How to treat a newly diagnosed young patient with multiple myeloma

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Survival rates of young patients with myeloma have increased markedly in the last decade, mainly due to the use of autologous stem cell transplantation (ASCT) and new, highly efficient rescue treatments. In order to improve the survival of newly diagnosed young patients further, the next steps need to focus on increasing the activity of upfront or debulking regimens, improving the efficacy of ASCT, mainly through the conditioning regimen, and increasing the duration of responses through more effective maintenance or consolidation therapies. Nevertheless, this approach is being challenged by the favorable results obtained with long-term treatment with novel agents and the possibility of reserving the ASCT until relapse. Allogeneic transplantation in newly diagnosed patients should be considered as an investigational procedure and used only in well-designed clinical trials. This review covers the new strategies that are currently under investigation with the aim of optimizing the outcome for newly diagnosed young patients with myeloma.

By the term "young myeloma patient" we understand not only people younger than 65 or 70 years old, but also those fit enough (that is, without severe co-morbidities) to be able to endure intensive treatments and the inconveniences of some intravenous (IV) or repetitive therapies. What should the aim of treatment be in these patients? Ideally it should be to provide a cure or at least ensure long-term survival (> 10 or 20 years) with good quality of life. Achieving such a goal implies the eradication, or at least a major reduction, of the tumor cell clone in most patients. Here we review the current data concerning the treatment of newly diagnosed young patients with myeloma. For this purpose we have divided the discussion into three phases, each with its particular burning question: (1) Induction treatment phase: what is the optimal induction regimen? (2) Intensification phase with autologous stem cell transplantation (ASCT): should ASCT be used upfront or at the time of relapse? and (3) Maintenance or consolidation phase: do we have enough reliable data with which to make general recommendations? We will also address the role of allogeneic transplant and the treatment of high-risk patients, and, first of all, try to shed some light into the controversial matter of determining the value of complete response (CR) as a treatment endpoint.

Should CR Be a Treatment Endpoint?

There is a large body of evidence showing an association between optimal response to ASCT therapy and long-term outcomes such as progression-free survival (PFS) and overall survival (OS) in patients with multiple myeloma (MM).[1,2] This association is not so well established for elderly patients mainly because in the era of melphalan-prednisone (MP) few patients achieved CR. However, the current definition of CR in MM is far from optimal since it is based only on the disappearance of the monoclonal component by immunofixation and the presence of fewer than 5% plasma cells in bone marrow (BM); the incorporation of new criteria, such as the normal free light chain ratio and the absence of clonal plasma cells by immunohistochemistry (stringent CR), though representing a step forward, has not greatly increased its low sensitivity.[3] In order to improve the assessment of treatment efficacy at the BM level, more sensitive tools are currently being investigated. These include multiparametric flow cytometry and RT-PCR, which may help to define immunophenotypic and molecular remission, respectively. These techniques can detect a single clonal cell among between 10^{-4} and 10^{-5} normal cells, which is a sensitivity at least two orders of magnitude greater than that of immunohistochemistry. Nevertheless, it is important to understand that, in contrast to acute leukemia, the BM pattern of infiltration in MM is not uniform; therefore, negative results from immunophenotyping or molecular techniques do not rule out the possibility that residual tumor cells are present at another BM location. In spite of this drawback, recent data indicate that these new tools are more sensitive and provide more accurate prognostic information than the conventional CR definition.[4,5] Another limitation of these BM investigations is the occurrence of extramedullary relapses, which is an emerging problem that is probably associated with the

prolonged survival of MM patients and the capacity of plasma cells to escape the BM milieu. Accordingly, the use of imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography–positron emission tomography (CT-PET) with (18F)2-fluoro-2-deoxy-D-glucose (PET-FDG), should be investigated in order to detect residual disease outside the BM.[6,7] Once the patient achieves CR, this must be lasting; in fact, duration of CR is the best predictor of OS.[8] Finally, it is important to emphasize that the prognostic impact of CR should only be evaluated within uniformly treated cohorts of patients, since differences in treatment duration and the use of consolidation or maintenance therapies may greatly modify the value of CR. For example, it is well established that maintenance treatment in acute lymphocytic leukaemia (ALL) or non-Hodgkin lymphoma (NHL) has a marked impact on the duration of CR and, eventually, on the probability of cure.

