LEADING ARTICLE

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Breakthroughs in the Management of Multiple Myeloma

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Abstract

Although multiple myeloma remains a terminal illness, the past four decades have seen a dramatic change in the outlook for a newly diagnosed patient in terms of therapies available, supportive care and insight into the pathogenesis of this disease. Among the newer agents available for treatment, thalidomide has been resurrected and discovered to be a valuable therapy for myeloma. Thalidomide appears to work, at least in part, through its anti-angiogenic properties, but much remains to be learned about its mechanism of action as well as optimal administration regimens.

With the development of increasingly more potent bisphosphonates it has become possible to diminish the painful skeletal complications of myeloma, one of the most devastating problems of this disease. The most recent generation of bisphosphonates, pamidronic acid and zoledronic acid, have provided a statistically significant decrease in the skeletal complications of myeloma when used in a prophylactic manner. These agents appear to work by inhibiting osteoclast function.

Progressive improvement in cytogenetic techniques has now demonstrated that almost all patients with myeloma have chromosomal abnormalities, some of which appear to confer varying degrees of prognostic significance. In particular, the changes in chromosome 13 are associated with an unusually poor outcome. These findings are serving as a guide toward learning more about the pathogenesis of myeloma as well as in identifying potential targets for therapy.

Stem cell transplantation has emerged as the standard treatment for the large majority of patients with myeloma following the demonstration of superior complete remission and survival, both disease-free and overall, in a French randomised trial. Unfortunately, virtually all patients will eventually relapse following autologous stem cell transplantation, prompting continuing efforts such as tandem transplants, CD34+ selection, as well as modifications in the conditioning regimen to improve outcomes. Allogeneic bone marrow transplants appear to offer a better chance for a possible cure of myeloma but have been associated with an unusually high mortality. However, this approach is being revived with the advent of the less toxic non-myeloablative transplant that has provided an 81% short-term survival in a trial combining this approach with an initial conventional autologous bone marrow transplant. Immunotherapy with dendritic cells appears now to be a feasible way to enhance innate or acquired immunity to help eliminate minimal residual disease following autologous bone marrow transplant. Unfortu-

nately, a cure for myeloma remains elusive but the continuing advances in management may significantly prolong survival in affected patients.

Before the introduction of melphalan therapy in 1962 the prognosis for patients with multiple myeloma was extremely poor with a median survival of 17 months from the onset of symptoms and nearly 100% mortality.[1] Although the gain in survival using melphalan was modest, this represented a breakthrough in treatment of a disease with an otherwise dismal outlook. The following two decades constituted a period of multiple clinical trials utilising a growing number of chemotherapeutic agents in varying combinations. Among these regimens vincristine, doxorubicin, dexamethasone (VAD) emerged as the most important for the reason that high-dose corticosteroid plus vincristine and doxorubicin could overcome resistance to alkylating agents that is associated with refractory disease. Indeed, VAD has become the standard for nearly 20 years. Despite an improvement in response rates, however, none of these regimens used during this 30-year period produced a change in survival.

In the early 1980s, allogeneic bone marrow transplantation and, soon thereafter, autologous bone marrow transplantation became established as a new modality of treatment for multiple myeloma. Indeed, high-dose chemotherapy and autologous stem cell transplantation has provided the first statistically significant increase in overall survival and now represents what many would consider the standard of care for the majority of patients with newly diagnosed myeloma. Furthermore, innovations and refinements of the transplant procedure continue to enhance the outcomes of this modality of treatment.

This past decade has brought forth an amazing insight into the molecular level of the pathogenesis of myeloma and along with it an array of new agents that represent the new breakthroughs in the treatment of myeloma and will likely change our management of this disease even more. This review details some of the more promising of these new developments but is not intended as an evidence-based treatment recommendation.

1. Thalidomide

Despite a worldwide withdrawal because of teratogenic effects in the 1960s, thalidomide continued to be studied for its immunologic effects and was recently approved in the US for use in erythema nodosum leprosum. Two observations published in 1994 coincided with growing evidence of the importance of anti-angiogenesis in tumour growth and led to the investigation of thalidomide in myeloma.[2] It was found that increased bone marrow vascularisation in myeloma correlated not only with disease activity but was also, independently, a poor prognostic factor for survival.[3] Simultaneously it was observed that thalidomide inhibited angiogenesis.[4]

Subsequently, Barlogie and his colleagues[5] initiated a clinical trial testing the efficacy of thalidomide in refractory myeloma. In this trial, 84 previously heavily pre-treated patients were given oral thalidomide for a median of 80 days at an initial dose of 200mg daily and escalated by 200mg every 2 weeks to a maximum of 800mg. Thirty-two percent of the patients had at least a 25% reduction in paraprotein usually within 2 months of treatment.[5] An extension of that trial showed that 37% of 169 patients had >25% reduction in paraprotein and two patients actually achieved a complete remission.[6] This high-risk population had an impressive 2-year overall survival rate of 48% and event-free survival rate of 20%.[6] These promising results have since been confirmed by other studies that have reported response rates in relapsed myeloma of 25–45%.[7,8]

