

Multiple Myeloma: Transplant Eligible

Effective Date: September 2023



Background

Multiple myeloma (MM) is an aggressive malignant neoplasm of plasma cells that accumulates in the bone marrow and contributes to approximately 15 percent of all hematologic malignancies. In Canada, MM make up 1.2 percent of all new cancer cases and 1.8 percent of all cancer deaths. Seventy-five percent of all myeloma cases are in patients over the age of 60 years, and the incidence increases steadily with age.

Guideline Questions

1. How should patients who are diagnosed with multiple myeloma who are transplant eligible be managed?

Search Strategy

Originally, the Medline and Pubmed databases were searched for relevant clinical trials, systematic reviews, and meta-analyses (1966-2012). This update involved informal literature searches and consensus discussions and the Alberta annual hematology tumour team meeting.

Target Population

The following recommendations apply to adult cancer patients with multiple myeloma, who are transplant eligible.

Recommendations

Treatment Guidelines for Newly Diagnosed Multiple Myeloma

Goal of therapy:

The goals of therapy for young patients with multiple myeloma is to achieve the deepest possible response and to maintain that response for as long as possible.

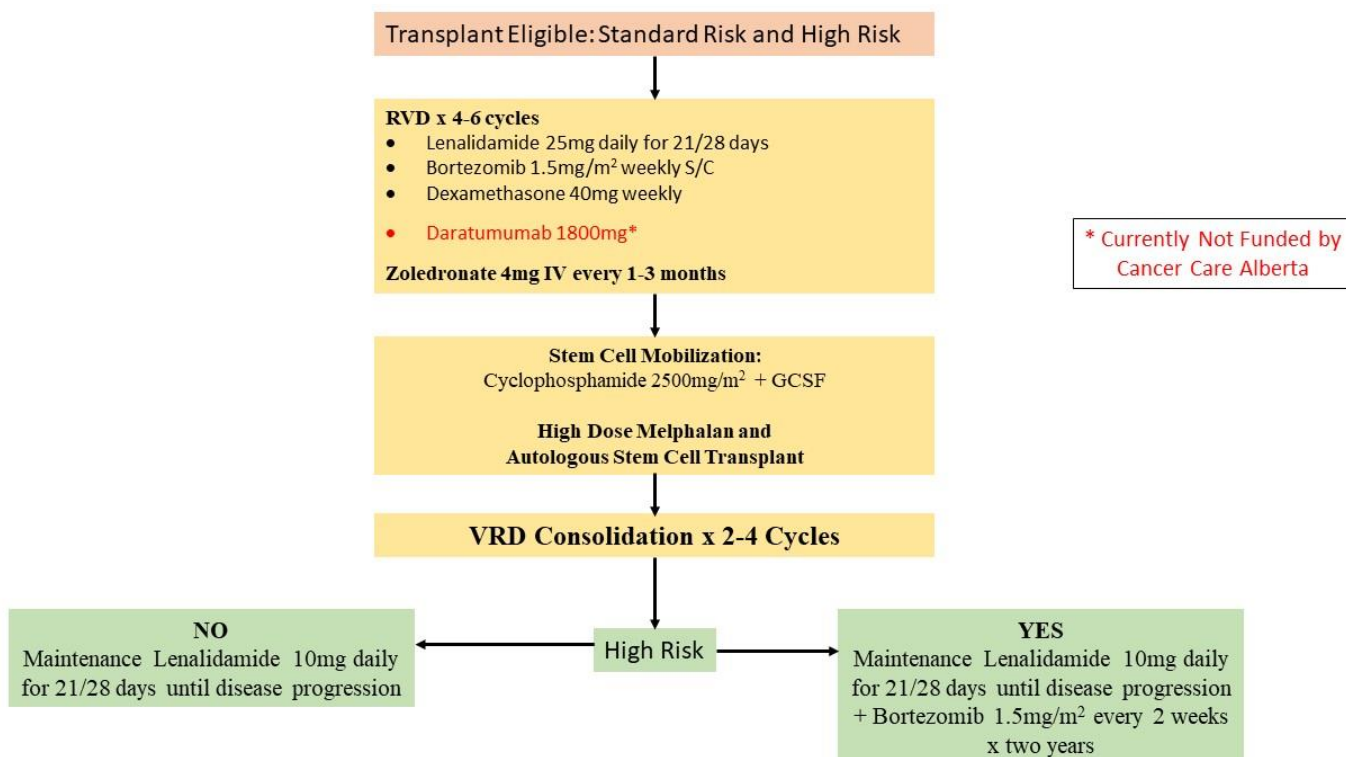
For elderly patients, the goal of therapy is to minimize symptoms and maximize response with as little toxicity as possible.

These guidelines identify effective, evidence based treatment regimens to be utilized. These treatment regimens can include multi-drug and multi-step approaches, cell therapy, radiation therapy, or single agents when appropriate. The use of the most effective therapy in that line of therapy for the patient's level of frailty should be emphasized.

