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State of the art therapy in multiple myeloma and future perspectives

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ABSTRACT

Treatment for multiple myeloma (MM) has changed beyond recognition in the past decades. While until the early 1980s, MM caused a slow progressive decline in quality of life until death after about two years, today's patients can expect a 50% chance of achieving a complete remission, a median survival time of five years and a 20% chance of surviving longer than ten years. State of the art therapy comprises: evidence-based supportive care; highly effective and well tolerated chemotherapeutic regimens; and for patients qualifying for intensive high-dose conditioning, autologous haematopoietic stem cell transplantation (HSCT) is an option. Maintenance therapy has become increasingly important since a majority of patients is able to achieve a good remission after front-line therapy which is aimed to be preserved as long as possible. In addition, improved understanding of the disease biology has led to the development of novel biological treatment agents, such as thalidomide, bortezomib and others, targeted at cellular mechanisms and interactions, e.g. with the bone marrow microenvironment. These strategies are incrementally integrated into modern MM care. This review considers recent clinical advancements in anti-myeloma strategies and provides an overview of the state of the art management of MM patients.

1. Introduction

MM is a malignant disorder characterized by an uncontrolled clonal proliferation of malignant plasma cells which normally produce a monoclonal paraprotein. In the majority of patients, the paraprotein is readily detectable in the serum and urine. Especially at later stages, MM may induce lytic bone lesions, renal function impairment and immunodeficiency caused by myelosuppression. With effective treatment, the median overall survival (OS) is approximately four years.

The central goal in improving MM treatment is the achievement of prolonged complete remission (CR) rates, long-term OS, and improvement in quality of life, with few MM-associated symptoms and with as few treatment cycles as possible. Over the last years, high-dose (HD) chemotherapy (CTx) followed by autologous peripheral blood stem cell transplantation (auto-PBSCT) has emerged as one effective approach to reach this objective.[1] Auto-PBSCT given with need for treatment after standard-CTx or early during the treatment course (at initial diagnosis) has been demonstrated to be very profitable in MM.[2] In patients with advanced disease and adverse prognostic factors, such as cytogenetic abnormalities, the therapeutic approach of an auto-, followed by an allogeneic (allo)-SCT is currently pursued in clinical trials.[3] Allo-SCT has been shown to be potentially curative for MM patients, although long-term results have to be awaited. The introduction of reduced intensity conditioning (RIC) regimens has decreased treatment-related morbidity and mortality (TRM) considerably.[2–4] The current use of earlier auto-PBSCTs, tandem transplants within clinical trials, and implementation of novel

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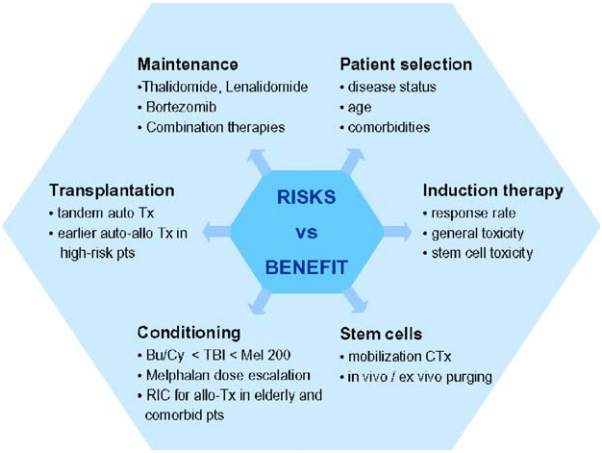

Fig. 1 – Hexagon of treatment considerations, improving outcome and patient safety. Abbreviations: TBI: total body irradiation, BuCy: Busulfan/Cyclophosphamide regimen, RIC: reduced intensity conditioning.

anti-MM drugs used upfront, as part of the HD-conditioning regimen or maintenance treatment, gives hope to improve the management of MM further. With increasing success, these more intensive treatment strategies are also used in older patients, which can be attributed to advances in reduced intensity conditioning and supportive care measurements.

Treatment considerations to improve the outcome and safety in MM patients are depicted in Fig. 1, and include optimal patient selection for highly effective and well-tolerated induction and conditioning regimens, single vs. multiple transplants, cell therapy issues, novel anti-MM drugs and maintenance therapy approaches.

