24]. MRD is increasingly used in daily clinical practice owing to its great clinical impact. However, this technique has also limitations and some patients with negative MRD can relapse. At the moment, a debate is open about the role of imaging techniques to help in the assessment of MRD. Therefore, PET/CT could be considered potentially as a complementary technique for the assessment of the MRD status.

PET/CT cannot be considered as a perfect imaging technique for MM, but its increasing use is allowing us to better understand the behavior of MM-related bone disease and to take appropriate action at the right time, thus contributing to improve the care of our patients. The more we know about PET/CT, the more we realize that we have a new ally in the fight against MM. Almost without realizing it, PET/CT is starring a silent revolution in the history of MM. As in other revolutions, time will tell.

References