Patients ≤ 65 Years Old and Transplant-Eligible:

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable clinical trial, patients who are 65 years old or younger and are transplant-eligible should receive a course of therapy consisting of:

- Pre-transplant induction with a 3-drug regimen that includes lenalidomide, bortezomib, and dexamethasone.
- High dose melphalan followed by autologous stem cell transplantation
- Post transplant consolidation
- Maintenance lenalidomide and/or bortezomib until disease progression.



Induction Regimens:

Depth of response is one of the most important prognostic factors in multiple myeloma¹. The goal of the transplant course is to achieve the deepest, most durable remissions possible, including stringent complete remission and minimal residual disease negativity². Three drug regimens that include a proteasome inhibitor, and IMiD, and dexamethasone have been shown in several prospective studies to provide superior outcomes when used as part of pre transplant induction.

RVD:

The combination of lenalidomide, bortezomib, and dexamethasone is associated with an improved overall response rate, depth of response, progression free survival, and overall survival³⁻⁵. This benefit is seen in all patient groups including those with high risk cytogenetics. A strategy of RVD induction and stem cell transplant followed by consolidation and maintenance therapy results in a complete response rate of 59%, median progression free survival of 50 months, overall survival at four years of 81%, and high rates of minimal residual disease negativity. **RVD for 4-6 cycles is considered standard initial induction regimen for transplant eligible myeloma patients.**

KRd:

The use of carfilzomib based inductions have been produced durable responses (FORTE study: Gay, F et al Lancet Oncology 2021) when combined with high dose melphalan and autologous stem cell transplant. However, when RVD was compared to KRd in the randomized phase 3 endurance trial, both treatments showed similar progression free survival. Median overall survival was not reached in either group. Toxicity was higher, however, in the KRd regimen⁶. A subsequent retrospective study of KRd versus RVD followed by stem cell transplant shows similar responses in the two groups⁷. As such KRd does not offer advantages over RVD for induction therapy prior to stem cell transplant.

CYBORD:

CYBORD has not been compared to RVD or Rd as induction therapy for transplant eligible myeloma. Historical response rates and outcomes in phase 2 studies and real world evidence, including Canadian Myeloma Research Group's database, offer inferior responses to those seen with the RVD combination, which have the strength of evidence of two phase 3 studies. As such, CYBORD is no longer considered standard for initial therapy in this setting. However, CYBORD remains an option for those who do not tolerate lenalidomide or have a contraindication to the drug. It may also be considered an option for initial cycles in patients presenting with renal failure with the intention of switching to RVD upon improvement of renal function.

Four Drug Regimens:

Anti-CD 38 monoclonal antibodies have been incorporated into frontline therapy for patients with non-transplant eligible multiple myeloma, dramatically improving responses and survival. RVD with daratumumab (D-RVD) was compared to RVD alone for transplant eligible patients in the randomized phase 2 Griffin study. Patients received induction with either D-RVD or RVD for four cycles followed by stem cell transplantation, consolidation and maintenance with the same regimen they received in induction. Stringent complete responses were higher in the daratumumab arm (62% versus 45%). Rates of minimal residual disease were also higher (51% versus 20%)⁸. Estimated progression free survival at four years was similar in the two groups (87% versus 70%). The Casseiopeia phase 3 study using D-VTD induction showed a difference compared to VTD in PFS (90% compared to 81%) at three years, however, we are awaiting longer term data. The value of the daratumumab in limited durations of 4 cycles pre-high dose melphalan with autologous stem cell rescue followed by 2 cycle in

consolidation appears to abrogate the need for continuous daratumumab in maintenance following consolidation in this trial. Although this regime has Health Canada approval, thalidomide does not have provincial funding and as such will not be listed in the recommendations in this guideline.

The GMMG-HD7 trial comparing Isatuximab plus RVD to RVD alone also showed an improvement in MRD negativity (50% vs 36%)⁹. Progression free survival is not yet reported.

Neither daratumumab nor Isatuximab are currently funded provincially for upfront treatment of patients with multiple myeloma who are transplant eligible, and alternate funding is required for its use.

Transplant eligible patients should receive 3-4 cycles of induction therapy before proceeding to ASCT. The achievement of CR is not required to proceed to transplant. Patients who fail to achieve CR after 3-4 cycles of induction, including those with primary refractory disease, can still benefit from high dose therapy and ASCT and should still be referred for transplant evaluation. Options for those demonstrating inadequate response to initial induction (<PR) include stem cell collection and transplant without re-induction, or second line salvage therapy prior to transplant. In the latter case, regimens containing anti-CD38 monoclonal antibody (daratumumab, isatuximab) can be considered.

