



POSITION PAPER

Treatment of patients with multiple myeloma who are eligible for stem cell transplantation: position statement of the Myeloma Foundation of Australia Medical and Scientific Advisory Group

H. Quach,^{1,2} D. Joshua,^{3,4} J. Ho,^{3,4} J. Szer,⁵ A. Spencer,⁶ S. J. Harrison,^{2,7} P. Mollee,^{8,9} A. W. Roberts,⁵ N. Horvath,¹⁰ D. Talulikar,^{11,12} B. To,¹⁰ A. Zannettino,¹⁰ R. Brown,³ L. Catley,^{9,13,14} B. Augustson,¹⁵ W. Jaksic,¹⁶ J. Gibson^{3,4} and H. M. Prince^{2,7}

¹Department of Haematology, St Vincent's Hospital, ²Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, ⁵Department of Clinical Haematology and BMT, Royal Melbourne Hospital, ⁶Department of Haematology, The Alfred Hospital, ⁷Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Victoria, ³Department of Haematology, Royal Prince Alfred Hospital, ⁴Faculty of Medicine, University of Sydney, Sydney, New South Wales, ⁸Amyloidosis Centre and Department of Haematology, Princess Alexandra Hospital, ⁹School of Medicine, University of Queensland, ¹³Department of Haematology, Mater Public Hospital, ¹⁴Mater Medical Research Institute, Brisbane, Queensland, ¹⁰Department of Haematology, South Australia Pathology, ¹⁶Department of Haematology, Queen Elizabeth Hospital, Adelaide, South Australia, ¹¹Department of Haematology, Canberra Hospital, ¹²Australian National University, Canberra, ACT, and ¹⁵Department of Haematology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

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Correspondence

Hang Quach, Department of Haematology, St Vincent's Hospital, 41 Victoria Parade, Melbourne, Vic. 3065, Australia.
Email: hang.quach@svha.org.au

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Abstract

The survival of patients with multiple myeloma (MM) has improved substantially since the introduction in the late 1980s of high-dose chemotherapy (HDT) supported by autologous stem cell transplantation (ASCT). Further improvements have been observed following the availability of immunomodulatory drugs (IMiD) such as thalidomide and lenalidomide, and the proteasome inhibitor, bortezomib. Here, we summarise the recommendations of the Medical Scientific Advisory Group to the Myeloma Foundation of Australia for patients considered suitable for HDT + ASCT as part of initial therapy. These recommendations incorporate the various phases of treatment: induction, HDT conditioning and maintenance therapy.

Introduction

The treatment paradigm for multiple myeloma (MM) has evolved considerably since the introduction of the so-called 'novel agents' namely the immunomodulatory drugs (IMiD) such as thalidomide and lenalidomide and the first-in-class proteasome inhibitor bortezomib. In the era predating these agents (1990s), high-dose chemotherapy (typically high-dose melphalan) supported by autologous stem cell transplantation (HDT + ASCT) was proven superior to conventional-dose chemotherapy as front-line therapy and considered standard of care for transplant-eligible patients.¹ At that time, standard-dose

chemotherapy was able to achieve a partial response in approximately 50–60% of patients, but patients rarely achieved a complete response (CR) unless the treatment was consolidated with HDT + ASCT. It is now recognised that deeper responses translate to longer duration of response² – the biological rationale for consolidative HDT + ASCT.

With the advent of IMiD and proteasome inhibitors, deep responses have become more readily achievable (see below). Indeed, with the use of multidrug combinations that incorporate IMiD and/or proteasome inhibitors, the CR rate that can now be achieved with induction and maintenance strategies is comparable with that observed with HDT + ASCT in the 1990s and early 2000s. Consequently, this has conceptually 'challenged' the place of front-line HDT + SCT as standard of care in transplant-eligible patients. This manuscript summarises

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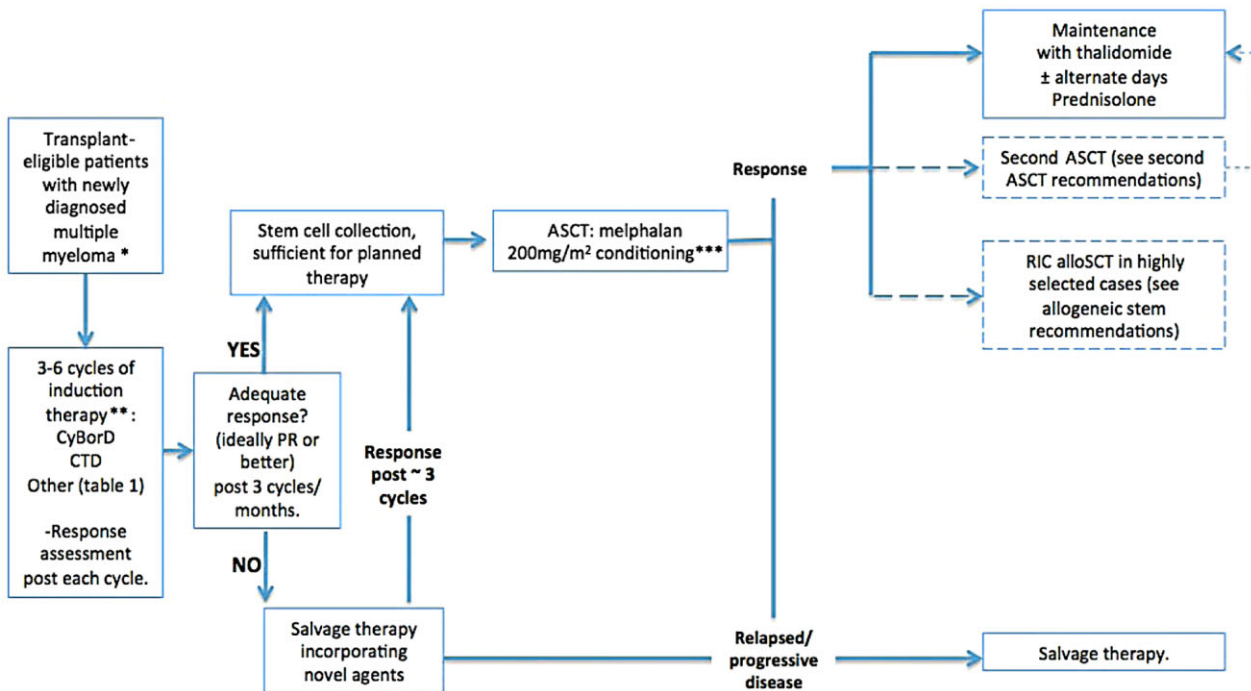