Despite these observations about the value of CR and how its assessment might be improved, it should be noted that within an apparently uniform diagnosis of myeloma, together with a large group of patients who may represent two thirds of all MMs, and whose quality of response is clearly associated with survival, three other small subgroups can be distinguished on the basis of their response pattern: (1) rapidly responding but early relapsing. This pattern is also observed in other hematological malignancies such as NHL, and these patients probably harbor distinct genotypic features that would require a different treatment approach; (2) non-responding, non-progressive patients; and (3) those that revert to an MGUS profile after treatment. The final goal would be the design of "risk-adapted" treatment strategies for these singular patient subgroups.[9] Thus, while rapidly responding but early relapsing patients may benefit from intensive-sequential therapy, those developing a monoclonal gammopathy of unknown significance (MGUS) profile and non-responding, non-progressing patients should probably not be over-treated. An additional treatment endpoint is to pay more attention to the individual response obtained with each line of therapy in order to avoid using consolidation or maintenance approaches with drugs that had low efficacy in that particular patient during previous treatment phases.

Induction Treatment: Will Novel Drug Combinations Replace the VAD Regimen?

For the answer to this question to be affirmative, novel drug combinations would need to demonstrate higher efficacy than VAD (vincristine, adriamycin, dexamethasone), in terms of response rate, both before and after ASCT, and this must also result in the prolongation of PFS. However, we do not think it would be so easy to demonstrate the impact on OS, since the heterogeneity of treatments at relapse precludes statistically sound analysis.

The VAD combination has long been the gold standard as a preparatory regimen for young patients who are candidates for ASCT. The efficacy of VAD results in a partial response (PR) rate of 52% to 63%, with 3% to 13% CR rates. The new alternative debulking treatment strategies are based on thalidomide, lenalidomide and bortezomib in combination with well-established anti-myeloma agents such as dexamethasone, adriamycin and cyclophosphamide, or even the combination of two novel agents plus corticosteroids. The results so far obtained with these regimens will be discussed in detail in the next paragraphs.

Thalidomide-based Induction Regimens

The use of thalidomide plus dexamethasone (TD) has been extensively studied (**Table 1**), and several pilot studies have shown 48% to 80% ≥ PR, including CR rates of 4% to 16%. Rajkumar et al[10] compared TD with dexamethasone alone in two randomized phase III studies and both showed a significantly superior results for the TD arm. As shown in **Table 1**, TD also proved to be superior to VAD as an induction regimen.[11] Two other randomized trials showed that the addition of adriamycin to TD (TAD)[12] or thalidomide to VAD (T-VAD) resulted in an increase in the response rate (RR) (72% and 81%, respectively) that was significantly greater than that obtained with VAD (54% and 66%, respectively). The CR rate was relatively low (4%-7%) in these two studies, but the CR plus very good PR (VGPR) was 32% and 38%, respectively, which are significantly higher values than those obtained with VAD (15% and 19%, respectively). The British group has compared cyclophosphamide + TD (CTD) with cyclophosphamide + VAD (CVAD) as induction regimens before transplant, and found the thalidomide arm to be significantly superior, with RRs of 87% and 75%, including 19% and 9% CR, for CTD and CVAD, respectively.[13]

To define the current role of novel agents as induction regimens, it is important to determine whether the apparent initial benefit is maintained after ASCT. In the study of Macro et al, which compared TD and VAD, the difference in VGPR was no longer evident following ASCT (44% vs 42%). In the Hovon study of TAD vs VAD,[12] the benefit in favor of TAD remained after ASCT when considering the VGPR rate (49% vs 32%; $P = .01$) but not for the CR rate (16% vs 11%). This translates into a superior PFS for TAD-compared with VAD-treated patients (33 vs 25 months, respectively; $P < .001$) but a similar OS (59 vs 62 months). Finally, in the UK trial, the CR rate after transplant also remained favourable for the thalidomide arm (51% vs 40% for CTD vs CVAD, respectively; $P = .08$).

Table 1. Results of novel agent-based combinations used as induction therapy: responses before and after autologous stem cell transplantation (ASCT).

