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REVIEW

Management of multiple myeloma: The changing landscape

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Summary Many changes have been incorporated into the approach to multiple myeloma over the last few years, due to improvements in our understanding of the disease biology. New diagnostic and prognostic criteria from the International Myeloma Working Group have clarified the initial clinical approach to this disease. The prognostic impact of chromosomal abnormalities is now recognized, and the detection of specific abnormal cytogenetics is beginning to influence therapeutic decisions. The introduction of the novel agents thalidomide, bortezomib and lenalidomide has expanded treatment options at different points in the disease course; these agents are being evaluated in conjunction with conventional chemotherapy and stem cell transplantation. This report highlights some of the key recent findings in multiple myeloma, and describes areas for future research.

Introduction

The diagnosis of multiple myeloma is made in approximately 15 000 US and 1800 Canadian patients per year. Although occasional patients may be cured with allogeneic stem cell transplantation, the median survival has typically been on the order of 3–4 years. The diagnosis of myeloma requires the detection of $\geqslant$ 10% plasma cells in a biopsy of the bone marrow (or another tissue), which usually produce a monoclonal antibody molecule in the serum and/or urine.[1] About 20% of newly diagnosed patients will have disease that is asymptomatic, also called smoldering myeloma. These patients are important to distinguish because therapy is not required until symptoms supervene.[2] The International Myeloma Working Group has published useful criteria for the establishment of symptomatic disease, which include any of the following manifestations of end-organ damage: hypercalcemia, renal insufficiency, anemia or bone lesions (referred to by the acronym ''CRAB'').[1]

Prognostic Factors in Multiple Myeloma

The new International Staging System (ISS) for multiple myeloma is based on two laboratory

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parameters: β2-microglobulin (β2M) level and serum albumin level. Patients with stage I disease have a β2M < 3.5 mg/L and albumin level ⩽3.5 g/dL (median survival 62 months) compared with stage II disease (neither stage I nor III) (median survival 44 months) and stage III with a β2M ⩾ 5.5 mg/L (median survival 29 months).[3]

Certain cytogenetic and molecular features have also emerged as key prognostic determinants. The first adverse cytogenetic abnormality reported involved deletion of the long arm of chromosome 13 (del 13q). Del 13q is present in about 15% of patients by conventional G-banding techniques and 50–60% using fluorescence in situ hybridization (FISH).[4] Detection of this abnormality by conventional cytogenetics appears to confer a more potent negative effect, likely related to the need for actively dividing tumour cells in order to obtain metaphases for analysis.[5]

More recently, two oncologic pathways have been proposed in the progression of normal plasma cells to monoclonal gammopathy of undetermined significance (MGUS) and ultimately multiple myeloma. First, almost 50% of patients manifest translocations between the immunoglobulin heavy chain gene locus on chromosome 14q32 and one of 5 non-random partner chromosomes—11q13 (CCND1), 4p16.3 (FGFR-3 and MMSET), 6p21 (CCND3), 16q23 (c-maf), and 20q11 (mafB)-which result in altered expression of the juxtaposed oncogenes. These translocations are already present in MGUS and may represent immortalizing events in the evolution from normal plasma cells to MGUS. Del 13q is often seen, and, as the disease progresses, additional cytogenetic abnormalities may occur including ras mutations, myc abnormalities and inactivation of p53 (17p13).[6,7]

On the other hand, about 50% of patients manifest hyperdiploidy of the odd-numbered chromosomes 1,3,5,7,9,11,15,19, and 21. Deletion of 13q and IgH translocations are less common in this group, and the prognosis is in general more favourable.[8] Both of these proposed pathogenetic pathways have in common the dysregulation of one of the three cyclin D genes (cyclin D1, D2 or D3), which is felt to be a unifying event in development of myeloma. Gene expression profiling has been used to further classify myeloma into eight subtypes according to the TC (translocation-cyclin) classification.[6,7]

Our myeloma program at Princess Margaret Hospital identified t(4;14) and p53 (17p13) deletion as negative prognostic factors for the outcome of autologous stem cell transplantation (ASCT). Del 13q was a less powerful adverse factor.[9–11] Of note, FISH or molecular testing is currently required to detect t(4;14). Other groups have described similar findings in both ASCT and non-ASCT patients.[4,12]

The ideal prognostic system would incorporate cytogenetic features with other parameters, and the Intergroupe Francophone du Myelome (IFM) has reported the first effort in this regard. They analyzed the outcome of approximately 1000 newly diagnosed myeloma patients treated with tandem transplant protocols using a battery of FISH cytogenetic studies and other clinical features. The most important factors for overall survival included the presence of t(4;14), p53 deletion, and an elevated β2M level > 3 mg/L. Notably, del 13q was not an independent prognostic factor, but the majority of patients with t(4;14) and p53 deletion also had deletion 13q. Only rarely did patients manifest both t(4;14) and p53 deletion, however.[13]

Although the results of cytogenetic and molecular testing do not yet routinely determine therapy decisions in individual patients, the development of novel strategies are desirable for those with unfavourable abnormalities, and the field is entering the era of so-called ''risk-adapted therapy.'' The first effort came from the IFM, which developed separate ASCT protocols for high-risk patients (IFM 99–03 and IFM 99–04) and lower-risk patients (IFM 99–02) based on adverse risk factors identified in their earlier trial—β2-microglobulin levels and presence of 13q deletion by FISH. Several centres, including our own, will be exploring alternative novel regimens, without first-line ASCT, in patients with t(4;14).

