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Editorial Comment

160 years of multiple myeloma: Progress and challenges

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Since the first description of the disease now known as Multiple Myeloma (MM) by Dr. Solly in 1844 (first case report of MM [Sarah Newbury]), there has been a continually increasing interest in the clinical and pathophysiological information on MM and related diseases, accompanying a dramatic change in the understanding of the biology of the disease itself, diagnostic procedures and therapeutic approaches. Diagnostic parameters include conventional disease determinants, characterisation of bone marrow (BM) plasma cells, cytogenetics, but may also involve bone markers, the BM microenvironment (BMM) and signalling pathways. As a result, the assessment of treatment outcome has also become more challenging, requiring considerations of the impact of stage, prognostic factors and age, the importance of preserving and improving the patient's quality of life and the wisest selection of standard care or novel treatment options. Whereas after the introduction of melphalan and prednisone, only minor advances had been made for the following 20 years, myeloablative doses of melphalan and autologous stem cell transplantation (auto-SCT), given as one or two sequential courses, and the identification of new drugs have lately been major advances in the management of this disease. New classes of agents include immunomodulatory drugs (IMiDs), proteasome inhibitors, modifiers of histone acetylation, farnesylation, heat shock proteins, direct AKT-targeting agents and monoclonal antibodies (either given alone or in combination with established anti-MM-therapeutics), as well as passive and active immunotherapeutics.[1] This special issue focuses on the biology, the advances in understanding and the treating of MM. It documents the demanding aspects of understanding and treating this complex disease, both for basic researchers and clinicians, and likewise for MM experts and novices in this promising field of haematological research. This series of reviews covers biomedical research, ranging from routine laboratory techniques to genomics and proteomics, as well as epidemiology and outcomes research, prognostic and predictive factors and treatment options. Familial risks and temporal incidence trends are also analysed, and epidemiology data, outcomes research and health economic aspects in MM are addressed, illustrating the range and complexity of the topics covered in this issue.

Laboratory investigations in MM and monoclonal gammopathy of undetermined significance (MGUS) are essential for correct diagnosis of the disease.[2] The paper by San Miguel reviews the most relevant laboratory techniques currently used in MM and MGUS patients. Although BM morphology and electrophoretic analysis remain the gold standard, other technologies such as immunophenotyping, DNA cell content and cell cycle analyses are now part of the diagnostic work-up. This paper allows the reader to understand which biochemical parameters are relevant and used as prognostic factors, but also what pitfalls (e.g. with flow cytometry, FACS) need to be considered, as FACS analysis represents a reliable technique for differentiating benign and malignant plasma cells and investigating minimal residual disease. However, as compared with BM morphology (cytology) and histology, this technique usually underestimates the amount of BM plasma cells. Since the determination of the frequent and complex genomic abnormalities in MM allows clarification

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of the pathogenesis of the disease and its prognosis, cytogenetics have become an important tool, and are currently used in the determination of risk factors for stratification in clinical trials. Liebisch and Döhner describe oncogenic pathways in the early development of clonal plasma cell disorders, where half of the tumours are non-hyperdiploid and carry translocations of the IgH locus and various oncogenes (e.g. cyclin D1,D3, FGFR3), and the remaining hyperdiploid tumours exhibit recurrent trisomies (typically of chromosomes 5,7,9,11,15,19 and 21), but infrequently exhibit IgH translocations. Certain chromosomal aberrations, such as deletion of chromosome 13q (Δ13), deliver independent prognostic information already used in risk stratifications. However, others (such as 17p13del (p53 del), t(4;14) or t(11;14)) are not consistently used and the prognostic significance of most genetic aberrations has to be further defined. We are now also acquiring a much clearer understanding of the fundamental steps in the pathogenesis of MM: disruption of the balance between cellular regulation of apoptosis and the acquisition of mutations involving chromosomal aberrations and defined molecular events. In order to understand these molecular changes, genetic analysis beyond the use of chromosome banding, FISH, comparative genomic hybridisation (CGH) and diploidy analyses is being approached, as well as global gene expression and proteomic profiling. These technologies are covered by Tassone *et al.*, who presents a series of novel indices to be evaluated in current and future clinical trials and who consider the major challenge in defining their potential role in the management of individual patients.

