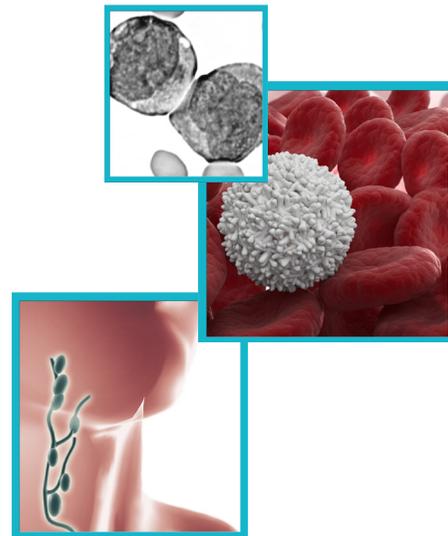


SPECIAL REPORT

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Impediments to curing myeloma in 2012



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Practice Points

- Multiple myeloma has long been considered an incurable disease.
- Advances in biologic understanding and targeted drug development have made it possible to consider curability as a goal in this disease.
- Current myeloma therapy can overcome some features that historically had been associated with poor prognosis (chromosome 13 deletion, translocation 4;14 and so on).
- Clinical features such as primary plasma cell leukemia, extramedullary disease and renal failure still remain poor prognostic markers, along with biologic features such as translocation 14;16, translocation 14;20, deletion 17p and amplification of chromosome 1q21.
- Imaging modalities, such as MRI and PET, are emerging diagnostic and prognostic markers.
- Future prognostic models will be more comprehensive and likely to incorporate host factors, biological and imaging features.

SUMMARY Our understanding of multiple myeloma biology over the last two decades has led to a marked improvement in progression-free and overall survival for the majority of patients. The introduction of novel agents, improvement in administration of high-dose therapy with autologous stem cell support, along with supportive care measures have enabled the myeloma researchers to once again debate the curability of this disease. The present article is a succinct review of the progress that has been made and the impediments to curability of this disease.

Multiple myeloma (MM) is the second most common hematologic malignancy [1] characterized by the presence of monoclonal plasma cells in the bone marrow, along with an increased production of monoclonal proteins in the serum and/or urine that leads to end organ damage (lytic bone lesions, hypercalcemia, anemia and renal failure). The last decade has witnessed

major progress in clinical outcomes in MM, attributable to the introduction of several novel agents which, when combined with either each other or conventional cytotoxic drugs, have imparted a high frequency of complete responses (CRs) [2–5]. These advances have re-ignited the debate on curability of MM, as has been advocated by the Arkansas Investigators in their Total

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Therapy program [6]. Fonseca *et al.* have elegantly demonstrated the heterogeneous nature of MM, even within the same patient during the course of disease, when treated sequentially with novel therapies, highlighting the genetic chaos that is present from the very onset of disease, which further evolves rapidly with each relapse so that eventually total resistance to salvage interventions ensues [7,8]. It has also been observed that, despite a lower CR frequency, patients with documented antecedent smoldering course and those presenting with a monoclonal gammopathy of undetermined significance-like gene-expression profiling (GEP) signature can have long-term overall survival (OS) of over 10 years (75% patients) after autologous stem cell transplantation [9]. The present manuscript reviews the available data on long-term survivors (>10 years) in terms of their presenting features, quality of response and management in order to guide therapeutic investigations aimed at long-term disease control. Toward this goal, published literature has been succinctly reviewed and the authors' clinical trials experience updated.

Long-term survival in MM

The best example of curability of a hematologic malignancy lies in experience in pediatric acute lymphoblastic leukemia, with a cure rate approaching 80% [10]. Unlike pediatric acute lymphoblastic leukemia patients who can endure intensive therapy, the median age of a MM patient at diagnosis is 70 years and poses a major therapeutic challenge. The assessment of curability on the MM patient population is also hampered by the presence of geriatric comorbidities that may confound patient survival. Another important aspect to consider in this elderly patient population is the genetic link to longevity (e.g., whether a patient outlives median survival of his/her ancestors).

Recently published population studies from Sweden and the USA that analyzed data separately in terms of calendar periods and age categories looked at relative survival ratios (RSRs) of patients diagnosed with MM. The Swedish group [11], which looked at 14,381 patients from 1973 to 2003 in four calendar periods and six age categories, reported improved 1-year survival over time in all age groups, but improvement in 5-year and 10-year RSR was observed only in patients younger than 70 and 60 years, respectively. Specifically, in patients with MM diagnosed at <60 years of age, a 29% ($p < 0.001$)

decrease in 10-year mortality was seen in the last calendar year from 1994 to 2003, compared with 1987–1993. They also reported that females had 3% ($p = 0.024$) less mortality than males. In the opinion of the authors, the most probable explanation for these results is the use of high-dose melphalan with subsequent autologous stem cell transplant, thalidomide and an improvement in supportive care. It is important to note that bortezomib and lenalidomide were not in routine clinical use during this study, with only four patients receiving the former, while none received the latter, respectively.

