



An Update of the Management of Multiple Myeloma: The Changing Landscape

Donna E. Reece

The management of multiple myeloma is rapidly changing. Cytogenetic, molecular and proteomic techniques have led to a better understanding of the pathophysiology of this heterogeneous malignancy. Novel agents designed to interrupt myeloma growth and survival pathways have entered into clinical usage with unprecedented speed, while new prognostic systems based on clinical and biologic features, such as cytogenetic abnormalities, have been developed. A plethora of clinical trials have been initiated

utilizing novel agents, alone or in conjunction with established modalities such as conventional cytotoxic agents and stem cell transplantation. These newer treatments have increased the antitumor response rates in this disease and have provided options for patients whose disease has become resistant to conventional therapy. A major challenge is to define the optimal use of these new agents and combinations in order to significantly impact the natural history of myeloma.

The diagnosis of multiple myeloma is made in approximately 15,000 US and 1800 Canadian patients per year. The median survival is 3-4 years, so the prevalence of this disease is considerably higher. The International Myeloma Working Group has published new criteria for the diagnosis of symptomatic myeloma, which include the detection of $\geq 10\%$ plasma cells in the bone marrow (or tissue biopsy), a monoclonal protein in the serum or urine and the presence of end-organ damage. Hypercalcemia, renal insufficiency, anemia or bone lesions (referred to by the acronym "CRAB") each fulfill the definition of end-organ injury¹ (Table 1). Patients without these features are considered to have asymptomatic myeloma, and are not offered therapy until symptoms supervene.²

Prognostic Factors in Multiple Myeloma

The new International Staging System (ISS) for multiple myeloma was derived and validated from a data set of over 10,000 patients and utilizes two straightforward laboratory parameters: β_2 -microglobulin (β_2M) level and serum albumin level. Patients with stage I disease have a β_2M level < 3.5 mg/L and albumin level ≥ 3.5 g/dL (median survival 62 months) compared with stage II disease (neither stage I or III) (median survival 44 months) and stage III with $\beta_2M \geq 5.5$ mg/L (median survival 29 months).³ The importance of cytogenetic and molecular features as determinants of outcome is being increasingly recognized. Deletion of chromosome 13 or 13q (del 13), detected by fluorescence in situ hybridization (FISH) or conventional G-banding techniques, the t(4;14) translocation and p53 deletion are all associated with a poorer prognosis. Patients

with unfavorable abnormalities are strong candidates for novel strategies and investigational agents.

Treatment of Multiple Myeloma

Initial therapy

Initial therapy in candidates for autologous stem cell transplantation (ASCT): Most newly diagnosed patients < 65 years of age (or older if fit) are candidates for ASCT, and initial therapy must avoid agents with cumulative myelosuppression in order to permit collection of an adequate number of stem cells. Common pre-ASCT induction regimens have included dexamethasone alone or with vincristine and doxorubicin in the so-called VAD regimen; VAD produces partial remission (PR) in about 50% patients, with complete remissions (CR) (no evidence of monoclonal protein by electrophoresis and immunofixation and $< 5\%$ marrow plasma cells) observed in 5%-10% patients.² The combination of oral thalidomide and dexamethasone, which

Table 1. Criteria for end-organ damage due to multiple myeloma (CRAB).¹

Hypercalcemia:

serum calcium > 0.25 mmol/L (1 mg/dL) above the upper limits of normal or > 2.75 mmol/L (11 mg/dL)

Renal insufficiency:

serum creatinine > 173 mmol/L (1.96 mg/dL)

Anemia:

Hgb 2 g/dL below lower limits of normal or Hgb < 10 g/dL

Bone lesions:

lytic lesions or osteopenia with compression fractures

Other:

symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

Correspondence: Donna E. Reece, MD, Princess Margaret Hospital, 610 University Ave., Ste. 5-207, Toronto ON M5G 2M9, Canada; Phone (416) 946-2824, Fax (416) 946-6546, donna.reece@uhn.on.ca

Abbreviations: Hgb, hemoglobin

avoids the inconvenience of a central catheter, has now been subjected to a randomized study through the Eastern Cooperative Oncology Group (ECOG). This regimen was compared with dexamethasone alone for 4 cycles before planned ASCT in 207 patients. The response rate for this combination was 58%, compared to 42% with dexamethasone alone. However, deep venous thrombosis (DVT) occurred in 18% versus 3% patients, respectively, and \geq grade 4 toxicity was noted twice as often in the combination group.⁴ Other investigators have added thalidomide to VAD-like regimens as initial therapy in ongoing trials. These regimens produce higher rates of CR or near CR (nCR) (same as CR but persistent immunofixation positivity), and do not compromise stem cell collection or ASCT.