Figure 1 Treatment algorithm for transplant eligible patients with newly diagnosed symptomatic multiple myeloma. *Suitable candidates for autologous stem cell transplants are generally patients who are aged <75 years with good performance status, no significant comorbidities or frailty. Individual assessment of biological fitness for high-dose chemotherapy (HDT) + autologous stem cell transplantation (ASCT) by the treating physician is advised. Clinical tools such as the haematopoietic stem cell transplant comorbidity index (HCT-CI) may be useful for patients aged above 65 years. **Induction regimens that incorporate bortezomib, thalidomide or lenalidomide improve quality of responses. Patients who are not immediate transplant candidates but in whom ASCT may still be a viable option at relapse should avoid the alkylating agent melphalan so as not to compromise potential stem cell harvest. ***Lower dose melphalan conditioning can be considered in patients aged ≥ 70 years or younger patients with impaired renal function and comorbidities. alloSCT, allogeneic stem cell transplantation; RIC, reduced intensity conditioning.

the treatment recommendations from the Medical Scientific Advisory Group (MSAG) to the Myeloma Foundation of Australia (MFA) for patients deemed eligible for HDT + ASCT (Fig. 1). These recommendations incorporate the various phases of treatment: induction, stem cell collection, HDT conditioning and maintenance therapy. Recommendations pertaining to patients who are considered to have 'high-risk' smouldering myeloma are discussed in our position statement on transplant ineligible patients. The complete guideline on diagnostic work up and treatment is outlined in the Multiple Myeloma Clinical Practice Guideline that is available on <http://www.myeloma.org.au>.

Have IMiD and proteasome inhibitor-based combinations superseded HDT and ASCT?

A key question addressed during the development of these recommendations was: are there any situations in which a HDT + ASCT should *not* be offered to transplant-eligible patients with MM? Firstly, it is important to

consider the aims of treatment of MM and whether these can be achieved without HDT + ASCT in the current era. MM remains incurable for the great majority of patients, with a median survival in the modern era of between 4–7 years (depending on prognostic factors), so new therapeutic strategies are aimed at improving overall survival (OS) and quality of life (QOL). It is important to note that the impact on survival by any new treatment strategy can be difficult to demonstrate as long-term follow up is required, and the effect may be confounded by the types of salvage therapy utilised following relapse. Consequently, recognised predictors for survival such as achievement of CR and progression-free survival (PFS) are used as surrogate end-points to facilitate comparisons with evolving treatment strategies. Prior to the era of IMiD and proteasome inhibitors, HDT + ASCT achieved CR in approximately 20–30% of patients³ with a correlation between the achievement of CR and survival²; a recent long-term follow up of 344 patients who received ASCT between the years 1989 and 1998 showed that 35% of patients who achieved CR were still alive after 17 years compared with 11% of non-CR responders.⁴

To improve OS, it is now routine practice to incorporate either IMiD and/or proteasome inhibitors into the pretransplant induction phase with the choice of agent often dependent on regional regulatory issues relating to drug availability. At the time of writing, only thalidomide or bortezomib are available on the pharmaceutical benefits scheme (PBS) in Australia and New Zealand for induction therapy. With double or triple combination induction therapy incorporating IMiD and/or proteasome inhibitors, CR/near(n) CR rates can now be achieved in up to approximately 30–50% of patients,^{5–9} even prior to ASCT. Although clearly a significant achievement, our current definition of CR (as defined by no detectable paraprotein, i.e. immunofixation negativity) is somewhat crude as tumour burden can still be readily detected by flow cytometry or by molecular studies. Indeed, more sensitive techniques in detecting minimal residual disease have demonstrated the prognostic differences between the different ‘depths of CR’; immunophenotypic CR (as defined by no abnormal plasma clone detected on flow cytometry) results in a much more sustained remission/PFS compared with the less sensitive ‘immunofixation negative’ CR (3-year PFS 50% vs 95% for immunophenotypic CR).¹⁰ The deeper the level of CR, the more durable the response appears to be.¹⁰ This in turn correlates strongly with improved survival.⁴

With the aim of maximising depth and durability of response, we believe the key issue is therefore not whether novel agent-based therapy should supersede the need for transplantation, but whether transplantation when incorporated as part of the front-line treatment strategy can augment the rate and quality of CRs to novel agent-based induction. Indeed, recent large trials have consistently shown that *pretransplant* induction with IMiD and/or bortezomib-based regimens translate into deeper responses *post-transplant*.¹¹ With a treatment-related mortality (TRM) of <5%, HDT + ASCT remains one of the most reliable treatment modalities capable of inducing durable and quality responses in MM, and remains integral to our treatment strategy.

