

Multiple Myeloma: Transplant Ineligible

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 ineligible 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 ineligible.

Recommendations

Not Transplant Eligible:
Standard Risk and High Risk

DRd, until disease progression

- Daratumumab 1800mg s/c
- Lenalidamide 25mg daily for 21/28 days
- Dexamethasone 40mg weekly

OR

- Dara-VMP
- Dara-CYBORD
- RVd

Zoledronate 4mg IV every 1-3 months

Patients Transplant Ineligible

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, combinations of daratumumab with novel agents (lenalidomide, or bortezomib) have been shown to be superior to similar regimens without daratumumab as initial therapy for transplant ineligible patients. The standard therapy for these patients should therefore include a novel agent, daratumumab, and steroids. However, in frail patients, and those with significant co-morbidities or advanced age (>75 years), there is an increased risk of toxicities¹¹. For these patients, consideration should be given to dose reductions or sequential addition of components of the initial regimen^{9, 10}.

Daratumumab, Lenalidomide, and Dexamethasone (DRd):

Lenalidomide and dexamethasone (Rd) has been one of the standard regimens for the initial therapy of myeloma in patients not eligible for stem cell transplant since the results of the FIRST study, which compared melphalan, prednisone, and thalidomide (MPT) for 12 cycles (18months) to Rd for 18 cycles (18months) and Rd until disease progression these patients². The continuous Rd strategy was superior to MPT with improved response rate, PFS and duration of response. Overall survival at 4 years was improved with continuous Rd, but this did not reach statistical significance (4-year OS 59% vs 51%, $p=0.0168$).

The addition of daratumumab to Rd significantly improved the outcomes compared to Rd alone. The phase 3 MAIA study randomized patients to either Rd or DRd. After 56 months of follow up, the median PFS was 34 months in the Rd group, and not yet reached in the DRd group⁴ DRd also showed higher CR rates (47.6 vs 24.9%) and MRD negativity (24.2 vs 7.3%)³.

DRd is the current standard of care for newly diagnosed myeloma patients who are not eligible for stem cell transplant.

Daratumumab with Bortezomib-Based Regimens:

The combinations of bortezomib, melphalan, and prednisone (VMP)⁵ and cyclophosphamide, bortezomib, and dexamethasone (CYBORD)⁶ have in the past been used as alternatives to Rd for newly diagnosed transplant ineligible patients, with CYBORD having been preferred for use over VMP in Alberta. The addition of daratumumab to bortezomib based regimens has also been shown to improve outcomes.

Daratumumab plus VMP (DVMP) was compared to VMP alone in patients not eligible for stem cell transplant⁷. DVMP resulted in higher overall responses (90.9% vs 73.9), complete responses or better (42.6%, versus 24.4%). MRD negativity (22.3% vs 6.2%) compared to VMP. PFS at 18 months was 71.6% for DVMP versus 50.2% for VMP alone.

There are no randomised trials comparing CYBORD with or without daratumumab. The single arm LYRA study treated both transplant eligible and ineligible patients with Dara + CYBORD. Among transplant ineligible patients, the rate of complete response (or better) was 29.8%, and 3 year PFS was 72.6%⁸.

Both DVMP and Dara-CYBORD are daratumab containing regimens that can be considered as alternatives to DRd when lenalidomide is not tolerated or otherwise contraindicated.

Other regimens that do not contain daratumumab are available, such as Rd² and VRD⁹, can be considered for use for newly diagnosed patients. These regimens, however, show outcomes that are inferior to daratumumab containing regimens and could be considered when daratumumab is not tolerated or otherwise not appropriate for use.

Regimens:

- DRd (4 week cycles):
 - o daratumumab 1800mg s/c weekly (cycle 1,2), every 2 weeks (cycles 3-6), then monthly until disease progression
 - o lenalidomide 25mg orally for 21/28 days per cycle
 - o dexamethasone 40mg orally weekly for 4 weeks per cycle

- DVMP (6 week cycles):
 - o daratumumab 1800mg s/c weekly (cycle 1), every 3 weeks (cycles 2-9), then monthly until disease progression
 - o melphalan 9mg/m² orally days 1-4 (cycles 1-9)
 - o prednisone 60mg/m² days 1-4 (cycles 1-9)
 - o bortezomib 1.3mg/m² s/c days 1,4,8,11,22,25,29,32 (cycles 1-4) then 1.3mg/m² s/c days 1,8,22,29 (cycles 5-9)

- Dara-CYBORD (4 week cycles):
 - o daratumumab 1800mg s/c weekly (cycle 1,2), every 2 weeks (cycles 3-6), then monthly until disease progression
 - o cyclophosphamide 300mg/m² orally weekly for 4 weeks per cycle
 - o bortezomib 1.5mg/m² subcutaneously weekly for 4 weeks per cycle
 - o dexamethasone 40mg orally weekly for 4 weeks per cycle
 - o Patients should receive 9-12 cycles followed by maintenance bortezomib (1.3mg/m² every 2 weeks for 2 years).

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 or pamidronate) or Denosumab. For further details refer to chapter on supportive care

Antibiotic Prophylaxis:

- Valacyclovir 500mg orally daily is recommended for all patients treated with a proteasome inhibitor such as bortezomib.
- Sulfamethoxazole-trimethoprim (one single strength tablet daily) is an option for PJP prophylaxis

Dose Adjustment for Elderly Patients

When therapy is started in elderly patients, frail patients, the very elderly (over 75 years of age) and those patients with significant co-morbidities are at an increased risk of toxicity from combination regimens. As a result of such toxicity, therapy is often terminated early resulting in poorer outcomes than if less intense but more tolerable therapy were to be given for a longer period of time. It is suggested that a frailty assessment be performed and that dose reductions be strongly considered for patients with one or more of these risk factors.¹¹ These scores can predict survival and toxicity and thus help determine appropriate therapy. For frail elderly patients treated with Rd, a randomised trial has shown no difference in outcomes when, after the initial 9 months of treatment, the dose of lenalidomide was reduced to 10mg and dexamethasone discontinued¹⁰. This has not been replicated using DRD but does suggest that these changes can be made to reduce toxicity without sacrificing effectiveness in this frail population, where side effects and infectious complications often limit therapy and result in increased mortality. Suggestions of layering therapy starting with a two drug approach like Rd and adding in the third drug in a subsequent cycle once tolerability is established. Using an approach tailored for the patient is the most important aspect of the frailty based treatment plan creation.

Table 1. Suggested dose reductions are as follows (adapted from Palumbo et al¹):

Dose Level 0 NO RISK FACTORS	Dose level -1 At least one risk factor	Dose Level -2 At least one risk factor and any grade 3/4 non hematologic toxicity
Lenalidomide 25 mg/day, d 1-21	15 mg/day, d 1-21	10 mg/day, d 1-21
Bortezomib 1.3mg/m ² d1,8,15,22 q5weeks	1.0mg/m ² d1,8,15,22	1.3 mg/m ² d1, 15 q 4 weeks
Dexamethasone 40 mg/ week	20mg/week	10mg/week

Summary:

- Daratumumab with lenalidomide and dexamethasone given until disease progression is the preferred treatment for patients with newly diagnosed multiple myeloma who are not eligible for stem cell transplant.
- Bortezomib based regimens that contain daratumumab (Dara-VMP, Dara-CYBORD may also be considered.

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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.

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Conflict of Interest Statements

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*Working group lead

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