Thalidomide regimens, particularly when given early in the disease course and in combination with chemotherapeutic agents, are associated with an increased risk of thromboembolism.⁵ The precise mechanism of this complication is unknown, as is the best method of prevention. Although some benefit of prophylactic aspirin or low-dose warfarin has been reported, the use of low molecular weight heparin (LMWH) or full doses of warfarin may be more effective.

Evaluation of new agents as part of initial therapy before ASCT: After the efficacy of bortezomib, a novel first-in-class proteasome inhibitor, was established in relapsed and refractory myeloma patients,^{6,7} a number of trials using this drug in combination with other agents, such as dexamethasone, anthracyclines and thalidomide, have been activated in newly diagnosed patients. Overall response rates have been impressive, ranging from 75% to 100%, with CR or nCR seen in 20%-30%. So far, no detrimental effects on subsequent ASCT have been observed. Lenalidomide, an investigational immunomodulatory agent that is a derivative of thalidomide, has also demonstrated efficacy, with a lower incidence of peripheral neuropathy, in relapsed/refractory myeloma patients.⁸ A pilot study of dexamethasone plus lenalidomide has been initiated in newly diagnosed patients. Prophylactic aspirin has been added after thrombotic events were seen in the early phase of the trial.⁹ This combination is being studied in a randomized trial through ECOG. So far, there are no data available on the ability to collect blood stem cells after lenalidomide therapy. Lenalidomide is not yet approved by the FDA or other regulatory bodies

The ability of newer regimens to achieve high CR or nCR rates pre-ASCT might translate into an improved survival rate after ASCT, as most studies have shown a better outcome for patients in CR or nCR after the procedure. However, longer follow-up is required to evaluate this hypothesis.

Initial therapy in patients not eligible for ASCT: Melphalan and prednisone (MP) has been the mainstay of treatment in the older or medically compromised patient population and yields partial remission in 50%-55%, with only occasional CR. Other combinations of alkylating agents, such as VBMCP, have been utilized by some groups.²

Palumbo et al have compared the outcome of MP with MP plus thalidomide 100 mg daily (MPT) in newly diagnosed patients.¹⁰ The interim analysis revealed that the overall response rate was 73% (31% CR/nCR and 42% PR) with MPT, compared with 48% (4% CR/nCR and 44% PR) 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% vs 2%) and grade 1-2 neurotoxicity (35% vs 5%); LMWH prophylaxis for the first 4 months has been recommended.¹⁰

The same team has compared MP with 2 cycles of intravenous melphalan 100 mg/m² followed by ASCT in newly diagnosed patients 50-70 years of age. The preliminary results showed a higher CR/nCR rate (25% versus 6%; $P = 0.0002$) and superior 3-year event-free survival (37% vs 16%; $P < 0.001$) in the ACST group. As expected, more hematologic toxicity, fever and mucositis was seen in the transplant arm.¹¹ Finally, the French IFM99-06 trial compares these three regimes—MP versus MPT versus intravenous melphalan 100 mg/m² and ASCT \times 2—in patients 65-75 years of age.¹²

Not unexpectedly, bortezomib has also been added to first-line treatment in older myeloma patients. The phase I trial of Mateos et al established that the full dose of bortezomib, 1.3 mg/m², could be combined with MP using a 6 week schedule,¹³ and a large international study has been initiated comparing this 3-drug regimen to standard MP.

Whether the use of these combination regimens upfront will ultimately improve the progression-free survival (PFS) and overall survival, thereby justifying the increased toxicity, is uncertain at this juncture. However, for the first time, several treatments have produced exceptionally high CR, nCR and PR rates in older patients and may prove preferable to MP.