RVD Regimen:

Patients should receive no more than 4 cycles prior to attempted stem cell mobilization. Cycles are repeated every 28 days. Each cycle consists of:

- o Lenalidomide 25mg orally daily for 21 days
- o Bortezomib 1.5mg/m² subcutaneously weekly for 4 weeks
- o Dexamethasone 40mg orally weekly for 4 weeks.

A 21-day schedule can be used for sicker patients requiring a more rapid initial response to therapy:

- o Lenalidomide 25mg orally daily for 14 days
- o Bortezomib 1.3mg/m² subcutaneously twice weekly for 2 weeks
- o Dexamethasone 40mg orally twice weekly for 2 weeks.

High Risk Myeloma:

Patients with high risk cytogenetic aberrations such as del17p or t(4;14) and t(14;16) have a worse outcome with ASCT than patients without these findings. They should be considered for clinical trials with novel frontline agents with or without SCT. However, in the absence of a clinical trial, patients with high risk myeloma should receive similar treatment as other myeloma patients including induction with a VRD followed by ASCT. All patients are recommended to have evaluation of cytogenetic abnormalities prior to initiation of therapy by bone marrow aspirate to screen for the double hit myeloma. Screening for tp53, del1q, amplification of 1p, in addition to current high risk

lesions of t(4:14) with assessment of the NSD2 breakpoint,⁴⁰ and t(14;16) are considered the global standard of care.

Stem Cell Transplantation:

Autologous Stem Cell Transplant (ASCT):

Four large randomized trials initially demonstrated the superiority of autologous stem cell transplantation to standard dose chemotherapy with significant prolongation of TTP and OS.¹⁰⁻¹³ Other trials, with several caveats, have failed to demonstrate the same benefit from ASCT.¹⁴⁻¹⁷ Details of these trials are outlined in Table 1 of Appendix A. Subsequent trials have confirmed the ongoing benefit of stem cell transplant over approaches that do not include transplant^{4,5}.

Deferral Of Transplant:

Deferral of transplant until first relapse has been explored as an approach for transplant eligible patients. The DETERMINATION trial randomized patients to a strategy of either RVD followed by lenalidomide maintenance, or RVD, stem cell transplant, and lenalidomide maintenance³¹. Progression free survival was 67.5 months in the transplant group versus 46.2 months in the no transplant group. There was no difference in overall survival between the groups, likely because of the availability of effective salvage therapies at relapse. Unfortunately, in the no transplant group, only 35% of those requiring subsequent therapy went on to receive stem cell transplant, suggesting that alternative effective salvage therapies influenced the study results. Among patients with high risk cytogenetics, PFS was 55 months for transplant and only 17 months for the RVD alone group. Because of the observed improvement in progression free survival, upfront stem cell transplant remains a recommendation for newly diagnosed multiple myeloma patients. However deferral of transplant can be considered an option. When the patient is planning for a deferred transplant stem cell should still be collected early in the course of first line therapy, given difficulties collecting stem cells after prolonged IMiD therapy.

Transplant Over the Age of 65:

Patients are considered transplant eligible if they are under the age of 65, meet minimal requirements for underlying organ function and all other transplant eligibility requirements of the Calgary or Edmonton transplant programs. There is no proven benefit to transplant over currently listed standard therapy for patients over the age of 65, and no randomised trials addressing this have been performed in the frontline daratumumab era. The Myeloma XI study did look at the outcomes for patients over 65 undergoing non-transplant and transplant approaches³⁷. However, the comparison was not randomized with the selected bias of the treating doctor assigning patients to the TE or NTE arms. In addition, only 62% of those aged 65-69, and 57% of those over 70 who were initially deemed to be transplant eligible went on to stem cell harvest at the end of induction, again resulting in considerable selection bias among those getting ASCT. Retrospective analysis of the CIBMTR show good outcomes for this population, but selection bias is demonstrated again with only 15% of patients

being over 65 with no published quality of life analysis studied specifically in this cohort³⁸. Given the improvement in outcomes seen in transplant free regimens for elderly patients (as described in the non transplant eligible section of these guidelines), stem cell transplant is not recommended as initial therapy for patients over the age of 65 or with significant comorbidities.

Renal Failure:

Patients with renal failure on dialysis are candidates for autologous stem cell transplant and should be referred without significant delays for transplant evaluation, based on the individual transplant program's ability to manage dialysis patients undergoing stem cell transplant.

Stem cell collection:

The standard regimen includes cyclophosphamide 2.5 gm/m² with G-CSF starting on day 7. The goal is to collect at least 3-5 x 10⁶ CD34 cells/kg for each planned transplant. Alternatively, mobilization may be attempted with GCSF (5-10mcg/kg) with or without plerixafor (0.24mg/kg).