The central topic of bone disease is covered by three groups: Durie, who describes novel diagnostic imaging technique advances (such as MRI, FDG-PET and whole body CT), which offer the opportunity to precisely stage patients by anatomic and functional techniques. His new, so called Durie/Salmon PLUS staging system integrates these imaging techniques and is described in comparison with more conventional staging systems.[2] Thereby, early disease, better discrimination of stage II versus III disease and early detection of the efficacy of novel agents seem to be accomplished. The second article by Heider *et al.* covers bone markers in MM and elucidates the pathophysiology of osteoclast activation and osteoclast inhibition. Biochemical markers of bone turnover and remodelling (such as ICTP, NTx, TRACP-5b, osteoprotegerin and receptor activator of nuclear factor kB [RANK] ligand [RANKL]) are discussed. In the third article by Yeh and Berenson, recent characterisation of osteoclast-activating-factors, RANKL-ostoprotegerin-RANK system, and inhibitors of Wnt signalling – all of which have provided a better understanding of MM bone disease on the molecular level – are described. Moreover, therapeutic options in MM bone disease, such as kyphoplasty, vertebroplasty, bisphosphonates and bone-seeking radiopharmaceuticals, are discussed.

The manuscripts by Mitsiades, Bommert and Jakob deal with the molecular mechanisms and biological behavior of myeloma cells and their microenvironment: Mitsiades describes recent progress in the studies of BM stromal cells and other constituents of the BM milieu, promoting the ability of MM cells to resist anti-MM therapies through cell adhesion- and cytokine-mediated mechanisms. Ongoing research into these mechanisms has provided several new molecular targets. Bommert demonstrates that although IL-6 has been considered to be the central growth factor, other cytokines, chemokines and cell to cell contacts provided by the BMM are also important players in supporting MM cells. Consequently, multiple targeting of a complex signalling network, rather than inhibition of a single pathway or growth factor, is required to efficiently induce myeloma cell death. Since tumour suppressor p53 is rarely mutated in MM, non-genotoxic activation of the p53-dependent death pathway is suggested as one promising therapeutic strategy. Albeit that considerable knowledge of the signalling and survival pathways has been accumulated, all authors conclude that only through the comprehensive understanding of these pathways will additional molecular targets be identified and novel and possibly more effective treatment strategies be developed. Apart from Δ13 and t(4;14) or t(14;16) translocations, the increased density in BM microvessels, endothelial cells (EC) and soluble angiogeneic factors have been identified as new prognostic markers. Although the relevance of angiogenesis is still controversially discussed, this seems less an epiphenomenon than relevant force in the progression of MM (reviewed by Jakob *et al.*). Correlation analysis on angiogenic growth factors (such as bFGF, HGF, VEGF) as EC seem to sustain growth and progression of myeloma, not only by giving vascular supply but also by providing essential proliferation and survival stimuli.

