Changing paradigms in the treatment of multiple myeloma

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The outcome of patients with multiple myeloma (MM) treated with conventional approaches, mainly alkylating agents and glucocorticoids with or without high-dose therapy/autologous stem cell transplant (HDT/ASCT), has been unsatisfactory with a median survival of 2-3 years and 5-6 years for older and younger patients respectively.[1] Moreover, the number of long-term survivors has been disappointingly small. The introduction of the so-called dose-reduced intensity conditioning allogeneic transplantation (Allo-RIC) and the availability of new effective drugs with novel mechanisms of action such as thalidomide, lenalidomide and bortezomib in the last decade have resulted in a new scenario in which there is an expectation for real improvement in long-term outcome for patients with MM. This improvement can come from a better initial therapy for patients eligible and not eligible for HDT/SCT, from more effective rescue regimens for patients with relapsed/refractory disease and finally from better supportive measures and general management.

Patients eligible for high-dose therapy/stem cell transplantation

High-dose therapy followed by autologous stem cell support (ASCT) is considered the gold standard in the initial therapy of younger patients with MM. It is important to highlight that the achievement of complete remission (CR) is the crucial step for a long-term outcome after ASCT in MM. On the other hand, the sensitivity to the initial induction therapy measured by the M-protein size at the time of transplant is the most important predictor of CR after ASCT. With the use of conventional chemotherapy regimens the post-transplant CR rate has been about 35% and the median overall survival of six years in the best circumstances.[2] The current availability of new drugs such as thalidomide, lenalidomide and bortezomib have provided the framework for improving the results of ASCT. Thus, thalidomide/dexamethasone (TD) was approved by the US Food and Drug Administration for use as pre-transplant induction regimen.[3] Another regimen with high anti-myeloma activity is the association of bortezomib and dexamethasone.[4,5] On the other hand, thalidomide and bortezomib are being explored in combination with dexamethasone in the so-called triple combinations: the PAD (bortezomib, adriamycin, dexamethasone) regimen results in pre- and post-transplant CR rates of 24 and 43% respectively[6] and VTD (bortezomib, thalidomide, dexamethasone) results in a post-transplant CR rate of 45%.[7] Moreover, the Total Therapy III used at the University of Arkansas using VTD-PACE plus tandem ASCT, consolidation with VTD and maintenance with TD results in a CR rate at two years of 56%.[8] The real impact of these increased CR rates, when incorporating novel agents in the pre-transplant induction regimens, on the long-term post-ASCT outcome require more prolonged follow-up. Hopefully, the remarkable results of Total Therapy I with 10-year OS of 33% and 7% of patients alive in continued CR after a median follow-up of 12 years will be improved.[9] Five studies on tandem versus single ASCT have been performed. Two showed a significant increase in CR rate, three a prolonged EFS, but only one a significantly longer OS.[2] There are many unsolved questions on the role of ASCT in MM: what will be the long-term impact of induction with novel agents? How to improve the efficacy of high-dose regimens? Is there a role for post-ASCT consolidation/maintenance? Do patients in CR with primary therapy benefit from ASCT intensification? Concerning the frequent question on whether or not there is still a role for ASCT in the era of novel agents it must be considered that ASCT is a therapeutic tool that increases CR in about 20% of the patients, irrespective of the induction regimen.

Because of its high transplant-related mortality (TRM) the myeloablative allogeneic transplantation with conventional conditioning has been almost universally replaced by the so-called dose-reduced intensity conditioning allogeneic transplantation (Allo-RIC) using fludarabine/melphalan or fludarabine/low dose total body irradiation as conditioning regimens. The TRM has been reduced to 10-20% and the CR rate is about 40-50%. The most important predictor of outcome is the disease chemosensitivity with a low tumor burden at the time of transplant. A promising approach is to perform Allo-RIC from related or unrelated HLA-identical donors after debulking with ASCT although results are still controversial.[10-12] The results of two large ongoing prospective studies, one in Europe and the other in the United States investigating the role of the tandem ASCT followed by Allo-RIC are awaited. In any event, there is a need to continue to investigate conditioning intensity and post-transplant strategies aimed at decreasing the TRM, and enhancing the graft-versus-myeloma effect while minimizing the graft-versus-host disease.

