Multiple myeloma: so much progress, but so many unsolved questions

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High-dose therapy (HDT) with autologous stem-cell transplantation (ASCT) for multiple myeloma (MM) was developed in the 1980s and has been considered the standard front-line treatment for younger patients with normal renal function since the mid-1990s.[1] The recent introduction of the novel agents, thalidomide, bortezomib, and lenalidomide is now changing the transplantation scenario in several ways. These agents are being incorporated into the pre-transplantation setting as part of induction regimens with the objective of increasing the response rate prior to ASCT, as well as following the transplantation procedure as consolidation or maintenance treatments.[1,2] Consolidation is aimed at increasing the quantity and depth of responses achieved with high-dose melphalan, while the goal of maintenance therapy is to prolong the duration of the first response and to delay relapse. The overarching goal of applying treatments in the post-ASCT setting is undoubtedly the extension of progression-free survival (PFS) and, importantly, overall survival (OS). Some authors are even considering that MM has become a potentially curable disease.[3] These major improvements have been widely adopted in the medical community. Nevertheless, important issues and challenges remain, and we would like to address some of these here.

Notably, the high efficacy of the novel agents has led some groups to investigate these agents upfront without the application of ASCT, and interesting results have been reported. Lenalidomide plus low-dose dexamethasone (Len/dex) as part of front-line therapy without ASCT yielded similar survival rates at two years as compared with Len/dex followed by ASCT in a non-randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG).[4] Furthermore, in a non-randomized phase II trial of lenalidomide-bortezomib-dexamethasone in the upfront setting, in which the choice of proceeding to HDT or not was left to the physician or patient, no difference in outcome was seen for the two approaches.[5] Based on these results, many colleagues have begun to consider the use of such novel agent-based therapies without the upfront application of ASCT as an alternative to early transplantation and the role of ASCT itself has become a matter of debate: should it be used upfront or as a salvage treatment at the time of progression for patients initially treated with novel agents? In 2013, we only have the preliminary data of a single prospective study addressing this issue to try to solve this burning question. The Italian Myeloma Network, GIMEMA, has reported in abstract form the results of the first randomized study comparing conventional chemotherapy plus novel agents to tandem high-dose melphalan and ASCT in 402 newly diagnosed MM patients.[6] At the time of the report, with a short follow up, there was no significant difference in OS between the two groups, but PFS was significantly improved in the early HDT arm. Two other ongoing trials, one conducted by the European Myeloma Network (NCT01208766) and one by the Institute Francophone du Myelome (IFM) together with a US consortium (NCT01208662), are investigating the same issue and will enrol 1500 and 1000 patients, respectively.

The debate surrounding HDT comes at the very time when important advances in the understanding of the biology of the disease, including the complexity and dynamics of the MM genomic landscape,[7] are leading some physicians to believe that a risk-adapted strategy should be routinely used, with serial biological examinations guiding treatment decisions in daily practice.

Up to now, the concept of a risk-adapted strategy relies on prognostic factors identified at the time of diagnosis, such as stage according to the International Staging System (ISS), chromosomal and genetic abnormalities detected through conventional cytogenetics, fluorescence *in situ* hybridization (FISH) or gene expression profiling, the combination of ISS and FISH, or other biological parameters. Currently, there are two groups who are routinely applying a risk-adapted strategy. In Little Rock, Arkansas, systematic gene expression profiling, performed at the time of diagnosis in all patients eligible for high-dose therapy, is used to segregate patients with high-risk *versus* standard-risk disease.[8] A specific total therapy 4 program is proposed to patients with standard-risk disease, while those with high-risk disease receive a more intensive approach (total therapy 5), which is aimed at sustaining the duration of complete remission (CR). The group at the Mayo Clinic is routinely using the mSMART algorithm to define patients with standard, intermediate, or high-risk disease, and recommended treatment options vary according to risk-group category.[9] These two different US options are interesting, and the development of a risk-adapted strategy is undoubtedly one of the most important goals in the 2010s. Nevertheless, we have to keep in mind that the choice of therapy proposed in the Little-Rock program is not based on the results of phase III trials. Similarly, the mSMART algorithm is not evidence-based.

