How to Think About Risk in Myeloma

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Abstract

An integral part of myeloma therapy is risk stratification of newly diagnosed patients. This method involves a combination of staging and genetic risk assessment. Although survival has dramatically improved for patients with genetically defined, standard-risk myeloma, those with high-risk disease remain a therapeutic challenge. Current treatment approaches might include the use of combination therapy for induction and maintenance. Future approaches are expected to involve drugs that are "risk agnostic," such as monoclonal antibodies and immunotherapy.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. S1, S135-8
Keywords: Bortezomib, Carfilzomib, Cytogenetics, Dexamethasone, Immunotherapy, Lenalidomide, Next-generation sequencing

Introduction

When assessing risk, perception is sometimes as important as reality. For instance, a "double black" advanced ski run would be perceived as risky to an average skier but not to a confident champion. The steep slope is a reality for both people, yet the risk is mitigated with the better skier. Similarly, in myeloma we might perceive risk in a patient who looks weak and frail, with a high tumor burden. Other times, cytogenetics and organ function are our own black diamond. The truth is, risk is different for everyone.

Median survival for myeloma has improved and is likely to continue to improve as a consequence of new agents.[1] However, there are subgroups of patients who are destined for early relapse despite these treatments. In general, such patients are considered to be high-risk. Genetically defined high-risk myeloma comprises 15% to 20% of patients with myeloma,[2,3] and advanced stage of disease as defined according to the International Staging System (ISS) at the time of presentation also confers a poor prognosis. In addition, I would also add that high risk might be determined on the basis of patient characteristics. With respect to significant comorbidities or frailty, therapeutic options might be limited, thus rendering treatments less effective and leading to a higher risk of relapse.

Consider 2 scenarios.

Case 1

A 65-year-old man who presents with back pain, nausea, and constipation. Blood work reveals hypercalcemia, elevated creatinine level at 2.5 mg/dL, hemoglobin 9.0 mg/dL, and β_2 microglobulin at 6.5 mg/mL. Skeletal x-rays show an L4 compression fracture and generalized osteopenia. A bone marrow biopsy shows 70% plasmacytosis with 17p deletion on 50% of cells using targeted fluorescence in situ hybridization (FISH) analysis, as well as trisomy 9.

Case 2

A 75-year-old man with diabetes, hypertension, and coronary artery disease with a previous myocardial infarction 3 years ago. The patient lives alone, and he requires some assistance for regular errands. He is able to dress himself; however, his activity outside the house is limited as he describes himself as unsteady on his feet. He develops increasing dyspnea on exertion. Cardiac work-up was negative. Blood work revealed a hemoglobin of 7.5 mg/dL, creatinine 3.0 mg/dL, and albumin 3.0 mg/mL. A bone marrow biopsy shows 70% plasmacytosis with normal karyotyping in FISH studies. Skeletal x-rays show scattered lucencies in the long bones.

Genetically Defined High-Risk Myeloma

Traditional karyotyping was one of the first methods of defining high-risk myeloma, with patients with deletion 13 classically defined as high-risk.[4] Further refinement with FISH analysis showed that deletion 13 did not confer the risk but that it was the commonly associated markers (17p, 4;14) that conferred the greater risk of relapse.[5] Other recognized high-risk markers in FISH analyses include t(4;14), t(14;16), and t(14;20). C-MYC might also be considered a poor-risk marker.[6]

In contrast, there are genetic abnormalities traditionally considered favorable, such as hyperdiploidy. In the case of the patient in case 1, the trisomy 9 could be considered a good-risk marker. However, the question arises as to whether it is able to abrogate the poor prognosis of the 17p deletion. A retrospective analysis from the Mayo Clinic[7] suggested that, indeed, this is the case. For patients

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Submitted: Feb 9, 2016; Accepted: Feb 9, 2016

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.02.015

with a high-risk lesion but without concurrent trisomy, the median overall survival (OS) was 3 years, whereas the median OS was not reached for high-risk patients with trisomy ($P < .001$). Related to this, among the group of patients with a trisomy, no survival difference was seen between those with high-risk abnormalities and those without. However, this study was limited by its retrospective nature and the heterogeneity of the treated patients. In contrast, a more recent publication of the Medical Research Council Myeloma IX trial[8] suggested the opposite; median OS for patients with hyperdiploidy and poor prognosis markers was 36 months versus 61 months for those with only hyperdiploidy ($P < .001$). Median progression-free survival (PFS) was 15 versus 23 months ($P < .001$). Examining each lesion individually, the authors observed shortened OS and PFS for every lesion, compared with hyperdiploidy alone. Patients with more than 1 lesion had the worst prognosis. It should be noted that the 2 studies used different therapies, which might have affected outcomes.