A trend of increasing response rates has been found by combining thalidomide with dexamethasone and /or chemotherapy as outlined in table I.[9] By moving thalidomide to front-line therapy Rajkumar and colleagues[10] and Weber et al.[11] found response rates of 38% and 36%, respectively, in patients with previously untreated myeloma. However, by combining thalidomide with dexamethasone, Rajkumar et al.[12] found a 64% response rate in an untreated population. Weber and col-

Table I. Summary of thalidomide trials in multiple myeloma[9]

Type of multiple myeloma	Treatment regimen	n	Patients with a reduction in paraprotein of >50%	Patients with a reduction in paraprotein of >75%
Refractory multiple myeloma	Thalidomide alone	392	36%	17%
	Thalidomide + dexamethasone	122	52%	NR
	Thalidomide + dexamethasone + chemotherapy	197	62%	35%
Untreated multiple myeloma	Thalidomide alone	68	51%	NR

n = number of patients; **NR** = not reported.

leagues confirmed this, reporting a 72% response rate in 28 previously untreated patients.[11]

Although its anti-angiogenic action is well documented, the exact mechanism of action of thalidomide in myeloma is not adequately established. Other possible ways that thalidomide may be acting on the myeloma cell include the modulation of the adhesion of the tumour cells to the bone marrow stromal cells,[13] the inhibition of cytokine secretion or activity,[14] a direct toxic effect on the myeloma cell[15] and through immunomodulatory properties resulting in cytotoxic T-cell proliferation.[16]

There are still unanswered questions about how best to use thalidomide in myeloma. The optimal administration schedule remains unclear. Responses have been documented at doses as low as 50 mg/day,[17] although it is generally recommended to start with 200 mg/day and escalate to a maximum of 800 mg/day, as tolerated.[18] Higher doses have been used but it is unknown whether there is a dose response. The duration of treatment is also unclear. While most investigators generally continue treatment until disease progression, this strategy becomes questionable if the drug is used in initial therapy of untreated disease in view of the unknown long-term toxicity. The use of thalidomide as a post-stem cell transplant maintenance strategy has been advocated but no data are yet available.[9] Well designed clinical trials will be necessary to answer these questions.

The adverse effects of thalidomide are, at times, a limiting factor but they do seem to be somewhat dose dependent. In addition to the well known teratogenic effects, thalidomide commonly causes sedation and constipation. One of the most serious adverse effects is the development of peripheral neuropathy, which generally improves after discontinuation of the drug but has been reported to be chronic in some patients.[19] Rashes are not uncommon, and are generally mild and resolve when the drug is withdrawn; however, severe cases have also been documented including toxic epidermal necrolysis.[20] Deep vein thrombosis has been reported with thalidomide, especially when combined with an anthracycline, along with a number of less common adverse effects including oedema, neutropenia, bradycardia and hypotension.[21] Above all, the use of thalidomide during pregnancy is absolutely contraindicated.

2. Bisphosphonates

One of the most devastating complications of myeloma is the development of bone involvement in the form of either fractures or painful lytic lesions. Management of these conditions has traditionally consisted of analgesics and/or radiation therapy and preventive measures have been generally unsuccessful. Nearly 65% of myeloma patients present with some element of bone disease and this involvement will extend to virtually every patient in the course of the disease.[22] In view of the high frequency of skeletal involvement in this disease it was clearly a major breakthrough in management of myeloma when bisphosphonates became available.

Bisphosphonates are synthetic analogues of the naturally occurring pyrophosphate-containing compounds. These agents were found nearly 30 years ago to inhibit bone resorption by inhibition of osteoclasts.[23] Although the early bisphosphonates, such as etidronic acid, were not very effective clinically, the addition of nitrogen-containing side chains produced much more potent bisphosphonates including

pamidronic acid and zoledronic acid. The different classes of bisphosphonates are outlined in table II. The mechanism of action on the osteoclasts has been the subject of considerable research in recent years with evidence for multiple mechanisms, including the inhibition of osteoclast maturation as well as suppression of mature osteoclasts.[24,25] A decrease in cytokine production and inhibition of adhesion of tumour cells to bone matrix have also been demonstrated.[26,27] On a molecular level, it appears that the nitrogen-containing bisphosphonates work in the mevalonate pathway by preventing post-translational modification (prenylation) of small guanosine 5-triphosphonate (GTP)-binding proteins, such as Ras, that are necessary for osteoclast metabolism.[28,29] Specifically, there is evidence that farnesyl pyrophosphate synthase may be the enzyme that is inhibited.[30]

The use of bisphosphonates has become the standard of care for tumour-induced hypercalcaemia, with the newer generation bisphosphonates showing superiority in the effectiveness and rapidity of reducing elevated calcium levels.[31] More importantly, the Myeloma Aredia Study Group demonstrated that monthly intravenous pamidronic acid in myeloma patients with at least one lytic bone lesion significantly reduced skeletal events defined as pathological fracture, irradiation of or surgery on bone, or spinal cord compression after a period of 21 months of treatment.[32,33] Toxicity from bisphosphonates has been minimal with rare allergic reactions, hypocalcaemia, uveitis and reversible elevation of creatinine being the most common events reported. Regular treatment for up to 6 years has been reported with continuing benefit and without biochemical abnormalities.[34] Limited bioavailability has precluded the use of most of the oral bisphosphonates, with the exception of clodronic acid, which is available in Europe.