ASCT

High-dose melphalan 200 mg/m² has become the standard conditioning regimen before ASCT in multiple myeloma, as regimens with multiple chemotherapeutic agents or total body irradiation (TBI) produce more toxicity without an added anti-tumor benefit; patients over the age of 70 years usually receive a dose of 140 mg/m² to lessen the morbidity and mortality. A single ASCT after older induction regimens typically produces CR in about 20%-40% of patients, with a median PFS in the range of 2.5-4 years and overall survival of 4-5 years.⁵ Two large randomized trials have established the superiority of ASCT to conventional therapy.² In contrast, the US Intergroup trial, which randomized 510 patients to receive a single ASCT after conditioning with melphalan 140 mg/m² plus TBI versus combination chemotherapy with VBMCP, showed a significantly longer PFS for the transplant arm without prolongation of survival. The fact that 52% of patients initially receiving VBMCP later underwent salvage ASCT may explain the

lack of survival advantage.¹⁴ Other studies in which transplant was deferred until relapse have also suggested similar overall survival, although post-ASCT remissions were shorter, compared with upfront ASCT.

Prognostic factors in patients undergoing ASCT

Adverse prognostic factors before ASCT, such as a high β 2M level, are similar to those identified at diagnosis. Detection of del 13 when detected by conventional cytogenetics, which requires dividing cells for analysis, may confer a particularly poor prognosis.⁵ We have performed FISH cytogenetics in over 100 patients treated with ASCT at Princess Margaret Hospital (**Table 2**). As noted by other investigators, patients with t(4:14) and p53 deletions (17p13) have an inferior prognosis; del 13 by FISH was a less powerful adverse factor. We have not been able to confirm the favorable results in patients with t(11:14) previously described. The number of abnormalities, excluding t(11:14), provided additional prognostic information.¹⁵ Although the use of cytogenetic data does not routinely affect treatment decisions in individual patients at this time, risk-adapted approaches are under investigation in clinical trials. For instance, the Intergroupe Francophone du Myelome (IFM) has developed separate transplant protocols in high-risk patients and lower risk patients based on β 2M level and presence of del 13 by FISH. Our group is exploring the use of novel agents, without ASCT, in patients with t(4;14).

Strategies to improve the outcome of ASCT

Approaches to improve the results of ASCT are listed in **Table 3**. For most oncologists, the primary questions in this regard are: 1) should tandem ASCT now represent the treatment of choice in newly diagnosed myeloma patients? and 2) should maintenance therapy, particularly thalidomide, be used routinely?

Tandem ASCT: Barlogie et al at the University of Arkansas pioneered the use of tandem ASCT in the early management of multiple myeloma in their Total Therapy I program. This program produced a CR rate of 41% and overall median survival of 79 months.⁵ The IFM94 trial was the first randomized study comparing single and tandem transplants. The 7-year probability of event-free survival doubled from 10% to 20%, with a concomitant improvement in

Table 2. Overall survival according to genetic abnormality in 126 patients treated with autologous stem cell transplantation (ASCT).¹⁵

Abnormality	N (%)	Median OS (months)	Relative Risk (95% CI)	p value
p53 del	10 (8)	14.7	4.5 (1.5-13.1)	0.0025
t(4:14)	15 (12)	18.3	4.8 (1.8-12.7)	0.0005
t(11:14)	16 (13)	37.2	1.5 (0.5-4.8)	0.5231
13q del	39 (31)	34.4	2.3 (1.0-5.2)	0.0498
None	43 (34)	not reached	1.0	

overall survival from 21% to 42%.¹⁶ Mature results are not available for the other randomized trials, as the median follow-up required to discern a benefit may exceed 4 years (**Table 4**). In general, the data indicate that tandem ASCT improves PFS with a variable effect on overall survival.¹⁷⁻²⁰ Two trials suggest that the second procedure provides the most benefit in patients not achieving a CR, nCR or very good PR (> 90% reduction in serum monoclonal protein).^{16,18} Therefore, offering tandem ASCT to this subset of patients is a reasonable approach.