Treatment schedule	Pts	Pre-trx ≥ PR (%)	Pre-trx CR +nCR (%)	Post-trx ≥ PR (%)	Post-trx CR + nCR (%)	Reference
Thalidomide-based combinations						
Thal-Dex vs Dex	207	63 vs 41	–	–	–	Rajkumar V et al. J Clin Oncol. 2006;24:431-436
Thal-Dex vs Dex	470	63 vs 46	7.7 vs 2.6	–	–	Rajkumar V et ak. J Clin Oncol. 2008;26:2171-2177
Thal-Dex vs VAD	200	76 vs 52	10 vs 8	–	–	Cavo M et al. Blood. 2005;106:35-39
Thal-Dex vs VAD	204	65 vs 47	35 vs 13*	–	44 vs 42*	Macro M et al. Blood. 2006:108:57a
TAD vs VAD	400	72 vs 54	4 vs 2	87 vs 79	30 vs 21	Lokhorst HM et al. Haematologica 2008;93:124-127.
T+VAD vs VAD	230	81 vs 66	38 vs 19*	–	–	Zervas K et al. Ann Oncol. 2007;18:1369-1375
CTD vs CVAD	254	87 vs 75	19 vs 9	88 vs 76	51 vs 40	Morgan G et al. Blood. 2007;110:3593a
Lenalidomide-based combinations						
Len-Dex vs Len-Dex	445	81 vs 70	17 vs 14	–**	–**	Rajkumar V et al. J Clin Oncol. 2008;26:8504a
Len-Dex vs Dex	198	85 vs 51	22 vs 4	–	–	Zonder J et al. Blood. 2007;110:77a
Len-Dex-Clarithromycin	72	90	46	–†	–†	Niesvizky R et al. Blood. 2008;111:1101-1109.
Len-Cy-Dex	53	83	2	–	–	Kumar S et al. Blood. 2008;112:91a
Bortezomib-based combinations						
Bz-Dex	48	66	21	90	33	Harousseau JL et al. Haematologica. 2006;91:1498-1505
Bz-Dex (alt)	40	60	13	88	30	Rosiñol L et al. J Clin Oncol. 2007;25:4452-4458
Bz-Doxil	63	79	28	–	–	Orlowski R et al. Blood. 2006;108:797a
Bz-Doxil-Dex	36	89	32	96	54	Jakubowiak AJ et al. Blood. 2006;11:3093a
Bz-Adriamycin	21	95	24	95	57	Oakervee HE et al. Br J Haematol. 2005;129:755-762
Bz-Cy-Dex	100	79	11	–	–	Knopp S et al. Blood. 2008;112:2776a
Bz-Cy-Dex	33	100	64	–	–	Reeder CB et al. J Clin Oncol. 2008;26:8517a
Bz-Dex vs VAD	482	82 vs 65	15 vs 7	91 vs 91	40 vs 22	Harousseau JL et al. J Clin Oncol. 2008;26:8505a
Bz-Adriamycin-Dex vs VAD	300	83 vs 59	5 vs 1	93 vs 80	23 vs 9	Sonneveld P et al. Blood. 2008;112:653a
Bortezomib and IMID-based combinations						
Bz-Thal-Dex	38	92	18	–	–	Wang M et al. Hematology. 2007;235-239
Bz-DTPACE	12	83	17	92	58	Badros A et al. Clin Lymph Myeloma. 2006;7:210-216
Bz-Thal-Dex vs Thal-Dex	460	94 vs 79	32 vs 12	–	55 vs 32	Cavo M et al. Blood. 2008;112:158a
VBCMP/VBAD-Bz vs Thal-Dex vs Bz-Thal-Dex	183	72 vs 66 vs 80	28 vs 12 vs 41	97 vs 97 vs 97	54 vs 53 vs 64	Rosiñol L et al. Blood. 2008;112:654a
Bz-Len-Dex	68	100	44	–	–	Richardson P et al. Blood. 2008;112:92a
Bz-Len-Cy-Dex	25	100	36	–	–	Kumar S et al. Blood. 2008;112:93a

* Including VGPR

**4-year OS after 4 cycles and trx: 92% in both arms

†Median EFS for patients receiving trx after Len-Dex clarithromycin: 37 months

Trx indicates transplantation; PR, partial response; CR, complete response; nCR, near CR; Thal, thalidomide; Len, lenalidomide; Dex, dexamethasone; Cy, cyclophosphamide; Bz, bortezomid; Doxil, doxorubicin; VAD, vincristine, adriamycin, dexamethasone; TAD, thalidomide, adriamycin, dexamethasone; CTD, cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide, VAD; VBCMP, vincristine, bleomycin, chlorambucil, melphalan, prednisone; VBAD, vincristine, bleomycin, adriamycin, dexamethasone; DTPACE, cisplatin, cyclophosphamide, dexamethasone, doxorubicin, etoposide, thalidomide.

The most relevant thalidomide-related side effects are peripheral neuropathy and deep venous thrombosis (DVT). Peripheral neuropathy (12%-17% of patients) limits the dose and duration of treatment.[12,14] The overall incidence of DVT ranged from 8% to 23%, and the greatest risk of its occurrence is when thalidomide is combined with chemotherapy, especially with adriamycin. Accordingly, in this setting, anticoagulant prophylaxis with low molecular weight heparin (LMWH) or aspirin is mandatory. Warfarin has been considered as an alternative in DVT risk-reduction strategies. However, therapeutic-dose warfarin is associated with an increased risk of severe hemorrhage, as well as reduced effectiveness in cancer patients receiving chemotherapy. In contrast, low-dose warfarin may not be efficacious in this setting.