Other methods of genetic assessment include gene microarray analysis. Several genetic signatures have been identified. These include the Erasmus Medical Center-92, the Intergroupe Francophone du Myelome (IFM)-15, and the University of Arkansas Medical Sciences signatures.[9-12] Standard use of this method of risk assessment has been hampered by lack of consensus or overlap in the signatures. Moreover, in the future, next-generation sequencing will likely supplant microarray analysis.[13] For example, deep sequencing of RNA was used to determine that many mutated genes have little or no detectable expression, and that mutant alleles are often differentially expressed in patients.[14] This development of new technologies might be driven in part by their widespread availability as well as the ability to leverage the results into targeted therapies.

In the 2 case scenarios, case 1 would fit into a definition of high-risk disease and be treated accordingly.

Clinically Defined High Risk

Clinically defined high risk is a more encompassing definition with multiple factors to be considered. Objective criteria include ISS staging.[15] The ISS staging system, when developed, had an advantage over the traditional Durie—Salmon staging in that it provided prognostic information.[15] Median survival varied from 29 months for advanced-stage patients to 62 months for stage I disease. Combining this information with cytogenetics as well as re-evaluating median survival in the era of modern myeloma therapy provides further relevance.

Indeed, the IFM used a combination of ISS staging and cytogenetics to define a particularly poor-risk group of patients.[16] They assigned a score for each risk factor: score 0, no adverse factor; score 1, 1 adverse factor; score 2, ISS stage III and high lactate dehydrogenase (LDH) level, without t(4;14) and del(17p); score 3, ISS stage III and/or high LDH, with t(4;14) and/or del(17p). Patients with a score of 3 were found to have a poor prognosis despite treatment with novel agents, specifically, a bortezomib-containing regimen.

Clinical presentation is also of import in our assessment of risk. Patients who present with renal failure are encompassed by the ISS staging system. A retrospective series from the Greek Myeloma Group included 756 newly diagnosed myeloma patients.[17] The presence of renal failure was associated with a trend for a higher early death rate; however, when corrected for ISS stage in multivariate analysis, it had no independent effect on survival. Extramedullary disease has been associated with worse prognosis even in the era of modern therapy: interestingly, again underscoring the interplay of genetic risk and clinical presentation, in a series of 1965 patients from the University of Arkansas, extramedullary disease was more prevalent in genomically defined high-risk disease.[18]

Elderly patients pose other issues to consider in assessment of risk. Older retrospective studies have suggested that elderly patients present with more advanced disease.[19] The incidence of del(13) and t(4;14) decreased with age, but not del(17p) in the IFM series.[20] However, despite this phenomenon, survival is worse for elderly patients with newly diagnosed myeloma.[21] Although life expectancy is naturally shorter for elderly patients compared with younger ones, further factors need to be taken into account, including treatment-related mortality and disease recurrence.

The elderly represent a heterogenous population, and frailty and geriatric assessment might also play a role in risk assessment, because these characteristics will ultimately influence aggressiveness of treatment as well as its associated risk. Palumbo et al studied 869 patients in the European Myeloma Network.[22] In an additive scoring system, a score of 1 was assigned for patients 76 to 80 years in age and a score of 2 for those older than 80 years. A score of 1 each was given to patients who scored ≤ 4 on the Katz Activity of Daily Living scale, ≤ 5 on the Lawton Instrumental Activity of Daily Living scale, and ≥ 2 on the Charlson comorbidity index. Their analysis showed that this frailty score encompassing age, functional status, and comorbidities could predict survival and toxicity. With these factors in mind, case 2 would therefore be high-risk, considering the 3-year OS of 57% in frail patients according to this scoring system.

Treatment of High-Risk Myeloma

Treatment is individualized, and cases 1 and 2 warrant different approaches. For case 1, my general approach would be a combination of induction chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant, with a subsequent consolidation/maintenance strategy.

Bortezomib would be a backbone of the induction regimen. The IFM 2005 trial of VAD (vincristine, doxorubicin, and dexamethasone) versus bortezomib-dexamethasone induction showed improved event-free survival and OS for bortezomib-treated patients with t(4;14) but not del(17p) (4-year OS 50% vs. 79%).[23] The HOVON65/GMMG-HD4 trial showed that bortezomib-based induction and maintenance after transplantation improved PFS and OS compared with VAD induction and thalidomide maintenance.[24] More recent trials using carfilzomib-based induction also suggest some abrogation of poor-risk cytogenetics. A small phase II trial of carfilzomib plus lenalidomide and dexamethasone induction showed no differences in response rate on the basis of ISS stage or high-risk cytogenetics and similar PFS for high-risk and standard-risk cytogenetics.[25]

The role of high-dose therapy separate from induction treatment in high-risk cytogenetics is less clear. In Total Therapy 3, the combination of bortezomib with tandem transplantation improved outcomes of patients with t(4;14).[26] Tandem autologous transplant might also provide a benefit, although it is less clear whether the

benefit is from the tandem procedure and moreover from the deepening of response. A meta-analysis of 4 European trials showed improvement in OS with double autologous transplantation for patients who failed to achieve a complete response after bortezomib-based induction or had high-risk cytogenetics.[27] The recently completed Blood Marrow Transplant Clinical Trials Network Stamina trial might more definitely answer this question, because it compares tandem autologous transplantation with a single transplant with consolidation therapy and single transplant alone, followed by maintenance lenalidomide in all arms.