An alternative strategy is to collect sufficient stem cell to support two transplants but to reserve the second for use only at the time of relapse. There are less data available for second ASCT in this setting. We have been utilizing such an approach at Princess Margaret Hospital and have reported a median time to progression after the second ASCT of 13 months (range 6-99). Not surprisingly, as noted by others, patients with a longer progression-free interval (at least 2 years) following the first transplant derived the most benefit from a second procedure.²¹ Definitive recommendations regarding about the optimal timing of second transplants are not clear at the current time, particularly in view of emerging information about the biologic subtypes of myeloma and the availability of more effective agents for recurrent disease.

Use of melphalan doses > 200 mg/m² before ASCT: Mucosal damage to the oropharynx and gastrointestinal tract represents the dose-limiting toxicity of melphalan. We have explored the use of melphalan doses of 240-300 mg/m² preceded by 2 doses of amifostine as a cytoprotective agent. Mucosal toxicity was acceptable in myeloma patients conditioned with 280 mg/m² and amifostine, and the CR rate with a single transplant was 60%.²² Further phase III evaluation of this regimen is planned.

Integration of novel agents into the conditioning regimen: The use of new drugs in conjunction with the pre-transplant conditioning regimen has not been well-stud-

Table 3. Strategies to improve the outcome of autologous stem cell transplantation (ASCT).

- Improved induction regimens
 - Integration of novel agents
- Improved pre-ASCT conditioning regimens
 - Escalation of melphalan dose
 - Integration of novel agents
- Tandem ASCT
- Improved post-ASCT measures
 - Maintenance therapy
 - Alpha interferon
 - Corticosteroids
 - Thalidomide
 - Combination chemotherapy
 - Novel agents
 - Allogeneic SCT
- Immunotherapy
 - Vaccines

Table 4. Randomized studies of tandem autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma.

Study	N	Age	Regimen	Maintenance	CR/VGPR Rate (%)		EFS		OS		Comment
					Single	Tandem	Single	Tandem	Single	Tandem	
Attal ¹⁶	399	≤ 60	MEL 140 + TBI vs MEL 140 → MEL 140 + TBI	α IFN	42	50	25	30*	48	58*	Greatest benefit of 2nd ASCT in pts in ≤ VGPR after 1st
Fermand ¹⁷	277	≤ 55	MEL 140 vs MEL 140 → CT + TBI		39	37	31	33	–	–	
Cavo ¹⁸	268	≤ 60	MEL 200 vs MEL 200 → MEL + BU		38	48	21	31	–	–	Greatest benefit of 2nd ASCT in pts in ≤ nCR after first
Goldschmidt ¹⁹	268	≤ 65	MEL 200 vs MEL 200 → MEL 200	α IFN	–	–	22	NYR*	–	–	No effect of del 13q
Sonneveld ²⁰	303	≤ 65	MEL 70 x 2 vs MEL 70 x 2 → CY + TBI	α IFN	13	28*	20	22*	55	50	Prognostic factors β2M, del 13q, abnormal 1p

*Statistically significant

Abbreviations: ASCT, autologous stem cell transplantation; α IFN, alpha interferon; β2M, β2-microglobulin; CR, complete remission; CT, chemotherapy; del 13, deletion of 13; EFS, event free survival; MEL, melphalan; OS, overall survival; TBI, total body irradiation; nCR, near CR (same as CR except immunofixation positivity); NYR, not yet reached; PR, partial remission; pts, patients; VGPR, very good PR (> 90% reduction in serum monoclonal protein; BU, busulfan.

ied. One preliminary report from Arkansas has assessed 2 doses of bortezomib just before melphalan conditioning.²³

The IFM companion trials for high-risk patients use one ASCT followed either by a second ASCT (IFM99-04) or reduced intensity conditioning (RIC) allogeneic SCT (IFM99-03) depending on the availability of an HLA-matched sibling donor.²⁴ A β2M level over 3 mg/L and presence of del 13 by FISH defined high-risk disease. In IFM99-04, conditioning for the second ASCT was melphalan 220 mg/m²; patients were also randomized to receive a short course of an anti-interleukin-6 monoclonal antibody or not. The final results, presented at the 10th International Myeloma Workshop, did not show a benefit with the antibody.²⁵ However, the 3-year survival rate for the higher-dose melphalan autografts exceeded 3 years, which represents an encouraging finding in this poor-risk group. The results of IFM99-03 will be discussed further in the section below on allogeneic transplantation.