Early versus delayed ASCT

Conceptually, it is generally accepted that the maximum benefit of HDT, with respect to depth and durability of response, is derived by concentrating the most effective treatment early in the disease course. This is when the existing malignant plasma cell clones are most drug sensitive and patients are more able to tolerate intensive treatment. Indeed, the optimal timing of HDT + ASCT prior to the era of IMiD and proteasome inhibitors was clear – transplantation as part of front-line therapy was considered superior to delaying transplantation until first

relapse on the basis of improved event-free survival (EFS) (39 vs 13 months) and average time without symptoms, treatment and treatment toxicity (27.8 vs 22.3 months) compared with when ASCT was ‘delayed’ until first relapse.¹² No difference in OS was demonstrated in this study.

The same question is being readdressed in the era of IMiD and proteasome inhibitors in two randomised phase III trials, the GIMEMA MM-RV-209¹³ and EMN MM-RV-441¹⁴ trials. In both trials, patients age <65 years were given lenalidomide-dexamethasone induction prior to stem cell collection, then randomised to either ASCT or a further six cycles of melphalan, prednisone and lenalidomide (GIMEMA trial) or cyclophosphamide, lenalidomide and dexamethasone (EMN trial). Preliminary combined analysis of these two trials showed superiority of ASCT as part of front-line treatment compared with when ASCT was delayed until relapse, with respect to PFS1 ($P < 0.001$) and 4-year OS (85 vs 76%, $P = 0.027$).¹⁵

In another prospective study that compared lenalidomide and high-dose dexamethasone with lenalidomide and low-dose dexamethasone (Ld) as induction for patients aged <65 years, patients were given the choice either to proceed to HDT + ASCT upfront after four induction cycles or continue with lenalidomide-dexamethasone until disease progression. With the caveats that this trial was not designed to assess the impact of early versus delayed transplant and that this component of treatment was not randomised, post-hoc analysis revealed the probability of survival was substantially higher for those patients undergoing early ASCT compared with patients who continued on with lenalidomide-dexamethasone (3-year survival probability 0.94 vs 0.78 respectively).¹⁶

In summary, current available data support an early transplant approach as it is associated with longer PFS, time without treatment and emerging OS benefit.¹⁵

Tandem versus single ASCT

Tandem ASCT, in which the second ASCT is planned to occur 3–6 months after the first, was developed in an attempt to increase dose intensity to achieve a deeper and sustained remission. Reported CR rates with single SCT have been approximately 25–35%; that for tandem transplant is approximately 40% with a median EFS and OS of 49 months and 62 months respectively.¹⁷ In a meta-analysis of six randomised control trials of 1803 patients, comparing tandem versus single ASCT for upfront treatment of MM, Kumar *et al.*¹⁸ reported that while there was a superior overall response rate with tandem ASCT (risk ratio 0.79), there was a significant

increase in TRM (risk ratio 1.71). Overall, tandem ASCT did not result in improved OS or EFS compared with single ASCT. However, the trials that were included in this meta-analysis were heterogeneous, mainly because of the inclusion of a trial that compared single transplant plus thalidomide maintenance therapy to tandem transplant, which favoured single transplant.¹⁹ This trial has been subsequently retracted. When this trial was excluded from the meta-analysis, the heterogeneity disappeared, and there was a statistically significant change in the hazard ratio for EFS but not OS favouring tandem transplant.

In the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON)-65/German Multiple Myeloma Group (GMMG)-HD4 trial that compared VAD (vincristine, doxorubicin, dexamethasone) with PAD (bortezomib, doxorubicin, dexamethasone) followed by ASCT then maintenance with thalidomide (VAD arm) or bortezomib (PAD arm), tandem ASCT emerged on multivariate analysis as a significant factor for improved OS ($P = 0.03$).²⁰ More recently, an integrated analysis was performed of data from phase III European studies in which patients were prospectively assigned to receive either single or double (tandem) ASCT. Double ASCT resulted in superior PFS (med 38 vs 50 months, $P < 0.001$) and OS (5-year estimates: 63% vs 75%, $P = 0.002$).²¹ Tandem ASCT may therefore be a reasonable strategy, perhaps in selected patients who have had a suboptimal response to first transplant given that subset analyses in previous phase III trials have indicated that tandem transplants seem to primarily benefit patients with less than very good partial response (VGPR) after the first transplantation.^{22,23} It must be emphasised that consolidation or maintenance therapies with newer agents, and effective salvage therapies in the current era, may well mitigate any OS advantage of tandem ASCT over single ASCT.

