

## Introduction to a series of reviews on multiple myeloma

Multiple myeloma (MM) is probably one of the hematologic malignancies in which major progress (from biology to therapeutics) has occurred over the last 15 years. Biology has moved from morphology and low-sensitivity protein analysis into genomics, while therapeutics has moved from only 1 active agent (melphalan) to almost uncountable potentially active drug combinations. We have learned that in the pathogenesis of MM, there are 2 key players: (1) the genetic lesions intrinsic to the malignant clone, and (2) the interaction between myelomatous plasma cells (PCs) and their microenvironment. Almost all MM patients display cytogenetic abnormalities, and cytogenetics has become one of the most important prognostic factors [particularly 17p (p53) deletion and t(4;14)]. Most recently, it has been shown that approximately two-thirds of MM patients have  $\geq 1$  of the following 11 recurrently mutated genes (*ACTG1*, *RBI*, *CYLD*, *PRDM1*, *TRAF3*, *BRAF*, *FAM46C*, *DIS3*, *TP53*, *NRAS*, and *KRAS*), with frequent intraclonal heterogeneity that plays a critical role in disease outcome and drug resistance. Accordingly, in the near future, MM will probably no longer be considered a single entity. The second player in MM pathogenesis consists of the interaction between the malignant clone and stromal cells through direct contact, soluble molecules, or exosomes, thus promoting tumor progression and drug resistance. The bone marrow (BM) microenvironment also includes T, natural killer, and dendritic cells, which play a critical role in immune surveillance; the importance of immune monitoring will likely increase with the revival of immunotherapy and the possibility of therapeutic intervention through the blockade of immune checkpoints. In this series, both players (tumor cell genetics and tumor microenvironment) are reviewed in detail by Bianchi and Munshi.

Another fascinating research area is the understanding of the transformation from a premalignant condition (monoclonal gammopathy of undetermined significance) to a malignant disease (MM). It is unfortunate that the key question in this process, “Why does a quiescent clone become aggressive in some patients while it remains stable in others?” is yet to be answered. Furthermore, are differences in behavior dictated by the genomic features of the tumor clone, or are they dictated by the dialogue between PCs and their microenvironment? This distinction is most relevant for patients with smoldering MM because under its diagnosis, there is marked heterogeneity in terms of risk of progression, including a high-risk subgroup with a median time to progression to symptomatic MM of only 2 years. These patients can be identified by the presence of  $\geq 3$  g/dL of monoclonal protein component plus  $\geq 10\%$  PCs in BM, or immune paresis plus  $>95\%$  phenotypically abnormal PCs within the BM-PC compartment determined by multiparameter flow cytometry. Interestingly, the Spanish Myeloma Group has shown that high-risk smoldering MM patients identified by the criteria described above may benefit from early therapeutic intervention. This study has not only opened the possibility of early treatment but also highlighted the need to revisit the diagnostic criteria for MM. Accordingly, the International Myeloma Working

Group has proposed 3 new myeloma-defining events for identification of “early myeloma”:  $\geq 60\%$  clonal BM PCs, involved/uninvolved serum free light-chain ratio  $\geq 100$ , and  $>1$  focal lesion identified by magnetic resonance imaging. The new criteria for MM include these myeloma-defining events because they were associated with an 80% risk of disease progression within 2 years, as demonstrated in 2 or more independent studies, and, therefore, consistently identify patients who are candidates for immediate treatment. This significant change in the diagnosis of MM is critically reviewed in this series by a group of experts from 3 different institutions.

Progress in MM treatment and patients’ survival has reinforced the need for better tools to prognosticate and monitor treatment efficacy. The current criteria for the definition of complete response are based on low-sensitivity techniques (immunofixation and morphology); therefore, more sensitive methods for assessing the depth of response (minimal residual disease), both inside the BM (multiparameter flow cytometry immunophenotyping and molecular methods such as allele-specific oligonucleotide polymerase chain reaction and next-generation sequencing) and outside the BM (positron emission tomography with computed tomography [PET/CT]), are required for optimal monitoring to avoid undertreatment and overtreatment. There is clear evidence that the better the quality of response, the longer the survival, and most likely, the concepts of immunophenotypic and molecular remission as well as remission determined by PET/CT will soon become widely applied as new response criteria. Accordingly, the present review by Paiva, van Dongen, and Orfao represents a unique opportunity to understand the pros and cons of each technique.

In this review series, 3 experts from the French Myeloma Group analyze the treatment options for newly diagnosed MM patients. As mentioned above, the outcome of MM patients has significantly improved over the last decade. This was first due to the introduction of high-dose therapy followed by autologous stem cell transplant, and in particular to the use of novel agents such as proteasome inhibitors (bortezomib [Btz]) and immunomodulatory agents (thalidomide [Thal] and lenalidomide [Len]).

In transplant-candidate MM patients, the new standard includes 4 to 6 cycles of bortezomib-based induction with 3 drugs (Btz/Thal/dexamethasone [Dex] or Btz/Len/Dex or Btz/cyclophosphamide/Dex) that induce 80% to 90% responses, including up to 30% complete response rates, followed by autologous stem cell transplant. Recent data have shown that consolidation and maintenance (particularly with Len) may significantly prolong progression-free survival, but optimal schedule and treatment duration are still under investigation. Allogeneic stem cell transplantation remains experimental due to transplant mortality (10%-15%) and the persistence of relapses. In elderly patients, the new standards are melphalan/prednisone/Btz or Len/Dex, but melphalan/prednisone/Thal is also frequently used. The value of maintenance in elderly patients is also under investigation.

Although survival of myeloma patients has at least doubled and a small fraction may even be operationally cured, most patients eventually relapse, and treatment at this stage may be particularly complex. The final review article of this series provides a complementary view from leaders in the United States and Europe. At the time of relapse, the use of alternative drugs to those given up front is current practice. Many new options are currently available for the treatment armamentarium of MM, including recently approved drugs (such as the second- and third-generation proteasome inhibitors carfilzomib and ixazomib and the immunomodulatory agent pomalidomide), as well as other emerging agents with novel mechanisms of action (eg, monoclonal antibodies, histone deacetylase inhibitors, and kinesin spindle protein inhibitors) that are under active investigation.

The final goal should be to find a balance among efficacy, toxicity, and cost and, at the end of the road, the dream of achieving the cure for this disease.

The articles in this review series, “Multiple myeloma: from the bench to bedside,” include the following:

“Pathogenesis beyond the cancer clone(s) in multiple myeloma” by Giada Bianchi and Nikhil C. Munshi

“New criteria for response assessment: role of minimal residual disease in multiple myeloma” by Bruno Paiva, Jacques J. M. van Dongen, and Alberto Orfao

“Smoldering multiple myeloma” by Vincent Rajkumar, Ola Landgren, and María-Victoria Mateos

“Frontline therapy of multiple myeloma” by Philippe Moreau, Michel Attal, and Thierry Facon

“Treatment options for relapsed and refractory multiple myeloma” by Ajay K. Nooka, Efsthios Kastiris, Meletios A. Dimopoulos, and Sagar Lonial

It is our hope that this review series will contribute to the stimulation of translational research and lead to a better understanding of new criteria for the diagnosis, monitoring, and treatment of MM.

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