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. As well, the recent Intergroup study mentioned above included a second randomization to alpha interferon or observation after ASCT or IBMCP, and did not demonstrate an advantage in PFS or overall survival with interferon maintenance.¹⁴ Corticosteroid maintenance has been shown to prolong remission after conventional therapy, but no data are available regarding its efficacy post-ASCT. Newer approaches such as those based on thalidomide are under evaluation. However, the duration of thalidomide is often limited by the development of side effects, including sedation, constipation, dizziness, rash, DVT and, most notably, peripheral neuropathy. The National Cancer Institute of Canada (NCIC) MY9 randomized phase II trial comparing maintenance with thalidomide 400 mg versus 200 mg daily revealed that, even with the lower dose, patient attrition was a concern.²⁶ The ongoing NCIC MY10 study randomizes patients to thalidomide 200 mg daily plus alternate day prednisone versus observation alone after high-dose melphalan and ASCT. Encouraging results have been reported in the IFM99-02 trial by Attal et al. In this trial, good-risk myeloma patients (neither or only 1 risk factor: β2M level over 3 mg/L and presence of del 13 by FISH) were randomized to receive no therapy, pamidronate alone, or pamidronate and thalidomide 100 mg daily after ASCT. The first interim analysis showed a statically significant improvement in PFS (median 27 vs 28 vs > 38 months, respectively), although no difference in overall survival has been noted.²⁷ One potential explanation for this finding is that patients can respond to thalidomide given at the time of relapse. As an alternative to thalidomide, the ongoing CALGB 100104 phase III study compares lenalidomide with placebo after ASCT.

The University of Arkansas Total Therapy programs have pioneered the use of repetitive cycles of myelosuppressive chemotherapy after ASCT. Total Therapy II—induction with sequential VAD, DCEP (dexamethasone, cyclophosphamide, etoposide and cisplatin), and CAD (cy-

lidomide are under evaluation. However, the duration of thalidomide is often limited by the development of side effects, including sedation, constipation, dizziness, rash, DVT and, most notably, peripheral neuropathy. The National Cancer Institute of Canada (NCIC) MY9 randomized phase II trial comparing maintenance with thalidomide 400 mg versus 200 mg daily revealed that, even with the lower dose, patient attrition was a concern.²⁶ The ongoing NCIC MY10 study randomizes patients to thalidomide 200 mg daily plus alternate day prednisone versus observation alone after high-dose melphalan and ASCT. Encouraging results have been reported in the IFM99-02 trial by Attal et al. In this trial, good-risk myeloma patients (neither or only 1 risk factor: β2M level over 3 mg/L and presence of del 13 by FISH) were randomized to receive no therapy, pamidronate alone, or pamidronate and thalidomide 100 mg daily after ASCT. The first interim analysis showed a statically significant improvement in PFS (median 27 vs 28 vs > 38 months, respectively), although no difference in overall survival has been noted.²⁷ One potential explanation for this finding is that patients can respond to thalidomide given at the time of relapse. As an alternative to thalidomide, the ongoing CALGB 100104 phase III study compares lenalidomide with placebo after ASCT.

clophosphamide, doxorubicin and dexamethasone), with or without thalidomide, followed by tandem ASCT, consolidation with DCEP and CAD chemotherapy, and interferon maintenance—showed the feasibility of this approach. The CR/nCR rate was 80% while PFS and overall survival were superior to Total Therapy I in the absence of loss of q13 by conventional cytogenetics and/or hypodiploidy.^{5,28} Updated results of Total Therapy II noted more CRs and a longer event-free survival in the thalidomide arm. However, overall survival was not improved, as patients in the thalidomide arm had a shorter survival after relapse. An important finding was the identification of a new adverse cytogenetic and molecular feature, amplification of 1q21(CKS1B) by FISH.²⁸

Novel agents have been integrated into post-ASCT chemotherapy in Total Therapy III, which includes VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide, etoposide) and VTD (bortezomib, thalidomide, dexamethasone) after tandem transplants.²⁹ It will be of considerable interest to see whether the addition of bortezomib, which has been reported to be able to overcome the negative impact of q13 deletion found by conventional cytogenetics,³⁰ will improve the outcome of patients in this and other poor-risk groups, such as those with t(4:14) and amplifications of 1q21.