Patients not eligible for high-dose therapy/stem cell transplantation

In patients not eligible for ASCT the conventional therapy has consisted of alkylating-based regimens, mainly melphalan and prednisone (MP) or dexamethasone-based therapies. With these regimens the overall response rate (ORR) has been between 40-50% and the CR rate less than 5% with median survivals of about three years. The novel agents thalidomide, bortezomib and lenalidomide have been associated with either MP or dexamethasone usually leading to improved results. Thus, five trials have compared MPT (melphalan-prednisone-thalidomide) versus MP.[1] In all these trials the

ORR and PFS were significantly superior with MPT. In two of these studies the OS was also significantly longer with MPT. Particularly remarkable are the results on PFS and OS achieved in patients older than 75 years with MPT using a daily dose of thalidomide of 100 mg.[13] The combination of MP with bortezomib (MPV) was superior to MP in ORR (71% *vs.* 36%), CR rate (30% *vs.* 4%), PFS (median, 24 *vs.* 16 months) and OS (82% *vs.* 69% at two years).[14] Importantly, MPV was superior to MP in all prognostic subgroups, including high-risk cytogenetics such as t(4;14), t(14;16) and 17p deletion. In a pilot study, the association of MP and lenalidomide (Revlimid) (MPR) resulted in a PR and CR rates of 81% and 24% respectively[15] and the accrual of a large phase III international study comparing MPR versus MP has recently been completed.

A recently published study compared the association of thalidomide and dexamethasone (TD) with MP.[16] TD produced a significantly higher ORR (68% *vs.* 50%) but was more toxic in elderly patients this resulting in a significantly shorter OS (41.5 *vs.* 49.4 months).[16] A large phase III trial has shown that TD was significantly superior to dexamethasone alone in ORR (63% *vs.* 46%) and TTP (22.6 *vs.* 8.5 months).[17] However the CR rate with TD was only 7.7% and this regimen could not be optimal for patients with extramedullary soft-tissue plasmacytomas. The preliminary results of a Medical Research Council trial showed that the association of TD with cyclophosphamide (CTD) resulted in an encouraging CR rate of 22%.

In one phase II trial the association of lenalidomide and dexamethasone resulted in an ORR of 91% with a 3-year survival rate of 88%.[18] On the other hand, an Eastern Cooperative Oncology Group study (ECOG) compared lenalidomide/dexamethasone at full doses of dexamethasone versus lenalidomide/dexamethasone at a dose of dexamethasone of 40 mg weekly.[19] The ORR was lower with low-dose dexamethasone. However, the OS at one and two years was significantly longer with lenalidomide/low-dose dexamethasone due to a significantly lower toxicity and early mortality.[19] This difference was higher in patients older than 65 years. Interestingly, the CR rate of the low-dose dexamethasone arm in patients who received more than 4 cycles was as high as 22%. This study requires longer follow-up. Concerning toxicity, peripheral neuropathy is the major concern in thalidomide- and bortezomib-containing regimens while the risk of deep vein thrombosis makes mandatory the use of antithrombotic prophylaxis when thalidomide or lenalidomide are combined with cytotoxic agents or with dexamethasone.

It seems that the association of MP or dexamethasone with a novel agent such as thalidomide, bortezomib or lenalidomide will become the standard of care for elderly patients with MM in the very near future, once all the three new drugs are approved by the health authorities for their use in up-front therapy. The first choice will depend on the patient age and clinical status as well as on the disease characteristics. A general guideline for the up-front treatment of elderly patients with MM is given in Table 1.