Treatment of Multiple Myeloma

Overview

Despite the excitement about new regimens that produce high initial response rates, the management of multiple myeloma is still mostly based on eligibility for ASCT. Newly diagnosed patients < 65 years of age (or older if fit) have typically been treated with high-dose dexamethasone-based regimens to avoid the hematopoietic stem cell damage that occurs with melphalan, while older or infirm patients usually receive alkylating agents, unless dexamethasone is needed for urgent tumour control, as in the case of pancytopenia or neurologic compromise. Neither of these approaches is curative and patients eventually require salvage regimens. Myeloablative allogeneic SCT (alloSCT) can produce cure in a proportion of selected patients, but is limited by donor unavailability, age limitations and significant risks of morbidity

Table 1 Novel agents in the treatment of multiple myeloma.

Agent	Class	Effects	Toxicity
Thalidomide	IMiD	Decreased adhesion, cytokine production, angiogenesis Increased anti-myeloma immunity	Teratogenicity, peripheral neuropathy, sedation, rash, constipation, VTE
Bortezomib	Proteasome inhibitor	Decreased adhesion, cytokine production, angiogenesis, NFkB, DNA repair	Fatigue, peripheral neuropathy, gastrointestinal toxicity Decrease in neutrophils, platelets and lymphocytes
Lenalidomide	IMiD	Decreased adhesion Increased T cell proliferation, NK cell cytotoxicity, IFN-γ and IL-2	Myelosuppression, VTE

IMiD = immunomodulatory derivative; NK = natural killer; IFN = interferon; IL-2 = interleukin-2; VTE = venous thromboembolism.

and mortality. Less intensive, reduced intensity conditioning (RIC) approaches have been introduced to try to mitigate these problems.

The approach to myeloma is rapidly evolving due to the introduction of the novel agents thalidomide, lenalidomide and bortezomib. These drugs are undergoing evaluation alone and in combination with other anti-myeloma strategies and at different time points in the disease course. These drugs were first studied in the relapsed/refractory setting, and Table 1 summarizes their major cellular effects and toxicities.

Initial Therapy

Initial therapy in candidates for ASCT

Pulsed high-dose dexamethasone with vincristine and doxorubicin, in the so-called VAD regimen, and dexamethasone alone were the most commonly used pre-ASCT induction regimens until recently. VAD produces partial remissions (PR) in about 50%, with complete remssions (CR) (no evidence of monoclonal protein by electrophoresis and immunofixation, and <5% marrow plasma cells) observed in 5—10% of patients.[2] The combination of oral thalidomide and dexamethasone has now been compared with dexamethasone alone in a randomized Eastern Cooperative Oncology Group (ECOG) trial involving 207 patients; four cycles were administered before planned ASCT. The response rate for this combination was 58%, compared to 42% with dexamethasone alone. On the other hand, venous thrombotic events (VTE) and $\geqslant$ grade 4 toxicity were significantly higher in the thalidomide group.[14] Many thalidomide combinations have since been reported in newly diagnosed patients, and these regimens typically produce high rates of CR or near CR (nCR) (same as CR but persistent immunofixation positivity) without compromising subsequent stem cell collection (Table 2).[15—21] Due to the high risk of VTE, some form of thromboprophylaxis is required, although the optimal approach is uncertain. Aspirin is often given unless there is a history of or predisposing factor for thrombosis, in which case full anticoagulation is preferred. The new immunomodulatory derivative of thalidomide lenalidomide, which has been approved by the FDA for relapsed myeloma, has been given with dexamethasone in a pilot study in newly diagnosed patients, with a very high response rate. Aspirin prophylaxis was mandated, and the risk of VTE was low in this pilot study.[22] Limited data are available so far on the ability to collect blood stem cells after regimens containing lenalidomide. Two cooperative group randomized trials of lenalidomide and dexamethasone as induction therapy are ongoing. Lastly, as shown in Table 3, the novel agent bortezomib can be combined with corticosteroids and other chemotherapy agents without prohibitive hematologic or non-hematologic toxicity, and a number of combination studies have been initiated in newly-diagnosed patients.[18,19,23—26] The results also show impressive initial response rates with no detrimental effects on subsequent ASCT.