Allogeneic SCT

Myeloablative allogeneic SCT (alloSCT) can produce cure in a small proportion of selected patients but is limited by lack of appropriate donors, age limitations and significant risks of morbidity and mortality due to graft-versus-host disease and other complications. Although 5-year survival rates may be comparable to less toxic ASCT,³¹ survival rates may be better after this time point in alloSCT recipients due to a lower relapse rate. Less intensive RIC alloSCT has been introduced in an effort to mitigate some of the problems while maintaining the benefits, such as a tumor-free graft and the “graft-versus-myeloma effect” of allogeneic transplantation. RIC allogeneic transplantation has less early non-relapse mortality, although late relapses and transplant-related deaths have become apparent.⁵ Unfortunately, the graft-versus-myeloma effect, a critical anti-tumor mechanism with RIC regimens, is associated with the undesirable clinical manifestations of GVHD. The prevailing opinion is that RIC allogeneic SCT should be performed after ASCT as a consolidation measure, preferably in the setting of a clinical trial. The preliminary results of two such studies have been reported. First, high-risk patients with a suitable donor in the IFM99-03 trial, after undergoing ASCT, were conditioned with fludarabine, anti-thymocyte globulin and low-dose busulfan and were compared with those treated with a second intensified autograft (with melphalan 220 mg/m² +/- anti-interleukin-6 monoclonal antibody as per IFM99-04); the median PFS and overall survival rates were similar.²⁴ Second, the Spanish Myeloma Group reported results in 141 patients < 70 years

of age who did not achieve a CR or nCR with initial ASCT. These patients were then treated with either a second ASCT or RIC allogeneic SCT with melphalan and fludarabine if a sibling donor was available. Of note, 56% could not undergo the second procedure, particularly in the older age groups. Although the CR rate was higher with alloSCT, the transplant-related mortality was greater, leading to comparable survival rates in the two groups.³² More information will become available with longer follow-up of these and other trials. The large Blood and Marrow Transplant Clinical Trials Network (CTN) protocol 0102 is in progress and compares tandem ASCT to ASCT followed by RIC allogeneic SCT with an HLA-matched donor in patients < 70 years of age.

Management of Relapse

The usual approach to progressive disease has been the use of sequential regimens designed to control the disease with the best quality of life for as long as possible. Fortunately, the number of options available has increased. Patients who experience a remission lasting several years after a single, or even double, ASCT, may derive benefit from another ASCT, just as elderly patients with at least a 1-year remission may respond again to melphalan and prednisone. Other strategies are listed in **Table 4**. Thalidomide has been extensively studied as a single agent or with corticosteroids in relapsed/refractory patients.^{33,34} Representative studies are listed in **Table 4**.

In Canada and Europe, combinations of corticosteroids and oral, rather than intravenous,² cyclophosphamide are often used as salvage therapy (**Table 5**).³⁵⁻³⁹ Our group has reported the use of a convenient combination of oral cyclophosphamide 500 mg per week and prednisone 50-100 mg every second day after relapse from ASCT. The PR rate among 59 patients with measurable disease was 41%. This regimen is well tolerated, with myelosuppression, responsive to dose reduction, noted in only 11%.³⁶ It represents an attractive base for the addition of other agents, and we are conducting a phase I trial in combination with bortezomib. Weekly oral cyclophosphamide plus dexamethasone and thalidomide is effective in the setting of relapsed disease, and now represents one arm of first-line therapy in the Medical Research Council (MRC) Myeloma IX trial.³⁸

The APEX trial has demonstrated the superiority of bortezomib over dexamethasone alone in terms of response rate and time to progression. The 1-year overall survival rates were 89% versus 72%, respectively. Patients with only one prior regimen had more favorable outcomes than those treated after 2 or 3 recurrences.⁷ In patients who do not respond to bortezomib alone, the addition of dexamethasone has resulted in additional partial or minimal responses in 15%-20% in phase II trials.⁶ Principal toxicities of bortezomib include fatigue, gastrointestinal side-effects, thrombocytopenia and peripheral neuropathy (which may be painful). With appropriate monitoring and dose modifi-

Table 5. Selected regimens for relapsed/refractory myeloma.

