Multiple Myeloma (MM) is probably one of the hematological 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 one active agent - melphalan - into almost uncountable potentially active drug-combinations. We have learned that in the pathogenesis of MM there are two 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 one or more of the following 11 recurrently mutated genes (e.g.: ACTG1, RB1, CYLD, PRDM1, TRAF3, BRAF, FAM46C, DIS3, TP53, NRAS, 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 as a single entity. The second player in the MM pathogenesis consists on 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, NK and dendritic cells which play a critical role in immune surveillance, and 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) will be reviewed in detail by Bianchi and Munshi.

Another fascinating research area is the understanding of the transformation from a premalignant condition (MGUS) to a malignant disease (MM). Unfortunately, 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 is most relevant for patients with smoldering MM (SMM) since under its diagnosis there is marked heterogeneity in terms of risk of progression, including a high-risk subgroup with only 2-years median time to progression to symptomatic MM. These patients can be identified by the presence of both ≥ 3g/dL of M-component plus ≥ 10% PCs in BM, or immune paresis plus > 95% phenotypically abnormal PCs within the BM PC compartment by multiparameter flow cytometry. Interestingly, the Spanish myeloma
group has shown that high-risk SMM 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 has also highlighted the need of revisiting the diagnostic criteria for MM. Accordingly, the International Myeloma Working Group (IMWG) has proposed three new myeloma-defining events for identification of “early myeloma”: ≥60% clonal BM PCs; involved:uninvolved serum FLC ratio ≥100; or >1 focal lesion by MRI. The new criteria for MM includes these myeloma-defining events because they were associated with an 80% risk of disease progression within 2-years demonstrated in two or more independent studies, and therefore consistently identify patients which 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 three 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 (CR) are based on low sensitive 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 ASO-PCR or next generation sequencing) and outside (PET/CT), are required for optimal treatment monitoring in order to avoid both under- and over-treatment. There is clear evidence that the better the quality of the response, the longer the survival and most likely, the concept of immunophenotypic or molecular remission as well as PET/CT remission 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 mini-review series three experts from the French myeloma group (IFM) analyze the treatment options for newly-diagnosed MM patients. As mentioned above, the outcome of MM has significantly improved over the last decade. This was first due to the introduction of high dose therapy followed by autologous stem cell transplant (ASCT), and particularly to the use of novel agents such as proteasome inhibitors (bortezomib-BTZ-) and immunomodulatory (IMID) agents (thalidomide -Thal- and lenalidomide –Len-).

In transplant-candidate MM patients, the new standard includes 4-6 cycles of bortezomib-based induction with three drugs (Btz-Thal-Dex or Btz-Len-Dex or Btz-Cyclo-Dex) that induce 80-90% responses, including up to 30% CR rates, followed by ASCT. Recent data have shown that consolidation and maintenance (particularly with lenalidomide) may significantly prolong progression-free survival, but optimal schedule and treatment duration are still under investigation. Allogeneic stem cell transplantation remains experimental due to the transplant mortality (10%-15%) and the persistence of relapses. In elderly patients, the new standards are MPV (Melphalan-Prednisone-Btz) or Len-Dex, but MP-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 United States and European leaders. At the time of relapse, the use of alternative drugs to those given upfront is current practice. Many new options are currently available for the treatment armamentarium of MM, including recently approved drugs (such as second and third generation proteasome inhibitors – carfilzomib, ixazomib - and IMIDS – pomalidomide -), as well as other emerging agents with novel mechanisms of action (monoclonal antibodies, HDAC inhibitors, KSP inhibitors,...) which are under active investigation.

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

The reviews in this series: “Multiple Myeloma: what should I know from the bench to bedside?” include the following:

- Pathogenesis beyond the cancer clone(s) in multiple myeloma by Giada Bianchi, Nikhil Munshi
- Smoldering Multiple Myeloma by Vincent Rajkumar, Ola Landgren, Maria-Victoria Mateos.
- Frontline therapy of multiple myeloma by Philippe Moreau, Michel Attal, Thierry Facon.
- Treatment options for relapsed and refractory multiple myeloma by Ajay K Nooka, Efstathios Kastritis, Meletios Dimopoulos, Sagar Lonial

We hope this review will contribute to stimulate translational research and lead to a better understanding of new criteria for diagnosis, monitoring and treatment of multiple myeloma.
Introduction to a series of reviews on multiple myeloma

Jesus F. San Miguel