The ability of these new induction regimens to produce high CR or nCR rates before ASCT has potential implications for the long-term results after ASCT, as most studies have shown a better outcome in patients entering CR or nCR after transplant. Randomized trials are now ongoing to compare bortezomib- and thalidomide-containing induction regimens with VAD or similar programs to test this hypothesis. Two of these trials were presented at the American Society of Hematology meetings in 2006. In the first, patients were randomized to receive induction with either VAD or thalidomide + dexamethasone for 3 cycles followed

Table 2 Thalidomide regimens as part of initial therapy before ASCT.

Study	N	Regimen	Response Rate (%)		VTE (%)
			CR/nCR	Overall	
[a]Rajkumar et al. 2006[14]	102	Thal + Dex	—	72	17
Chanan-Khan et al. 2004[15]	11	VAD + Thal	27	91	12
Hussein et al. 2006[16]	53	DVdt Doxil + Vincristine + Dex + Low-dose Thal	—	87	25
Hassoun et al. 2006[17]	45	Doxo + Dex → Thal + Dex	36	84	11
Badros et al. 2005[18]	57	VDT-PACE	17	83	—
Wang et al. 2005[19]	36	VTD	19	92	—
Williams et al. 2006[20]	27	CTD Cyclophosphamide + Thal + Dex	55	96	11
[a]Goldschmidt et al. 2005[21]	203	TAD Thal + Doxo + Dex	7	80	4-8

CR = complete remission; Dex = dexamethasone; Doxil = pegylated liposomal doxorubicin; Doxo = Doxorubicin; DT-PACE = dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; V = Velcade™ (bortezomib); VTE = venous thromboembolism.
[a] *One arm of phase III trial.*

Table 3 Bortezomib regimens as part of initial therapy before ASCT.

Study	N	Regimen	CR/nCR Rate (%)	CR + PR Rate (%)
Jagannath et al. 2005[23]	32	B +/— Dex	25	88
Oakervee et al. 2005[24]	21	PAD B + Adria + Dex	29	95
Harousseau et al. 2005[25]	48	B + Dex	21	67
Wang et al. 2005[19]	36	VTD B + Thal + Dex	19	92
Badros et al. 2005[18]	57	VDT-PACE	17	83
Orlowski et al. 2006[26]	55	B + Doxil	16	74

Adria = doxorubicin; B = bortezomib; CR = complete remission; Dex = dexamethasone; Doxil = pegylated liposomal doxorubicin; DT-PACE = dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; nCR = near CR; PR = partial remission; Thal = thalidomide; V = Velcade™ (bortezomib).

by melphalan 200 mg/m^2 and ASCT. Although the overall response rate and very good partial remission (at least 90% reduction in serum monoclonal protein = VGPR) rate was significantly better with thalidomide plus dexamethasone before ASCT, the 6 month post-transplant responses were comparable and no survival benefit has been realized.[27] The second study compared VAD and bortezomib + dexamethasone. Again, the response rate, including CR, was improved in the bortezomib arm in this interim analysis,[28] and the long-term results are awaited with interest.

Therapy in patients not eligible for ASCT

Melphalan and prednisone (MP) has been the cornerstone of treatment in this patient population for several decades; CRs are uncommon while partial remission is observed in about 50% of patients. Other combinations of alkylating agents such as VBMCP have yielded higher response rates, but no consistent survival benefit.[24] The addition of thalidomide to MP has been evaluated in two randomized studies, with similar results. Palumbo et al. reported an overall response rate of 73% when thalidomide 100 mg daily was added to 7 days of oral melphalan (4 mg/m^2/day) and prednisone (40 mg/m^2/day) every 4 weeks (MPT) compared with 48% with MP alone. The CR/nCR rate with MPT was 31% versus 4% with MP. The event-free survival at 26 months was 68% for MPT and 32% for the control arm ($P < 0.001$), while the median overall survival had not been reached for either group. Toxicities were more common in the MPT group, particularly DVT (19% versus 2%), grade 3—4 infections (13% versus 2%) and grade 1—2 neurotoxicity (35% versus 5%); low molecular weight heparin prophylaxis for the first 4 months has been recommended.[29] The French IFM 99—06 trial compared MP and MPT, in which thalidomide was stopped when chemotherapy was completed after 12 cycles, with a third regimen of intravenous melphalan 100 mg/m^2 and ASCT twice in patients 65—75 years of age.[30] The superiority of MPT was confirmed, and even produced a better outcome than the double ASCT regimen. Specifically, the median progression free survival (PFS) was 17.2 months for MP, 29.5 months for MPT and 19.0 months for ASCT while the median overall survival (OS) was 30.3, over 56 and 38.6 months, respectively.[30] Palumbo

et al. have now completed a phase I–II trial of lenalidomide and MP and established the maximal tolerated doses in this combination. Response rates were high, but, not surprisingly, myelosuppression was common, and hematopoeitic growth factors were frequently utilized.[31] Mateos et al. in Spain have reported a phase I–II trial in which bortezomib was added to MP. The CR/nCR rate was 46% and the toxicity profile was tolerable.[32] An international phase III of MP versus MP-bortezomib is ongoing.