Lenalidomide-based Induction Regimens

Lenalidomide is also undergoing first-line evaluation, although the information is more scarce (**Table 1**). Two large randomized trials, one conducted by ECOG[15] and the other by SWOG, have shown that the majority of patients respond to induction with lenalidomide plus dexamethasone (RR of 82 and 85% with a CR rate of 4% and 22%, respectively). In the ECOG trial, 90 of the initial 431 patients went off therapy after the initial 4 cycles and received an ASCT; information about CR rate after ASCT is not available, but the 3-year OS of this cohort of patients was 92% (Rajkumar SV et al, personal communication). Niesvizky et al,[16] in a pilot study of 72 patients, showed that the combination of lenalidomide plus dexamethasone plus clarithromycin was associated with an RR of 90%, including 41% CR (most of which qualified as stringent CR), although after 4 to 6 cycles the CR rate was in the range of 5% to 10%. In this study, 30 patients underwent ASCT and achieved a median EFS of 37 months. Finally, lenalidomide plus dexamethasone has been combined with cyclophosphamide in a dose-finding pilot study that produced a RR of 83% (**Table 1**).

With respect to toxicity, lenalidomide is better tolerated than thalidomide from several perspectives: it does not usually produce clinically significant somnolence, constipation or neuropathy, although the incidence of myelosuppression is higher, mainly neutropenia and thrombocytopenia, which are manageable with dose reduction and growth factor support. Lenalidomide is also associated with risk of DVT and anticoagulant prophylaxis with LMWH or aspirin is also mandatory.

Bortezomib-based Induction Regimens

Numerous phase II clinical trials have been designed to assess the activity of bortezomib-based combinations as frontline therapy in transplant candidate patients. As shown in **Table 1**, the RR ranges from 60% to 95% with 10% to 32% CRs. In all these pilot studies the CR markedly increased after transplant (31%-54%). Results from two large phase III randomized trials have recently been reported. The IFM trial compared bortezomib plus dexamethasone with VAD.[17] After 4 cycles the RR with bortezomib plus dexamethasone was significantly higher than that with VAD (82% vs 65%, including 15% vs 7% CR/nCR) and this benefit remained after transplant (CR/nCR: 40% vs 22%). A significant prolongation of PFS had already been observed for bortezomib plus dexamethasone relative to the VAD arm (69% vs 60% at 2 years, respectively; $P < .01$), although no significant differences in OS have been detected so far. This trial also explored the value of two consolidation DCEP cycles before ASCT, and concluded that this strategy apparently has no benefit since the CR rate did not increase. The Hovon group is currently comparing the combination of bortezomib plus adriamycin and dexamethasone (PAD) vs VAD. The bortezomib arm induced a significantly higher VGPR rate (42% vs 15%) but few CRs (5% vs 1%); nevertheless, the CR significantly increased after transplant, particularly in the PAD arm (23% vs 9% $P < .001$).[18]

The most frequent side effects of bortezomib included gastrointestinal symptoms, cyclical thrombocytopenia and, in particular, peripheral neuropathy. This latter side effect is less frequent in newly diagnosed patients (6%-7%) than reported in previously treated patients, probably because only 3 or 5 cycles are administered as induction therapy.

Bortezomib in Combination with Thalidomide or Lenalidomide

Several pilot studies have explored the feasibility and efficacy of the combination of bortezomib with thalidomide (**Table 1**) in untreated MM patients. The high and rapid response rate (88%-92% ≥ PR, with 18%-22% CR) prompted the design of phase III trials. Thus, the Italian group compared bortezomib plus thalidomide and dexamethasone (VTD) with thalidomide-dexamethasone (TD) and again found the first option to be significantly superior both before ASCT (RR: 94% vs 79% with 32% vs 12% CR/nCR) and after ASCT (55% vs 32% CR/nCR; $P < .001$).[19] In addition this translated into a significantly longer PFS (90% vs 80% at 2 years for VTD vs TD, respectively; $P < .009$), but no significant differences in OS have yet been observed (96 vs 91% at 2 years).The Spanish group has performed a similar comparison (VTD vs TD), but in addition a third arm, based on chemotherapy (VBCMP/VBAD plus bortezomib), was included in the trial.[20] Preliminary results indicate that the TD arm is inferior to the two others in terms of CR rate both before (30%, 6%, 20%) and after (49%, 34%, 43%) ASCT.

