High-risk myeloma: when to transplant-or not.

High-Risk Myeloma: When To Transplant—Or Not

Donald M. Eicher , Sagar Lonial, Federica Cavallo, Antonio Palumbo, Bijay Nair, Sarah Waheed, Craig Hofmeister, Heesun J. Rogers

The diagnosis of multiple myeloma requires findings of a clonal plasma cell disorder and myeloma-related organ dysfunction, such as hypercalcemia, renal insufficiency, anemia, and bone disease.[1] Myeloma evolves from a premalignant state, monoclonal gammopathy of undetermined significance,[2] which is present in 3%–4% of the general population,[3] progressing to multiple myeloma at a rate of 1% per year.[4] Prognosis in patients with multiple myeloma depends on several variables, including age, performance status, renal function, disease stage, β_2-microglobulin, and cytogenetic abnormalities.[5] The treatment of multiple myeloma continues to improve due to the development of several new active agents, new drug combinations, and autologous transplantation.[6 and 7] From new information on risk stratification by genetic and molecular prognostic markers, chromosomal abnormalities such as deletion of the long arm of chromosome 13 [del13(q)] or monosomy 13, and t(4:14)(p16.3;q32) [t(4;14)] have been associated with poor prognosis.[8] Patients with high-risk disease do poorly with most therapies and have inferior survival in the absence of complete remission (CR). Their median overall survival (OS) is 3 years, even with aggressive therapy.[9] Thus, questions have arisen now as to the best initial and subsequent use of novel drugs, the role of high-dose therapy, and auto- or allo-transplantation, endpoints for therapy, and the role of consolidation and maintenance therapies.

THE PROBLEM

- A 58-year-old white woman was found to be anemic with hemoglobin of 7 g/dL (normal, 11.5–15.5). She underwent screening colonoscopy and was placed on iron supplementation. She then developed blurred vision, saw an optometrist, was found to have a retinal hemorrhage, and was referred to an ophthalmologist who obtained laboratory testing, the results (normal range bracketed) of which revealed elevation of serum total protein at 15.8 g/dL (6–8.4) and serum IgG of 11,316 mg/dL (717–1,411), borderline creatinine elevation at 1.4 mg/dL (0.7–1.4), and decreased IgA 22 mg/dL (78–391), and IgM 13 mg/dL (53–334). Serum calcium was normal at 8.9 mg/dL (8.5–10.5). Further evaluation revealed serum IgG kappa monoclonal protein, 9.16 g/dL, by serum protein electrophoresis and immunofixation electrophoresis. Serum β_2-microglobulin was elevated (7 mg/dL; normal, 0.3–1.9), albumin was decreased (2.4 g/dL; normal, 3.5–5.0), and the lactate dehydrogenase (LDH) was within normal range (164 U/L; normal, 100–220). Complete blood cell count showed white blood cells 3.8 x 10^3/μL (normal, 3.8–11.0), Hemoglobin 5.7 g/dL (normal, 11.5–15.5), hematocrit 18.8% (normal, 36.0%–46.0%), and platelets 152 x 10^3/μL (normal, 150–400), with 4% circulating plasma cells in peripheral blood (see Figure 1). Bone marrow aspirate smear (see Figure 2) and core biopsy (see Figure 3) identified involvement by plasma cell neoplasm comprising 70% of the total marrow cellularity. Immunostains performed on the core biopsy demonstrated that markedly increased plasma cells were positive for CD138 (syndecan-1) and kappa light chains, and negative for CD79a (mb-1; Ig-α), CD56 (NCAM-1), cyclin D1, and lambda light chain. Cytogenetics demonstrated a normal female karyotype. Interphase fluorescence in situ hybridization (FISH) analysis of the marrow specimen showed

monosomy 13 (see Figure 4), and IgH/FGFR3 fusion, t(4;14) (see Figure 5). Skeletal survey identified partial compression fracture at T8 vertebral body.

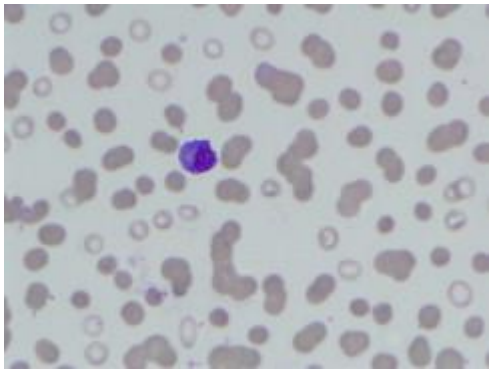

Figure 1. Peripheral blood smear (x50, Wright stain) shows normocytic anemia with remarkable rouleaux formation in red blood cells and circulating plasma cells.