Induction therapy prior to ASCT

Induction therapy prior to ASCT serves to promptly reduce tumour burden. Deeper pretransplant response is associated with better post-transplant outcome.²⁴ Induction regimens that incorporate IMiD and/or proteasome inhibitors (Table 1) are superior to chemotherapy-only regimens such as the classic infusional VAD, particularly in poor-risk patients such as those with poor cytogenetics or other adverse prognostic features.^{28,32,40} Two-drug combinations where dexamethasone is combined with thalidomide (TD), lenalidomide (Ld) (low-dose dexamethasone) or bortezomib (BD) are superior to VAD.^{28,32,40} Of note, Ld or BD achieves CR/VGPR rates of 20–40% prior to ASCT, which is superior to the TD combination

that induces CR/VGPR rates of approximately 10–16%.²⁸ Three-drug combinations appear to further improve efficacy with respect to depth of initial response; the addition of a chemotherapy agent, either cyclophosphamide or doxorubicin to thalidomide (CTD, TAD),^{5,6} bortezomib (CyBorD, PAD)^{7,8} or lenalidomide (LCD)⁹ induces CR/VGPR rates between 37% and 65%. Similar impressive efficacy is seen with three-drug regimens that combine IMiD and proteasome inhibitors.^{24,41} In contrast, no further advantage was seen with a four-drug combination, which instead results in greater toxicity.⁴¹ It should be noted that combinations of IMiD and proteasome inhibitors are not currently available through PBS reimbursement in Australia.

There have been no clinical trials that directly compare bortezomib-based regimens to IMiD-based regimens for induction prior to ASCT. One meta-analysis showed that bortezomib-based regimens (BD or BTD) were superior to non-bortezomib-based regimens with respect to PFS and OS,⁴² but this was not surprising given that the non-bortezomib comparator was VAD or TD, both of which are known to induce only modest responses. Nonetheless, bortezomib certainly induces rapid and quality responses, and given that it can partially mitigate the impact of adverse cytogenetics, bortezomib-based regimens are often used preferentially as first-line induction in transplant eligible patients. A weekly schedule of bortezomib 1.5 mg/m² appears to result in reduced toxicity without compromising efficacy compared with the traditional schedule of bortezomib 1.3 mg/m² days 1, 4, 8, 11 every 21 days.⁷ Similarly, it appears that weekly subcutaneous bortezomib is better tolerated than intravenous without compromising efficacy in transplant eligible patients, based on preliminary results of a phase II study.⁴³ Please refer to Box 1 for summary of recommendations.

Stem cell mobilisation

The most common regimen used to mobilise peripheral blood stem cells for MM patients is high-dose cyclophosphamide with recombinant human granulocyte colony stimulating factor (rhG-CSF), such as filgrastim, 5–10 mcg/kg. The addition of high-dose cyclophosphamide for mobilisation does not necessarily improve depth of response over induction therapy and does not improve CR rates or time to progression (TTP) in patients undergoing ASCT.⁴⁵ However, using cyclophosphamide for mobilisation has the advantage of increasing the CD34 + cell yield.⁴⁶ A higher dose of cyclophosphamide (4 g/m²) will give a better CD34 + yield, but may also cause more toxicity requiring hospital admissions compared with cyclophosphamide 2 g/m².⁴⁷ More recently, plerixafor

Table 1 Induction treatment regimens for upfront treatment of myeloma prior to autologous stem cell transplantation