Moreover, these strategies do not take into account two major points: 1) the disease response to therapy and its evaluation; 2) the clonal evolution of the disease and the intrinsic genomic instability of the myeloma clone. Let us take each of these one at a time.

1) Over the last decade, it has been unambiguously shown that the response achieved both prior to and after ASCT is a major prognostic factor.[1-3] Disease response, which cannot be anticipated or predicted at the time of diagnosis, is evaluated according to the criteria developed by the IMWG.[10] Improvements in therapeutic strategies have resulted in stringent or molecular CRs and minimal residual disease (MRD) negativity being achieved more frequently.[11,12] A neg-

ative MRD, evaluated either by flow cytometry or polymerase chain reaction (PCR), strongly correlates with improved outcomes, both before and after ASCT.[13] Nevertheless, with the exception of the ongoing MRC XI trial, in which induction therapy is modified in case of a suboptimal response,[14] there is currently no other ongoing trial which is designed to adapt the treatment strategy according to the results of response evaluation at any time of the therapeutic schedule, especially on completion of therapy when the probability of achieving MRD negativity is the highest. In addition, the issue of routine evaluation of prognostic parameters at diagnosis and of MRD status over time is of importance. Several study groups, including the IFM, the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON), the Medical Research Council (MRC) and the Little Rock group, have demonstrated that gene expression profiling is currently one of the most important prognostic parameters at diagnosis.[8,15-17] However, this test is not routinely performed outside clinical trials. Similarly, MRD assessment is difficult and cumbersome, while PCR evaluation is not suited to the follow up of large numbers of patients, is not cost-effective, and requires an experienced laboratory. Flow cytometry evaluation is hampered by the quality of bone marrow samples and is not routinely performed on a multicenter basis. Although these techniques, which are mostly performed in specialist centers, are reliable, they have a major drawback in that they do not permit the assessment of MRD status outside the bone marrow. A recent study has evaluated the impact of PET-CT negativity after ASCT and has clearly shown that among patients reaching CR, the subgroup of patients achieving PET-negativity had a more favorable outcome.[18] This emphasizes the necessity of MRD evaluation not only in bone marrow, but also outside the bone marrow, using the most sensitive, appropriate, cost-effective and easy-to-use tools, which have been validated in specifically designed clinical trials.

2) In the future, an important new concept will guide our therapeutic strategies both at the time of diagnosis and at relapse. Several groups in the US and Europe have clearly demonstrated that there is substantial genetic heterogeneity not only between myeloma patients but also within individual cases.[19-22] At diagnosis, three different groups of patients may be described. Firstly, there are patients who present with stable genomes, particularly those with low-risk hyperdiploid disease. A second group includes patients whose disease is composed of a mosaic of minor subclones that evolve through complex and branched trajectories. In the third group of patients, a pattern consistent with a linear evolution of one major clone is the dominant characteristic.[20] The intrinsic genetic instability of aggressive myeloma subclones in addition to the selective pressures introduced by therapies during the course of the disease are the two driving forces of the dynamics of clonal evolution and diversification observed in MM. Myeloma therapies introduce profound changes in the bone marrow microenvironment that create new selective pressures, and recent results suggest that the patterns of clonal evolution are different among patients treated with conventional chemotherapy and those treated with new drugs, such as proteasome inhibitors that target specific pathways.[21] Gene expression profiling, as well as data from high-density single nucleotide polymorphism arrays, have revealed particular features of genomic instability in patients with high-risk disease, such as specific signatures of chromosomal instability and chromothripsis, as well as significant increases in copy number alterations with disease progression.[23] Given these recent results, which confirm the concept of subclonal instability and competition between subpopulations for survival during the disease course, it could be proposed that therapeutic options should be chosen depending on the results of serial clonal evaluations, comparing the disease genome at the time of diagnosis and at relapse. The timing and the choice of a specific therapy could also be important in order to reduce the clonal diversity at diagnosis or at the time of relapse in case of the emergence of a new clone, or, on the contrary, in case of a stable clone that remains sensitive to a former regimen.

In the attempt to define the best therapeutic strategy, future trials should not only be designed to investigate prognostic parameters at diagnosis, but also to evaluate disease response in and outside of the bone marrow, and to assess the dynamics of clonal expansion of the disease. An enormous challenge awaits us!

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