The combination of bortezomib with lenalidomide and dexamethasone has also been investigated in a phase I/II trial in which 68 patients were enrolled. All patients responded, including 74% ≥ VGPR and 44% CR/nCR. Moreover, responses were independent of cytogenetics and toxicities were manageable with an incidence of only 3% of grade 3 peripheral neuropathy and DVT. Kumar et al have explored the same combination but with the addition of cyclophosphamide in 25 patients; all responded with 20% of stringent CR plus additional 16% of CR (**Table 1**).[21] Taken together, these data suggest that the upfront combination of a proteasome inhibitor plus one immunomodulatory drug (IMID) is highly effective, although longer follow-up is needed to define the effect on survival and, in particular, to exclude the possibility of inducing more resistant relapses or to burn out drugs that could be very valuable at relapse.

These data lead us to conclude that VAD is no longer the gold-standard induction regimen. TD is probably suboptimal and higher response rates could be achieved if adriamycin or cyclophosphamide were added to TD. A similar possibility may exist for Len-based induction regimens. Bortezomib-dexamethasone +/- thalidomide has proved to be highly effective as a debulking treatment and is significantly superior to VAD or TD before and after ASCT. A similar pattern would be expected for bortezomib + lenalidomide + dexamethasone.

Rationale for Autologous Stem Cell Transplantation

High-dose therapy (HDT) (usually based on melphalan 200 mg/m^2) followed by ASCT prolonged OS as compared with standard-dose therapy (SDT) in prospective randomized trials conducted by the French (IFM) and English (MRC) groups and has provided evidence for longer than 10-year survivorship in at least a subset of patients.[22,23] Nevertheless, the US (SWOG 9321) and French (MAG91) studies and the Spanish (PETHEMA-94) trial, though confirming the benefit of ASCT in terms of RR and event-free survival (EFS), found no greater OS than with SDT[24-26] (**Table 2**). These discrepancies can at least be partly explained by differences in (1) the study designs (the Spanish study randomized only patients who responded to initial therapy while randomization was performed upfront in the others), (2) in the conditioning regimens and, particularly,and (3) the intensity and duration of the chemotherapy arm (the dose of alkylating agents and steroids were higher in the SWOG and Spanish trials, which may explain why OS for conventionally treated patients was longer in these two studies than in the IFM and MRC trials).

Table 2. Results of randomized trials comparing autologous stem cell transplantation (ASCT) with chemotherapy.

	Study	EFS/PFS	OS	*P*	Reference
SDT vs ASCT					
	IFM				Attal M et al. N Engl J Med. 1996;335:91-97
	SDT	18 m (10% 5 y)	37 m (12% 5 y)	S	
	HDT	27 m (28% 5 y)	NR (52% 5 y)		
	MRC				Child JA et al. N Engl J Med. 2003;348:1875-1883
	SDT	19 m	42 m	S	
	HDT	31 m	54 m		
	SWOG				Barlogie B et al. J Clin Oncol. 2006;24:929-936
	SDT	14% 7 y	39% 7 y	NS	
	HDT	17% 7 y	38% 7 y		
	PETHEMA				Blade J et al. Blood. 2005;106:3755-3759
	SDT	33 m	66 m	NS	
	HDT	42 m	61 m		
	MAGG				Fermand JP et al. J Clin Oncol. 2005;23:9227-9233
	SDT	19 m	47 m	NS	
	HDT	25 m	47 m		
Single vs Double ASCT					
	IFM			NS	Attal M. N Engl J Med. 2003;349:2495-2502
	Single	25 m (10% 7 y)	48 m (21% 7 y)		
	Double	30 m (20% 7 y)	58 m (42% 7 y)		
	GIMEMA				Cavo M. J Clin Oncol. 2007;25:2434-2441
	Single	23 m	46 m	NS	
	Double	35 m	43 m		

EFS indicates event-free survival; PFS, progression-free survival; OS, overall survival; SDT, standard-dose therapy; S indicates significant *P*-value; NS, non-significant *P*-value; NR, not reached

In spite of these discrepancies, ASCT is currently considered to be the standard care for younger patients with multiple myeloma, mainly because of its low treatment mortality rate (1%-2%), the benefit in response rate, and, particularly in EFS, which ranges between 25 and 42 months, representing a prolongation of 9 to 12 months compared with conventional chemotherapy. Moreover, soon after ASCT, patients enjoy an excellent quality of life with a long treatment-free interval, which also makes ASCT a cost-effective therapy. In fact, compared with the cost of novel agents, ASCT is no longer an expensive treatment.