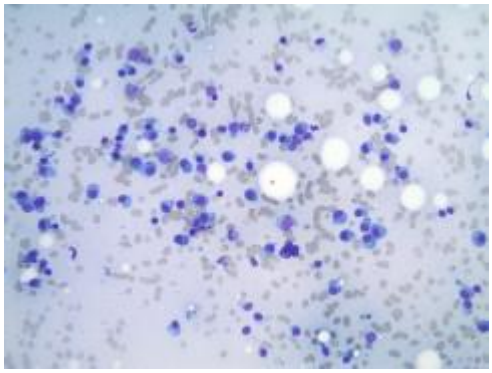

Figure 2. Bone marrow aspirate smear (x50, Wright stain) shows markedly increased atypical plasma cells with anisocytosis, and occasional immature forms with prominent nucleoli or double nuclei (not shown in the photograph).

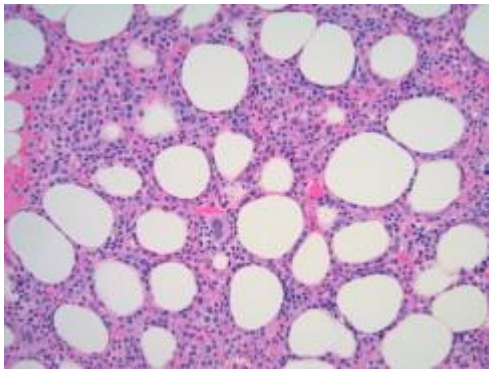

Figure 3. Bone marrow core biopsy (x20, hematoxylin and eosin) shows increased cellularity for age (approximately 60%) with reduced trilineage hematopoietic maturation, and markedly increased plasma cells with atypia and immature forms with nucleoli replacing approximately 70% of the marrow cellularity. Immunohistochemical stains (not shown in the picture) show the plasma cells are positive for CD138 and kappa light chain, and negative for lambda light chain, CD56, CD79a and cyclin D1.

Figure 4. Interphase FISH picture shows a cell with two blue signals from normal two centromeres, one red signal from the locus-specific 13q14 (Rb1) probe, and one green signal from 13q34 (LAMP1) probe. This pattern demonstrates monosomy 13.

Figure 5. Interphase FISH picture shows a cell with a green signal from the locus-specific 14q32 (IgH) probe, an orange signal from 4p16 (FGFR3) probe, and fusion of two signals in proximity. This pattern demonstrates t(4;14)(p16;q32).

By Durie-Salmon Stage[10] and the International Staging System[11] (ISS) the patient had stage III, high-risk myeloma. She received packed red blood cell transfusions. Treatment with bortezomib,

revlimid, and decadron (VRD), was complicated by moderate to severe fatigue, diarrhea, neuropathy, dysgeusia, and weight loss. The serum monoclonal paraprotein decreased to 0.16 g/dL with no detectable urine monoclonal protein after therapy. A very good partial remission was achieved after five cycles of therapy.

Several questions arise in the management of this patient with high-risk multiple myeloma. Is bortezomib-based therapy necessary to overcome her high-risk disease[12]? Should a change of the initial treatment regimen be used if she does not achieve initial CR? Will autologous stem cell transplantation (ASCT) or tandem ASCT (a tandem or double transplant is a procedure involving the administration of a second cycle of high-dose melphalan and a second stem-cell infusion within a few months after the first procedure.) improve her chance of OS and is it currently the standard of care? Or should allogeneic marrow transplantation be considered for this patient with high-risk disease, despite higher treatment-related mortality? What are proper endpoints of therapy: CR, progression-free survival (PFS), and/or OS? Finally, what is the appropriate maintenance therapy for this patient?

EXPERT OPINION 1

The identification and definition of high-risk myeloma represents an important clinical question for newly diagnosed myeloma patients. High-risk disease was previously defined as deletion of chromosome 13 or signs of "proliferation" such as an elevated lactate dehydrogenase (LDH),[13] elevated β_2-microglobulin, or increased plasma cell labeling index, but has more recently been replaced with FISH or gene expression based definitions of high-risk disease.[14] While the use of ISS stage 3 or high LDH does have value, the presence of deletion of 17p, t(4:14), t(14:16),[9 and 15] as well as the presence of circulating plasma cells, is now used more commonly to define high-risk patients at the time of diagnosis.[16]

Practically, it is important to know that if one is to rely on FISH or gene expression profiling at the time of diagnosis, the test must be performed on purified plasma cells, as the use of unselected FISH may result in false negative allocation of patients to a standard risk category. The presence or absence of a FISH-defined risk category may be further enhanced through the use of the ISS stage. Specifically, with the t(4:14) translocation, prognosis was defined further by the concomitant ISS stage such that the outcomes for patients with t(4:14) who had ISS stage 1 disease was very different from those with ISS stage III disease.[17] Thus, older techniques and newer molecular tests are likely complementary, and are useful as one seeks to make optimal decisions when treating patients.

