Cancer Treatment Reviews 36S2 (2010) S3–S11

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Multiple myeloma – current issues and controversies

Shaji Kumar*

Division of Hematology, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Keywords:
Multiple myeloma
IMiDs®
Thalidomide
Lenalidomide
Bortezomib
MGUS
Smouldering myeloma
Plasma cell dyscrasia
Monoclonal protein

SUMMARY

The outcome of patients with multiple myeloma has dramatically improved in the past decade, due to the introduction of new, more effective treatments, wider use of high-dose therapy, and better appreciation of potential complications and their management. Increasing treatment options have also raised several important questions regarding the optimal use of novel therapies such as thalidomide, lenalidomide, and bortezomib to realise their full potential and to maximise the survival of patients with myeloma. The high response rates seen with the new regimens have led to increasing debate about the goal of therapy for this disease, including the concept of cure. While we still lack definitive data answering some of these questions, we have attempted to interpret the current state of knowledge, and provide a perspective on the current issues and controversies in this disease.

Introduction

Multiple myeloma (MM) is a plasma cell malignancy that is characterised by accumulation of clonal plasma cells, predominantly in the bone marrow, leading to one or more clinical manifestations of bone destruction, anaemia, hypercalcaemia, and renal insufficiency. It is the second most common haematological malignancy after lymphoma, and affects over 20,000 patients each year in the United States, with nearly 11,000 deaths during the same time period.[1] The past decade has witnessed unprecedented progress in our understanding of the disease biology,[2] as well as improvements in the treatment of this disease.[3,4] While this has led to improved survival of patients with MM in general, it is also questioning the 'conventional wisdom' in the management of this disease. As a result, our approaches to myeloma therapy have undergone a paradigm shift, and new questions have arisen regarding the optimal management strategies and treatment goals.[5]

Timing of therapy

MM represents a late stage in the evolution of monoclonal gammopathies, and is preceded by a phase of monoclonal gammopathy of undetermined significance (MGUS) in all patients. Although MGUS resembles MM, it manifests with a lower number of plasma cells in the bone marrow and is not associated with end-organ damage attributable to plasma cell proliferation.[6] It is further differentiated from MM by a low serum monoclonal protein level. MGUS has an increasing prevalence with age, affecting nearly 6% of those over 60 years of age, and represents the most common plasma cell disorder.[6] Although no treatment is indicated in patients with MGUS, recent studies showing an association between MGUS and bone loss suggest that routine evaluation of bone status can facilitate timely prophylaxis.[7] Moreover, large epidemiological studies have suggested that patients with MGUS have a risk of progression to myeloma or another related condition requiring treatment of approximately 1% per year.[8] Patients with certain clinical and laboratory features, such as higher levels of M protein and those with abnormal free light chain ratios, are at a higher risk.[8] Patients with MGUS may therefore benefit from risk stratification to guide follow-up. Those at low risk can be reassessed in 6 months then once every 2 years; whereas patients at higher risk require initial reassessment at 6 months then yearly thereafter.[6] An intervening stage, designated as smouldering multiple myeloma (SMM), can be identified in a proportion of patients where the measures of tumour burden are higher than that of the threshold for MGUS.[7] In contrast to MGUS, patients with SMM have a higher risk of progression to symptomatic myeloma requiring therapy, with nearly 10% of patients progressing each year during the first 5 years after diagnosis of SMM.[9] The current standard of care for these patients is disease monitoring every few months until disease progression, and then treatment of the progressed disease.[10] Following this time period, patients often seem to follow a course similar to that of MGUS patients, highlighting the heterogeneous nature of patients given the label of smouldering myeloma.

As with other cancers, the presence of such a presymptomatic phase has raised significant interest in developing interventional strategies to prevent disease progression. However, efforts have been hampered by three important considerations: lack of effective therapies; significant toxicity of existing therapies; and an inability

* Correspondence: Division of Hematology, Department of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
Tel.: +1 507 266 0523; fax: +1 507 284 0161.
E-mail address: kumar.shaji@mayo.edu (S. Kumar).

0305-7372/$ – see front matter

to identify which patients are truly at risk of early progression. Two critical advances in the past decade have allowed us to readdress this issue, namely: availability of novel therapies with a much higher efficacy to toxicity ratio, and the introduction of a well-characterised scheme for the identification of patients at the maximum risk of progression. The early results of a phase III trial by Spanish investigators have provided a glimpse into how we might manage these patients in the future.[11] In this trial, patients with high-risk SMM (defined as those with >3 g/dl M spike and >10% plasma cells in the marrow or either one of these along with evidence of immunoparesis were randomised to receive induction therapy of lenalidomide (25 mg/day) on days 1–21 and dexamethasone (20 mg/day) on days 1–4 and 12–15 over the course of nine 28-day cycles, followed by a maintenance dose of lenalidomide (10 mg/day) on days 1–21 every 2 months until disease progression, or the current standard of care of close observation without treatment. The preliminary results suggested a significant improvement in the risk of progression in patients assigned to active therapy,[11] a result that was not unanticipated.