Unfortunately, efforts directed towards improving the efficacy of the conditioning regimen have been very limited, and melphalan 200 mg/m^2 (Mel200) continues to be the gold standard. Nevertheless, unpublished data from the Spanish group suggest that the combination of melphalan and busulfan (particularly in its IV formulation) may be superior to Mel200. In addition, the possibility of adding new agents (such as bortezomib) to the conditioning regimen is also under investigation. The IFM Group conducted a pilot study of Mel200 plus Bz (1 mg/m^2 on days -6, -3, +1, +4).[27] Three months after ASCT, 70% of patients achieved VGPR or better, including 34% with CR. Kaufman et al conducted another pilot study of Mel200 plus Bz, administered as a single dose 24 hours before or after Mel200.[28] The VGPR rate was 53% and the PR rate was 94%.

When considering novel agents it is also important to determine whether ASCT enhances the high response rates already obtained with these new induction regimens. As mentioned above, studies with bortezomib-based combinations, including four randomized trials,[17-20] as well as data from thalidomide (TAD regimen)[12] and probably from Len,[15,16] indicated an improved CR rate following ASCT (**Table 1**), which already translates into prolonged PFS. These data imply that induction with novel agents and ASCT are complementary rather than alternative treatment approaches.

The use of tandem ASCT will decrease for two reasons. First, according to the experience of the IFM and Italian groups, only patients achieving less than a VGPR with the first transplant benefit from the second[29,30] (**Table 2**). Second, a similar benefit accrues when using thalidomide as a consolidation/maintenance therapy.[31,32] Moreover, a second transplant at relapse may be performed increasingly often, providing that the duration of the response to the first transplant has lasted for more than 2 or 3 years.

Autologous Stem Cell Transplantation Upfront or at the Time of Relapse?

The favorable results obtained with long-term treatment with novel combinations (for example, the 79% 3-year OS for patients treated with Len-Dex beyond 4 cycles)[15] are challenging the role of upfront ASCT. In fact, one of the current major debates surrounding the treatment of young MM patients concerns whether to use high-dose chemotherapy followed by ASCT upfront or to reserve this treatment until relapse. In other words, the debate is between a more intensive approach with an induction debulking scheme (3-6 cycles) followed by ASCT plus the possibility of a consolidation treatment or a more gentle approach based on an optimized treatment with novel agents until relapse or disease progression occurs, at which time ASCT would be performed. Several groups are currently evaluating these two approaches and it is hoped that these randomized trials will clarify the utility of ASCT.

The "total therapy (TT) programs" are the opposite of the "gentle approach." In TT2, the addition of thalidomide to induction therapy and its use in consolidation and maintenance therapy produced a significantly higher rate of CR compared with that in patients not receiving thalidomide (62% vs 43%) and a significantly greater 5-year EFS rate (56% vs 45%).[33] Although there were no significant differences in the 8-year OS rate, a significant survival advantage was apparent among the group of patients who had cytogenetic abnormalities (46% vs 27%). Overall post-relapse survival was significantly shorter in the group of patients who were randomly assigned to receive thalidomide than in those of the control group, whereas this was not the case among the patients with cytogenetic abnormalities.[34] In the TT 3 program the addition of bortezomib to the previous TT2 approach yielded a higher CR rate (63%), sustained at 4 years from response onset in 87%, with a 4-year estimated OS and EFS of 78% and 71%, respectively. The superiority of the TT3 program over its predecessor, TT2, was also noted in the low-risk subgroup of patients; nevertheless, in the high-risk MM group, outcomes also remained poor with TT3. Based on these results, the Arkansas group has developed a gene-expression profile (GEP)-risk-based algorithm for assigning separate therapies to good-risk (TT4) and poor-risk (TT5) MM.[35]

Maintenance or Consolidation Treatment

Maintenance treatment with interferon and/or corticosteroids has been employed for many years after ASCT. Two extensive meta-analyses showed a median prolongation of both PFS and OS of 4 to 8 months for patients receiving interferon maintenance. However, this approach has been abandoned due to its side effects and what was considered to be only a modest survival advantage. The availability of