Regimen	Schedule	Responses
CD ²⁵	Cyclophosphamide 1g/m ² IV D1 Dexamethasone 40 mg D1-4, 9-12 Cycles repeated every 21 days for 2-3 cycles prior to ASCT	Post-transplant ORR 81% (similar to VAD with ORR of 80%)
CID ²⁶	Cyclophosphamide 100 mg/m ² po D1, 2, 3, 4 Idarubicin 10 mg/m ² po D1, 2 Dexamethasone 40 mg po daily, D 1-4, 8-11, 15-18 for cycle 1; days 1-4 for cycles 2-4 Cycles repeated 21 days for 3-4 cycles prior to ASCT	ORR 66% (CR 9%) post-CID ORR 80% (34% CR) post-AuSCT
PCAB ²⁷	Doxorubicin 30 mg/m ² IV D1 Carmustine 30 mg/m ² IV D1 Cyclophosphamide 600 mg/m ² IV D Prednisolone 60 mg/m ² po D1-5 Pegfilgrastim 6 mg sc D2 Cycles repeated every 4 weeks up to 12 cycles	ORR 48% (41% PR, 7% CR)
TD ²⁸⁻³⁰	Thalidomide 200 mg po daily Dexamethasone 40 mg po daily D1-4 Cycles repeat every 4 weeks for 3-4 cycles prior to ASCT	Pretransplant ORR varies from 64% to 76% ORR 76% with thalidomide-dexamethasone versus 52% VAD, <i>P</i> < 0.001 ²⁸
CTD ^{5,31}	Thalidomide 100 mg po daily Cyclophosphamide 500 mg po/IV weekly Dexamethasone 40 mg po daily 1-4, 12-15, or Dexamethasone 40 mg weekly Cycles repeated every 28 days for 3-4 cycles prior to ASCT	ORR 89%
TAD ⁶	Thalidomide 200 mg po daily Doxorubicin 9 mg/m ² IV rapid infusion, D1-4 Dexamethasone 40 mg po, days 1-4, 9-12 and 17-20 Cycles repeated every 28 days for 3-4 cycles prior to ASCT	ORR with TAD 72% versus 54% with VAD, <i>P</i> < 0.001 CR + VGPR higher post-ASCT in TAD arm (49% vs 32%, <i>P</i> < 0.001)
BD ^{32,33}	Bortezomib 1.3 mg/m ² IV D1, 4, 8, 11 Dexamethasone 20 mg on day of and day after bortezomib Cycles repeat every 21 days for 3-4 cycles prior to ASCT	CR/nCR 22% post-induction CR/nCR 38% post-ASCT
PAD ^{8,20,34}	Bortezomib 1.3 mg/m ² IV D1, 4, 8, 11 Doxorubicin 20/m ² IV D1 and 4 or doxorubicin 9 mg/m ² IV D1, 2, 3, 4 (daily bolus or continuous infusion) Dexamethasone 20 mg po daily, D1, 2, 4, 5, 8, 9, 11, 12 Cycles repeated every 3 weeks for 3-4 cycles prior to ASCT	ORR 95%; 65% ≥ VGPR, 24% CR Assessment following ± ASCT: ORR 95%, 81% ≥ VGPR, 43% CR
CyBorD/BCD ^{7,35,36}	Bortezomib 1.3 mg/m ² IV D1, 4, 8, 11 Cyclophosphamide 300 mg/m ² po D1, 8, 15, 22 (or cyclophosphamide 900 mg/m ² IV D1) Dexamethasone 20 mg po on day of and day after bortezomib Cycles repeated every 21 days x for 3-4 cycles prior to ASCT Or Bortezomib 1.5 mg/m ² wc D1, 8, 15, 22 Cyclophosphamide 300 mg/m ² po D1, 8, 15, 22 Dexamethasone 20 mg po on day of and day after bortezomib Cycles repeated every 28 days x for 3-4 cycles prior to ASCT	ORR 88%, ≥VGPR 61% post-induction ORR 93%, ≥VGPR 60% post-induction
Ld ³⁷	Lenalidomide 25 mg po daily D1-21 every 28 days D Dexamethasone 40 mg po weekly Cycles repeated every 28 days for 3-4 cycles prior to ASCT, otherwise, until disease progression	CR/VGPR 42% post-induction
LCD ^{9,38}	Lenalidomide 25 mg po daily D1-21 every 28 days Cyclophosphamide 300 mg/m ² po daily D1, 8, 15 Dexamethasone 40 mg po daily, D1, 8, 15 and 22 Cycles repeated every 28 days for 3-4 cycles prior to ASCT	VGPR 38%, CR 2% post-induction
BTD ²⁴	Bortezomib 1.3 mg/m ² IV D1, 4, 8, 11 Thalidomide 200 mg po D1-21 Dexamethasone 40 mg po on day of and day after bortezomib Cycles repeated every 21 days for 3-4 cycles prior to ASCT	CR/nCR 31% post-induction CR was 57% post-ASCT
(BTDC) ³⁹	Bortezomib 1.3 mg/m ² IV D1, 4, 8, 11 Dexamethasone 40 mg po D1-4, 9-12 Thalidomide 100 mg po daily Cyclophosphamide 400 mg/m ² IV D1, 8 Cycles repeated every 21 days for 3 cycles prior to ASCT, or additional 4 cycles for patient who became ineligible for ASCT	ORR 96%; CR/nCR 44% post-induction ORR 100%; CR/nCR = 78% post-ASCT

This table summarises the commonly used induction regimens and is not intended to be exhaustive. Please refer to recommendations regarding induction therapy. ASCT, autologous stem cell transplantation; CR, complete response; IV, intravenous; nCR, near CR; ORR, overall response rate; VAD, vincristine, doxorubicin, dexamethasone; VGPR, very good partial response.

Box 1 Recommendations regarding induction therapy

- Transplant-eligible patients should be treated with three to six cycles of induction prior to ASCT (grade A recommendation, level 1B evidence).
- VAD is no longer a recommended induction regimen (grade A recommendation, level 1B evidence).
- The incorporation of proteasome inhibitors, thalidomide or lenalidomide as part of front line induction therapy (Table 1) improves quality of responses and is considered standard of care. Currently, only bortezomib and thalidomide but not lenalidomide are available on the Australian PBS for induction therapy for patients with newly diagnosed MM.
- Three-drug combinations appear more efficacious than two-drug combinations (grade B recommendation, level 2A evidence). Four-drug combinations are more toxic without added efficacy and are not recommended (grade A recommendation, level 1B evidence).
- The choice of induction therapy (Table 1) is dependent on local availability/access to novel therapeutic agents and should take into consideration the patient's prognostic indices and comorbidities, for example:
 - For patients categorised as having high-risk MM (Table 2) or with renal impairment, the use of bortezomib early in the disease course should be considered (grade A recommendation, level 1B evidence).
 - For patients with pre-existing neuropathy, thalidomide or bortezomib should be used with caution with appropriate dose attenuation upon worsening of neuropathic symptoms. A weekly schedule of bortezomib 1.5 mg/m² and subcutaneous route of administration appear to significantly reduce neurotoxicity compared with the traditional bortezomib schedule of 1.3 mg/m² IV on days 1, 4, 8, 11 every 21 days.
 - For patients with severe renal impairment, lenalidomide-based regimens are not the induction of choice because of renal clearance of lenalidomide.
 - For patients with previous history or at high-risk of thromboembolic complications, thalidomide and lenalidomide, although not absolutely contraindicated, should be avoided if other effective induction options are available. For recommendations with respect to thromboembolic prophylaxis for patients treated with thalidomide or lenalidomide, please refer to the MSAG Multiple Myeloma Clinical Practice Guideline (<http://www.myeloma.org.au>).