Just over 5% of patients ever go on to a second transplant. With the availability of highly effective therapies for 2nd and subsequent lines, the use of a second transplant for salvage at relapse has become very infrequent. In addition, it would not be pursued in elderly patients at the time of relapse, nor in patients who had a short remission with their first transplant. As such, collection targets should be for a single transplant for those over the age of 60. For younger patients who may benefit from a transplant in later lines of therapy, or for those for whom a tandem transplant is being considered a higher collection target would be indicated.

Conditioning regimen:

The standard transplant conditioning regimen is high dose Melphalan 200 mg/m² on day -1.

Tandem Autologous Transplantation:

Four large randomized trials have addressed the role of tandem transplantation in multiple myeloma, and have shown that tandem transplantation improves survival in patients who fail to achieve a VGPR after the first transplant. Details of these trials are outlined in Table 2 of Appendix A.¹⁸⁻²¹ For standard risk patients the results have otherwise been equivocal. The BMT CTN trial included strategies of transplant followed by maintenance, transplant followed by consolidation followed by maintenance, and tandem transplant followed by maintenance. Tandem transplant did not show any benefit until 8 years of followup in only patients with high risk cytogenetics³². Gagleman et al reported on 488 patients with extramedullary disease who received single or tandem transplant for newly diagnosed myeloma³⁴. Forty-one percent (202) had high risk cytogenetics of whom 42 received a tandem transplant. A second transplant improved both OS and PFS (84% and 45% at 4 years) compared to single transplant (41% and 22%), however no p-value was reported for this comparison and this study was not powered for this comparison.

The EMN02/HO95 randomized phase III trial compared a bortezomib-based induction followed by either continued bortezomib-based therapy vs transplant (single or double) with a second randomization examining the impact of VRD consolidation with all patients receiving lenalidomide maintenance until progression¹³. Tandem ASCT improved the 5-year PFS (53.5% vs 44.9%, $p=0.036$) and overall survival (80.3% vs 72.6%, $p=0.022$) compared to single ASCT. When only those with standard risk cytogenetics is considered, the effect was no longer significant with the hazard ratio for disease progression or death 0.84. The difference in the median PFS for those with high-risk cytogenetics was larger at 46 months following tandem ASCT compared to 26.7 months for single ASCT but did not reach statistical significance ($p=0.062$). The study included only 81 patients in the high risk cytogenetic group who underwent transplantation and thus was not powered for this comparison. A more focused look at those with del17p ($n=40$) favored double ASCT over single ASCT (5 year-OS 80% vs 57%, $p=0.066$) although it still did not meet statistical significance.

There does not appear to be a benefit to tandem transplant in patients with standard risk multiple myeloma. Published studies have not been powered to assess this modality in high risk patients would have showed a trend to benefit especially in those with p53 mutation. Tandem autologous transplant should not be routinely performed, but can be considered for patients with high risk cytogenetics.

Allogeneic Stem Cell Transplant:

Four studies have been conducted to date comparing tandem autologous to tandem autologous-allogeneic stem cell transplant. The details of these trials are outlined in Table 3 of Appendix A. In a French study trial (IFM99-03) of high risk patients (del13 and high $\beta 2$), no difference in outcome was seen between the two approaches.²³ In a study by Bruno and colleagues, allogeneic transplant was superior however in this study the results of the tandem autologous arm were lower than expected and the study had several reporting caveats.²⁴ Early results from the PETHEMA group suggest superior results with allogeneic transplant; however they only report a trend for better PFS, not OS.²⁶ The largest study comparing autologous to transplantation was performed by the US Blood and Marrow Clinical Trials Network. 625 patients were biologically assigned to receive either a tandem ASCT or ASCT followed by an allogeneic SCT. The 3-year PFS was 46% for the tandem autologous arm versus 43% for the autologous-allogeneic arm ($P = .67$). OS at 3 years was also not significantly different between the groups: 80% for the tandem autografts versus 77% for the autologous-allogeneic arm. Assignment to the autologous-allogeneic arm was associated with worsened survival in patients with stage I and II disease, but not in those with stage III disease. At this point, allogeneic transplant is not considered a standard part of therapy for newly diagnosed or relapsed myeloma and should be performed only in the setting of a clinical trial.

Post Transplant Therapy:

Consolidation:

All patients should be considered for 2 cycles of consolidation therapy with VRD following ASCT, and up to four cycles for those patients with high risk disease at diagnosis by cytogenetics, or who do not achieve a VGPR post transplant. For patients with alternate funding access to daratumumab, it can be included in post-transplant consolidation.

- Bortezomib 1.5 mg/m² on days 1, 8, 15, and 22
- Lenalidomide 5-15mg/d, days 1-21/28
- Dexamethasone 40 mg on days 1, 8, 15, 22

Maintenance Therapy:

Lenalidomide:

Two phase III trials have examined the role of lenalidomide maintenance following ASCT. The CALGB 100104 (n=460) trial compared a strategy of maintenance with lenalidomide (10mg daily) to placebo following ASCT²⁷. At a median follow up of 34 months, maintenance resulted in an improved TTP of 46 months versus 27 months for placebos (p<0.001). Overall survival was also improved, with HR for death 0.62 (p<0.03). Lenalidomide maintenance was associated with an increase in second primary malignancies (SPM) (7.8% vs 2.6%). However event free survival analysis including SPM as study related events continued to show improved survival outcomes in favor of the maintenance arm.