The real proof of benefit will depend on the ability to demonstrate improved survival with early intervention, confirming that we have been able to alter the natural history of the disease. Even if this approach does not improve survival, if it leads to better quality of life (QoL) by avoiding the complications that myeloma patients typically present with, it will represent an advance in the field and alter current views. However, until evidence for these benefits emerges, careful close observation of patients with SMM should be considered the standard of care outside a clinical trial.

Initial therapy of myeloma

While the past decade has seen improvements in all aspects of myeloma care, the maximum impact has been in the area of initial therapy of newly diagnosed disease. There have been several large trials examining the role of treatment regimens incorporating one or more of the novel agents.[12–20] While these studies have addressed important questions and advanced the treatment strategy for patients with MM, the results of these trials also have raised several important questions.

Patient characteristics that affect choice of initial therapy

The choice of initial therapy should be based on several factors: eligibility for stem cell transplant (SCT), age, performance status, presence of comorbidities, presence of disease-related complications, and, most importantly, patient choice following a thorough discussion of the pros and cons of different approaches. Among these, eligibility for high-dose chemotherapy and autologous peripheral blood stem cell transplantation (auto-SCT) have been the primary factors for treatment selection, both in clinical trials and in routine practice. This has been based on the results of randomised clinical trials demonstrating survival improvement with auto-SCT compared with conventional alkylator-based therapies.[21] While randomised trials have shown equivalent outcomes between an early or delayed auto-SCT, the possibility of alkylating agents hampering subsequent stem cell collection had necessitated this early treatment decision after diagnosis, so that subsequent possible use of SCT is not jeopardised.

Another closely related aspect is the patient's age, often used as one of the criteria for determining transplant eligibility. While selected patients up to 75 years can be considered for SCT, randomised trials of SCT have only included patients up to 65 years old. Age remains one of the most powerful prognostic factors in this disease,[22] and often limits treatment choices due to higher risk of adverse events from the currently available treatment options. Similarly, performance status is an important factor to be included in the initial treatment decision making, as patients with poor performance status tend to have inferior outcomes, likely a composite effect of disease-related complications, age, and comorbidities. Unfortunately, limited prospective data are available for these patients in terms of optimal approaches, since they are often excluded from clinical trials.

Myeloma-related factors that affect choice of initial therapy

Another aspect of the disease that has led to the development of specific treatment recommendations has been the presence of genetic risk factors. Although there are different definitions used across various studies, in general, the presence of cytogenetic abnormalities, such as deletion 17p [del(17p)] or translocation of the immunoglobulin heavy chain (IgH) locus on chromosome 14 [t(4;14)], indicate high-risk disease in MM. Based on this practical definition, approximately 25% of MM patients are deemed to be high-risk.[23] The prognostic value of del(13q) is related to its frequent association with t(4;14) and del(17p).[24] Patients with t(14;16) and t(4;14) translocations, p53 abnormalities due to del(17p) detected by interphase fluorescence in situ hybridization (FISH), chromosome 13 abnormalities observed through conventional cytogenetics, and those with high rates of plasma cell proliferation have very short survival with short response duration to prior therapies.[23–25] Several studies have so far demonstrated that use of bortezomib can improve the outcome of patients with IgH translocations or chromosome 13 abnormalities,[26,27] leading to a recommendation to use bortezomib upfront in these patients. The duration of bortezomib therapy may also influence the specific efficacy of the drug in this setting, since recent data from France do not reflect a complete amelioration of the poor risk when bortezomib is used for short duration as induction therapy in contrast to that previously reported from Arkansas.[27,28] One study has evaluated the efficacy of lenalidomide in newly diagnosed MM patients with high-risk cytogenetic abnormalities defined as hypodiploidy, del(13q) by methaphase cytogenetics, del(17p), IgH translocations of t(4;14) or t(14;16) by FISH or cytogenetics, or plasma cell labelling index (PCLI) ≥3%.[29] Results of this study showed that although median progression-free survival (PFS) and time to progression were significantly shorter in the high-risk group than the standard-risk group, overall survival and response rates were comparable between groups.[29] The outcomes achieved in high-risk patients with lenalidomide plus dexamethasone in this study were comparable to those obtained with other therapies.[30] Approximately 10% of newly diagnosed MM patients have del(17p), which is associated with shorter overall survival, aggressive disease, and higher prevalence of extramedullary disease and hypercalcaemia.[24–33] However, there is no conclusive evidence that any currently available treatment options are effective for the treatment of MM in patients with del(17p). Recent data from a cohort of patients primarily treated with immunomodulatory agent-based therapy failed to demonstrate prognostic value for proliferation measures, suggesting the inability of the newer drugs to overcome the impact of this aspect of disease biology.[25,30] New therapeutic strategies need to be investigated in patients with del(17p). Studies that have assessed the efficacy of various treatment options in MM patients with high-risk cytogenetics have included small numbers of patients and limited duration of follow-up, making it difficult to draw meaningful conclusions.

Toxicity concerns that affect choice of initial therapy

Peripheral neuropathy has long been associated with monoclonal gammopathy, but has been pushed to the forefront more recently due to the side effects of drugs such as bortezomib and thalidomide. Presence of baseline neuropathy in patients with myeloma is much