For the first time, regimens designed for use in elderly patients have produced exceptionally high CR, nCR and PR rates, and an improvement in measures of survival. The toxicities, however, are not inconsequential, and prophylaxis against VTE is an important feature of treatment when thalidomide or lenalidomide is used. The outcome of patients treated with MPT approximates that seen with ASCT in younger patients, an observation which has raised the question of whether transplant is actually necessary in any age group. This determination will depend on several factors, including the durability of responses, toxicity and quality of life considerations and, possibly whether a robust marrow reserve, without significant exposure to chronic oral melphalan or other myelosuppressive agents, is important for the optimal use of salvage regimens. Finally, as myeloma patients are anticipated to live longer, the delayed risk of secondary acute myelogenous leukemia from alkylating agents should be monitored. As our understanding of different risk groups of myeloma becomes more sophisticated, it may be possible to identify patient subsets that can be treated successfully without ASCT.

ASCT

Single agent melphalan at a dose of 200 mg/m^2 is the standard high-dose regimen before ASCT in multiple myeloma, as total body irradiation (TBI)-containing or combination chemotherapy regimens result in more toxicity without additional anti-tumour benefits. The dose of melphalan is usually reduced to 140 mg/m^2 in patients over the age of 70 years and those with significant renal insufficiency to decrease toxicity.

When a single ASCT is performed after older induction regimens such as VAD, CR is observed in about 20–40% of patients. The median PFS ranges from 2.5 to 4 years, with a median overall survival of 4–5 years.[2] Although two large randomized trials have demonstrated that ASCT was superior to conventional therapy, the US Intergroup trial showed only a significantly longer PFS, without a significant prolongation of survival, in the transplant arm. This trial randomized 899 patients to receive a single ASCT after melphalan 140 mg/m^2 plus TBI versus combination chemotherapy with VBMCP; a second randomization to receive alpha interferon versus observation for the maintenance phase was also included.[33] Possible explanations for the lack of survival benefit with ASCT include the use of a TBI-containing regimen, now known to be inferior to high-dose melphalan alone, the low rate of CR observed in the ASCT arm, or the fact that 52% of patients initially receiving VBMCP later underwent salvage ASCT. Other studies in which transplant was delayed until relapse have also shown overall survival that is comparable to that seen when ASCT is as part of initial therapy, although post-ASCT remissions are shorter than those seen with upfront ASCT.

Strategies to improve the outcome of ASCT

Table 4 outlines several strategies designed to enhance the benefit of ASCT. In addition to the exploration of more potent induction regimens before ASCT, as discussed above, the use of tandem ASCT and/or maintenance therapy have been proposed as strategies to improve the results of autologous transplants. Post-ASCT immunotherapy with vaccines is also under evaluation. The use of an allogeneic transplant, after ASCT, represents an aggressive form of immunotherapy in that the ''graft-versus-myeloma'' effect mediated by donor T cells is considered a key anti-tumour component of this modality.

Table 4 Strategies to improve the outcome of ASCT.

Improved induction regimens
-Integration of novel agents
Improved pre-ASCT conditioning regimens
-Escalation of melphalan dose
-Integration of novel agents
Tandem transplantation
-Tandem ASCT
-ASCT followed by allogeneic SCT
Improved post-ASCT measures
-Maintenance therapy
Corticosteroids
Thalidomide
Novel agents
-Cyclic combination chemotherapy
Immunotherapy
-Vaccines

Tandem ASCT

The first results of a large-scale tandem transplant program for newly diagnosed patients were reported by Barlogie et al. at the University of Arkansas. This multiphase program produced a CR rate of 41% and overall median survival of 79 months.[34] The randomized IFM trial comparing single and tandem transplants demonstrated a doubling of both the 7-year of event-free survival probability from 10% to 20% and overall survival from 21% to 42%.[35] The final results are not available for all the other randomized trials, but the data suggest that tandem ASCT improves PFS with a variable effect on overall survival (Table 5).[35–39] Two trials suggest that the second procedure provides the most benefit in patients not achieving a CR, nCR or VGPR.[35,37] A number of centres, including our own, offer second transplants to patients who do not achieve high-grade remission after the first procedure.

An alternative strategy is to collect sufficient stem cell to support two transplants initially but to reserve the second for use only at the time of relapse. We have utilized this approach at Princess Margaret Hospital, and have reported a median time to progression after the second ASCT of 13 months (range 6–99 months), which was longer, not unexpectedly, in patients with a longer progression-free interval (at least 2 years) following the first transplant.[40] The transplant group in Tunisia has shown a benefit with this approach in a randomized trial in which better results were obtained in the arm given a single transplant followed by 5 months of thalidomide maintenance therapy and ASCT performed at relapse, compared with tandem ASCT.[41] Definitive recommendations regarding the optimal timing of second transplants are not clear at the current time, but it is likely that either an ''early'' or ''delayed'' second transplant may afford longer periods of disease control, and perhaps a longer survival, compared with a single procedure during the entire course of the disease.