Table 1. Up-front therapy in elderly patients.

"Aggressive" disease	MPV
"Non-aggressive" disease	MPT
Poor cytogenetics	MPV
Renal failure	Vel/Dex
History of peripheral neuropathy	Len-based
Very elderly	MPT (Thal 100 mg/day)
Logistics	MPT/Len-based

Treatment of relapsed/refractory myeloma

The treatment of patients with relapsed/refractory disease constitutes a real challenge. A review on the use of thalidomide in MM shows that in patients with relapsed/refractory disease the ORR is about 30%, that thalidomide in combination with dexamethasone with or without cytotoxic agents results in an ORR of 40-65%[20] and that soft-tissue plasmacytomas do not respond to thalidomide.[21] Bortezomib administered as a single agent induces an ORR and a CR rate up to 43% and 9% respectively.[22,23] The association of bortezomib with pegylated liposomal doxorubicin is superior to bortezomib alone in VGPR plus CR (27 *vs.* 19%), TTP (median, 9.3 *vs.* 6.5 months) and OS at 15 months (75% *vs.* 65%).[24] The combination of lenalidomide plus dexamethasone was superior to dexamethasone alone in ORR (60 *vs.* 22%), CR rate (15 *vs.* 2%), TTP (median 11 *vs.* 5 months) and OS (median, 29.6 *vs.* 20 months).[25,26] A number of three and even four drug combinations showing an encouraging ORR in patients with relapsed/refractory myeloma are being reported. However, most of these studies have important shortcomings: low number of patients, possible favorable patient selection, short follow-up, considerable toxicity and economic cost.[1] We favor the use of a sequential treatment approach for successive relapses. Considering that dexamethasone has only an additive effect when it is combined with thalidomide or bortezomib and that it shows an evident synergism with lenalidomide, we recommend the use of thalidomide or bortezomib either alone or in association with dexamethasone or lenalidomide/dexamethasone rather than multiple agent combinations. The choice of the rescue treatment should depend on many factors: the components of the initial therapy, the degree and duration of response to primary therapy (deep responses with TTP longer than two years and relapsing off therapy might benefit from re-treatment with the initial therapy), performance status and age at the time of relapse (fragile patients must be treated with more gentle approaches), type of relapse (*aggressive* relapses should be treated with bortezomib-based regimens while more *indolent* relapses may benefit from thalidomide- or lenalidomide-containing regimens saving bortezomib for subsequent relapses) and previous toxicity (avoid thalidomide and bortezomib in patients with peripheral neuropathy). In younger patients with chemosensitive relapse an ASCT or an Allo-RIC rescue (if there is an available HLA–identical donor) should be considered.

Current survival prospects for patients with multiple myeloma

From all the above it becomes evident that considerable progress has been made with the introduction of ASCT and with the incorporation of the new drugs thalidomide, bortezomib and lenalidomide. In fact, three studies have shown a significant improvement in the survival of patients with MM diagnosed in more recent years.[27-29] Thus, a Swedish study showed a continuous improvement over a 30-year-period (1973-2003), the maximum improvement being observed in patients younger than 60 years and in the last period of the study (1994-2003).[27] The authors concluded that the improved survival was likely due to the increased use of ASCT. Brenner *et al.*[28] reported a 5-year relative survival increase from 29% to 35% and a 10-year increase from 11% to 17% between 1990-1992 and 2002-2004 respectively. As in the Swedish study, the strongest increase was observed among patients younger than 60 years. By contrast, only a moderate improvement was seen in the age group of 60-69 years and no improvement among older patients. The authors attributed the improvement, at least in part, to the benefit of ASCT and they emphasized that perhaps the impact of the incorporation of novel agents on 5- and 10-year survival was not yet maximized and that hopefully a further improvement on survival derived from the use of novel agents will be seen in the forthcoming years.[28] Finally, the Mayo Clinic group reported improved survival in patients with MM in recent years both in the relapsed and in the newly diagnosed setting.[29] Thus, patients relapsing from ASCT after the year 2000 had a significantly longer survival from the time of relapse than those relapsing in the previous period (median, 24 *vs.* 12 months). Furthermore, in a series of 2,981 patients with newly diagnosed MM those diagnosed within the last decade had a significant improvement in overall survival (median, 45 *vs.* 30 months).