Table II. Classes of bisphosphonates

Simple aliphatic side chain	Nitrogen-containing aliphatic side chain	Heterocyclic ring side chain
Etidronic acid	Pamidronic acid	Zoledronic acid
Clodronic acid	Alendronic acid	Risedronic acid
	Ibandronic acid	Minodronic acid

Table III. Recurring cytogenetic abnormalities with prognostic implications in multiple myeloma[39-43]

Translocations involving 14q32
t(11;14)
t(4;14)
t(14;16)
Chromosome 13 abnormalities
monosomy
deletion 13
13q translocations
17p deletions
22q deletions

3. Cytogenetics

For years we laboured under the mistaken assumption that chromosomal changes were uncommon and of little utility in myeloma. This was mainly due to the low numbers of dividing plasma cells and the relatively unsophisticated cytogenetic techniques. Indeed, not long ago the prevailing opinion was that most patients with myeloma have only normal metaphases.[35] However, even in the early 1980s, conventional cytogenetics showed a variety of numerical and structural chromosome changes in the malignant plasma cell.[36] Furthermore, the frequency and number of these chromosomal abnormalities were found to correlate with the aggressiveness of the disease.[36] Arguably these findings could also be possibly secondary to prior alkylator therapy in these early studies.

Just as there are widely varying presentations and clinical outcomes in patients with myeloma it is now recognised that there is a considerable heterogeneity found in the chromosomal changes in this disease. Karyotypic abnormalities occur in approximately 50% of patients who are tested using conventional cytogenetics, with a predominance of hyperdiploidy, although certain recurring abnormalities have been found.[37] Table III shows some examples of recurring cytogenetic abnormalities. With the advent of the fluorescent in-situ hybridisation (FISH) technique it is now found that at least 90% of all myeloma patients have chromosome abnormalities and that some of these specific changes occur with considerable frequency and appear to have a direct bearing on prognosis.[38,39] Armed with this data the

stage has been set for further understanding of the molecular basis of myeloma and subsequent development of targeted therapy to improve response and survival rates.

The Arkansas group demonstrated a strong correlation between the presence of chromosome 13 abnormalities (Δ13) [found using conventional cytogenetics] and poor disease outcome.[39] This has been confirmed by others using both conventional cytogenetics and FISH analysis.[40,44,45] Chromosome 13 abnormalities occur in approximately 45% of patients who are tested, of whom 85% have monosomy and 15% have interstitial deletions of the 13q14 locus.[46] Facon et al.[45] found a median survival time of 65.1 months in patients lacking Δ13 compared with 26.7 months for patients with Δ13 ($p < 0.0001$) [figure 1].

Structural changes involving chromosome 14q32 area even more common, found in 65–71% of patients and 100% of cell lines using FISH technology.[41,42,47] Multiple partner chromosomes in this translocation have been identified, the three most common being CCND1 at 11q13, FGFR3/MMSET at 4p16, and c-maf at 16q23.[48] While these translocations do not result in a fusion protein as seen in the t(9;22), they result in the juxtaposition of oncogenes with promoter regions in 14q32. Other structural abnormalities including chromosome 1 (1p or 1q), chromosome 16 [t(1;16)] and chromosome 17 (17q or 17p) have been found in a recurring fashion but have been studied incompletely.[38,43] Numerical changes are also found, especially in more advanced disease and may confer a poor prognosis as in other related B-cell tumours, while structural changes may be an initiating event in tumour development. More detailed cytogenetic techniques, such as multiple colour spectral karyotyping and comparative genomic hybridisation, will add even more information in the future.

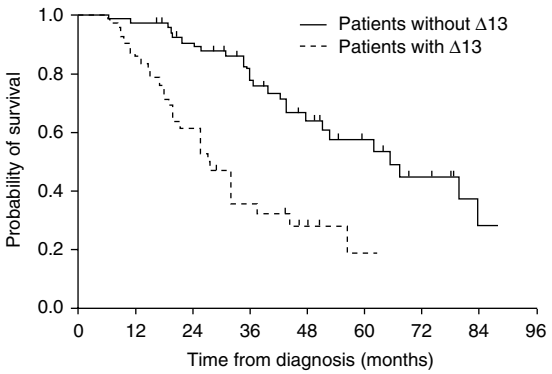

Fig. 1. Overall probability of survival by presence or absence of chromosomal 13 abnormalities (Δ13) in patients with multiple myeloma. The proportion of deaths occurring in patients with and without Δ13 was 64.2% (27/42) and 38.2% (26/68), respectively. The median survival time for patients with Δ13 was 26.7 ± 4.1 months and for patients without Δ13 was 65.1 ± 9.8 months; $p < 0.0001$ (reproduced from Facon et al.,[45] with permission).