Use of melphalan doses >200 mg/m^2 before ASCT

The dose-limiting toxicity of melphalan is potentially severe damage to the oral and gastrointestinal mucosa. The use of the cytoprotective agent amifostine has permitted the safe administration of melphalan doses of 240–300 mg/m^2. The CR and nCR rate after a single transplant using this regimen was approximately 50% in a pilot study,[42] and a phase III trial of this regimen versus tandem

Table 5 Studies of tandem ASCT in newly diagnosed multiple myeloma.

Study	N	Age (years)	Regimen (mg/m^2)	Post-ASCT Maintenance Therapy	CR or VGPR Rate (%)		Median EFS (months)		Median OS (months)	
					Single	Tandem	Single	Tandem	Single	Tandem
Attal et al. 2003[35]	399	⩽60	MEL 140 + TBI vs MEL 140 → MEL 140 + TBI	α IFN	42	50	25	30[a]	48	58[a]
Fermand et al. 2003[36]	277	⩽55	MEL 140 vs MEL 140 → CC + TBI	None	39	37	31	33	49	73
Cavo et al. 2003[37]	268	⩽60	MEL 200 vs MEL 200 → MEL + BU	None	38	48	23	35[a]	65	71
Goldschmidt et al. 2005[38]	268	⩽65	MEL 200 vs MEL 200 → MEL 200	α IFN	–	–	22	NYR[a]	23	NYR
Sonneveld et al. 2004[39]	303	⩽65	MEL 70 × 2 vs MEL 70 × 2 → CY + TBI	α IFN	13	28[a]	20	22[a]	55	50

ASCT = autologous stem cell transplantation; α IFN = alpha interferon; CR = complete remission; CC = combination chemotherapy; CY = cyclophosphamide; EFS = event free survival; MEL = melphalan; NYR = not yet reached; OS = overall survival; PR = partial remission; TBI = total body irradiation; VGPR = very good PR; vs = versus.
[a] $p < 0.05$.

transplants has been undertaken by the Seattle group. The IFM has utilized melphalan 220 mg/m^2 following a short course of an anti-interleukin 6 monoclonal antibody before a second, planned ASCT in high-risk patients with acceptable toxicity.[43] The patients had longer PFS and overall survival (41 versus 29 months) compared to historical controls, and had outcomes similar to those seen in patients with the same risk profile who were able to undergo related donor HLA matched reduced intensity conditioning (RIC) allogeneic stem cell transplantation (alloSCT) in a companion trial.[44]

Integration of novel agents into the conditioning regimen

The group in Arkansas has assessed the use of bortezomib 1.0—1.3 mg/m^2 on days −4 and −1 before melphalan conditioning (100—250 mg/m^2 in fractionated doses). No fatal complications were seen and the response rates were high.[45] Subsequently, this group has designed a trial in which total melphalan doses up to 240 mg/m^2 have been divided and each dose given after bortezomib on days 1, 4, 7 +/−10 of the conditioning regimen; oral thalidomide and dexamethasone have also been integrated during this period. A CR/nCR rate of 59% has been reported using this approach in patients with advanced and refractory disease,[46] and a randomized trial of this regimen is planned.

Post-ASCT measures

Although interferon has been utilized in several large trials, including those shown in Table 2, its use is not routine due to the cost, toxicity and limited efficacy. For example, the most recent randomized assessment from the Intergroup study mentioned above did not demonstrate an advantage in PFS or overall survival with alpha interferon maintenance.[33]

Prednisone 50 mg on alternate days has been shown to prolong PFS and overall survival in patients treated with VAD alone,[47] but minimal data regarding its use after ASCT are available. The IFM 99—01 trial by Attal et al. randomized good-risk myeloma patients (neither or only 1 risk factor: β2M level over 3 mg/L or presence of 13q deletion by FISH) to receive no therapy, pamidronate alone, or pamidronate and thalidomide 100 mg daily after ASCT. The analysis demonstrated a statistically significant improvement in PFS (4 year PFS 52% versus 36% without thalidomide, p = 0.002) and OS (4 year OS 87% versus 75% without thalidomide, p = 0.04) from the time of randomization. The benefit was restricted to patients who achieved less than a VGPR with ASCT and in those who lacked del 13q.[48] The first interim analysis of the Australasian maintenance trial, which compared 1 year of prednisolone to prednisolone plus thalidomide after ASCT, demonstrated an improved PFS and overall survival in the arm given thalidomide.[49] Long-term administration of thalidomide can be difficult due to toxicity, and the median onset of the adverse event that led to discontinuation of this agent was 8 months in the IFM 99—01 study.[48] Moreover, the optimal dose and duration of thalidomide maintenance are not yet known, and thalidomide maintenance has not been formally compared to a strategy in which thalidomide is given at the time of disease recurrence.