The IFM 2005-02 trial²⁸ randomized 614 patients to maintenance with lenalidomide 10-15mg daily following ASCT. All patients received two cycles of consolidation with lenalidomide 25mg daily for 21 of 28 days prior to starting maintenance. With a median follow up of 45 months, the 4 year PFS was 43% for lenalidomide compared to 22% for placebo (p<0.001). There was no difference in OS (73% vs 75%). There were 23 second primary malignancies in the lenalidomide group and 9 in the placebo group.

A meta-analysis of the 4 main lenalidomide maintenance studies, including an Italian study and the British myeloma XI, revealed an overall survival advantage, emerging at the 5 year post ASCT mark. The use of continuous lenalidomide was used in 2 of the 4 studies, where as a schedule of 21 days out of a 28 day regime was used in the remainder. The use of the 3 week schedule was adopted in Alberta upon approval of lenalidomide maintenance.

A retrospective analysis of 11 clinical trials of lenalidomide-based therapy for relapsed/refractory multiple myeloma including 3846 patients reported an incidence rate of second primary malignancies (SPMs) of 3.62²⁹. Incidence rate of invasive (hematologic and solid tumor) SPMs was 2.08, consistent with the background incidence of developing cancer. In a separate analysis of pooled data from

pivotal phase 3 trials of relapsed or refractory MM (n = 703), the overall IR of SPMs was 3.98 (2.51-6.31) with lenalidomide/dexamethasone and 1.38 (0.44-4.27) with placebo/dexamethasone. IRs of non-melanoma skin cancers were 2.40 (1.33-4.33) and 0.91 (0.23-3.66), respectively. IRs of invasive SPMs were 1.71 (0.86-3.43) and 0.91 (0.23-3.66), respectively.

Proteasome inhibitors:

The phase III HOVON-65/ GMMG-HD4 trial randomized 827 patients to receive VAD induction followed by ASCT and maintenance therapy with thalidomide (arm A) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by ASCT and maintenance with bortezomib every 2 weeks for 2 years (arm B)³⁰. The strategy of bortezomib-based induction with bortezomib maintenance resulted in superior response rates (\geq VGPR 76% vs 56%, $p < 0.001$) and PFS (35 vs 28 months, $p = 0.02$). The study was not designed to evaluate the benefit of bortezomib maintenance on its own. However, the number of patients achieving a response upgrade after starting maintenance was similar between the thalidomide and bortezomib maintenance arms suggesting similar effects of these two strategies. An analysis of PFS calculated from the time of last HDM showed a significant difference in favor of the bortezomib arm (31 versus 26 months). This indicates that although post-transplantation bortezomib and thalidomide both achieved similar response upgrades, bortezomib contributed more to improvement of PFS. Importantly in this study, for patients with del17p, PAD followed by bortezomib maintenance significantly improved PFS (mPFS in arm B vs arm A: 26.2 vs 12.0 months; $P = .024$) and overall survival (3-year OS rate in arm B vs arm A: 69% vs 17% $P = .028$)

Maintenance therapy with ixazomib, lenalidomide and dexamethasone (IRd) was compared to lenalidomide with dexamethasone in the GEM2014MAIN trial³⁵. With a median follow-up of 56 months, they demonstrate there was no difference in PFS between the two maintenance arms (median not reached, PFS at 5 years: 62% vs. 63% with IRd and Rd, respectively, $p = 0.785$). As such, ixazomib maintenance is not recommended following ASCT.

Similarly, concurrent carfilzomib with lenalidomide was also compared with lenalidomide as part of a second randomization in the FORTE study. Here, the 3-year PFS from the second randomization was 75% in patients treated with carfilzomib + lenalidomide (95% CI, 68–82, median, not reached [NR]; 95% CI, NR–NR) versus 65% with lenalidomide alone (95% CI, 58–72, median, NR; 95% CI, NR–NR) (hazard ratio, 0.64; 95% CI, 0.44–0.94; $p = 0.023$). Carfilzomib is currently not funded for first line therapy, including maintenance therapy.

Supportive Care:

Thrombosis Prophylaxis

Thrombosis prophylaxis is required with the use of lenalidomide. There is no consensus at the present time regarding the optimal DVT/pulmonary embolism prophylaxis. Acceptable options include:

- Daily ASA (81 or 325 mg)
- Prophylactic dose of low molecular weight heparin (LMWH)
- Coumadin with therapeutic INR (2-3)
- Novel oral anticoagulant (Apixaban, Rivaroxaban, etc)

Bone Targeted Agents

All patients should receive a therapy with either a bisphosphonate (zoledronate 4mg or pamidronate 30 – 90mg every 4 – 12 weeks) or Denosumab, as determined by the renal function of the patient. For further details refer to the chapter on supportive care.

