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REVIEW

Treatment for patients with newly diagnosed multiple myeloma in 2015

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ABSTRACT

Multiple myeloma is the second most frequent haematological disease. The introduction of high-dose melphalan followed by autologous haematopoietic cell transplant (HDT/ASCT) for young patients and the availability of novel agents for young and elderly patients with multiple myeloma have dramatically changed the perspective of treatment. However, further research is necessary if we want to definitively cure the disease. Treatment goals for transplant-eligible and non-transplant-eligible patients should be to prolong survival by achieving the best possible response, while ensuring quality of life. The treatment should be individualized on the basis of host and disease features and better monitoring of the response upon use of high-sensitivity techniques for evaluating residual disease.

For young patients, HDT/ASCT is a standard of care for treatment and its efficacy has been enhanced and challenged by the new drugs. For elderly patients, treatment options were limited to alkylators, but new upfront treatment combinations based on novel agents (proteasome inhibitors and immunomodulatory drugs) combined or not with alkylators have significantly improved outcomes.

Extended treatment for young and elderly patients improves the quality and duration of clinical responses; however, the optimal scheme, appropriate doses and duration of long-term therapy have not yet been fully determined.

This review summarises the progress in the treatment of patients with newly diagnosed multiple myeloma, addressing critical questions such as the optimal induction, early *versus* late ASCT, consolidation and/or maintenance for young patients, and how we can choose the best option for non-transplant-eligible patients.

1. Introduction

Multiple myeloma (MM) is a neoplastic plasma cell disorder characterised by clonal proliferation of malignant plasma cells in the bone marrow, and usually monoclonal protein in the blood and/or urine. It is associated with end-organ damage consisting of anaemia, renal insufficiency, bone lesions and/or hypercalcaemia. It is the second most frequent haematological neoplastic disease after non-Hodgkin lymphoma and comprises 1% of all cancers and 10% of haematological malignancies. It primarily affects older individuals; the median age at the time of diagnosis is 70 years, and two-thirds of MM patients are over 65 years of age when first diagnosed [1].

The outcome of MM patients has significantly improved in the last decade. Initially, the benefit mainly accrued to young patients, based on the introduction of high-dose therapy followed by autologous stem cell transplantation (HDT-ASCT) upfront and novel agents at the moment of relapse of disease progression. More recently, the use of these novel agents to treat elderly patients has also resulted in a significant benefit with respect to outcome [2,3].

By considering that depth of response is one of the most important prognostic factors in MM, and that the achievement of deep remissions represents a therapeutic goal for a significant fraction of MM patients, we will start by reviewing the relationship between depth of response and survival, as well as the emerging role of new cellular and imaging techniques in monitoring minimal residual disease (MRD). We will then focus on the current treatment algorithm for patients with MM, and discuss the goals of therapy and the options for young and elderly patients in the upfront setting.

2. The relationship between depth of response and survival: the rationale for implementing MRD monitoring in MM

Achieving deep levels of response is a prerequisite for prolonged progression-free survival (PFS) and, very probably, overall survival

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(OS) of patients with haematological malignancies. MM is no exception to this paradigm, and published data on currently approved regimens for transplant-eligible patients (*e.g.*, bortezomib, thalidomide, dexamethasone, VTD) [4,5], upfront induction for the elderly (*e.g.*, bortezomib, melphalan, prednisone or melphalan, prednisone and thalidomide) [6,7], and even approved regimens for the relapse/refractory setting [8,9] have shown a clear association between increasing rates of complete response (CR) and prolonged PFS/OS.

However, some evidence contradicts this paradigm. It is known that: 1) some patients failing to achieve CR have an excellent outcome (those with an MGUS-like signature at baseline) [10]; 2) some patients in CR have dismal survival (those with unsustained CR or high-risk cytogenetics) [11–14]; 3) similar CR rates are associated with different PFS/OS; and, most importantly, 4) different CR rates from various trials are associated with a similar OS. These observations have three possible explanations: 1) distinct, small biological subgroups (5–10% of the whole population), such as patients with an MGUS-like signature or who are not able to sustain CR, have different clinical behaviours (Fig. 1); 2) the sensitivity of the criteria used to define CR may differ, *i.e.*, the CR rates may be similar in two arms, but a variety of outcomes may result from different levels of undetectable residual disease; and 3) it is only valid to compare CR rates within homogenously treated series of patients (*i.e.*, comparisons of the OS of patients in CR after induction is inappropriate if subsequent consolidation or maintenance approaches differ between the distinct arms).

The classic definition of CR was introduced by Blade et al. on behalf of the European Group for Blood and Marrow Transplantation (EBMT) more than 15 years ago. CR was defined as the disappearance of any soft tissue plasmacytomas, a negative immunofixation of serum and urine, and <5% bone marrow plasma cells (BMPCs) [15]. Since then, the International Myeloma Working Group (IMWG) has added the stringent CR (sCR) category to the conventional CR definition, and it includes the normalisation of serum free light chain ratio plus absence of clonal PCs by immunohistochemistry or 2- to 4-colour flow cytometry [16]. Kapoor et al. [11] have analysed sCR in a series of patients after ASCT and shown it to be associated with better PFS and OS than CR. As the treatment of MM has significantly advanced, other ways of measuring the various disease manifestations have also emerged. Table 1 shows a detailed characterisation of the different methods for measuring MRD in MM.