Conventional approaches such as combinations of alkylators and corticosteroids are not effective in improving outcomes for patients with high-risk disease. Additionally, many randomized studies now have demonstrated that the use of allogenic transplant does not improve outcomes for these patients. The Blood and Marrow Transplant Clinical Trials Network group presented results recently of a randomized trial comparing tandem autologous transplant with autologous followed by non-myeloablative allogenic transplant and demonstrated that among both standard- and high-risk patients, there was no improvement in PFS or OS.[18 and 19] Furthermore, the use of allogenic transplant is associated with very high treatment-related mortality as well as complications of graft-versus-host disease and relapse, making this a much less attractive option even for those with high-risk disease where the graft-versus-myeloma effect may not have sufficient time to be a long-term disease control mechanism.

For the specific high-risk feature described in the current case, there have been signs of improved outcomes through the use of new treatment approaches. A study of bortezomib-thalidomide-

dexamethasone induction, followed by high-dose therapy and autologous transplant followed by consolidation and maintenance therapy suggested that among those randomized to receive thalidomide-dexamethasone induction, there continued to be a detrimental impact on PFS for patients who carried the t(4:14) translocation at diagnosis.[20] However, for patients randomized to receive bortezomib-thalidomide-dexamethasone at induction, the negative impact of t(4:14) was no longer seen, suggesting that the combination of a proteasome inhibitor and immunomodulatory drug (IMiD) at diagnosis and as consolidation therapy is a strategy that can be used to help overcome or mitigate the negative impact of high-risk features at diagnosis.

While the use of combination therapy in the induction and consolidation phase may serve to help mitigate certain high-risk subsets of myeloma, it is clear this is not always the case for all poor-risk patients. However, it is important to realize that in an era where we have many more effective agents at our disposal, it is no longer appropriate to treat with induction therapy and have no plans for consolidation or maintenance therapy. This is especially the case among patients with high-risk disease, where patients may achieve a CR but in the absence of ongoing therapy are likely to rapidly relapse, often with a more resistant and genetically complex plasma cell clone. For this reason, the concept of CR duration, first introduced by Barlogie and colleagues, is of value.[21]

In summary, the identification of patients with high-risk features at initial diagnosis is an important part of treatment planning. While the absence of high-risk features does not change the initial recommendation for combination therapy with a proteasome inhibitor, IMiD, and steroids, it does have an impact on the approach towards high-dose therapy, consolidation, and maintenance therapy. For patients with high-risk disease, the ongoing use of autologous transplant following combination induction continues to remain a standard consolidation approach, although this should not be where therapy ends. Additonal therapy in the maintenance setting following transplant, also with combinations such as VRD, are critically important to ongoing suppression of the malignant clone.[22] Thus, the choice of bortezomib and ImID-based induction, high-dose melphalan-based consolidation, and combination maintenance are critical as we attempt to overcome the genomically unstable high-risk plasma cell clone. For patients who have disease that has progressed in the context of bortezomib-based therapy, the use of newer proteasome inhibitors such as carfilzomib,[23 and 24] or alternative partners with bortezomib such as the histone deactelyase inhibitors in combination with bortezomib[25] may offer some patients a way to overcome bortezomib resistance. Trials testing these approaches are currently underway.

Only through early identification and intense combination-based approaches can we hope to improve outcomes for patients with high-risk myeloma. For this particular patient with high-risk t(4;14) multiple myeloma, I recommend combination therapy including a proteasome inhibitor and IMiD both at induction and as consolidation following high-dose therapy and autologous transplant. It is likely that further biological understanding will help in the development of personalized approaches for patients with high-risk disease, and perhaps will help us to ultimately cure patients with standard- and high-risk myeloma.

Sagar Lonial, MD

Department of Hematology and Medical Oncology

Winship Cancer Institute

Emory University School of Medicine

Atlanta, GA

EXPERT OPINION 2

Despite tremendous improvements obtained with the introduction of novel drugs such as thalidomide, bortezomib, and lenalidomide, patients with high-risk features still have poor prognosis. Novel agents, in particular bortezomib, may be able to overcome the adverse influence of cytogenetic abnormalities such as t(4;14) in patients with multiple myeloma who are eligible for transplantation.[12 and 26] The Intergroupe Francophone du Myélome (IFM) used a short-term bortezomib-dexamethasone regimen and found a significant advantage in both PFS and OS of patients with t(4;14), in comparison with patients treated with the combination of vincristine, doxorubicin, and dexamethasone.[12] In the Total Therapy 3 (TT3) trial, with incorporation of bortezomib upfront into the tandem transplant regimen, the presence of high-risk features was not associated with a shorter event-free survival (EFS) and OS.[26] A recent published randomized trial showed that three cycles of VTD (bortezomib-thalidome-dexamethasone) followed by double ASCT induced higher rates of CR or near CR and longer PFS in comparison to TD (thalidomide-dexamethasone) across subgroups of patients with poor prognostic factors, such as t(4;14) and high β_2-microglobulin.[20]

The patient in this case was treated with one of the best available novel three-drug combinations, and obtained a very good partial response after five cycles of treatment. The young age and the high-risk features of this patient justify an aggressive approach targeting CR. This patient is a candidate for a double high-dose chemotherapy with melphalan 200 mg/m^2 and ASCT approach.

