Consensus statement on the treatment of transplant-eligible patients with newly diagnosed multiple myeloma in New Zealand

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ABSTRACT

Multiple myeloma is the second most common blood cancer in New Zealand with higher incidence in Māori and Pacific Island populations. It remains an incurable disease but the rapidly changing treatment landscape has led to improved outcome. In response to recent changes in funding of anti-myeloma therapy in New Zealand, the New Zealand Myeloma Interest Group has reviewed the latest literature and updated the treatment pathway of transplant-eligible patients with newly diagnosed multiple myeloma.

In New Zealand, around 400 new cases of multiple myeloma (MM) are reported each year. This equates to an age standardised incidence rate of 5.19 cases per 100,000 population, which is similar to other western countries and is increasing with time. The incidence is higher in Māori and Pacific Islanders.[1] The MM treatment landscape has rapidly evolved over the last two decades, with increasing number of novel agents and immunotherapies available. These agents are effective and usually well tolerated. They have led to a significant improvement in outcome in MM patients.[1,2] PHARMAC, the pharmaceutical management agency in New Zealand, has recently made changes to funding for anti-myeloma therapy, which included unrestricted access to bortezomib and lenalidomide maintenance therapy. The New Zealand Myeloma Interest Group has taken this opportunity to review and update the national treatment pathway accordingly. These recommendations aim to unify upfront therapy for transplant-eligible MM patients in New Zealand and form the basis of ensuring equity and consistency of MM care in New Zealand. This goal is in line with national Cancer Action Plan, as published by the New Zealand Cancer Control Agency.[3] However, these recommendations are for guidance only, and final patient treatment decisions should be made at clinicians' discretion, taking into consideration all patient factors.

Method

The New Zealand Myeloma Interest Group is comprised of representative haematologists from District Health Boards around the country with a special interest and expertise in MM. We reviewed the currently available evidence, including randomised controlled trials, retrospective data and conference abstracts, and interpreted these in the context of treatment options available in New Zealand to form a recommendation that is best suited for our population.

Induction chemotherapy

The funded front-line option for induction chemotherapy remains bortezomib-based treatment for transplant-eligible patients. The preferred regimen is to combine bortezomib with an alkylating agent such as

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cyclophosphamide and dexamethasone. In younger patients or those with suboptimal response, defined as less than a very good partial response by International Myeloma Working Group (IMWG) criteria, changing to bortezomib–thalidomide–dexamethasone (VTD) regimen (Table 1) prior to autologous stem cell transplant (ASCT) can be considered. VTD has been shown to improve responses in the upfront setting compared to bortezomib–cyclophosphamide–dexamethasone combination; however, whether this translates to survival outcome is unknown.[4] The decision will need to be balanced against the increased risk of neurological toxicity with the VTD regimen, as reported in the IFM2013-04 study,[4] although this trial used twice-weekly bortezomib instead of the weekly regimen used in New Zealand. The optimal number of induction cycles has not been clearly defined by current evidence but, based on international practice, a minimum of four cycles is recommended.[5,6]

The group recognises that the more effective regimen of lenalidomide–bortezomib–dexamethasone is currently recommended in many countries as upfront induction chemotherapy, based on its improved response and outcome.[7] However, this regimen is not currently available as induction, as lenalidomide is not funded for front-line induction treatment in New Zealand.

High-dose therapy and autologous stem cell transplant

High-dose therapy with autologous stem cell transplant remains an integral part of front-line therapy in newly diagnosed MM, even in the era of novel agents. ASCT has been shown to significantly improve the depth of response and progression-free survival (PFS) but not overall survival (OS).[8,9] This may be partly due to the short follow-up in trials and the availability of effective salvage agents. Based on the improved PFS, it is recommended that eligible patients should be considered for front-line ASCT rather than delaying to relapse. This recommendation is further supported by the result of IFM2009 trial, which showed 21% patients were unable to receive ASCT at relapse due to disease refractoriness.[8]

Until recently, the role of tandem ASCT has been unclear, and published data have shown conflicting results. However, recently, two large randomised controlled trials, the EMN02 trial and updated result

Table 1: Recommended regimens and dosing.