To evaluate any soft tissue plasmacytomas, as well as medullary and, in particular, extramedullary disease, highly sensitive imaging techniques have recently been proposed to help redefine CR. Accordingly, the number of focal lesions with whole-body or conventional magnetic resonance imaging (MRI) was found to be of prognostic significance for OS [17]. However, it should be noted that focal lesions might remain hyperintense in responding and non-responding patients for several months after therapy due to treatment-induced necrosis and inflammation. This may explain some of the inconsistency found between serological and MRI CR [18]. For this reason, it is recommended that MRI be performed during the follow-up with caution because lesions may remain many months or even years after the end of the treatment [19]. 18-Fluoro-deoxyglucose positron emission tomography/computed tomography (PET/CT) evaluation has proved to be of prognostic value as early as day 7 of induction therapy [20] and, more importantly, among patients in conventional CR at day 100 after high-dose therapy (HDT) [21]. Accordingly, PET/CT may be useful for detecting active foci of disease as a complementary assessment to the MRD evaluation by other techniques and predicting long-term outcomes, whereas its sensitivity to detecting medullary or extramedullary MRD in patients in immunophenotypic and/or molecular CR remains to be addressed. Furthermore, PET/CT results may also be difficult to interpret, running the risk of drawing false-positive and false-negative conclusions [22].

Novel assays have also been developed to measure levels of monoclonal immunoglobulin. The serum free light chain (sFLC) assay was introduced in 2006, and the normalisation of its ratio is one of the requirements for defining stringent CR. The new heavy-light assay allows to identify the different light chain types of each heavy chain to be discriminated (*i.e.*, to separate the amount of IgGK from IgGL), and may have a greater prognostic value than the sFLC assay [23]. However, its advantages over immunofixation have yet to be demonstrated and the heavy light assay does not work well for light chain secretors MM [23].

Cellular response in MM is defined when <5% BMPCs are detectable by conventional morphology. However, it has already been shown that, under the microscope, approximately 10% of patients qualified for CR (including those with a normal sFLC ratio) have >5% BMPCs, which

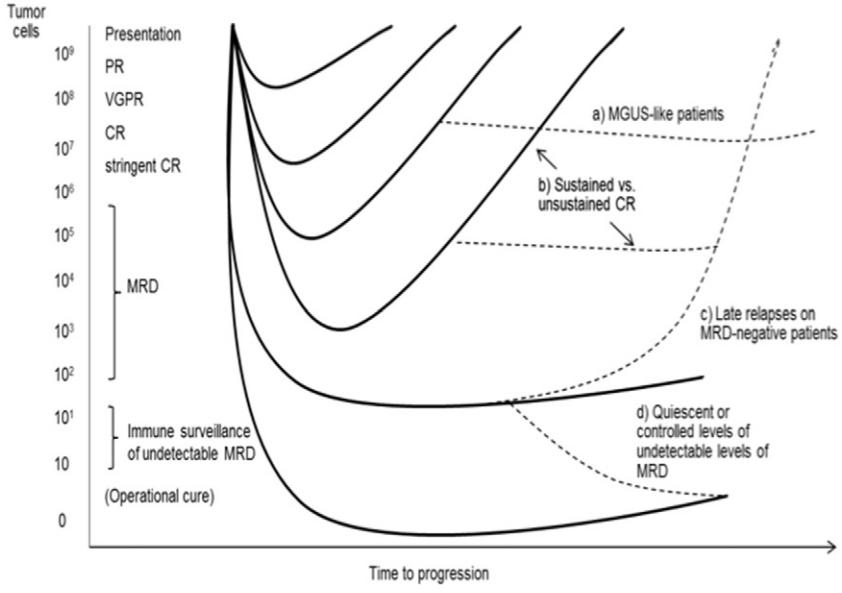

Fig. 1. The deeper the response, the longer the (progression-free) survival. This paradigm has been consistently demonstrated by a large number of studies using different levels of response (Table 1). However, it should be noted that the clinical course may differ from this paradigm in distinct biological subgroups: those patients with a baseline MGUS-like signature (a) and extended survival irrespective of CR; and those patients with persistent MRD plasma cells harbouring high-risk cytogenetics (b) who are unable to sustain CR for long periods of time. So far, the absence of MRD has consistently translated into extended survival it cannot be considered a marker of a "cure" (c). However, an "operational cure" could be achieved if a very small undetectable MRD clone is quiescent (like MGUS) or under control (*e.g.*, by immune cells) (d), but the prospective identification of such patients is currently not possible, and may imply serial MRD monitoring in order to prevent cellular relapse (earlier than biological and/or clinical relapse).