It is becoming clear that in multiple myeloma, as in other hematologic malignancies, a deeper response correlates with longer survival.[27, 28, 29 and 30] Among patients with high-risk multiple myeloma, those who achieve a CR have a longer OS than those who do not. This was demonstrated in a landmark survival analysis of 44 patients with high-risk myeloma defined by gene expression profiling.[26] This study demonstrated significantly higher rates of 24-month OS for those achieving a CR compared with those who failed to achieve a CR (approximately 80% v 30%, respectively).

The available data confirm the role of ASCT as standard care for young multiple myeloma patients. In patients with high-risk myeloma, the value of ASCT may be augmented by using post-ASCT maintenance or consolidation therapy to delay time to relapse. Iterative long-term re-inductions with bortezomib-lenalidomide-dexamethasone combinations appear to be promising for patients with t(4;14).[31] In a randomized multicenter trial, the quality of response rates improves across induction, transplant, and consolidation, with 60% of patients achieving CR or near CR after consolidation post-ASCT.[20] Importantly, the three-drug approach after consolidation significantly improved the probability of molecular remission, thus confirming the results of a previous trial.[29]

This patient experienced significant toxicity during induction with the three-drug combination. We may consider a short consolidation course (four cycles) with lenalidomide plus steroids, followed by maintenance with lenalidomide. We have previously shown that a sequential approach including bortezomib as induction and ASCT followed by lenalidomide consolidation-maintenance improved the quality of response, with 66% of patients achieving CR after lenalidomide/prednisone-lenalidomide consolidation-maintenance.[32] The role of lenalidomide maintenance also has been investigated in two large trials, the IFM 2005-02 study and the Cancer and Leukemia Group B (CALGB) trial, where maintenance with lenalidomide significantly improved PFS, irrespectively of risk and quality of response.[33 and 34] However, the safety of long-term maintenance has been questioned because of the issue of second malignancies, and longer follow-up is needed to assess benefit in terms of OS.

In case of an available HLA-matched sibling donor, we would consider the option of an allogeneic transplant approach at first relapse. The introduction of reduced-intensity conditioning regimens has resulted in excellent responses with lower transplantation-related mortality[35 and 36] and stimulated interest in allogeneic transplantation. However, a recent phase III trial showed that non-myeloablative allogeneic stem cell transplant after ASCT was not more effective than tandem ASCT for patients with standard-risk multiple myeloma.[19] However, there are data suggesting a role of allogeneic transplantation in high-risk patients, where this approach showed that t(4;14) was not associated with a worse CR rate or shorter EFS or OS,[37] but further follow-up is needed before final conclusions regarding the utility of ASCT followed by allogeneic stem cell transplant in high-risk patients can be made. We think that allogeneic stem cell transplant is reasonable in the setting of a clinical trial addressing specifically the issue of high-risk patients.

In conclusion, fit patients with adverse prognostic factors such as ISS 3 and poor-risk cytogenetic abnormalities should probably benefit from a sequential approach and prolonged therapeutic schemas, within prospective trials.

Federica Cavallo, MD, PhD

Antonio Palumbo, MD

Department of Hematology

University of Torino

Torino, Italy

EXPERT OPINION 3

The patient has had an excellent response to the bortezomib, lenalidomide, and dexamethasone combination with M protein decreasing from 9.16 g/dL to 0.16 g/dL, albeit at the cost of some side effects. Based on her age and lack of other comorbidities, she appears to be a candidate for ASCT. We recommend as the next step proceeding with cyclophosphamide and granulocyte colony-stimulating factor–based stem cell mobilization followed by melphalan-based stem cell transplant, which would be considered standard of care at this time. We recommend doing a tandem ASCT in her case with the second ASCT being done within 6 months of the first.[38] This should be followed by maintenance with velcade, lenalidomide, and dexamethasone; the duration and dosing will depend on tolerance. This recommendation is based on data from TT3, which had 3 years of VRD maintenance with 5-year OS approaching 80%. In CALGB 100104 there was a benefit in risk of progression and death in the lenalidomide arm compared to placebo after ASCT.[33] Considering the patient's disease is positive for t(4;14), which is known to be sensitive to bortezomib, it makes sense to add this as well. This point is also supported by the Dutch–Belgian Hemato-Oncology (HOVON) Cooperative Group study[39]. The addition of lenalidomide for maintenance carries an added small risk of secondary malignancies, but at this time the benefit of improvement in survival seems to outweigh this risk.