Antibiotic Prophylaxis:

- Valacyclovir 500mg orally daily is recommended for all patients treated with a proteasome inhibitor such as bortezomib, and for all patients following stem cell transplant
- Sulfamethoxazole-trimethoprim (one single strength tablet daily) is recommended for all patients following stem cell transplant, and should be considered for patients receiving multidrug regimens such as RVD
- Levoquin 500mg orally daily x 3 months³⁹

Summary of Recommendations

Regimens containing bortezomib and dexamethasone as well as a third agent (cyclophosphamide, lenalidomide) are the standard induction regimen prior to stem cell transplantation for transplant eligible patients with standard risk or high risk myeloma requiring treatment. VAD or single agent dexamethasone should not be used.

- RVD is the recommended regimen for initial therapy of newly diagnosed transplant eligible patients. Patients should receive 4-6 cycles prior to stem cell collection. Cycles are repeated every 28 days.
- Cyclophosphamide followed by growth factor administration or growth factor alone is used for stem cell collection
- The standard stem cell transplant regimen consists of a single transplant conditioned with high dose (200mg/m²) Melphalan.
- Following transplant:
 - o All patients are eligible for 2 cycles of VRD. While high risk patients and those who fail to achieve VGPR are eligible for 4 cycles
 - o Following consolidation, patients with 17p deletion or t(4:14) should receive maintenance with lenalidomide and bortezomib (1.3mg/m²) every 2 weeks for 2 years. All others should receive lenalidomide 10mg daily for 21-28/28 days every 4 weeks until disease progression

References

1. Martinez-Lopez J, Blade J, Mateos M-V, Grande C, Alegre A, García-Laraña J, et al.. Long-Term Prognostic Significance of Response in Multiple Myeloma After Stem Cell Transplantation. *Blood* (2011) 118:529–34.
2. Munshi NC, Avet-Loiseau H, Anderson KC, et al.. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv.* 2020;4(23):5988-5999.
3. Durie BGM, Hoering A, Abidi MH, et al.. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial. *Lancet.* 2017;389(10068):519-527.
4. Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med.* 2017;376(14):1311-1320.
5. Richardson PG, Jacobus SJ, Weller EA, et al; DETERMINATION Investigators. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med.* 2022;387(2):132-147.
6. Kumar SK, Jacobus SJ, Cohen AD, et al.. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomized, controlled trial. *Lancet Oncol.* 2020;21(10):1317-1330.
7. Gaballa MR, Ma J, Rauf M, et al.. KRD vs. VRD as induction before autologous hematopoietic progenitor cell transplantation for high-risk multiple myeloma. *Bone Marrow Transplant.* 2022;57(7):1142-1149.
8. Voorhees PM, Kaufman JL, Laubach J, et al.. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood.* 2020;136(8):936-945.
9. Goldschmidt H, Mai EK, Nievergall E, et al. Addition of isatuximab to lenalidomide, bortezomib and dexamethasone as induction therapy for newly-diagnosed, transplant-eligible multiple myeloma patients: the phase III GMMG-HD7 trial. *Blood.* 2021;138(suppl 1):abstr 463.
10. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996;335(2):91-7.
11. Morgan GJ, Davies FE, Hawkins K, Brown J, Bell SE, Drayson MT, et al. The MRC Myeloma VII Trial of standard versus intensive treatment in patients <65 years of age with multiple myeloma [abstract]. *Blood* 2002;100: 178a. Abstract 668.
12. Palumbo A, Bringhen S, Petrucci MT, Musto P, Rossini F, et al. Intermediate dose melphalan improves survival of myeloma patients aged 50 to 70 : results of a randomized phase 3 study. *Blood* 2004 Nov;104(10):3052-7.
13. Palumbo A, Cavallo F, Gay F, et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. *N Engl J Med* 2014; 371:895-905 September 4, 2014
14. Femand JP, Katsahian S, Devine M, Leblond V, Dreyfus F, Macro M, et al. High dose therapy and autologous blood stem cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long term results of a randomized control trial from the Group Myelome-Autogreffre. *J Clin Oncol* 2005 Dec;23(36):9227-33
15. Bladé J, Sureda A, Ribera JM, Diaz-Mediavilla J, Palomera L, Fernandez-Calvo J, et al. High-dose therapy autotransplantation/intensification vs. continued conventional chemotherapy in multiple myeloma patients responding to initial treatment chemotherapy. Results of a prospective randomized trial from the Spanish Cooperative Group PETHEMA [abstract]. *Blood* 2001;98:815a. Abstract 3386.
16. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol* 2006 Feb;24(6):929-36.
17. Segeren CM, Sonneveld P, van der Holt B, Vellenga E, Croockewit AJ, Verhoef GE, et al. Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study. *Blood* 2003 Mar;101(6):2144-51.
18. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003 Dec;349(26):2495-2502.
19. Cavo M, Tosi P, Zamagni E, Cellini C, Ronconi S, De Vivo A. The "Bologna 96" clinical trial of single vs.. double autotransplants for previously untreated multiple myeloma patients [abstract]. *Blood* 2002;100(11/2):179a.

