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Introduction to the review series on advances in multiple myeloma

Multiple Myeloma (MM) is a B-cell malignancy arising from a post-germinative cell or a plasmablast, leading to the accumulation of malignant plasma cells mainly in the bone marrow. They are responsible for osteoclast activation and osteoblast downregulation, with resultant bone destruction and painful fractures. Despite tremendous progress in the treatment and outcome of the patients (more than ten year median overall survival for young transplant-eligible patients), thanks to the availability of many novel drugs in the past ten years, MM remains an almost incurable disease, with multiple relapses. Considerable work has been performed to try to dissect the molecular landscape of the disease, with the goal to identify sub-entities that could benefit from specific treatments. We have to acknowledge that we have failed to deliver in this aim to date, and molecular studies confirm the huge heterogeneity of MM, with few recurrent genetic abnormalities. Despite this setback, we continue to observe progress in the management of the patients, with a significant improvement of survival.

In this Blood issue, three major topics are reviewed:

- What is the optimal imaging assessment at diagnosis and during follow-up?
- In the era of so many novel drugs, is frontline high-dose melphalan with stem cell support still the standard of care?
- Are we ready for patient-adapted therapy, or should we continue to propose the same treatments to all the patients?

In the first review, Zamagni, Tacchetti and Cavo comprehensively describe what are the optimal tools to detect and monitor bone lesions. Bone disease establishes the diagnosis and dictates the immediate need of therapy. For this reason, imaging plays a significant role in the management of MM patients. Although conventional radiography has traditionally been the standard imaging modality, its low sensitivity in detecting osteolytic lesions and inability to evaluate response to therapy has called for the use of more sophisticated techniques, such as whole body low dose computed tomography (WBLDCT), whole body magnetic resonance imaging (WBMRI), and 18F fluorodeoxyglucose positron emission tomography (FDG-PET/CT).

In the second review, Kumar, Buadi and Rajkumar discuss the role of frontline high-dose melphalan (HDM) in the management of transplant-eligible patients. In the era of many available novel drugs, with novel mechanisms of action, the role of HDM in the frontline setting is debatable, with divergent opinions on both side of the Atlantic ocean. In Europe, HDM is the standard of care for all MM cooperative groups, whereas in USA, it is becoming either a salvage treatment option, or not considered in the treatment pathway for MM patients. The main point of discussion is whether we should just look to overall survival (OS) as a treatment goal, or if the first progression free survival (PFS) is important. Currently, it is demonstrated that frontline HDM produces a significant longer first PFS, but with no OS advantage. However, will this still be the case with the frontline use of monoclonal antibodies is a question that will need to be address in the future.

Finally, in the third review, Pawlyn and Davies address the question of personalized treatment based on molecular characteristics of the disease. To date, the choice of therapy for an individual MM patient has been based on clinical factors such as age and co-morbidities. The widespread evolution, validation and clinical utilization of molecular technologies, such as fluorescent in-situ hybridization and next generation sequencing has enabled the identification of a number of prognostic and predictive biomarkers for PFS, OS, and treatment response. They argue that in order to continue to improve myeloma patient outcomes, incorporating such biomarkers into the routine diagnostic

workup of patients will allow for the use of personalized, biologically rationalized treatments. In this setting, it is now clear that especially high-risk patients should be managed with different therapies in order to improve their poor outcome.

I am pleased to introduce this series on MM, and I trust that it will be of value to those interested in MM management.

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