With advances in therapeutics, EFS and OS outcomes in non-transplant regimens at short follow-up times of 2–3 years are comparable to transplant regimens with rates of 80%–90%, but how this pans out on long-term follow-up will determine in the next few years if upfront autologous SCT should be done or if it is safe to delay this until disease progression or relapse. Until such data are available, autologous stem cell transplant should be considered standard of care.

There is some controversy about the appropriate outcome endpoint for clinical trials in myeloma. It is becoming clear that response rates (RR) and CR rates do not correlate well with long-term survival in newly diagnosed patients with myeloma and should not be used as primary endpoints. As has been pointed out, PFS or more appropriately called "progression-free interval" and OS might be better used[40]. There are subgroups of patients who take a long time to achieve CR, while having excellent CR duration and OS (eg, molecular subgroup CD-2), while others who are quick to achieve CR (eg, molecular subgroup CD-1) have a poorer CR duration and OS.[31 and 41] CD-1 and CD-2 are molecular subgroups of myeloma defined by gene expression profiling.[41]

If her response to VRD was not adequate the other considerations should again be a bortezomib-based regimen such as bortezomib/liposomal doxorubicin/ dexamethasone, bortezomib/cyclophosphamide/dexamethasone, or VTDPACE (bortezomib/thalidomide/dexamethasone/cisplatin/doxorubicin/ cyclophosphamide/etoposide). If neuropathy is an issue consideration should be given to administering bortezomib subcutaneously, which has a lesser risk of neuropathy. One should avoid alkylators such as melphalan and bendamustine prior to stem cell mobilization because of their ability to adversely affect stem cell reserve.

In case the patient is not a candidate for stem cell transplantation because of comorbidities or poor functional status, we recommend continuing VRD at lower doses so that she tolerates the treatment regimen better and continuing the same regimen even after the patient has achieved CR. If the tolerance is poor, two drug regimens might be considered: thalidomide/dexamethasone in case of cytopenias and lenalidomide/dexamethasone if neuropathy is a concern. Bortezomib/ melphalan/dexamethasone, melphalan/prednisone/thalidomide, melphalan/prednisone, and bendamustine/dexamethasone are other options.

Considering her age, we would not recommend an upfront allogenic stem cell transplant. If there is disease relapse within a short interval of ASCT (within 2 years) and if she is in good performance status at the time, this should be considered. If not, newer agents such as carfilzomib, pomalidomide, elotuzumab, etc, should be considered.

Bijay Nair, MD, MPHLittle Rock Hematology/Oncology Little Rock, AR

Sarah Waheed, MD

Myeloma Institute for Research and Therapy University of Arkansas for Medical Sciences Little Rock, AR

EXPERT OPINION 4

The often unassuming veneer over high-risk disease in myeloma makes it appear less dangerous at diagnosis. The response proportion is often identical for patients with low- and high-risk disease, but patients with high-risk disease quickly reveal themselves when data for PFS and OS become apparent. These patients are poorly managed with lenalidomide- or ASCT-based therapies, and bortezomib has proven to be the most effective component.[42 and 43] There are insufficient randomized trial data regarding the benefit of tandem transplantation in this group, although results from single-arm studies are clearly not encouraging.[44]

These patients should be referred for novel clinical trials whenever applicable, primarily studying novel agents with mechanisms of action previously not explored in myeloma, allogeneic transplants with interventions likely to both augment the graft-versus-myeloma effect while easing the burden

of graft-versus-host disease, or cell therapies targeting unique markers on the myeloma cell surface similar to the published advances in chronic lymphocytic leukemia using chimeric antigen receptors.[45] The exact wrong approach is to add on currently available therapies, hoping that this Sisyphean task can be achieved with a combination of the drugs we have had available for years.

With treatments available now, patients with high-risk disease should be treated continuously with effort to limit treatment-related mortality—avoiding treatment-induced neutropenic infections, disabling bortezomib-related neuropathy, and the now rare event of thalidomide-associated cardiac morbidity. The goal is to maximize treatment intensity while not spoiling the patient's quality of life with fatigue, neuropathy, or steroid myopathy. For this patient, early use of autologous transplant will provide the maximum benefit of high-dose melphalan, a benefit that appears marginal in patients with P53-deleted disease. Maintenance therapy incorporating both subcutaneous bortezomib and low-dose lenalidomide until the development of toxicity or progression extrapolates the survival benefits from CALGB 100104[33] and follows the lead of Spanish[46] and Italian phase III trials.[47]

Craig C. Hofmeister, MD

Division of Hematology

Ohio State University

Columbus, OH

SUMMARY

There is significant agreement among experts on most, though not all, major points of management in this case. Identification and definition of high risk disease is seen as an important first step in management. This is achieved by FISH or gene expression profiling and generally includes such mutations as 17p, t(4:14), and t(14:16). The molecular profile may be complemented by more traditional features such as ISS stage. Endpoints of therapy such as response rate and CR may be imperfect measures or may be achieved only after ongoing therapy with novel agents. PFS, OS, and CR duration are more appropriate endpoints.