Newer trials are evaluating other novel agents as maintenance therapy. For example, the ongoing CALGB 100104 phase III study compares lenalidomide with placebo post-ASCT, while the HOVON/GMMS group trial randomizes patients to receive either bortezomib or thalidomide for 2 years after ASCT.

A strategy in which repetitive cycles of myelosuppressive chemotherapy was given post-ASCT has been evaluated by the Arkansas group. In the Total Therapy II program, patients received induction therapy with sequential courses of VAD, DCEP (dexamethasone, cyclophosphamide, etoposide and cisplatin), and CAD (cyclophosphamide, doxorubicin and dexamethasone), with or without thalidomide given continuously throughout the program. After tandem ASCT, patients then received consolidation with DCEP and CAD followed by interferon maintenance. The CR/nCR rate was 80% while PFS and overall survival were superior to Total Therapy I in the absence of loss of 13q by conventional cytogenetics and/or hypodiploidy. In the initial publication, although the CR rate and PFS were longer in the group given thalidomide, the overall survival rate was not improved because the post-relapse survival was shorter in this group than in those not assigned to thalidomide.[50] This observation raises the important question of whether it is better to utilize all the effective agents initially to obtain high CR rates, or to reserve some for later use at the time of disease progression. An updated analysis of this study now shows a survival benefit for the thalidomide arm, as the post-relapse survival times were similar,[51] possibly related to the availability of other effective novel agents/regimens. Of note, the benefit of thalidomide was restricted to a subgroup of patients found to be at high risk using standard risk factors or risk factors defined by the presence of the amplification of chromosome 1q21 or a

previously described gene expression profile. These results once again highlight the need to consider different risk groups in defining optimal therapy.

The subsequent Total Therapy III program from the University of Arkansas integrates novel agents into the pre- and post-ASCT chemotherapy; VDT-PACE and VTD are given after tandem transplants[52] (Table 2). It will be of considerable interest to see if the addition of bortezomib, which has previously been reported to be effective despite the presence of del 13q or t(4;14), will be able to overcome the negative impact of these and other adverse risk factors.[53,54]

Allogeneic SCT

Myeloablative and reduced intensity conditioning (RIC) allogeneic SCT

The disadvantages of conventional myeloablative alloSCT are well described and include patient ineligibility, donor unavailability, regimen related toxicity and graft-versus-host disease (GVHD). These challenges have offset the lower relapse rate compared with ASCT. Case control studies have suggested that ASCT results in similar 5-year survival rates, with considerably less toxicity.[55] RIC allogeneic transplantation has a lower early non-relapse mortality rate, but the graft-versus-myeloma effect is typically associated with clinical GVHD and its potential adverse clinical consequences. Several ongoing randomized trials involving newly diagnosed patients are comparing tandem ASCT with sequential ASCT given first to reduce the tumour burden— followed by RIC alloSCT in patients in whom a suitable donor is identified (Table 6). The IFM 99—03 trial used fludarabine, anti-thymocyte globulin and low-dose busulfan as the conditioning regimen for alloSCT, and, as mentioned above, the median PFS and overall survival rates were similar to those seen with a second autograft using melphalan 220 mg/m^2 +/— anti-interleukin 6 monoclonal antibody (IFM 99—04).[44] Second, the Spanish Myeloma Group has reported preliminary results in 141 patients < 70 years of age who did not achieve a CR or near CR with initial ASCT. These patients were then treated with either a second ASCT or RIC with melphalan and fludarabine if a sibling donor was available. Over 50% of the eligible patients could not receive the second procedure, particularly in the older age groups. In the preliminary analysis, the survival rates in the two groups were similar, because the improved CR rate was offset by a higher transplant-related mortality among patients undergoing RIC alloSCT.[56] The only trial to date reporting

Table 6 Autologous followed by allogeneic stem cell transplantation in newly diagnosed multiple myeloma.

Study (Year)	Age (years)	N	Regimen Autologous/Allogeneic	CR (%)	PR (%)	TRM (%)	Median PFS (months)	Median OS (months)
Garban et al. 2006[44]	<65	166	Mel 220 mg/m^2 +/ — B-E8	30	60	5	30	41
		65	Flu + ATG + Bu	11	73	11	25	35
Rosinol et al. 2005[56]	<70	59	CBV	7	10	5	—	—
		23	Flu + Mel	26	4	17	—	—
Bruno et al. 2007[57]	<65	46	Mel 100-200 mg/m^2	26	63	2	33	58
		58	TBI	53	31	10	43	NYR

ATG = anti-thymocyte globulin; B-E8 = monoclonal anti-interleukin 6 antibody; Bu = busulfan; CBV = cyclophosphamide + carmustine + etoposide; CR = complete remission; Flu = fludarabine; Mel = melphalan; PR = partial remission; TRM = transplant-related mortality; PFS = progression free survival; OS = overall survival; TBI = total body irradiation.