4. Emerging Drugs

Other agents currently undergoing development have not progressed sufficiently to become established as new standards of care but look extremely promising. Most notably, the proteasome inhibitor, bortezomib (PS-341), has now been evaluated in a phase II trial for relapsed/refractory myeloma. Patients were treated twice weekly with bortezomib followed by a 1 week rest to a maximum of eight cycles. In the first cohort of 78 patients there was a 32% overall response rate using the Blade criteria, including 9% who had complete remission. At 10.2 months of follow-up the median overall survival had not been reached.[49]

Analogues of thalidomide known as immunomodulatory drugs show activity against myeloma cell lines and may be associated with fewer adverse effects. A phase I trial of one of these agents, CC-5013, in 27 relapsed/refractory myeloma patients at doses up to 50 mg/day by mouth showed no dose-limiting toxicity at 28 days, although there was grade 3 myelosuppression in all patients who were receiving 50 mg/day after 28 days. Seventy-one percent of evaluable patients had a ≥25% reduction in paraprotein and 79% had stable disease or showed signs of clinical improvement.[50] Of note, there were no reports of neuropathy, constipation or somnolence. A phase II trial assessed the use of CC-5013 (30 mg/day for 3 weeks with a 1-week rest) in a relapsed/refractory myeloma population. In a preliminary report of the first 19 evaluable

patients there was a ≥25% reduction of paraprotein in 33% of cases.[51]

Arsenic trioxide, now a proven treatment for acute promyelocytic leukaemia, also shows activity in myeloma. Several mechanisms of action have been demonstrated, including induction of apoptosis,[52] anti-angiogenesis[52] and immunologic mechanisms.[53] In three small phase II trials in advanced relapsed/refractory myeloma patients, arsenic trioxide resulted in response rates of 23–40%.[54-56] A phase II trial evaluating the possible synergistic action of arsenic trioxide with dexamethasone is also underway. Perhaps the most significant point is that these new agents appear to work through a targeted therapy approach rather than the historical cytotoxic mechanism approach to myeloma and other malignancies.

5. Bone Marrow Transplantation

Historically, bone marrow transplantation was a therapy largely reserved for young patients with multiple myeloma, for whom more aggressive strategies directed at long-term disease free survival was a viable option. Small studies using autologous bone marrow transplantation as a rescue treatment after high-dose chemotherapy/radiotherapy demonstrated what appeared to be improvements in disease-free survival compared with historical cohorts of patients treated with standard therapy alone, but these studies were prone to selection bias and could not be generalised to all patients.

In 1997, the French myeloma group (IFM) published convincing data from a trial (IFM 90) evaluating patients who received standard induction therapy with alternating VMCP (vincristine, melphalan, cyclophosphamide, prednisone) and BVAP (vincristine, carmustine, doxorubicin, prednisone) for 4–6 cycles.[57] Patients were then randomised to receive transplantation with melphalan 140 mg/m^2 and total body irradiation (TBI), or continued standard chemotherapy for a total of nine cycles. All patients received maintenance therapy with interferon. Response and survival rates in the transplant arm were significantly improved, with 38% of patients in the high-dose arm achieving a complete response or very good partial response compared with 14% of patients in the standard therapy arm. The event free survival and overall survival rates at 5 years were 28% and 52%, respectively, for patients receiving high-dose, compared with 10% and 12%, respectively, for patients receiving standard therapy ($p < 0.05$ for both). A recent update of this study, extended to 7 years of follow up, demonstrated continued superiority for high-dose therapy, which was associated with event free survival and overall survival rates of 16% and 43%, respectively, compared with 8% and 23%, respectively, with standard therapy.[58] Unfortunately, high-dose therapy alone results in few patients who are ultimately cured as the survival curves continue to decline, and nearly all patients will eventually relapse.

5.1 Autologous Transplantation

The pivotal study by Attal et al.[57] has corroborated the finding that high-dose therapy resulted in superior event-free survival and overall survival rates compared with standard therapy.[59-63] On the basis of these findings, the early use of autologous bone marrow transplantation after initial induction chemotherapy to cytoreduce the patient has become a standard approach for most patients younger than age 70 (see table IV).[64] In addition to the use of autologous transplantation for newly diagnosed patients, patients with refractory/relapsed disease,[65,66] renal failure[67] or who are older than 70[68] may also benefit from high-dose therapy (table V). However, because most patients will eventually relapse, work continues to develop methods aimed at improving response rates, reducing transplant-related toxicity, and ultimately improving the duration of post transplant remissions using autologous bone marrow transplantation.