novel agents (particularly those in oral formulations: thalidomide and lenalidomide) has renewed the concept of maintenance in an attempt to prolong the duration of the responses after transplant. The IFM group was the first to show that thalidomide as maintenance after tandem ASCT was superior to no maintenance or pamidronate alone,[31] and the Australian group obtained similar results upon comparing thalidomide (for 12 months) plus prednisone (until progression) with prednisone alone.[32] In total, 3 of 5 randomized trials showed a benefit in PFS and OS with thalidomide maintenance (**Table 3**). In spite of these positive results there are several caveats that currently preclude a general recommendation about maintenance with thalidomide outside of clinical trials. Thus, although the Australian trial indicated that maintenance for only one year did not adversely affect the outcome after relapse, two studies[33,35] suggested that the long-term use of thalidomide may induce more resistant relapses. Moreover, the benefit of thalidomide maintenance to patients with poor cytogenetics is not well established. Thus, while the French group found no benefit to patients with 13q deletion[31] and the MMRC found a negative influence of thalidomide treatment in patients with 17p,[36] the TT2 program revealed a survival advantage for patients with abnormal cytogenetics.[34] Finally, there is no consensus about the benefit to patients who are already in CR. Considering all this information together, maintenance with thalidomide could only currently be recommended for less than 12 months and for patients who do not achieve CR after ASCT. The more favorable toxicity profile of lenalidomide makes it an ideal maintenance agent and has prompted several ongoing trials designed to compare continuous treatment until relapse with non-maintenance or treatment for only a short period after ASCT.

The alternative would be to use 3 or 4 courses of consolidation therapy after ASCT. The Italian group showed that the combination of Bz-T-Dex upgraded the responses obtained with ASCT (36% converted from VGPR to CR and 22% became PCR-negative).[37] The Hovon group is currently investigating the role of bortezomib, given every 15 days after ASCT; preliminary results suggest an improvement in CR rate from 23% to 37%.[18]

Allogeneic Transplantation

Allogeneic transplantation (Allo-trx) offers the possibility of a curative approach in MM patients. However, it is associated with high transplant-related mortality (TRM) of up to 30%-50%) and morbidity (mainly due to chronic graft-versus-host disease). Accordingly, it should be only used in carefully defined situations and, preferably, in the context of clinical trials. In order to decrease TRM, various reduced-intensity conditioning regimens (RIC) have been developed (mainly based on fludarabine and melphalan or fludarabine plus radiotherapy [2 Gy]). With this approach the TRM decreased to 12% to 25% but this was associated with a higher incidence of relapses. To try to overcome this problem, several tandem "auto-allo" programs, summarized in **Table 4**, have been employed. In a prospective randomized trial, the French group compared double ASCT with ASCT followed by Allo-RIC among patients displaying poor prognostic features [high β_2-microglobulin and del(13q)]. Unfortunately, there were no event-free survivors at 5 years either after double ASCT or after ASCT followed by Allo-RIC.[38] By contrast, the Italian group described an improvement in terms of OS among patients receiving ASCT followed by Allo-RIC compared with double autologous transplant.[39] The Spanish group recently reported on a similar comparison but in patients failing to achieve at least near-complete remission (nCR) after a first ASCT. Although there was a greater increase in CR rate and a trend towards a longer PFS in favor of Allo-RIC, this was associated with a trend towards a higher TRM (16% vs 5%, $P = .07$), and there were no statistically significant differences in EFS and OS.[40] The Hovon group found these two

Table 3. Studies evaluating the role of maintenance therapy with thalidomide in newly diagnosed patients with multiple myeloma (MM).

				Maintenance vs No Maintenance			
Cooperative Group	N	Initial dose (mg)	Duration of T-maintenance	CR+ VGPR, %	EFS or PFS, %	OS, %	Reference
IFM	597	400	Until PD	67 vs 55	3-y EFS 52 vs 36	4-y OS 87 vs 77	Attal et al. Blood. 2006;108:3289-3294
Australian	243	200	12 months	63 vs 40	3-y PFS 42 vs 23	3-y OS 86 vs 75	Spencer et al. J Clin Oncol. 2009;27:1788-1793
Arkansas	668	400	Throughout study	62 vs 43	5-y EFS 56 vs 45	5-y OS 67 vs 65	Barlogie et al. Blood. 2008;112:3115-3121
MRC (UK)	820	100	Until PD	NA	HR:1.9 $P = .007$	Similar OS	Morgan et al. Blood. 2008;112:656a

CR indicates complete response; VGPR, very good partial response; EFS, event-free survival; PFS, progression-free survival; OS, overall survival; PD, progression of disease; NA, not available.

Table 4. Results of the trials evaluating the role of tandem autologous stem cell transplantation (ASCT) versus ASCT followed by allogeneic reduced-intensity chemotherapy (Allo-RIC).