an advantage for ASCT-RIC alloSCT over tandem ASCT is that from an Italian series of 245 newly diagnosed patients with Durie Salmon stage II or III who were less than age 65 and received an alloSCT using TBI conditioning alone if an HLA sibling donor was identified. Of the entire group, 58 underwent an ASCT-RIC alloSCT while 46 received tandem ASCT. These patients were not risk stratified, and the 2-year treatment related death rate was 10% versus 2%, respectively. The median overall survival had not been reached in the allogeneic recipients, compared with 58 months in the tandem ASCT group; the corresponding median event-free survival was 43 months and 33 months, respectively, from the time of diagnosis. Fewer relapses were seen in the alloSCT group, and some of these patients may be cured of myeloma.[57] The large North American Transplant Clinical Trials Network (CTN) protocol 0102 will complete accrual soon and provide more information about the role of RIC alloSCT. This trial compares tandem ASCT to ASCT followed by RIC alloSCT in patients < 70 years of age with an HLA matched donor; a second randomization in the ASCT arm evaluates the use of thalidomide + dexamethasone maintenance versus observation alone.

Management of Relapse

Since myeloma is not curable, patients typically receive sequential regimens, with each regimen given until toxicity or progression supervenes. Data from the Mayo Clinic, albeit collected before the availability of novel agents, indicated that the PFS progressively shortens with each relapse;[58] whether the newer agents will alter this pattern is uncertain. However, the number of options available for relapsed myeloma has increased considerably over the last few years.

Patients who experience a remission lasting several years after a single, or even double, ASCT may derive benefit from another ASCT, [40,59] just as elderly patients with at least a 1-year remission may respond again to melphalan and prednisone. Other strategies are more commonly used, however, and include regimens of high-dose dexamethasone, thalidomide, oral cyclophosphamide, bortezomib and lenalidomide.

Thalidomide has been extensively studied as a single agent or with corticosteroids in relapsed/refractory patients. In general, the PR rate is on the order of 30% when thalidomide is given alone, and 50% when combined with high-dose dexamethasone. The time to progression ranges from 4 to 12 months.[2,60,61] One retrospective study has suggested that better results are obtained with thalidomide and dexamethasone rather than a second ASCT,[62] although this has not yet been formally tested. The toxicity profile, particularly peripheral neuropathy, may limit the dose and duration of thalidomide administration. Thalidomide is not myelosuppressive, however, and many combinations with cytotoxic agents have been described. Response rates are generally high, although the incidence of VTE is increased particularly when doxorubicin is used.[63–71]

Regimens that include oral cyclophosphamide and corticosteroids have been widely used outside of the United States as treatment for progressive myeloma. In our centre, the PR rate of 59 patients with myeloma in first or second relapse after ASCT were given a simple combination of oral cyclophosphamide 500 per week and prednisone 50—100 mg every other day was 41%, while 20% achieved a minimal response. Although CR was uncommon, the median PFS was 19 months and overall survival 29 months.[72] Myelosuppression was uncommon, in contrast to the use of oral melphalan, which may be difficult to administer post-ASCT. Given the favourable toxicity profile, all 3 novel agents –thalidomide, bortezomib and lenalidomide— have been combined with oral cyclophosphamide and corticosteroids with high response rates.[64,65,72–76]

The international APEX trial demonstrated the superiority of single agent bortezomib over dexamethasone alone in terms of response rate and time to progression in patients with relapsed myeloma who have previously received 1 to 3 prior regimens. The initial response rate to bortezomib was 38% compared with 18% for dexamethasone; with longer follow-up, the response rate to bortezomib has increased to 43%. The median time to progression was 6.2 versus 3.5 months while the overall survival was 29.8 versus 23.7 months, respectively, even though over half of the dexamethasone patients were switched to bortezomib during the trial. Patients with only one prior regimen fared better with bortezomib than those treated after two or three recurrences.[77,78] Phase II trials have indicated that the addition of dexamethsone results in PR or minimal response in 15-20% of patients who fail to respond or progress on bortezomib alone.[79,80] The most important side effects include gastrointestinal toxicities, fatigue as well as peripheral neuropathy which may have a painful component. Thrombocytopenia and neutropenia may be observed in a reversible cyclic pattern.[77–79] These toxicities can be anticipated and are usually manageable with dose adjustments. Many bortezomib combinations have been evaluated in the setting of relapsed/refractory disease, including a number that are now being assessed

Table 7 Bortezomib combination regimens in relapsed/refractory myeloma.