ASCT, autologous stem cell transplantation; IV, intravenous; MM, multiple myeloma; PBS, pharmaceutical benefits scheme; VAD, vincristine, doxorubicin, dexamethasone.

(Mozobil, Sanofi-Aventis, Bridgewater, NJ, USA), a chemokine receptor-4 antagonist, has been shown to be a potent stem cell mobiliser. Its use in combination with rhG-CSF significantly improves stem cell mobilisation compared with rhG-CSF alone.⁴⁸ Because of high cost, plerixafor is generally reserved for patients who fail to mobilise adequately as either a rescue strategy or during a second mobilisation attempt under the PBS reimbursement criteria in Australia.

Box 2 Recommendations regarding stem cell mobilisation

- Stem cell mobilisation regimen should follow institution protocol.
- Stem cells can be mobilised with rhG-CSF alone or rhG-CSF (10 mcg/kg) in combination with high-dose cyclophosphamide (2–4 g/m²).
- The use of high-dose cyclophosphamide has the advantage of increasing CD34 + yield but is also associated with more toxicity.
- rhG-CSF alone may be adequate for the initial attempt of stem cell mobilisation after thalidomide or bortezomib-based induction therapy. However, combination rhG-CSF and high-dose cyclophosphamide may be required after lenalidomide-based induction therapy, and it is recommended that stem cell mobilisation is attempted before patients have received more than four treatment cycles (grade B recommendation, level 2B evidence).
- Plerixafor in combination with rhG-CSF significantly improves stem cell mobilisation and is reserved for patients who fail to mobilise adequately on cyclophosphamide plus rhG-CSF, or rhG-CSF alone (grade B recommendation, level 2B evidence).

rhG-CSF, recombinant human granulocyte colony stimulating factor.

Box 3 Recommendations regarding follow up post-ASCT

Post-ASCT, patients should be followed up monthly until stable, then 3 monthly or less frequent if there appears to be disease stability (grade C recommendation, level 4 evidence).

Follow up assessment should include:

- Clinical assessment.
- Serum \pm urinary protein electrophoresis (immunofixation not required).
- Serum free light chains.
- FBE, U&E, Ca²⁺.
- Targeted radiographic imaging if indicated.

ASCT, autologous stem cell transplantation; FBE, full blood evaluation; HDT, high-dose therapy; U&E, urea and electrolytes.

Bortezomib and thalidomide on their own do not appear to impair stem cell mobilisation⁴⁹ in patients who have received fewer than four induction treatment cycles. Recent reports have indicated that thalidomide and oral cyclophosphamide, two agents that have not been shown to impact stem cell mobilisation individually, may induce a higher rate of stem cell mobilisation failure when used in combination.⁵⁰ Lenalidomide has been reported to reduce the number of CD34 + cells collected.⁵¹ Mobilisation using rhG-CSF alone after lenalidomide-based induction therapy may be inferior

Box 4 Recommendations regarding maintenance therapy post-ASCT

- Maintenance therapy with thalidomide 100 mg daily with or without corticosteroids is recommended in patients following first-line treatment with HDT and ASCT (grade A recommendation, level 1A evidence).
- Thalidomide ± prednisolone maintenance post-ASCT should continue for approximately 12 months. The benefit of maintenance beyond 12 months remains to be proven (grade A recommendation, level 1A evidence).
- Lenalidomide maintenance post-ASCT is well tolerated, improves PFS and possibly OS (grade A recommendation, level 1B evidence). At present, lenalidomide is not registered for this indication, and hence we cannot currently routinely recommend lenalidomide maintenance.
- The dose schedule and role of maintenance bortezomib is still unclear, and bortezomib is not registered for this use. Bortezomib maintenance is not recommended (grade C recommendation, level 4 evidence).

ASCT, autologous stem cell transplant/transplantation; HDT, high-dose chemotherapy; OS, overall survival; PFS, progression-free survival.

Box 5 Recommendations regarding alloSCT

- Currently, alloSCT is still considered investigational and should ideally be performed in the setting of a clinical trial (grade C recommendation, level 4 evidence).
- Young patients with high-risk MM (Table 2) who are considered potentially suitable for alloSCT should be referred early to the transplant physician at the outset of treatment (grade C recommendation, level 4 evidence).

alloSCT, allogeneic stem cell transplantation; MM, multiple myeloma.

to combination therapy using rhG-CSF and high-dose cyclophosphamide,⁴⁶ and the latter should be considered for stem cell mobilisation. It is strongly advised to mobilise patients prior to receiving four cycles of lenalidomide-based induction therapy. Please refer to Box 2 for summary of recommendations.