A second population study analyzed 26,523 patients using data from the 1973–2004 limited-use database of the Surveillance, Epidemiology and End Results (SEER) Program of the US National Cancer Institute issued in 2007 [12]. The RSR was calculated for five calendar periods from 1992 to 2004 and five age groups ranging from <50 to 80 years of age. At time of diagnosis, half of the population was 70 years of age or older and less than 10% were <50 years. The results of this study showed that 5-year survival increased for all age groups by 2002–2004 compared with previous years, but a significant increase was seen in patients <50 years to 50–59 years of age, and this increase was even more pronounced when calculating the 10-year relative survival; 40–60% respectively. On the other hand, no improvement was noticed in the 80 years of age or older population.

Achieving CR has been shown to prolong survival in MM patients, especially if sustained for 3 years after treatment initiation [13,14]. Several important factors such as β 2-microglobulin, albumin, CRP, LDH, bone marrow plasma cell burden, cytogenetic abnormalities and GEP, which are used for disease staging and risk stratification, also play a defined role as prognostic markers in patients with MM. Baseline presence of high-risk cytogenetics and minimal residual disease detected by multiparameter flow cytometry persisting beyond 100 days after initial therapy were identified as independent factors that affect CR adversely [15].

Imaging techniques are also considered as important prognostic tools. The metastatic bone survey, a whole body x-ray, has been used as a standard for evaluating bone disease (osteolytic lesions or osteopenia), but can sometimes underestimate bone involvement. MRI and, more recently, PET integrated with computed tomography (PET/CT) using radionuclide ^{18}F -labeled

with fluorodeoxyglucose, are effective in detecting bone lesions, marrow involvement and, in the case of the latter, demonstrating active or inactive disease, and their use can also provide vital prognostic information. Studies utilizing PET/CT and MRI by the University of Arkansas Myeloma Group [16] and the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) [17] looked at the number of focal lesions, the uptake of fluorodeoxyglucose, expressed as standardized uptake value, and the presence of extramedullary disease (EMD) at baseline and after treatment in previously untreated myeloma patients. The results from these studies showed that the number of focal lesions adversely affected OS and event-free survival independently, as did presence of EMD and failure of fluorodeoxyglucose suppression. It was observed that complete suppression of fluorodeoxyglucose before the start of the first autologous stem cell transplant (ASCT) conferred a favorable affect on outcome, especially in the GEP 70-gene (GEP70)-defined high-risk patients [18]. On the basis of the presented data, MRI and PET/CT imaging in diagnosis and prognosis of MM are being used as an important adjunct to the treatment plan. However, PET/CT is not yet established as a standard for diagnosis and disease evaluation, as concerns have arisen regarding the heterogeneity of visual criteria and inconsistency in the interpretation of results [19].

There is certainly evidence that a subset of MM patients will have long-term survival based on available data. With the unprecedented advances in MM drug development, the proportion of long-term survivors (and potentially cured) will continue to grow.

Clinical & biological features associated with poor outcome in 2012

■ Adverse clinical factors

There are a number of clinical variables and their interaction helps in determining the initial therapy and patient outcomes, and in assessing cancer patients involved in clinical trials. Most of these factors are not unique to MM patients, but rather become more prominent due to advanced age of diagnosis. The most important clinical variables include host factors such as age, performance status, presence of comorbidities and complications secondary to disease with the eligibility for ASCT being the primary one. Age as a prognostic factor is very important, as patients of older age tend to fare worse than

younger patients; one reason for this could be that in younger patients more aggressive treatment options can be used that might be limited in the older age group [20]. Other examples of factors that have an adverse effect on prognosis are a poor performance status (by standardized systems such as Karnofsky scale or Zubrod scale), high β 2-microglobulin (representing International Staging System stage III disease) and high bone marrow plasma cell percentage. The presence of EMD [21] and primary plasma cell leukemia [22] has been associated with poor outcome even with intensive approaches, such as Total Therapy employed by the authors.

■ Adverse biologic factors

Like most cancers, MM has both interpatient and inpatient heterogeneity. The last 15 years have seen major progress in both the understanding of MM disease biology and development of biologically relevant MM therapies. Even in the era of novel agents, there are prominent biologic factors associated with the disease that also play a major role in overall prognosis. Patients can be categorized into genomically defined low risk or high risk depending upon underlying molecular cytogenetic abnormalities identified using either FISH or GEP. The poor prognostic cytogenetic abnormalities include translocations (4;14), (11;14), (14;16), (6;14) and (14;20), hyperdiploidy and deletion 17p [23], and their presence is associated with shorter OS and duration of response to therapy. GEP also helps identify different signatures that confer an adverse outcome, as shown by the Arkansas GEP70 model that identifies 13–20% high-risk newly diagnosed patients with short progression-free survival and OS, even when with the Total Therapy approach [24]. Different therapies are being employed by investigators in order to overcome these factors, especially with the introduction of the immunomodulatory drugs. The TT3A study has shown that prolonged use of bortezomib with tandem ASCT can overcome poor prognosis associated with translocation (4;14) [25], while it has also been demonstrated that the introduction of bortezomib in the modern era has improved outcome in patients who have chromosome 13 abnormalities [26]. Patients with low-risk disease usually have a median survival of 6–7 years or longer when compared with those with high-risk disease, who survive for a median of 3 years. On the other hand, those with intermediate risk have been shown to