Conventional therapies for myeloma such as alkylating agents and corticosteroids are not effective in high-risk disease. Newer combinations of proteasome inhibitors and IMiDs are important in high-risk disease. Bortezomib may overcome high-risk features such as t(4:14) in patients who can undergo transplantation. Novel three-drug combinations such as bortezomib/lenalidomide/dexamethasone or similar combinations are favored for induction therapy. All experts would choose such a combination induction therapy and then proceed to melphalan-based high-dose therapy and autologous stem cell transplant as a current standard of care for this patient's age and risk group. There is some support among discussants for tandem ASCT based on IFM results and other data. Alternative induction regimens can be considered after inadequate response to bortezomib/lenalidomide/dexamethasone.

Perhaps the strongest recommendation given by the panel is the need in this high-risk myeloma patient for ongoing maintenance therapy after auto-transplantation. Bortezomib can be given subcutaneously to reduce neuropathy with low-dose lenalidomide, maintaining quality of life and reducing toxicity. Experts agree these drugs should be used not only at induction but continuously in ongoing phases of therapy. Allogeneic transplant would be considered at first relapse by some

experts but in general is considered exploratory; treatment-related mortality and graft-versus-host disease complications make this modality less attractive.

A repeat bone marrow biopsy/aspirate after five cycles of induction therapy showed normal hematopoietic maturation with no morphologic evidence of residual involvement by plasma cell myeloma. Skeletal survey was negative. She then underwent stem cell mobilization utilizing filgrastim and plerixafor and collected 11.2 x 10^6/kg CD34 cells. The patient received high-dose chemotherapy with melphalan 200 mg/m^2 with autologous hematopoietic progenitor cell transplantation. Her nausea, vomiting, and electrolyte abnormalities were controlled. Pancytopenia was treated with red blood cell and platelet transfusions. She had mucositis and neutropenic fever. Blood cultures were negative. She was started on intravenous antiobiotics and pain medications for the mucositis. Subsequent follow-up showed appropriate recovery with good marrow function. Fevers and mucositis resolved. Nausea improved with prednisone. She was able to tolerate her pre-release medications and drink a sufficient amount of fluids.

After discharge she experienced pronounced fatigue, anorexia, shortness of breath, palpitations, and tachycardia. She developed a cardiomyopathy with evidence of congestive heart failure and ejection fractions down to 15%. Whether this is due to chemotherapeutic agents, effects of the stem cell transplant, or intercurrent viral infection could not be determined. Subsequently with medical therapy, she improved, with echocardiogram ejection fraction increased to 45%. She has no evidence of heart failure, although she still has minor shortness of breath when climbing stairs. There have been no arrhythmias. Her symptoms improved, and she returned to work full time. She lost 70 pounds over 5 months. Other expected toxicities also resolved.

She started lenalidomide maintenance therapy (10 mg/d) at 4.5 months after the transplant. The dose of lenalidomide was reduced to 5 mg daily at 10.5 months after transplant due to leucopenia. She remains in CR at 25 months after transplant and is on lenalidomide maintenance. She had no other significant adverse effects on lenalidomide.

Two recent trials of lenalidomide maintenance after stem cell transplantation show improved PFS.[33 and 34] Review of cytogenetic abnormalities is ongoing in one[33]; in the other, adverse cytogenetic profiles, including the t(4;14) and the 17p deletion, were more common in the lenalidomide group, and patients with a 13q deletion had higher PFS 3 years after randomization in patients who received lenalidomide maintenance therapy, as compared with those who received placebo.[34] In another recent double-blind, phase III, multicenter, randomized trial in patients who were ineligible for stem cell transplantation, lenalidomide given as part of induction therapy as well as in maintenance therapy significantly improved PFS.[48] An OS benefit may emerge in lenalidomide maintenance studies with longer follow-up.[49]

References

1. R.A. Kyle, S.V. Rajkumar

Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma

Leukemia, 23 (2009), pp. 3–9

2. O. Landgren, R.A. Kyle, R.M. Pfeiffer, J.A. Katzmann, N.E. Caporaso, R.B. Hayes, et al.

Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study

Blood, 113 (2009), pp. 5412–5417

3. R.A. Kyle, T.M. Therneau, S.V. Rajkumar, D.R. Larson, M.F. Plevak, J.R. Offord, et al.

Prevalence of monoclonal gammopathy of undetermined significance

N Engl J Med, 354 (2006), pp. 1362–1369

4. R.A. Kyle, T.M. Therneau, S.V. Rajkumar, J.R. Offord, D.R. Larson, M.F. Plevak, et al.

A long-term study of prognosis in monoclonal gammopathy of undetermined significance

N Engl J Med, 346 (2002), pp. 564–569

5. R. Fonseca, P.L. Bergsagel, J. Drach, J. Shaughnessy, N. Gutierrez, A.K. Stewart, et al.

International Myeloma Working Group molecular classification of multiple myeloma: spotlight review