Monitoring after ASCT

The average TTP for patients after HDT and ASCT is in the order of 2–4 years for younger patients and shorter for older patients. The final magnitude of response post-ASCT should be assessed after 2–3 months. Patients should be followed up with clinical and laboratory assessments, looking for evidence of relapse/progression. Testing should include serum or urinary paraprotein levels (SFLC levels are used in patients with unmeasurable paraprotein

Box 6 Recommendations for patients with high-risk MM

The optimal management for patients with high-risk MM remains uncertain. There is no proven risk stratification approach:

- Consider using bortezomib-based regimen as part of induction treatment (grade A recommendation, level 1B evidence).
- Consider early referral for allogeneic stem cell transplant consideration for selected patients with HLA-matched sibling. However, the role of allogeneic stem cell transplant, even in the high-risk setting is still unclear and requires discussions with both the transplant and treating haematologist early in the disease course (grade C recommendation, level 4 evidence).
- Consider tandem autologous stem cell transplant (grade B recommendation, level 2B evidence).

HLA, human leucocyte antigen; MM, multiple myeloma.

in blood or urine), full blood count, serum calcium levels and renal function. In assessing response, it is important not to misinterpret the emergence of oligoclonal bands as relapsed disease or clonal evolution. Oligoclonal response after primary therapy is a well-recognised event, and can appear as multiple oligoclonal bands in serum and/or urine immunofixation; it is thought to be related to immune reconstitution and is associated with a favourable outcome.⁵² Initial follow up for patients is usually monthly until stable, then 3 monthly or less frequent subsequently if there appears to be disease stability. Please refer to Durie *et al.*⁵³ for uniform response criteria to assess response and relapse after treatment. Please refer to Box 3 for summary of recommendations.

Consolidation and maintenance therapy post-ASCT

Consolidation following ASCT refers to a short treatment course that improves depth of response.²⁴ At the current time, there are insufficient data to determine if consolidation therapy improves long-term outcome in MM. The VCAT (Bortezomib Consolidation after Transplant) study is currently ongoing and may answer this question in due course. In contrast, maintenance therapy with thalidomide post-ASCT has proven to prolong both PFS and OS.⁵⁴ Treatment is generally tolerated for a median of approximately 12 months. Toxicity, in particular peripheral neuropathy, is the main reason for early thalidomide discontinuation. Lenalidomide maintenance post-ASCT has been assessed in two phase III studies. A reduced risk of disease progression by 50–52% ($P < 0.001$)^{55,56} was seen, and one study showed a significant reduction in

risk of death.⁵⁶ Grade ≥ 3 neutropenia was the most frequent adverse events. A higher incidence of secondary malignancies was noted in the lenalidomide arm in both studies (7.8–8.5% lenalidomide vs approximately 3% placebo). With respect to lenalidomide-associated second primary malignancies, a recent meta-analysis has shown that the risk pertains to secondary haematological malignancies and is closely related to the use of oral melphalan.⁵⁷ The current general consensus is that the benefits of lenalidomide treatment with lenalidomide until disease progression appear to outweigh the risks, although longer-term follow up is required. It is unknown whether maintenance with lenalidomide is equivalent to maintenance with thalidomide in terms of efficacy or toxicity. It is assumed that bortezomib, like thalidomide or lenalidomide, likely improves depth of response when used as consolidation or maintenance. However, the design of available studies, which incorporated different induction and consolidation arms, makes it difficult to elucidate the impact of bortezomib maintenance on survival.²⁰ As such, no firm conclusions regarding bortezomib maintenance can be made. Please refer to Box 4 for summary of recommendations.

Allogeneic stem cell transplant

'Graft versus myeloma (GVM)' effect has been shown to exist in the setting of allogeneic stem cell transplantation (alloSCT).⁵⁸ However, while this may give rise to some long-term durable remissions,⁵⁹ myeloablative alloSCT is associated with a high TRM of up to 50%. The subsequent introduction of reduced intensity conditioning (RIC) alloSCT has led to a lower TRM, approximately 10–15% at 1 year, while maintaining the GVM effect. Three prospective trials have been published that assessed the role of alloSCT as part of planned initial therapy in patients with MM. In the Intergroupe Francophone du Myelome (IFM)99-03 study,⁶⁰ patients with high-risk (del13q + β_2 -microglobulin > 3 mg/mL) and available sibling donors underwent MEL200 (melphalan 200 mg/m²) ASCT followed by RIC alloSCT with antithymocyte globulin, busulphan and fludarabine conditioning. Patients without a donor had a second ASCT. At the time of initial reporting, median EFS and OS were similar in the two cohorts, EFS 35 versus 32 months, $P = ns$ (not significant), and OS 47 versus 35 months, $P = ns$, in ASCT + RIC alloSCT versus tandem ASCT respectively. However, after longer follow up, OS was found to be significantly inferior in patients assigned to RIC alloSCT.⁶¹ An Italian randomised study also compared tandem ASCT versus ASCT followed by RIC alloSCT (non-myeloablative total body irradiation conditioning). Poor prognostic features were not required for trial entry. A superior long-term outcome was seen in

patients who had available sibling donors (OS: 80 vs 54 months, $P = 0.01$; EFS: 35 vs 29 months. $P = 0.02$).⁶² In the Spanish PETHEMA (Spanish myeloma group) trial,⁶³ comparisons were made between a second ASCT and RIC (melphalan and fludarabine) alloSCT in a group of patients who achieved <VGPR to their first ASCT. A higher rate of CR and a plateau in PFS in favour of RIC alloSCT was seen (40% vs 11%, $P = 0.001$) in this group. However, because of a higher TRM and graft versus host disease, no statistical difference in EFS and OS was observed. Finally, interim results from the Blood and Marrow Transplant Clinical Trials Network 0102 Trial showed equivalent 3-year PFS and OS for tandem auto-auto versus auto-allo stem cell transplant both high-risk⁶⁴ and standard-risk⁶⁵ MM patients; 2 Gy total body irradiation was used as the non-myeloablative conditioning regimen in the alloSCT arm. There was a trend to lower late PFS and TTP/relapse in the auto-alloSCT arm in the high-risk group ($P = 0.09$); however, no added benefit from auto-alloSCT was seen in the standard-risk group over tandem ASCT because of increased TRM. Please refer to Box 5 for summary of recommendations.