Regimen	Dosing
CyBorD induction	Bortezomib 1.5mg/m^2 SC Cyclophosphamide 300mg/m^2 PO Dexamethasone 40mg PO All given on days 1, 8, 15 and 22 of 28-day cycle
VTD induction	Bortezomib 1.5mg/m^2 SC, days 1, 8, 15 and 22 Thalidomide 50–100mg daily PO Dexamethasone 40mg PO, days 1, 8, 15 and 22 28-day cycle
Modified RVD consolidation	Bortezomib 1.5mg/m^2 SC, days 1, 8, 15 and 22 Lenalidomide 10mg daily PO, days 1–21 Dexamethasone 20–40mg PO, days 1, 8, 15 and 22 28-day cycle

from STaMINA trial (on as-treated analysis), have shown improvements in PFS for patients treated with tandem ASCT over single ASCT in patients with high-risk cytogenetic abnormalities.[9,10] However, in the EMN02 trial this difference did not reach statistical significance. The definitions of high-risk disease were different between these two trials and the number of patients with high-risk cytogenetic was small. The subgroup analysis showed the PFS improvement to be significant in those with 17p deletion (del17p) in the EMN02 study, while the benefit in other high-risk groups have yet to be published.[9] There does not appear to be an OS difference between tandem or single ASCT.[9,10] Based on these results, the group is recommending tandem transplant for patients with del17p by fluorescence in situ hybridisation (FISH). Tandem ASCT is currently not uniformly recommended for other high-risk patients based on clinical or genetic factors, due to a lack of strong evidence supporting this approach and potentially increased toxicities. However, this should be reviewed on an individual patient basis.

Most international guidelines are moving away from using chronological age to determine transplant eligibility. Instead, assessment should be based on biological age, performance status and coexisting comorbidities. Multiple retrospective studies have shown the feasibility of ASCT in elderly patients to achieve equivalent survival outcomes compared to younger patients.[11,12] Although toxicity during ASCT appears to be increased in the older transplant patients, including length of hospital stay and infection, transplant related mortality is reported to be between 1% and 1.5%, which is comparable to the younger population.[13,14] The definition of elderly differed between trials but generally used cut off between 65 to 70 years of age. It is worth noting that these evidences are mainly based on large retrospective analyses, and therefore an inherent bias cannot be excluded. Consideration should be given to reduce the conditioning melphalan dose to 140mg/m^2 in older or frailer patients, but this should also be balanced against treatment efficacy, as the reduced dose may compromise outcomes in patients with suboptimal response prior to ASCT.[11,15] Assessment using tools like the haematopoietic stem cell comorbidities index has been shown to correlate with survival outcome and may aid in patient selection and decisions on conditioning intensity.[16]

Post-transplant consolidation therapy

In New Zealand, bortezomib-based consolidation has been given to patients, as maintenance therapy was not available and bortezomib was funded for up to nine cycles in the front-line setting. Recently, lenalidomide maintenance has become available, prompting a review of the need for consolidation therapy.

When conventional chemotherapy was used as induction and maintenance therapy was not given, consolidation with proteasome inhibitor (PI)- or IMiD-based regimens have been shown to deepen responses and improve PFS outcomes, although no consistent OS benefit has been demonstrated.[17–19] However, in the era of novel agent-based induction treatment and post-ASCT maintenance, the role of consolidation is less clear. In the STaMINA trial, there was no advantage of RVD consolidation compared to patients who received single ASCT followed immediately by lenalidomide maintenance.[20] The EMN02 trial showed consolidation therapy improves PFS in the upfront setting, but the follow-up is too short at this stage to determine if this benefit is maintained in the ASCT cohort.[9]

As the benefit of consolidation therapy in the post-ASCT setting is unclear at this stage, its routine use is not supported by the group. However, it remains a valid option for patients who have a high-risk disease or suboptimal response. Traditionally, up to four cycles of consolidation were given post ASCT in New Zealand. In more recent international trials, if consolidation therapy is included, two cycles are typically used. Based on these factors, we propose that if consolidation is to be used, it can be given for two to four cycles. One proposed consolidation regimen is the modified RVD regimen (Table 1). Although this modified regimen has not been tested in prospective studies, it has the same bortezomib and lenalidomide dosing schedule as other commonly used anti-MM regimens in New Zealand.

The dose of 10mg of lenalidomide was proposed, as this would still fall within the latest PHARMAC Special Authority funding criteria for lenalidomide maintenance. The group will aim to collect data on the use of this consolidation regimen and its impact on patient outcome.