Leukemia, 23 (2009), pp. 2210–2221

6. H. Brenner, A. Gondos, D. Pulte

Recent major improvement in long-term survival of younger patients with multiple myeloma

Blood, 111 (2008), pp. 2521–2526

7. S.K. Kumar, S.V. Rajkumar, A. Dispenzieri, M.Q. Lacy, S.R. Hayman, F.K. Buadi, et al.

Improved survival in multiple myeloma and the impact of novel therapies

Blood, 111 (2008), pp. 2516–2520

8. R.A. Kyle, S.V. Rajkumar

Treatment of multiple myeloma: a comprehensive review

Clin Lymphoma Myeloma, 9 (2009), pp. 278–288

9. H. Avet-Loiseau, M. Attal, P. Moreau, C. Charbonnel, F. Garban, C. Hulin, et al.

Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome

Blood, 109 (2007), pp. 3489–3495

10. B.G.M. Durie, S.E. Salmon

A clinical staging system for multiple myeloma

Cancer, 36 (1975), pp. 842–854

11. P.R. Greipp, J. San Miguel, B.G. Durie, J.J. Crowley, B. Barlogie, J. Bladé, et al.

International staging system for multiple myeloma

J Clin Oncol, 23 (2005), pp. 3412–3420

12. H. Avet-Loiseau, X. Leleu, M. Roussel, P. Moreau, C. Guerin-Charbonnel, D. Caillot, et al.

Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p)

J. Clin. Oncol, 28 (2010), pp. 4630–4634

13. Hose D, Reme T, Hielscher T, et al. Proliferation is a central independent prognostic factor and target for personalized and risk-adapted treatment in multiple myeloma. Haematologica; 96:87-95.

14. R. Fonseca, B. Barlogie, R. Bataille, et al.

Genetics and cytogenetics of multiple myeloma: a workshop report

Cancer Res, 64 (2004), pp. 1546–1558

15. A.K. Stewart, P.L. Bergsagel, P.R. Greipp, et al.

A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy

Leukemia (2007)

16. Munshi NC, Anderson KC, Bergsagel PL, et al. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. Blood;117:4696-4700.

17. P. Moreau, M. Attal, F. Garban, et al.

Heterogeneity of t(4;14) in multiple myeloma. Long-term follow-up of 100 cases treated with tandem transplantation in IFM99 trials

Leukemia, 21 (2007), pp. 2020–2024

18. Stadtmauer EA, Krishnan A, Pasquini MC, et al. Tandem autologous stem cell transplants (auto-auto) with or without maintenance therapy versus single autologous transplant followed by HLA-matched sibling non-myeloablative allogeneic stem cell transplant (auto-allo) for patients (pts) with high risk (HR) multiple myeloma (MM): results from the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) 0102 Trial. ASH Annual Meeting Abstracts. 2010;116:526.

19. A. Krishnan, M.C. Pasquini, B. Logan, E.A. Stadtmauer, D.H. Vesole, E. Alyea 3rd, et al.

Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial

Lancet Oncol, 12 (13) (2011), pp. 1195–1203

20. M. Cavo, P. Tacchetti, F. Patriarca, M.T. Petrucci, L. Pantani, M. Galli, et al.

Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study

21. A. Hoering, J. Crowley, J.D. Shaughnessy Jr, et al.

Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in Total Therapy protocols

Blood, 114 (2009), pp. 1299–1305

22. Kaufman JL, Nooka A, Muppidi S, et al. Survival outcomes of early autologous stem cell transplant (ASCT) followed by lenalidomide, bortezomib, and dexamethasone (RVD) maintenance in patients with high-risk multiple myeloma (MM). In: ASCO; 2012 June 2012; Chicago, IL ASCO; 2012. p. 8100.

23. R. Vij, D.S. Siegel, S. Jagannath, et al.

An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib

Br J Haematol, 158 (2012), pp. 739–748

24. D.S. Siegel, T. Martin, M. Wang, et al.

A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma

Blood, 120 (14) (2012), pp. 2817–2825

25. Richardson PG, Alsina M, Weber DM, et al. Phase II study of the pan-deacetylase inhibitor panobinostat in combination with bortezomib and dexamethasone in relapsed and bortezomib-refractory multiple myeloma (PANORAMA 2). ASH Annual Meeting Abstracts. 2011;118:814.