Thus, the optimal post-transplant strategy for the high-risk patient remains undefined beyond incorporating proteasome inhibitors as either maintenance or consolidation therapy. Some small trials also have shown particularly promising depths of response and PFS using the combination of proteasome inhibitors and immunomodulatory agents post-transplantation. A single-institution study of RVD (bortezomib, lenalidomide, and dexamethasone) for up to 3 years after transplantation followed by single-agent lenalidomide included patients with plasma cell leukemia and 17p deletion. The 3-year PFS for this high-risk group was 57%, and the OS 100%.[28] Carfilzomib would be an alternate proteasome inhibitor of choice, especially if the patient has neuropathy that would preclude long-term bortezomib use. Studies of newly diagnosed patients treated with carfilzomib/lenalidomide/dexamethasone showed equal response in patients with high-risk cytogenetics.[25] Its use in the maintenance setting is less clear, but similar efficacy would be expected.

Future treatments that might be incorporated in these high-risk patients could include monoclonal antibodies. There is a growing database of high-risk patients with relapsed myeloma treated with varied antibodies targeting CD38, CD138, and signaling lymphocytic activation molecule F7.[29,30] To the best of our knowledge, surface antigen expression does not appear to differ in high-risk patients; therefore, these antibodies maintain a high level of activity even in genetically defined high-risk patients. In addition, the antibodies also induce responses relatively quickly, thereby conferring benefit to patients who are clinically high-risk either before or after transplantation.

Treatment of the elderly high-risk patient, however, is a very different paradigm. In these patients the emphasis is on balancing efficacy with side effects and treatment-related mortality. For the patient in case 2, assessing frailty and comorbidities would be important. Indeed, his comorbidities of diabetes and renal insufficiency would place him at higher risk of experiencing the side effects of steroids, and would necessitate a dose adjustment of renally excreted drugs, such as lenalidomide.

I would likely treat him with a doublet regimen, such as subcutaneously administered bortezomib with dexamethasone at a reduced dose of 20 mg weekly. His age and diabetes might predict the occurrence of bortezomib-induced neuropathy.[31]

The use of subcutaneous bortezomib should reduce the risk of peripheral neuropathy from 53% to 38%.[32] However, there are still practical considerations that are also paramount in the elderly patient. For instance, weekly transportation to the clinic to receive the bortezomib would be needed. His blood sugar levels would also require close monitoring, because of the potential risk of dexamethasone inducing the need for insulin. The alternative of an oral regimen such as lenalidomide and dexamethasone in that context seems more attractive. However, lenalidomide would need to be reduced in dose because of his low creatinine clearance. In addition, because he is relatively sedentary, he is at greater risk of deep venous thrombosis (DVT). The Eastern Cooperative Oncology Group trial 4A03 of lenalidomide with dexamethasone in a traditional high-dose schedule versus 40 mg weekly dexamethasone (the low-dose arm) confirmed that this regimen is well tolerated when the drug is reduced in the elderly.[33] Notably, however, the side effects of DVT (12%), and infections (9%) were still observed with the modified regimen.

It should also be accepted that the use of a doublet regimen would lead to a lower overall response rate and depth of response compared with a triplet regimen. In a phase II trial using the triplet regimen of RVD, the response rate was 100%.[34] However, the median age was 59 years. In contrast with the doublet of lenalidomide-dexamethasone, the overall response rate is 68%, and the complete remission rate is 2% after 4 cycles. An attempt to maintain efficacy while mitigating toxicity has led to an ongoing phase II trial of "RVD Lite." In this regimen, the bortezomib is given weekly subcutaneously at a reduced dose. The lenalidomide is reduced to 15 mg, and the dexamethasone to 20 to 40 mg weekly. The median age of patients in the trial was 73 (range, 65-91) years. Thus far, the regimen appears to be well tolerated and with high response rates (81%).[35]

Conclusion

In summary, our understanding of myeloma has evolved to recognize the clonal heterogeneity of the disease—as well as the heterogeneity of the patient. Our ability to risk-stratify will continue to evolve on account of the wider availability of genome sequencing. These advances might ultimately allow better targeted therapy while ideally decreasing side effects. In addition, as we improve our assessment tools of elderly patients, we might also be able to further tailor therapy for maximum benefit.

Disclosure

Consultant for Celgene, Janssen, Takeda Speakers bureau for Celgene, Janssen, Takeda, Onyx.

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