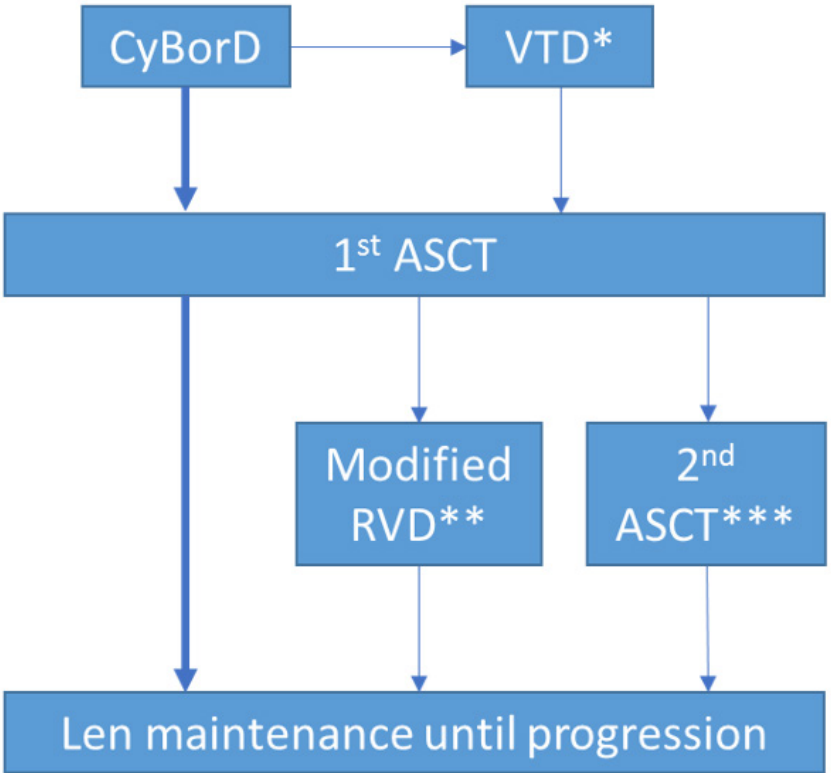
Maintenance therapy

Lenalidomide maintenance has become the standard of care as part of front-line therapy, based on results of multiple trials showing that it deepens responses, which translates to a PFS benefit, although OS benefit is less consistently shown.[21–25] The benefit is particularly seen in patients who have not achieved a complete response prior to maintenance; however, patients who are minimal residual disease (MRD) negative also benefited.[24,26]

Not all trials included baseline cytogenetic results, and therefore the evidence for patients with high-risk cytogenetic abnormalities has been less robust. In a meta-analysis and the Myeloma XI trial, there appears to be PFS benefit for those with high-risk cytogenetic compared to observation.[24,25] Based on these results, lenalidomide maintenance should be recommended for all patients post ASCT unless there is a contraindication.

Lenalidomide maintenance therapy can be started up to six months post ASCT, as per the current funding criteria, although in the studies it was generally started around 100 days after the ASCT. Lenalidomide should be continued until disease progression or if patients experience intolerant side effects. Recent data suggest that a shortened length of maintenance compromises outcome.[10] There is a small increase in secondary malignancies, but the benefit outweighs this risk.[21,24,25]

Figure 1: Treatment pathway for transplant-eligible, newly diagnosed multiple myeloma patients.



*May consider VTD induction for younger patients (<65) or those with a suboptimal response to CyBorD.
** Modified RVD maybe considered for patients who have a suboptimal response to ASCT (ie, less than VGPR) or have high-risk clinical features.
*** Tandem/double ASCT maybe considered for patients with high-risk FISH cytogenics

PI-based maintenance strategies have been investigated in clinical trials. In HOVON-65/GMMG-HD4, bortezomib-based maintenance improved outcome particularly for patients with high-risk cytogenetic.[27] However, the standard arm used conventional chemotherapy for induction versus bortezomib-based induction, making it difficult to determine whether the improved outcome is solely due to bortezomib maintenance. There is no randomised controlled trial comparing a PI-based with an IMiD-based maintenance strategy. Retrospective single-centre data suggest they may be equally efficacious, especially in high-risk cytogenetic patients.[28,29] Based on the currently available data, bortezomib maintenance therapy is not recommended routinely but can be considered for patients who cannot tolerate lenalidomide maintenance and have high-risk diseases. Ixazomib maintenance has been tested as post-transplant maintenance treatment in a prospective study. Although it has shown an improved progression-free survival compared with placebo, the degree of clinical benefit appears to be small.[30] Currently, this is not funded in New Zealand.

Conclusion

The treatment landscape of MM changes rapidly as evidence evolves. The increasing number of novel agents available continues to improve outcomes, although the cost is making public funding difficult in many countries. The New Zealand Myeloma Interest Group has formed the above consensus recommendation (Figure 1) based on best available evidence and modified to suit the New Zealand setting.

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