One approach, directed at improving complete response and survival rates after autologous transplant, is a programme incorporating tandem or back-to-back autologous transplantation, pioneered by Barlogie and colleagues[76] at the Arkansas Myeloma Center. In their recent series of over 1000 patients, the use of sequential tandem autologous transplantation increased the complete response rate

Table IV. Response to autologous bone marrow or stem cell transplantation for patients newly diagnosed with multiple myeloma

Study	Study design	Transplant	n	Median age	Median follow up (m)	CR after therapy (%)	Median survival (m)	Median EFS (m)	Actuarial survival (%)	Actuarial EFS (%)	TRM (%)
IFM 90 (Attal	Randomised trial	HDT	100	57	41	22	NR	27	52	28	2.7
et al.[57])		SDT	100	58	37	5	37.4	18	12 (5y)	10 (5y)	NR
IFM 94 (Attal	Randomised,	sBMT	79	NR	60	43[a]	NR	NR	35	19	NR
et al.[51,58,69])	single vs tandem	sPBSCT	88	NR	60	50	NR	NR	40	20	NR
	transplant; BMT	tBMT	85	NR	60	50	NR	NR	43	27	NR
	and PBSCT	tPBSCT	92	NR	60	61	NR	NR	60 (5y)	35 (5y)	NR
Fermand	Randomised	Early BMT	91	48	58	19	64	39	NR	NR	10
et al.[59]	transplant timing	Late BMT	94	47	58	5[b]	64	13	NR	NR	14
Majolino et al.[60]	Retrospective analysis	PBSCT	290	52	23	40	67.2	26.4	47 (6y)	28 (6y)	3
Tribalto et al.[61]	First line therapy	PBSCT	52	49	55	31	57	21	48 (6y)	24 (6y)	4
Blade et al.[62]	Retrospective	HDT	31	53	NR	39	62	43	NR	NR	0
	study, first line therapy	SDT	33	58	NR	6	38	21	NR	NR	0
Lenhoff et al.[63]	Retrospective review	PBSCT	274	51	32	41	NR	32	NR	45 (3y)	4
Harousseau et al.[70]	Phase II study	PBSCT	133	52	35	37	46	33	43 (5y)	35 (4y)	4
Barlogie et al.[71]	Planned tandem transplant	PBSCT	231	51	31	41	68	43	58 (5y)	42 (5y)	7
Cunningham et al.[72]	MRC phase II	BMT	53	52	31	40	Not reached	23	63 (54m)	30 (3y)	2

a CR rate includes CR and very good partial response.

b CR rate only reflects primary therapy.

BMT = bone marrow transplant; **CR** = complete response; **EFS** = event free survival; **HDT** = high dose therapy; **IFM** = Intergroupe Francophone du Myelome; **MRC** = Royal Marsden College; **n** = number of patients; **NR** = results not reported; **PBSCT** = peripheral blood stem cell transplant; **sBMT** = single bone marrow transplant; **SDT** = standard dose therapy; **sPBSCT** = single peripheral blood stem cell transplant; **tBMT** = tandem bone marrow transplant; **tPBSCT** = tandem peripheral blood stem cell transplant; **TRM** = treatment related mortality.

Table V. Response to autologous bone marrow transplantation for special patient populations with multiple myeloma

Reference	Study group	n	CR after therapy (%)	Median survival (m)	Median EFS (m)	Actuarial survival (%)	Actuarial EFS (%)	TRM (%)
Vesole et al.[65]	Refractory multiple myeloma	66	27	19	11	31 (3y)	25 (3y)	9
Rajkumar et al.[66]	Relapsed off multiple myeloma treatment	30	39	21	13	NR	NR	9
	Relapsed on multiple myeloma treatment	33	30	12	7	NR	NR	NR
	Primary refractory multiple myeloma	12	17	30	26	NR	NR	NR
Lahuerta et al.[73]	Melphalan 200 mg/m^2	315	43	45	22	37	16	6.1
	Melphalan /TBI	127	31	37	20	43	21	9.1
	Busulfan/melphalan	121	49	64	32	47 (5y)	16 (5y)	6.8
Badros et al.[68]	Patients >70y[a]	70	20	24	15	31 (3y)	20 (3y)	7
Badros et al.[67]	Patients with renal failure[a]	81	26	>52	23	55 (3y)	48 (3y)	6
Shimoni et al.[74]	TBC regimen[a]	120	26	38	17	29 (5y)	12 (5y)	13
Bjorkstrand et al.[75][a]	Allogeneic BMT	189	48	18	11	NR	NR	41
	Autologous PBSCT	189	40	34	20	NR	NR	13

a Previously treated and newly diagnosed patients included.

BMT = bone marrow transplant; **CR** = complete response; **EFS** = event free survival; **n** = number of patients; **NR** = results not reported; **PBSCT** = peripheral blood stem cell transplant; **TBC** = thiotepa, busulfan, cytoxan; **TBI** = total body irradiation; **TRM** = treatment related mortality.

from 24% after the first transplant to 43% after the second transplant.[77] This increase in complete response is itself an important finding, as multiple series, including the IFM 90 trial, have demonstrated that patients who achieve a complete response have a significantly improved rates of overall survival and event free survival, rationalising the use of strategies directed at improving complete response rates for patients undergoing autologous transplantation for multiple myeloma.