High-risk multiple myeloma

Several factors are known to confer a poorer prognosis in patients with MM (Table 2). These include older age,⁶⁶ higher International Stage System (ISS) stage, high lactate dehydrogenase (LDH), high plasma cell labelling index and the cytogenetic abnormalities: 13q deletion (identified by standard cytogenetic), t(4;14), t(4;16) and 17p deletion (as identified by fluorescent *in situ* hybridisation (FISH)).^{44,67,68} Amplification of chromosome 1q21 (by FISH) has also been shown to be associated with both shorter time to disease progression and poorer prognosis.^{69,70} By definition, patients with high-risk MM are considered those with an OS of 2 years or less despite treatment with IMiD and proteasome inhibitors.⁷¹ The most robust factors that are consistently associated with such poor survival are higher ISS stage and the cytogenetic abnormalities 17p deletion and t(4;14). Recently, this has led to a proposed revised(R)-ISS risk stratification system that incorporates ISS stage, LDH and high-risk iFISH (del17p and t(4;14)). The R-ISS risk stratification system (Table 2) was recently shown to identify clearly three different MM prognostic groups in patients who were treated in the era of IMiD and proteasome inhibitors. If this is confirmed by prospective evaluation, it will likely supersede the current ISS staging system.^{71,72}

Several reports have confirmed that bortezomib is effective even in the presence of poor risk cytogenetics (13q deletion, t(4;14), amp1q21 and perhaps even 17p deletion).^{20,70,73–75} Preliminary data suggest that the same

Table 2 Factors associated with poorer prognosis in multiple myeloma

High-risk factors	The following tests for high-risk disease are routinely available in Australia and are recommended
ISS (International Stage System) III (Serum β_2 microglobulin >5.5 mg/L)	β_2 microglobulin Albumin
Conventional cytogenetics	Conventional cytogenetics‡
• Del17p • Hypodiploidy • Deletion of chromosome 13†	
Fluorescent <i>in situ</i> hybridisation (FISH)	Fluorescent <i>in situ</i> hybridisation (FISH)‡
• t(4;14) • t(14;16) • Del17p • 1q21 amplification	• t(4;14) • t(14;16) • Del17p • 1q21 amplification.
Plasma cell labelling index $\geq 3\%$	Plasma cell labelling index (by flow cytometry)§
High lactate dehydrogenase (LDH)	LDH
Revised (R)-ISS risk stratification model ⁴⁴	5-year OS (%)
R-ISS I	81
• ISS I (serum β_2 M < 3.5 mg/L and serum albumin > 35 g/L) AND	
• Normal LDH AND	
• No high-risk iFISH profile (defined as del17p and/or t(4;14) and/or t(14;16))	
R-ISS II	62
• Patients failing to meet criteria for R-ISS I or III	
R-ISS III	39
• ISS III (serum β_2 microglobulin > 5.5 mg/L) AND	
• High-risk iFISH OR	
• High LDH	

†t(4;14) and del(17p) are often associated with del(13q), and it appears that most of the negative impact of del(13q) is related to t(4;14) or del(17p). ‡Cytogenetics and FISH should only be requested in patients in whom the identification of high risk would impact management. Cytogenetics is often only possible in patients with >15% plasma cells in the aspirate as the yield of metaphases is low with a lesser plasma cell burden. §Available at Royal Prince Alfred Hospital, NSW, Australia. LDH, lactate dehydrogenase; OS, overall survival.

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may apply to lenalidomide.⁷⁶ A possible beneficial role of tandem ASCT in patients with poor prognostic features was suggested in an integrated analysis of phase III European studies, in which patients were prospectively assigned to receive either single or tandem ASCT. Tandem ASCT resulted in OS benefit compared with single ASCT, which was particularly evident in patients with high-risk cytogenetics and who failed to achieve CR post-bortezomib-based induction (5-year OS estimate 70% vs 17% with single ASCT, $P < 0.001$).²¹ The role of alloSCT in patients with high-risk MM remains uncertain but is an area of active investigation. Please refer to Box 6 for summary of recommendations.

Conclusion

In transplant-eligible patients, ASCT remains a cornerstone of front-line therapy to maximise depth and durability of CR in our ultimate quest for improved survival while maintaining QOL. Based on current available data, we recommend that the most appropriate strategy for frontline treatment in transplant-eligible patients with MM should include an induction regimen containing either bortezomib or an IMiD, followed by HDT + ASCT, then thalidomide maintenance (Fig. 1). The routine use of bortezomib or lenalidomide post-transplant as consolidation or maintenance is yet to be proven superior to thalidomide maintenance. We believe that a national consensus for treatment algorithm of MM will improve patterns of care in Australia; the clinical practice guideline for MM will be updated by the MSAG to the MFA on an annual basis.

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