Author/Year	N	Regimen	Response Rate		Median TTP	Median PFS
			CR	PR		
Thalidomide +/- dexamethasone						
Barlogie ³³	169	Thal 200–800 mg/d	2%	28%	–	~ 5 mo
Dimopoulos ³⁴	44	Thal + Dex d 1-4, 9-12 & 17-20 x 1 (then d 1-4) q 28 d	–	55%	> 10 mo	–
Oral cyclophosphamide-containing						
De Weerd ³⁵	42	CY 100 mg/m ² /d + P 10–20 mg/d	2%	38%	–	–
Stewart ³⁶	59	CY 500 mg/wk P 50–100 mg q 2d	0	41%	–	18.6 mo
Garcia-Sanz ³⁷	71	CY 50 mg/d + Dex d1–4 + Thal 200–800 mg/d q 21 d	2%	53%	–	NYR (53% at 24 mo)
Williams ³⁸	29 VAD rel	CY 500 mg d 1, 8 & 15 + Thal 100–200 mg/d +	–	83%	–	–
	17 rel	Dex d1-4 & 14-17 q 28d	–	71%	–	–
Hovenga ³⁹	38	CY median dose 95 mg/d + Thal median dose 100 mg/d	0	64%	–	30 mo
Bortezomib +/- dexamethasone						
Richardson ⁶	202	B 1.3 mg/m ² d1, 4, 8 & 11 +/- Dex 20 mg d1-2, 4-5, 8-9 & 11–12 q 21 days	4%	31%	7 mo	–
Richardson ⁷ (phase III trial)		B 1.3 mg/m ² d1,4, 8 & 11 q 21d	6%	32%	6.22 mo	–
		Dex 40 mg d1–4, 9–12 & 17–20 q 35 d	< 1%	18%	3.49 mo	–
Lenalidamide +/- dexamethasone						
Richardson ⁸	101	L 15 mg BID vs 30 mg q d	6%	18%	–	–
		L + Dex 40 mg d 1–4 & 14–17	0	33%	–	–
Weber ⁴⁰ (Phase III trial)	171	L 25 mg d1–21 + Dex 40 mg d1–4, 9–12 & 17–20 x 4 (then d 1–4) q 28d	19%	51%	–	NYR at 15mo
		vs Dex same	4%	23%	–	5 mo

Abbreviations: B, bortezomib; CR, complete remission; CY, cyclophosphamide; Dex, dexamethasone; L, lenalidamide; NYR, not yet reached; P, prednisone; PFS, progression free survival; PR, partial remission; rel, relapsed; ref, refractory; thal, thalidomide; TTP, time to progression; VAD, vincristine, doxorubicin, dexamethasone.

cation, these are largely reversible.

Recently, lenalidomide plus dexamethasone has been shown to be superior to dexamethasone alone in another large randomized trial in patients with progressive myeloma; neutropenia, thrombocytopenia and fatigue represent the main toxicities.⁴⁰ Lenalidomide has been submitted to the FDA for approval.

Some patients are candidates for aggressive re-induction, particularly younger individuals with rapidly progressing disease who might undergo salvage transplants. The DT-PACE regimen from the Arkansas group may be useful in this regard.⁵ In addition, a myriad of clinical trials utilizing thalidomide and/or bortezomib in combination with other drugs in the relapsed/refractory setting are accruing patients worldwide.

Future Directions

The landscape of myeloma therapy is shifting rapidly. At this time, it is uncertain whether aggressive multi-modality treatment upfront, using all or most of the new agents with stem cell transplantation, can significantly extend survival, or perhaps produce cure, in this malignancy. The alternative approach is to reserve different regimens or novel agents for the treatment of sequential relapses. The findings of the numerous ongoing trials will be informative. With any treatment strategy, the use of new cytogenetic,

molecular and proteomic information will be paramount to develop optimal risk-adapted care.

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