In an effort to further evaluate the efficacy of tandem transplantation, the IFM initiated a randomised trial to evaluate the impact of single versus tandem transplantation on event free survival and overall survival rates.[78] Early analyses of this randomised trial showed that there was no advantage for tandem transplant over single transplant. However subsequent analyses have demonstrated a survival advantage for the group receiving the tandem transplant. In the groups receiving stem cell grafts, the 5-year event free survival rates were 20% versus 35% for single and double transplants, respectively, and overall survival rates were 40% versus 60% for single and double transplants, respectively.[78] It is important to note that the survival curves did not separate until after 3 years.

A more recent update of this analysis demonstrated a significant survival for patients receiving the tandem transplant approach. Overall survival for the patients in the tandem autologous transplant group was 42% at 7 years compared with 21% for those in the single transplant arm. Event-free survival was also improved in the tandem transplant arm.[51] Whether tandem transplant should be routinely used for all patients remains unclear. Patients in the single transplant arm in the tandem trial had a poorer overall survival than was seen in the original IFM90 trial. Subset analysis presented during this plenary session talk did not demonstrate a survival advantage for patients receiving tandem transplant vs a single transplant if the response to the first transplant was a CR or very good partial response (VGPR >90% paraprotein reduction).

Three additional randomised trials have also been performed evaluating the benefit of tandem autologous transplantation.[58] To date, none of these trials have demonstrated significant advantages of tandem transplant, however, the follow-up period is rela-

tively early in all three trials and further follow-up investigations are ongoing.

Other areas of investigation relating to autologous transplantation have addressed either changes in graft composition or changes in the transplant procedure itself. These have included changing the conditioning regimen (TBI vs no TBI), source of graft (bone marrow vs peripheral stem cells) and the use of CD34+ selection. Most centres have now adopted the use of peripheral blood stem cells (PBSC) as the primary transplant graft source, because patients engraft quicker and it is easier to obtain PBSC compared with a bone marrow graft. It is also believed that there is less tumour cell contamination with PBSC grafts, although tumour can still be detected within most PBSC grafts if sensitive enough techniques are used.[79]

The issue of tumour cell contamination does, however, lead to a discussion of graft purging using CD34+ selection. CD34+ selection can result in as much as a 2.5–3.0 log depletion of tumour cells contained within the graft, and pilot studies have demonstrated the safety and feasibility of using selected grafts in this patient population and others.[80-82] A 1999 randomised phase III trial cast doubt on the clinical utility of this procedure as there was no difference in the rates of event free survival or overall survival between the selected and unselected groups.[83] This was also reflected in randomised trial data from the European Group for Blood and Marrow Transplantation, in which a survival advantage for CD34+ selection was not demonstrated.[84] Thus, while tumour cell contamination is significantly reduced, residual host tumours may play a major role in relapse after autologous transplantation. Recent data also demonstrated a higher incidence of varicella-zoster virus reactivation in patients who received selected grafts.[85] Slower T-cell recovery after the use of CD34+ selected PBSC grafts has also been reported.[86] In the context of additional recent data describing immune reconstitution of the CD19+ and CD4+ compartments having a positive impact on survival in patients with multiple myeloma,[87] the use of CD34+ selected autologous PBSC grafts does not appear to confer either theoretical or practical advantages.

Finally, preparative regimens for autologous transplantation of multiple myeloma have historically used a combination of TBI and melphalan. The IFM 90 trial used this approach, however, a subsequent IFM randomised trial assessed the use of melphalan alone. This trial compared melphalan 200 mg/m^2 with TBI 8 Gy/melphalan 140 mg/m^2.[78] This trial demonstrated equivalent response rates between the two treatment groups but a higher overall survival in the melphalan 200 mg/m^2 group, related primarily to an absence of transplant related deaths in that group (compared with five deaths in the TBI/melphalan group). Additionally, there were fewer patients with >grade 3 mucositis, and a shorter duration of neutropenia in the melphalan 200 mg/m^2 group. Other groups have reported similar outcomes with melphalan 200 mg/m^2 and, thus, for most centres this has become the standard conditioning regimen for autologous PBSC transplants.[88] The use of alternative conditioning regimens to increase the proportion of patients entering complete response is still being explored in retrospective studies[73,74] or for patients with poor risk disease.

5.2 Allogeneic Transplantation

The rationale behind the use of allogeneic cell therapy for the treatment of multiple myeloma came from the observation that a small subset of patients with refractory myeloma could be cured with a standard ablative transplant from a syngeneic donor.[89,90] This was then broadened to include transplantation from matched related or unrelated donors in an effort to capitalise upon a postulated graft versus myeloma effect. Unfortunately, the transplant-related mortality associated with a standard allogeneic transplant is often between 30% and 50%, making this a difficult option to offer to all patients.[75,88,91-93] Because of the high transplant-related mortality associated with allogeneic transplantation (see table VI), most patients will opt for a standard autologous transplant as initial therapy, making the risk associated with a standard allo-

Table VI. Historical experience of allogeneic transplantation for multiple myeloma

Reference	Years	n	Transplant type	Early death/ TRM (%)	Chemosensitive disease (%)	CR after BMT (%)
Gahrton et al.[93] (EBMT)	1983–1993	334	Ablative	38	73	44
	1994–1998	223[a]	Ablative	21	75	54
	1994–1998	113[b]	Ablative	31	74	50
Bensinger[92] (IBMTR)	1988–1993	265	Ablative	50	42	NR
Bensinger[92] (Seattle)	1987–1999	136	Ablative	49	21	34
Badros et al.[94] (Arkansas)	2001	16	NMA	0[c]	31	38
Alyea et al.[95] (Boston)	2001	24	Ablative and TCD	21	100	NR
Badros et al.[96] (Arkansas)	2002	93	Ablative	29	NR	NR
		31	NMA	10	45	61
Maloney et al.[97] (Seattle)	2001	32	NMA	6	57	53

a Patients who had bone marrow transplants.

b Patients who had peripheral bone stem cell transplants.

c TRM before day 100 was 0%.