	Tandem Auto vs Auto/Allo-RIC					
Cooperative Group	Patients	CR, %	EFS, mo	OS, mo	*P*	Ref.
IFM*	166 vs 46	37 vs 55	25 vs 21	57 vs 41	NS	35
GIMEMA	82 vs 80	26 vs 55	33 vs 37	64 vs NR	S	36
PETHEMA**	82 vs 25	11 vs 40	20 vs 26	58 vs 60	NS	37
HOVON†	101 vs 115	42 vs 45	34 vs 39	63 vs 56	NS	38
EBMT	250 vs 110	41 vs 52	15 vs 36	50 vs 65	S	39

*Only high-risk patients (high β2-microglobulin and/or del(13q); worse survival for patients with del(13q)
**Only patients with < CR/nCR after first ASCT
†Patients after first ASCT were randomized to receive maintenance versus Allo-RIC
S indicates significant *P*-value; NS, non-significant *P*-value

approaches equivalent,[41] while recent results from an EBMT study showed a significant advantage of the Allo-RIC approach, whereby at 6 years the PFS was 36% and 15% and the OS was 65% and 50% for the Allo-RIC and double Auto groups, respectively.[42]

Differences in patient characteristics, graft-versus-host disease prophylaxis and conditioning regimens may help to explain these discrepant results. An emerging problem with Allo-RIC is the large proportion of patients who develop extramedullary relapses without bone marrow involvement, indicating that although the disease may be under control in the bone marrow milieu, extramedullary spread may occur. Regarding the use of Allo-trx as rescue therapy, CR or a VGPR is a prerequisite for transplantation, since otherwise patients with active disease will not benefit from this procedure. Once again, these transplants should be performed by experienced groups and within clinical trials. Donor lymphocyte infusions (DLI) given for relapsed myeloma following allogeneic transplantation induce responses in 30% to 50% of patients, but unfortunately the long-term efficacy is limited. Interestingly, the combination of DLI with thalidomide, lenalidomide or bortezomib may improve the response rate and contribute to modulate the immune response, although further studies are required to confirm this.

In summary, due to the high morbidity and mortality incurred, Allo-trx should still be considered as an investigational approach and performed in well-controlled trials. Our current policy is not to use it upfront but at relapse in high-risk patients (including early relapses after ASCT), providing the disease is under control before the allo-transplant is performed.

Can Novel Drugs Overcome the Adverse Prognosis of the High-risk Patients?

We could include several cohorts of patients in the high-risk category: (1) those with poor cytogenetics (particularly *p53(17p13)*,*t(4;14); t(14;16)* or complex karyotype), (2) those with early disease progression under induction therapy, and (3) those presenting with plasma cell leukemia. Recent data indicate that bortezomib combinations can overcome the adverse prognosis of the aforementioned cytogenetic abnormalities.[17,19,20] Nevertheless, both the number of patients with these signatures and their follow-up is still very short. As far as thalidomide is concerned, as previously discussed in the maintenance section, the results are contradictory, since while the TT2 program developed by the Arkansas group suggests that its use throughout the entire treatment programme mainly favors patients with cytogenetic abnormalities,[34] the data from IFM and MMRC suggest no benefit from thalidomide treatment,[31,36] and in the HOVON study patients with del(13q) detected by FISH or conventional karyotyping, had not different outcome. Lenalidomide apparently also overcomes the prognostic influence of del(13q), t(4;14) but not that of 17p deletion.[9] On the basis of these data we would not at this time propose a risk-stratification programme for these patients, but we would favor enrolling them in large clinical trials providing that these include one or two novel agents (particularly bortezomib) plus corticosteroids and/or one alkylating agent. Combinations such as Bz-T-Dex, Bz-Len-Dex or Bz-Len-Dex+ cyclophosphamide are very attractive.

A second possibility, for patients with specific genetic lesions, is to include them in experimental pilot studies in which a targeted therapy (such as FGFR kinase inhibitors in t(4;14) or cyclin-dependent kinase inhibitors) is added to a scheme such as VRD. A third possibility for these patients, particularly those with primary refractory disease, would be to add novel drugs with a complementary mechanism of action (eg, proteasome inhibitors and/or IMIDs plus Hsp90 or HDAC inhibitors). If CR or VGPR is achieved, patients should be exposed to high-dose therapy (ASCT) or to the experimental possibility of a tandem ASCT plus Allo-trx with a reduced-intensity conditioning regimen (Allo-RIC). However, we must emphasize that the choice of option should be made in the context of controlled clinical trials.[9]

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Disclosures

Conflict-of-interest disclosures: JFS-M received honoraria and serves on advisory committees/boards of directors of Celgene, Millennium, and Janssen-Cilag. M-VM received

honoraria from Janssen Cilag and Celgene Corporation. Off-label drug use: Lenalidomide is not approved for the treatment of patients with untreated multiple myeloma who are candidates for autologous stem cell transplantation, and for this indication bortezomib is not approved in the EU.

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