The subsequent articles deal with current treatment strategies in MM. The central goal in improving MM treatment is the achievement of long-term survival as well as the improvement in quality of life. Whether this is best achieved by treating the disease as intensively as possible, thereby inducing long-term remission (and, rarely, even cure), or transferring the disease into an indolent course, is still a matter of debate. Long-term survival beyond three years can be achieved with high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) which has emerged as one effective approach to treat myeloma patients. The results on auto-PBSCT and alternative therapy modalities are described by Denz *et al*. Since for defined adverse risk factors, (Δ13, t(4;14)), an extremely high risk of relapse has been observed (despite tandem auto-PBSCT), other aggressive treatment options in innovative clinical trials should be performed whenever possible. Allogeneic-SCT as discussed by Zeiser and Finke has been shown to be potentially curative for MM patients (although long-term results are still awaited) and the introduction of reduced intensity conditioning regimens has decreased treatment related morbidity and mortality. An excellent overview on the results of thalidomide, lenalidomide and actimid trials is provided by Kumar and Rajkumar for relapsed/refractory disease as well as a first-line approach, suggesting potent combinations for both clinical settings. This article underlines major advances that have been made in the understanding of IMiDs, but also that we still need to better understand their mechanism of action, to determine predictors of response based on pharmacogenomics and proteomics, and to find more active drugs for MM. The ubiquitin–proteasome pathway and data on the proteasome inhibitor Bortezomib are elucidated by Kropff *et al*. Preclinical and clinical studies,[3,4] single agent and combination usage, effects and side-effects[5] and future directives are

discussed. Of note with novel substances is the consideration of cost (although no price can argue against the value of an effective drug) which is significantly increased compared with standard-anti-MM strategies. Immunotherapeutic strategies, apart from allo-SCTs, are reviewed by Chatterjee *et al.*, describing recent developments on monoclonal antibodies, (radio)-immunoconjugates, targeted immunotherapeutics and targeted radiotherapy. Active immunotherapy options are discussed by Houet and Veelken, using immunisation against the clonal immunoglobin (idiotype), and immunisation of stem cell donors with myeloma antigens.

In the concluding manuscripts of this special issue, familial risks and temporal incidence trends, epidemiology, outcomes research and health economic data are reviewed. Altieri *et al.* elegantly describes a contributing hereditary etiology due to shared genetic factors in MM. Pedigree studies of families with multiple affected siblings[6] and cancer registry data have supported this hypothesis. This article describes that the incidence of MM (through Swedish cancer registry data analysis) has been constant for several decades and that the apparent increase in the elderly seems – at least in part – to be attributable to improved diagnostics and our increased age of life expectancy.[7,8] Their results provide evidence for a strong familial clustering of MM, CLL and possibly other Non-Hodgkin's lymphomas and strongly suggest that family history may be a risk factor for MM that can be measured with reasonable accuracy. Family histories of disease have an important role to play in targeting cancer screening procedures and genetic counselling. Other epidemiological factors that may play a role in the pathogenic pathway of MGUS and MM and outcomes research are elucidated by Sirohi and Powles. One key question relating to disease outcome is whether progress in its management is being achieved. Their analysis of outcomes research support our progress and understanding of the disease.[9,10] Many patients will live with MM for extended periods of time. Finally, health economic issues in MM treatment are discussed by Moeremans and Annemans, which – similarly to data on quality of life assessments – are increasingly important to consider. This is undoubtedly the case for novel drugs that demand a higher investment, while our resources are being restricted. Nevertheless, with these albeit more expensive 'targeted' therapies, the future seems bright, as they allow prolonged progression (and hopefully survival) in MM.

In summary, modern treatment concepts provide a safe and highly effective therapy with which a substantial proportion of MM patients survive for more than three years, and with favourable prognostic parameters beyond five and ten years. Although residual disease may be detectable with molecular methods, we are aiming at a normal life for MM patients, without symptoms relating to the disease or its complications. An increasing understanding of disease biology is the prerequisite for novel and even more effective targeted therapies. Despite impressive advances in MM therapy, there are still important challenges to overcome in the future: in addition to targeted therapies, chemotherapeutic regimens with an increased antineoplastic efficacy are needed, and well-designed, randomised trials should not only guide our selection of the most beneficial therapy combinations, but should also help to decipher the molecular basis of MM and help to develop novel, rational targeted therapies. The reviews in the current issue, covered by many of the leading specialists and investigators in MM, allow us to understand the progress that has been made and to see further advances in the years ahead. We hope that this special issue will appeal and be of value to the MM community, both to specialists and novices, providing in depth understanding and novel information for the former and an appropriate and enlightening introduction for the latter.

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