Ablative = standard myeloablative transplant; **BMT** = bone marrow transplant; **CR** = complete response; **EBMT** = European Group for Blood and Marrow Transplantation centres; **IBMTR** = International Bone Marrow Transplant Registry; **n** = number of patients; **NMA** = nonmyeloablative or 'mini' transplant; **NR** = not reported; **TCD** = T-cell depleted graft; **TRM** = transplant related mortality.

geneic transplant even greater as it becomes a second transplant.

Recently, the use of non-myeloablative transplant manoeuvres has opened up the possibility of allogeneic cell therapy for older patients, and for patients with heavily pretreated diseases and resultant poor performance status.[98,99] This approach is well suited for allogeneic transplantation of multiple myeloma patients because they are often older, heavily pretreated and have already had an autologous transplant. Numerous pilot studies have demonstrated a lower transplant-related mortality using the mini-transplant approach; however, a higher incidence of graft-versus-host-disease (GVHD) continues to be a problem even when T-cell depleted allogeneic grafts are used, as patients are then treated with donor lymphocytes to enhance immunity post transplant.[94,95,100,101]

Badros et al.[96] recently reported their experience with mini transplants in the setting of advanced myeloma. Their approach used less intense conditioning followed by rapid tapering of GVHD prophylaxis and early donor lymphocyte infusion (DLI) for patients with progressive disease or mixed chimerism. Early treatment-related mortality was 10% for patients receiving non-myeloablative transplant early DLI compared with 29% among 93 similarly matched patients who underwent standard ablative transplants previously at Arkansas. The response rate using this reduced intensity conditioning was quite high (61%), and early mortality was considerably reduced; however, late mortality remained high. Twelve patients had died at the time of the report; the deaths were due to progressive myeloma (n = 3), early transplant-related mortality (3) and late transplant-related mortality (6). Late onset causes of death were most commonly related to GVHD or complications associated with the intense immunosuppression required to control GVHD. This higher incidence of GVHD may be a function of the tumour cell ontogeny or related to older age of patients undergoing allogeneic transplant for myeloma.

Data recently presented by Maloney et al.[97] outlined a novel tandem autologous/allogeneic approach for the transplantation of patients with newly diagnosed myeloma. This protocol utilised a standard melphalan 200 mg/m^2-based autologous PBSC transplant followed, in short succession, by a low dose TBI only (200cGy) allogeneic conditioning with mycophenolate mofetil and cyclosporin as GVHD prophylaxis. The results from this study demonstrated an 81% survival with a median follow

up of 323 days after allogeneic transplantation. While this approach also had high incidences of GVHD associated with it, it may represent a novel approach for the safe delivery of allogeneic cell therapy for patients with multiple myeloma.

The impact of the graft versus myeloma effect after allogeneic transplantation is part of the motivation behind the use of allogeneic cell therapy for the treatment of myeloma. Data from Tricot et al.[102] initially described a patient, treated at Arkansas for relapsed myeloma shortly after an unrelated donor transplant, who went into remission quite rapidly after infusion of donor lymphocytes. While that case was complicated by significant GVHD, many additional groups have demonstrated that responses can be seen with DLI therapy as part of a pre-emptive treatment approach or as part of the treatment protocol for patients with relapsed disease after allogeneic transplantation.[101,103,104] Mehta and Singhal[105] reviewed the literature and calculated that 22 out of 33 evaluable patients treated with DLI, based upon published series, achieved a response to DLI in the setting of relapsed disease. Nearly all of those patients who responded to DLI developed some form of GVHD that required additional therapy. This response rate is somewhat higher than that seen by Salama et al.[106] who reviewed, via the international bone marrow transplant registry (IBMTR), 25 patients with allogeneic transplantation for relapsed myeloma and found a response rate of 40% (complete response + partial response). Again, responses to DLI was closely correlated with the subsequent development of GVHD.

Recently, Bellucci and colleagues[107] evaluated the impact of DLI, not on disease control, but on immune recovery after ablative allogeneic transplant with a T-cell depleted graft. Their data demonstrated that the use of CD8+–depleted DLI at 6 months significantly enhanced immune recovery, as measured using TREC analysis (T-cell receptor rearrangement excision circles) and improvement in T-cell receptor β-chain variable region (TCR Vβ) repertoire complexity. Thus, DLI not only adds a measure of anti-tumour immunity, it also can significantly enhance immune recovery in the setting of T-cell depleted allogeneic transplantation. When this data is viewed in the context of more recent transplant trials using non-myeloablative transplant approaches with or without pre-emptive DLI, it is clear that a graft versus myeloma effect exists, and that further attempts to intensify conditioning should give way to novel approaches to enhance graft immune function after allogeneic cell therapy.