Study	N	Regimen	Response Rate (%)		Median TTP/PFS	Median OS
			CR/nCR	PR		
Hollmig et al. 2004[67]	20	VATD Bortezomib + Doxorubicin + Thal + Dex	0	50	–	–
Zangari et al. 2005[68]	85	VTD Bortezomib + Thal + Dex	16	55	–	NYR (53% at 24 mos)
Ciolli et al. 2006[69]	18	VTD × 8	12	35	–	>11 mos
Chanan-Khan et al. 2005[70]	21	VDT × 4–6 Bortezomib + PLD + Thal	14	43	–	–
Jakubowiak et al. 2005[81]	20	VDD × 6 Bortezomib + PLD + Dex	33	23	–	–
Biehn et al. 2006[82]	22	Bortezomib + PLD	36	37	9.1 mos (TTP)	NYR (med f/u 36 mos)
Teoh et al. 2006[83]	14	Bortezomib + Dex + Zoledronic acid	64	29	–	–
Berenson et al. (2006)[84]	35	Bortezomib + po Mel	15	32	8 mos (PFS)	–
Popat et al. 2005[85]	22	Bortezomib + iv Mel +/− Dex × 8	5	38	6.8 (TTP)	–
Terpos et al. 2006[86]	60	VMDT × 8 Bortezomib + iv Mel + Dex + intermittent Thal	11	48	9.5 mos (PFS)	–
Palumbo et al. 2006[71]	30	VMPT Bortezomib + Mel + Pred + Thal	17	50	12 mos (PFS)	84% (1 year OS)
Kropff et al. 2005[73]	53	VDC Bortezomib + Dex + daily po Cyclophosphamide × 8	12	70	12 mos (PFS)	–
Davies et al. 2006[74]	11	CVD Bortezomib + weekly po Cyclophosphamide + Dex	22	42	–	–
Reece et al. 2006[75]	13	Bortezomib + weekly po Cyclophosphamide + Pred × 8	54	31	–	–

CR = complete remission; Dex = dexamethasone; f/u = follow-up; iv = intravenous; med = median; Mel = melphalan; mos = months; nCR = near CR; NYR = not yet reached; OS = overall survival; PLD = pegylated liposomal doxorubicin; PFS = progression free survival; po = per os; PR = partial remission; Pred = prednisone; Thal = thalidomide; TTP = time to progression; V = Velcade™ (bortezomib).

as initial therapy (Table 7).[67–71,73–75,81–86] Recently, the interim results of a large randomized trial reported by Orlowski et al. of bortezomib versus bortezomib plus pegylated liposomal doxorubin found that the time to progression was significantly better with the combination, specifically 9.3 versus 6.5 months, and that toxicities were acceptable. In the most recent analysis, a survival advantage was observed in the combination arm.[87]

Also, the combination of lenalidomide plus dexamethasone has recently been shown to be superior to dexamethasone alone in another large randomized trial; neutropenia, thrombocytopenia and fatigue represent the main toxicities, although anemia, rash and diarrhea may occur.[88] The risk of thromboembolism is increased, particularly when erythropoietin is given concomitantly, and prophylaxis is recommended.[89] Preliminary data indicate that, like bortezomib, lenalidomide and dexamethasone may be effective in the setting of del 13q and t(4;14) disease.[90]

The myelosuppression associated with lenalidomide must be considered when this agent is combined with other agents, as hematopoietic growth factor support may be utilized as an option to dose reduction.[91] Nevertheless, the drug has been effectively combined with doxorubicin and dexamethasone (''RAD''),[92] pegylated liposomal doxorubicin, vincristine and dexamethasone (''lenalidomide + DVd'')[93] and cyclophosphamide plus dexamethasone (CRD),[76] as well as with the novel agent bortezomib.[94]

These trials illustrate the limited utility of dexamethasone alone in relapsed/refractory disease, and future randomized trials will need an alternative comparator. Newer combinations of novel agents and other anti-myeloma agents produce excellent remission rates, which are expected to confer a longer progression free and overall survival. However, there are only limited data to support this contention at the present time, as randomized trials of combination regimens are relatively uncommon, and the studies that are underway have not yet matured. Nevertheless, encouraging results were reported by Offidani et al., who conducted a case-matched study in which continuous thalidomide along with monthly pulsed dexamethasone was compared to the same regimen plus pegylated liposomal doxorubicin (ThaDD) in advanced myeloma patients. They observed a superior overall response rate with the addition of the anthracycline (92% versus 63%) with three times the CR/nCR rate (30% versus 10%). The median progression free survival (21 versus 11 months) and overall survival (35 versus 20 months) were also longer with ThaDD, although toxicity was increased and more supportive care measures were

needed with ThaDD.[66] In addition, just as in the setting of newly diagnosed disease, an aggressive combination strategy has not yet been formally compared with the use of one or two of these agents at a time, in sequence.

Summary and Future Directions

Options for the management of myeloma are rapidly evolving. Better prognostic systems have been devised to characterize this heterogeneous malignancy, which will allow the development of optimal risk-adapted strategies. At this time, it is uncertain whether aggressive multi-modality treatment upfront, using all or most of the new agents followed by stem cell transplantation, can improve the long-term disease-free and overall survival, compared with the approach more often used now in which different less intense regimens/novel agents are given sequentially for multiple relapses. Ongoing clinical trials will help define some of the questions regarding the best approach to induction therapy, post-ASCT maintenance and management of relapsed disease. Moreover, newer effective agents are in the developmental pipeline, and will hopefully be able to extend the survival of myeloma patients even further.

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