26. M. Pineda-Roman, M. Zangari, J. Haessler, E. Anaissie, G. Tricot, F. van Rhee, et al.

Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2

Br J Haematol, 140 (2008), pp. 625–634

27. J.J. Lahuerta, M.V. Mateos, J. Martínez-López, L. Rosiñol, A. Sureda, J. de la Rubia, et al.

Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival

J Clin Oncol, 26 (2008), pp. 5775–5782

28. B. Paiva, M.B. Vidriales, G. Mateo, J.J. Pérez, M.A. Montalbán, A. Sureda, et al.

The persistence of immunophenotypically normal residual bone marrow plasma cells at diagnosis identifies a good prognostic subgroup of symptomatic multiple myeloma patients

Blood, 114 (2009), pp. 4369–4372

29. M. Ladetto, G. Pagliano, S. Ferrero, F. Cavallo, D. Drandi, L. Santo, et al.

Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma

J Clin Oncol, 28 (2010), pp. 2077–2084

30. J.L. Harousseau, M. Attal, H. Avet-Loiseau

The role of complete response in multiple myeloma

Blood, 114 (15) (2009), pp. 3139–3146

31. B. Nair, F. van Rhee, J.D. Shaughnessy Jr, E. Anaissie, J. Szymonifka, A. Hoering, et al.

Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance

Blood, 115 (21) (2010), pp. 4168–4173

32. A. Palumbo, F. Gay, P. Falco, C. Crippa, V. Montefusco, F. Patriarca, et al.

Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients

J Clin Oncol, 28 (5) (2010), pp. 800–807

33. P.L. McCarthy, K. Owzar, C.C. Hofmeister, D.D. Hurd, H. Hassoun, P.G. Richardson, et al.

Lenalidomide after stem-cell transplantation for multiple myeloma

N Engl J Med, 366 (19) (2012), pp. 1770–1781

34. M. Attal, V. Lauwers-Cances, G. Marit, D. Caillot, P. Moreau, T. Facon, et al.

Lenalidomide maintenance after stem-cell transplantation for multiple myeloma

N Engl J Med, 366 (19) (2012 May 10), pp. 1782–1791

35. A. Badros, B. Barlogie, C. Morris, R. Desikan, S.R. Martin, N. Munshi, et al.

High response rate in refractory and poor-risk multiple myeloma after allotransplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions

Blood, 97 (9) (2001), pp. 2574–2579

36. A. Badros, B. Barlogie, E. Siegel, M. Cottler-Fox, M. Zangari, A. Fassas, et al.

Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning

J Clin Oncol, 20 (5) (2002), pp. 1295–1303

37. G. Schilling, T. Hansen, A. Shimoni, T. Zabelina, J.A. Pérez-Simón, N.C. Gutierrez, et al.

Impact of genetic abnormalities on survival after allogeneic hematopoietic stem cell transplantation in multiple myeloma

Leukemia, 22 (6) (2008), pp. 1250–1255

38. B. Barlogie, M. Attal, J. Crowley, F. van Rhee, J. Szymonifka, P. Moreau, B.G. Durie, J.L. Harousseau

Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the Intergroupe Francophone du Myelome, Southwest Oncology Group, and University of Arkansas for Medical Sciences

J Clin Oncol, 28 (7) (2010), pp. 1209–1214

39. P. Sonneveld, I.G. Schmidt-Wolf, B. van der Holt, L. El Jarari, U. Bertsch, H. Salwender, et al.

Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial

J Clin Oncol, 30 (2012), pp. 2946–2955

40. S.V. Rajkumar, G. Gahrton, P.L. Bergsagel

Approach to the treatment of multiple myeloma: a clash of philosophies

Blood, 118 (12) (2011), pp. 3205–3211

41. F. Zhan, Y. Huang, S. Colla, J.P. Stewart, I. Hanamura, S. Gupta, et al.

The molecular classification of multiple myeloma

Blood, 108 (6) (2006), pp. 2020–2028

42. K. Neben, H.M. Lokhorst, A. Jauch, et al.

Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p.

Blood, 119 (2012), pp. 940–948

43. D. Reece, K.W. Song, T. Fu, et al.

Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13

Blood, 114 (2009), pp. 522–525

44. S. Waheed, J.D. Shaughnessy, F. van Rhee, et al.

International staging system and metaphase cytogenetic abnormalities in the era of gene expression profiling data in multiple myeloma treated with Total Therapy 2 and 3 protocols

Cancer, 117 (2011), pp. 1001–1009

45. D.L. Porter, B.L. Levine, M. Kalos, A. Bagg, C.H. June

Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia

N Engl J Med, 365 (2011), pp. 725–733

46. M.V. Mateos, A. Oriol, J. Martinez-Lopez, et al.

Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial

Lancet Oncol, 11 (2010), pp. 934–941

47. A. Palumbo, S. Bringhen, D. Rossi, et al.

Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial

J Clin Oncol, 28 (2010), pp. 5101–5109

48. A. Palumbo, R. Hajek, M. Delforge, M. Kropff, M. Petrucci, J. Catalano, et al.

Continuous lenalidomide treatment for newly diagnosed multiple myeloma

N Engl J Med, 366 (2012), pp. 1759–1769

49. A.Z. Badros

Lenalidomide in Myeloma-a high-maintenance friend

N Engl J Med, 366 (2012), pp. 1836–1838