In this issue of the journal, Brenner *et al.*[30] report on the "Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010" in order to provide early estimates of survival expectations by age groups for concurrently diagnosed patients using the so-called model-based projection approach. The data presented by Brenner *et al.* are derived from the 1973-2005 data base of the SEER Programe of the United States National Cancer Institute including data from 32,932 patients with MM from population-based cancer registries of the United States updated in April 2008 and covering a population of about 30 million people. This study shows that the 5- and 10-year relative survival for patients diagnosed in 2006-2010 younger than 45 years is 68% and 55% respectively. This is 15.5% and 19.7% longer than that observed in the traditional cohort analysis. By contrast, survival projections hardly exceeded the estimates from traditional survival analysis for older patients. Therefore, improved survival perspectives for elderly patients remains a major challenge in clinical practice.

From the encouraging results of clinical trials in both the up-front and the relapse setting, and from the improvement in survival in single institution series during the last decade, we can foresee an improved long-term outcome for patients with MM through several actions/interventions: i) the availability of more effective pre-ASCT regimens resulting in a higher post-ASCT CR rate and hopefully a better long-term outcome, ii) the possible use of a tailored front-line therapy for elderly patients by optimizing the use of MPT, MPV or lenalidomide/dexamethasone according to age, performance status, aggressiveness of the disease and co-morbidities, iii) selecting the best rescue regimens after relapse and exploiting all the effective drugs preferably in a sequential use according to previous drug exposure, depth and duration of response and previous toxicity, iv) a careful evaluation of response, serological relapse and clinical progression ensuring a timely, appropriate administration of therapy, v) adequate prophylaxis and/or management of toxicities, in particular peripheral neuropathy and deep vein thrombosis and vi) supportive care with an optimal use of erythropoietin, bisphosphonates, prophylaxis and treatment of infectious complications and appropriate management of patients with renal failure. We are certain that, if the application of all the above expands to large populations, future model-based projection analyses such as the one just reported by Brenner *et al.*[30] will show real enhanced survival perspectives for both young and elderly patients with multiple myeloma.

This work has been supported in part by Spanish Grants from Instituto Carlos III RD06/0020/0005 and 08/0147.

Joan Bladé and Laura Rosiñol have received honoraria for lectures and advisory boards from Janssen-Cilag and Celgene.

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Inherited thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder characterized by thrombocytopenia and microangiopathic hemolytic anemia accompanied by variable neurological dysfunction, renal failure and fever.[1]

Lesions consist of vessel wall thickening (mainly arterioles or capillaries), with endothelial cell swelling and/or detachments from the basement membrane with accumulation of fluffy material in subendothelial space, intraluminal platelet thrombosis and partial or complete obstruction of the vessel lumina. Thrombocytopenia is the likely consequence of platelet consumption in the microcirculation. The reason for hemolytic anemia is not as clear, but it may be a consequence of the mechanical fragmentation of erythrocytes as they flow through partially occluded microvessels.

TTP is a rare disease, with an estimated incidence of 2-10 cases per million/year in all racial groups. Recently, a greater awareness and perhaps improved diagnostic facilities have given the impression that the incidence is increasing.

In the microvasculature of patients with TTP, systemic platelet thrombi develop, mainly formed by platelet and von Willebrand factor (VWF). This protein plays a major role in primary hemostasis forming platelet plugs at sites of vascular injury under high shear stress. VWF is a large glycoprotein secreted by endothelial cells as ultra large (UL) multimers.