20. Sonneveld P, van der Holt B, Segeren CM, Vellenga E, Croockewit AJ, Verhoe GE, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. *Haematologica* 2007 Jul;92(7):928-35.
21. Femand JP, Ravaud PH, Katsahian S, Divine M, Leblond V, Belanger C, et al. High dose chemotherapy (HDT) and autologous blood stem cell (ABSC) transplantation versus conventional treatment in multiple myeloma (MM): results of a randomized trial in 190 patients 55 to 65 years of age [abstract]. *Blood* 1999;94(10 Suppl 1):396a.
22. Femand JP, Ravaud PH, Katsahian S, Divine M, Leblond V, Belanger C, et al. High dose chemotherapy (HDT) and autologous blood stem cell (ABSC) transplantation versus conventional treatment in multiple myeloma (MM): results of a randomized trial in 190 patients 55 to 65 years of age [abstract]. *Blood* 1999;94(10 Suppl 1):396a.
23. Garban F, Attal M, Michallet M, Hulin C, Bourhis JH, YakoubAgha I, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood* 2006 May;107(9):3474-80.
24. Bruno B, Rotta M, Patriarca F, Mordini N, Allione B, Carnevale-Schianca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med* 2007 Mar;356(11):1110-20.
25. Rosinol L, Perez-Simon JA, Sureda A, de la Rubia J, de Arriba F, Lahuerta JJ, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood* 2008 Nov;112(9):3591-3.
26. Krishnan A, Pasquini MC, Logan B, et al: Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol.* 2011 Dec;12(13):1195-203.
27. McCarthy PL, Owzar K, Hofmeister CC, et al: Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366:1770-1781
28. Attal M, Lauwers-Cances V, Marit G, et al: Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366:1782-1791.
29. Dimopoulos MA, Richardson PG, Brandenburg N, et al: A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. *Blood.* 2012 Mar 22;119(12):2764-7
30. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet.* 2010;376:2075-2085.
31. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *N Engl J Med.* 2022 Jul 14;387(2):132-147.
32. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous trans-plantation, consolidation, and maintenance therapy in multiplemyeloma: results of the BMT CTN 0702 trial. *J Clin Oncol.* 2019;37(7):589-597.
33. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, withor without bortezomib-lenalidomide-dexamethasone consolidationtherapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label,phase 3 study. *Lancet Haematol.*2020;7(6):e456-e468.
34. Gagelmann N, Eikema DJ, Koster L, et al. Tandem autologous stemcell transplantation improves outcomes in newly diagnosed multiple myeloma with Extramedullary disease and high-risk cytogenetics: astudy from the chronic malignancies working Party of the EuropeanSociety for Blood and marrow transplantation. *Biol Blood MarrowTransplant.* 2019;25(11):2134-2142
35. Rosinol L, Oriol A, Ríos Tamayo R, et al. Ixazomib Plus Lenalidomide/Dexamethasone (IRd) Versus Lenalidomide /Dexamethasone (Rd) Maintenance after Autologous Stem Cell Transplant in Patients with Newly Diagnosed Multiple Myeloma: Results of the Spanish GEM2014MAIN Trial. *Blood* 2021;138:466.
36. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2021;22:1705-20.
37. Palwyn C, C.Cairns DA, Menzies T, et al. Autologous stem cell transplantation is safe and effective for fit, older myeloma patients: exploratory results from the myeloma XI trial. *Haematologica.* 2022 Jan 1; 107(1): 231–242.
38. Auner, HW. Autologous Hematopoeitic cell transplantation in elderly patients with multiple myeloma. *Bone Marrow Transplant.* 2015;50(2):209-215.
39. Drayson M, Bowcock S, Planche T et al. Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo controlled, randomised phase 3 trial. *Lancet Oncol.* 2019 Dec12(12)1760-1772

40. Strong N, Ortiz-Estevez M, Towfic F, et al. The location of the t(4;14) translocation breakpoint within the NSD2-gene identifies a subset of patients with high-risk NDMM. *Blood* 2023 Mar 30; 141(13): 1574-1583

Appendix A: Evidence Tables for Treatment Regimens in Multiple Myeloma

Table 1. Comparison of Autologous Stem Cell Transplantation to Standard Chemotherapy for Multiple Myeloma