6. Immunotherapy

Immunotherapy is the basis for allogeneic cell therapy (graft versus myeloma effect) making efforts to enhance either innate or acquired immunity against tumour-related antigens a logical next step. Immunotherapy in the autologous setting has the added advantage of low toxicity and can be an adjunct to a tumour debulking procedure such as autologous transplantation. Current immunotherapeutic approaches involve either the use of dendritic cell vaccines or antigen-specific adoptive T-cell therapy. When using either of these strategies, one of the key issues relates to deciding what the target antigen will be for the dendritic cell or T-cell clone.

Investigators have used a variety of tumour and plasma cell related antigens, but thus far the approach with the greatest success is the use of idiotype vaccines. This is similar to the approach taken with follicular lymphomas in which the tumour cell has a specific antigenic determinant in the immunoglobulin variable region, the idiotype, which can be used to prime an autologous dendritic cell against this tumour specific antigen.[108,109] This antigen-primed dendritic cell is then given back as a subcutaneous injection to initiate a specific anti-tumour response. The advantage of the idiotype vaccine is that it is specific to the tumour cell, as opposed to other plasma cell antigens, which may be present on normal host tissues or normal plasma cells as well.

However, in myeloma, the tumour specific antigen is often found circulating free in the plasma and at lower densities on the tumour cell surface. This means that antigen-specific cells may be 'soaked up' with soluble antigen and tumour cells may then escape immune-mediated death.[110] Nonetheless, at least one group has successfully used the idiotype

approach to generate dendritic cell vaccines for the treatment of multiple myeloma.[111] Reichardt et al.[111] conjugated myeloma specific idiotype proteins with keyhole limpet haemocyanin (KLH), a marine animal protein known to be highly immunogenic and a neo-antigen. The fusion protein is used to pulse autologous dendritic cells *in vitro*. In this small study, patients were vaccinated after autologous PBSC transplant in an effort to address the issue of minimal residual disease. Two of the 12 patients developed idiotype specific cellular responses, but all patients developed KLH specific cellular and humoral responses. This is an important point to note, as immunocompetence after PBSC transplantation can be an issue, especially if CD34+ selected grafts are used and T-cell repertoire recovery and diversity are delayed.[86]

In an attempt to capitalise on functional differences between mature and immature dendritic cells, Munshi and colleagues[112] predicted that the use of mature dendritic cells derived from peripheral blood monocytes would serves as better antigen stimulators than immature dendritic cells. Data from numerous sources have demonstrated that immature dendritic cells are more effective at processing antigens, while mature dendritic cells are more effective at antigen presentation.[113] Munshi and colleagues' group had already demonstrated that monocyte derived dendritic cells were capable of processing and priming T-cell responses in an effective manner.[114,115] In their study, purified paraprotein from patients with myeloma was used to prime immature monocyte derived dendritic cells, which were then matured with tumour necrosis factor and interleukin-1β. These cells were then injected subcutaneously and antigen-specific T-cell responses were measured at various time-points after treatment. Of the five patients treated with this approach, one had a clinical response, while four had demonstrable antigen-specific T-cell responses.[112]

Finally, Wen et al.[116] recently reported the use of whole myeloma cell lysates to prime dendritic cells and generate specific anti-myeloma T-cells. This was done in an attempt to increase the response rates reported in the literature using idiotype protein alone as the primer of the immune response. This *in vitro* study demonstrated that the use of myeloma cell lysate resulted in enhanced cytotoxic T-cell generation and responses were seen in all of the four assays, whereas responses were seen in two out of four assays when only the idiotype protein was used. The responses were specific to myeloma cells, or dendritic cells pulsed with autologous myeloma cells. When allogeneic myeloma cells, normal B-cells, peripheral blood mononuclear cells or Epstein-Barr virus transformed B-cells were used as the target, minimal cytotoxic T-cell mediated killing was demonstrated. These data illustrate the impact of dendritic cells on the generation of cell-specific immune responses, and the use of myeloma cell lysate may have the added benefit of increasing the number of tumour antigens which are presented, thus increasing the overall chance of response to immunotherapy in the autologous setting. While the overall response rates in these studies are low, they have paved the way for further exploration in methods to enhance innate anti-tumour immunity alone or in concert with autologous PBSC transplantation.

7. Conclusion

This is an exciting time in the management of patients with multiple myeloma. The breakthroughs that have occurred in treatment, supportive care and knowledge of the pathogenesis of this disease give patients more hope than ever before. The challenge will be to build on these discoveries and conduct well designed clinical trials to demonstrate, conclusively, the apparent benefits. Unfortunately, a cure for myeloma remains elusive but the continuing advances in management may well significantly prolong survival in affected patients.

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