have comparable survival to low-risk patients in studies where there was early use of bortezomib plus ASCT [27]. The disease subset with GEP70 high risk, translocations (14;16) and (14;20), and deletion 17p remains a challenge. Clinical trials addressing this difficult group of newly diagnosed patients are now being conducted, such as the SWOG-1211 (NCT01668719) study [101], to establish guiding posts for future trials.

Long-term sequelae of MM therapy

The increase in survival of MM patients has presented a new challenge in the form of development of secondary malignancies. The association between acute myeloid leukemia and myelodysplastic syndrome (MDS) with MM has been known for a while, with initial trials implicating melphalan as the drug responsible for these secondary malignancies [28]. After the introduction of ASCT, studies have reported that use of conventional chemotherapy before transplant was more responsible for acute myeloid leukemia/MDS than myeloablative therapy used in combination with ASCT [29], and recent reports that show an increased risk with the use of lenalidomide as maintenance therapy have brought this problem to the forefront [30–32]. In addition to the treatment-related factors mentioned above, the following other etiologic factors are also implicated: disease-related factors, for example, IgG/IgA monoclonal gammopathy of undetermined significance; host-related factors either genetic or nongenetic, for example, decreased production of glutathione *S*-transferase enzymes in the presence of mutagens and/or carcinogens, pre-existing bone marrow abnormality, 5q- syndrome, age and concomitant therapy; environmental risk factors, for example, ionizing radiation; and autoimmune and behavioral factors, for example, obesity [33].

As treatment for patients who develop MDS, hematopoietic stem cell transplantation offered a possibility for cure, but only in a minority of patients owing to the problem of relapse and nonrelapse mortality. Hypomethylating agents – azacitidine and decitabine – have been approved by the US FDA for the treatment of high-grade MDS, and these have a role based on the finding that cytosine methylation is implicated in the pathogenesis of MDS, but again approximately half of patients fail to respond [34]. As MDS in the setting of MM can be devastating, better prediction models for second

malignancies/therapy-related MDS are needed so that patients who are at risk for developing secondary malignancies are identified early at diagnosis with the potential of pre-emptive incorporation of hypomethylating agents in induction/maintenance.

Conclusion

With the introduction of ASCT in the late 1980s, until the late 1990s the treatment mainly consisted of high-dose chemotherapy with or without ASCT and this regimen increased OS at 12 years to 35% in patients with CR [14]. The surge of novel agents developed since the late 1990s has also had a positive impact on OS when used in patients ineligible for stem cell transplantation (SCT), and in those with relapsed or refractory disease, as reported by clinical trials [35]. Their incorporation in upfront therapy for newly diagnosed MM with or without SCT has also shown improved results over conventional chemotherapy [36,37]. Newer agents such as pomalidomide (thalidomide analogue) and carfilzomib (a novel keto-epoxide tetrapeptide proteasome inhibitor) have shown potent single agent efficacy in patients with relapsed/refractory MM and are undergoing FDA/EMA approval process [38]. There are a number of exciting compounds in the clinical development pipeline, including HDAC, PI3K, oral proteasome, JAK, IRE1a and BRAF inhibitors as well as monoclonal antibodies (anti-CS1, anti-CD38). With the growing armamentarium of effective anti-MM drugs and a better genomic understanding of myeloma, it appears that the era of a truly personalized, risk-adaptive MM therapeutic strategy is on the horizon.

The road to MM curability lies in overcoming both adverse host factors (e.g., advanced age, comorbidities and poor performance status) and disease factors (poor risk based on clinical features such as plasma cell leukemia and EMD; genomic features such as GEP70 high-risk, deletion 17p, translocation [14;16] and [14;20], and amplification of chromosome 1q21). There is an emerging need to develop evidence-based prognostic models that take into account a combination of clinical, biologic and imaging variables to determine choice of therapeutic agents during induction, utility of high-dose therapy and autologous stem cell transplantation, the choice of maintenance therapy drugs and duration of maintenance therapy.

Future perspective

MM research and therapy is at an important juncture in the year 2012. The OS of MM patients has been extended more than three-fold in the last decade. With a continued better understanding of the heterogeneity of disease within a given MM patient, as well as between different MM patients, the field will likely evolve into a more personalized, risk- and response-adaptive therapeutic schema. Over the coming decade, one can envision that MM may become curable for a subset of MM patients, and a chronic disease for the rest. More comprehensive prognostic models that incorporate clinical

features, biologic features and novel imaging will likely be developed to help choose the right therapeutic strategy for any given patient.

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