2. To treat or not to treat

Criteria that aid the classification of MGUS, asymptomatic (smoldering) versus (vs.) symptomatic and non-secretory MM, as well as of solitary-, extramedullary- and multiple solitary-plasmocytomas have been defined by the 'International Myeloma Working Group':[5] MGUS shows a monoclonal protein <30 g/l, bone marrow (BM) clonal plasma cells <10% and no evidence of MM, other B-cell proliferative disorders or amyloidosis. In asymptomatic MM, the M-protein is $\geqslant$30 g/l and/or clonal BM plasma cells $\geqslant$10%, but no related organ or tissue impairment (ROTI). Symptomatic MM shows the pathologic findings as described for asymptomatic MM and ROTI, which is typically manifested by hypercalcaemia, renal

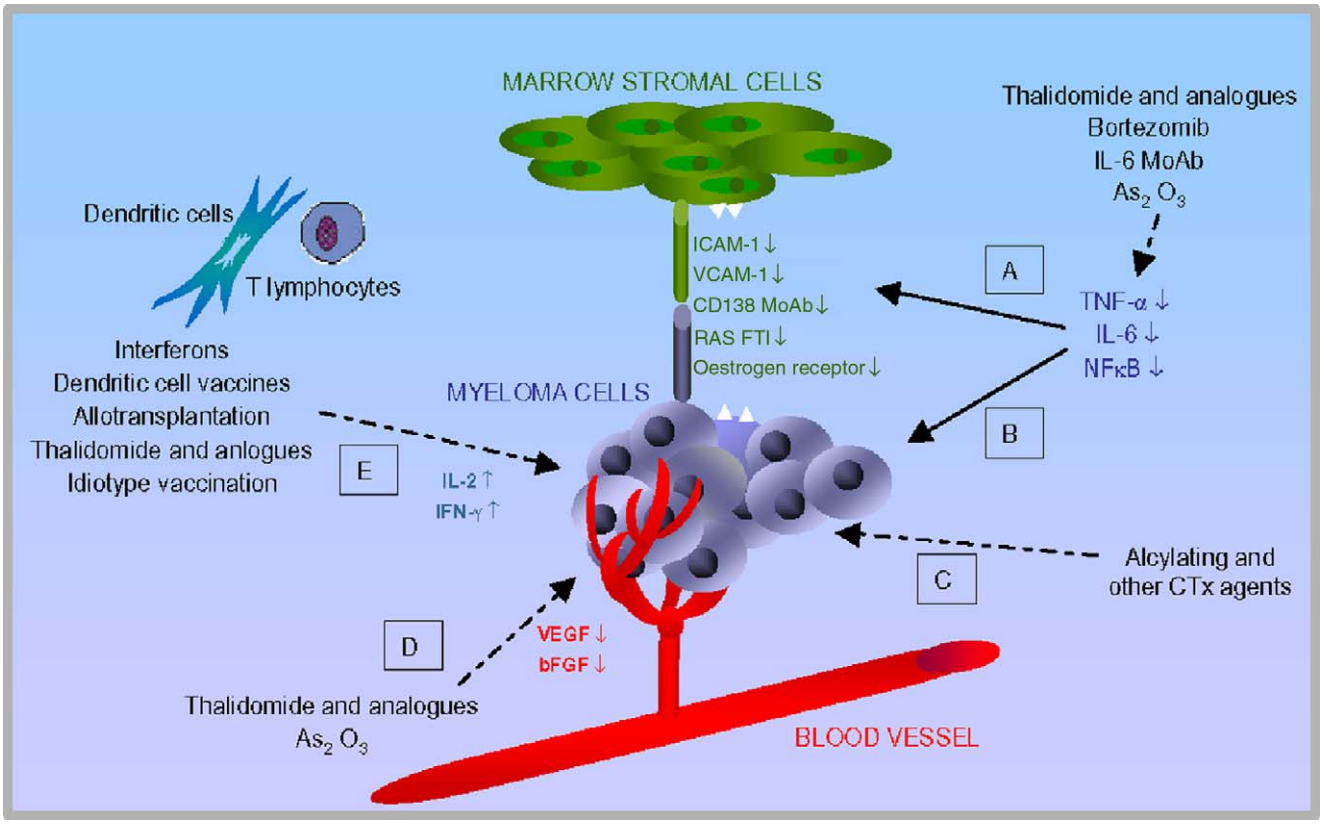

Fig. 2 – Targets of myeloma treatment. Changes of microenvironment by reduction of TNF-I, IL-6 and indirectly NFκB lead to A) impaired interaction of myeloma and stromal cells and B) induction of apoptosis in myeloma cells. C) Direct cytotoxic effect. D) Antiangiogenic effect. E) Stimulation of immunological effect versus myeloma cells.
***Abbreviations*: MoAb – monoclonal antibody. As_2O_3 – arsenic trioxide. TNF-I – tumor necrosis factor alpha. IL-6 – Interleukin-6. NFκB – nuclear factor kappa B. ICAM-1 – intercellular adhesion molecule 1. VCAM-1 – vascular cell adhesion molecule. FTI – farnesyl-transferase inhibitor. VEGF – vascular endothelial growth factor. bFGF – basic fibroblast growth factor. IL-2 – Interleukin-2. IFN-γ – Interferon gamma. Solid arrows indicate stimulation or secretion and dashed arrows inhibition.**