Randomized Study	N	Age	SDT vs. HDT/ASCT		
			CR (%)	mEFS (months)	mOS (months)
IFM90 ¹⁰	200	≤ 65	5 vs. 22 (p<0.001)	18 vs. 22 (p=0.01)	44 vs. 57 (p=0.03)
MRC VII ¹¹	401	≤ 65	8 vs. 44 (p<0.001)	19 vs. 31 (p=0.001)	42 vs. 54 (p<0.001)
IMMSG M97G ¹²	194	50 to 70	6 vs. 25 (p=0.0002)	15.6 vs. 28 (p<0.0001)	42.5 vs. 58+ (p<0.001)
MAG* ¹⁴	190	55 to 65	20 vs. 36 (p=NR)	18.7 vs. 25.3 (p=0.07)	47.6 vs. 47.8 (p=0.91)
PETHEMA ^{‡ 15}	164	≤ 65	11 vs. 30 (p=0.002)	33 vs. 42 (p=ns)	61 vs. 66 (p=ns)
US Intergroup ^{§ 16}	510	≤ 70	15 vs. 17 (p=ns)	21 vs. 25 (p=0.05)	53 vs. 58 (p=ns)
HOVON ¹⁷	261	≤ 65	13 vs. 29 (p=0.002)	21 vs. 22 (p=0.28)	50 vs. 47 (p=0.41)
Palumbo ¹³	524	≤ 65		22 vs 43 (p<0.001)	65% vs 81% at 4 y (p=0.02)

*22% Salvage transplant @ relapse in SDT arm. ‡Only responding patients were randomized.

§Cross-over rate of 52% in US Intergroup study.

Table 2. Comparison of Single versus Tandem Stem Cell Transplantation for Multiple Myeloma

Randomized Study	n	EFS	OS
IFM94: Single vs. Tandem SCT (Attal et al, 2003) ¹⁸	399	7 yrs: 10% vs. 20% (p<0.03)	7 yrs: 21% vs. 42% (p<0.001)
Bologna 96: Single vs. Tandem SCT (Cavo et al, 2002) ¹⁹	321	median: 23 mo vs. 35mo (p<0.001)	7 yrs: 46% vs. 43% (p=0.90)
HOVON 24: Single vs. Tandem SCT (Sonneveld et al, 2007) ²⁰	304	median: 22 movs. 21 mo 6 yrs: 15% vs. 7% (p=0.013)	Median 50 movs. 55 mo (p=0.51)
MAG 95: Single vs.. Tandem SCT (Femand et al, 1999) ²¹	193	No difference	No difference

Table 3. Comparison of Tandem Autologous and Autologous-Allogeneic Stem Cell Transplantations for Multiple Myeloma

Randomized Study	n	TRM	EFS	OS	Reference
Auto mel 200/200 vs. Auto mel 200 > Allo bu,flu,ATG	219 65	5% 11%	0% at 5 yrs 0% at 5 yrs	44% at 5 yrs 33% at 5 yrs	(Garban et al, 2006) ²²
Auto mel 200/200 vs. Auto mel 200 > Allo 2Gy TBI	80 82	4% 10%	20% at 4 yrs 42% at 4 yrs	53% at 4 yrs 75% at 4 yrs	(Bruno et al, 2007) ²⁴
Auto mel 200 >> cyclophosphamide, etoposide, BCNU- or melphalan-200 vs. Allo-RIC flu, mel	85 25	5% 16%	31 months Not reached*	60% at 5 yrs 61.8% at 5 yrs	(Rosinol et al, 2008) ²⁵

* survival for PFS $p=0.08$

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Hematology Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2023.

Maintenance

A formal review of the guideline will be conducted in 2024. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; CCA, Cancer Care Alberta

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Copyright © (2023) Alberta Health Services

This copyright work is licensed under the [Creative Commons Attribution-NonCommercial-NoDerivative 4.0 International license](#). You are free to copy and distribute the work including in other media and formats for non-commercial purposes, as long as you attribute the work to Alberta Health Services, do not adapt the work, and abide by the other license terms. To view a copy of this license, see <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

The license does not apply to AHS trademarks, logos or content for which Alberta Health Services is not the copyright owner.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the [Outpatient Cancer Drug Benefit Program Master List](#).

Conflict of Interest Statements

***Dr. Peter Duggan** reports honoraria from FORUS, Sanofi and Janssen.

Dr. Syliva McCulloch reports honoraria from Janssen, Sanofi, and FORUS and travel support from Janssen.

Dr. Jason Tay has nothing to disclose.

Derek Tilley has nothing to disclose.

*Working group lead

Citation

Duggan P (lead), McCulloch S, Tay J, Tilley D. Cancer Care Alberta, Alberta Health Services (2023). Clinical Practice Guideline on [Multiple Myeloma: Transplant Eligible, Version 1]. Accessed [Month, Year]. Available from: www.ahs.ca/guru