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Multiple Myeloma: Management of Relapsed/Refractory Disease

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Cancer Care Alberta

Clinical Practice Guideline LYHE-015 – Version 1
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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 with relapsed or refractory myeloma be managed?

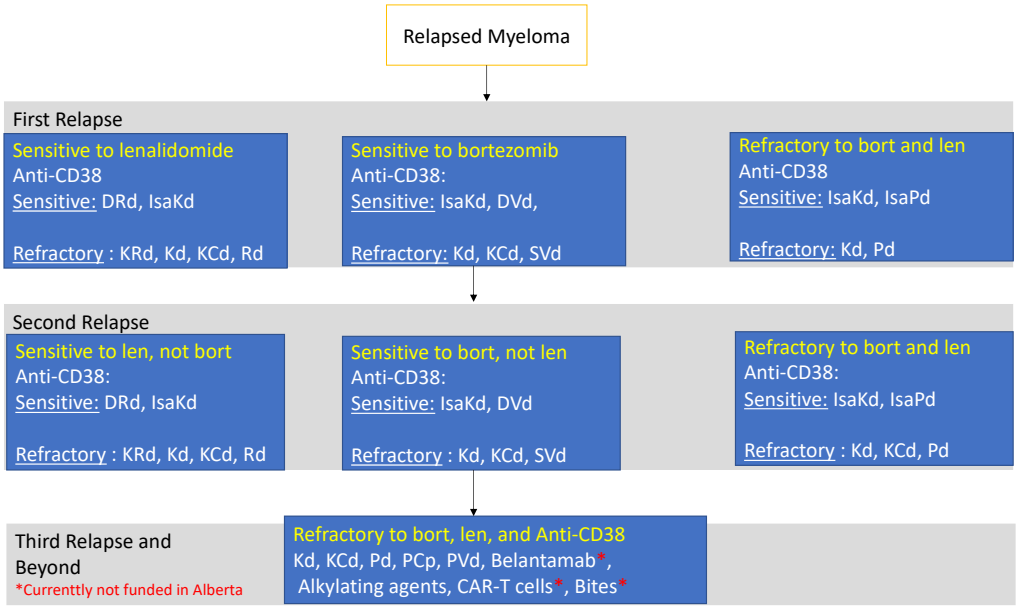
Search Strategy

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 relapsed or refractory myeloma.

Recommendations



Summary of Recommendations

1. ASCT is recommended for transplant eligible patients who did not undergo ASCT as part of initial therapy.

2. ASCT can be considered at relapse for transplant eligible patients with an initial remission following first line ASCT of 24 months or more *and* who have at least partial response to salvage therapy.

3. An anti-CD38 monoclonal antibody in combination with lenalidomide or bortezomib (daratumumab) or pomalidomide or carfilzomib (isatuximab) and dexamethasone should be used in first or subsequent relapse for patients who have not previously received daratumumab or isatuximab.

4. KRd can be considered in first relapse for patients not previously treated with anti-CD38 monoclonal antibody who are lenalidomide sensitive.

5. For patients who have previously received anti-CD38 monoclonal antibody, carfilzomib containing regimens (Kd, KRd, KCd), Velcade containing regimens (SVd, CYBORd), and IMID based regimens (Rd) are options for use in first relapse

6. Doublet or triplet combinations using pomalidomide and carfilzomib are options for patients refractory to lenalidomide and proteasome inhibitors.

7. For subsequent relapses, appropriate regimens will be based on a patient's prior therapies, and should include anti-CD38 monoclonal antibody if not previously used and otherwise eligible.

Discussion

Relapsed Guidelines

Whenever possible, patients should be considered for clinical trials at the time of relapse. In the absence of a suitable clinical trial the treatment of relapsed disease should be determined on an individual basis dependent of drug sensitivities, timing of relapse, age, prior therapy, bone marrow function, co-morbidities and patient preference.

A repeat bone marrow examination with cytogenetic testing should be performed at relapse as high-risk features frequently develop as the disease evolves and may affect the choice of therapy[35-37] Evaluation should include screening for t(11;14), which gets enriched over time with every relapse and which may affect future therapy with BCL2 inhibition [24-25]. A short duration of remission is also a high-risk feature, with poor long-term prognosis for those with initial remission lasting less than a year[38,39].

Autologous Stem Cell Transplant

Although it is recommended that ASCT be included as part of initial therapy for transplant eligible patients, there are some for whom ASCT may be deferred in favour of later transplant. Several clinical trials suggest that deferred ASCT results in shorter PFS but may not affect overall survival[1,2,3,4,5,49]. Most recently, the DETERMINATION trial randomized patients to a strategy of either RVd followed by lenalidomide maintenance, or RVd, stem cell transplant, and lenalidomide maintenance[49]. PFS was 67.5 months in the transplant group versus 46.2 months in the no transplant group. There was no difference in OS between the groups, likely because of the availability of effective salvage therapies at relapse. Among patients with high risk cytogenetics, PFS was 55 months for transplant and only 17 months for the RVD alone group. In the no transplant group, only 35% of those requiring subsequent therapy went on to receive stem cell transplant. Because of the observed improvement in progression free survival especially in those with high risk cytogenetics, upfront stem cell transplant remains the recommendation for newly diagnosed multiple myeloma patients If transplant is deferred, stem cells should still be collected early in the course of first line therapy, and transplant should be considered as early as possible during first relapse. If the stem cells were collected in first line, but the patient became transplant ineligible during the first line of therapy, it is recommended that transplant be strongly considered for second line, should transplant eligibility be determined by the bone marrow transplant program.

In patients who underwent ASCT as part of primary therapy and remain eligible for ASCT, a second transplant may be considered. However, the duration of remission is expected to be shorter than with a first transplant (**Table 1**). The median time to progression after a salvage second autologous stem cell transplant is typically 1-2 years[40-44]. A number of factors predict a poor response to second transplant, including short remission duration with first transplant, ISS stage II/III, elevated LDH at relapse, lack of response to re-induction therapy, and presence of high risk cytogenetics[6], [7]. Of these, response duration after first transplant and response to salvage chemotherapy are most consistently reported. Second ASCT therefore is generally not preferable to non-transplant regimens containing novel agents and an anti-CD38 monoclonal antibody, and should only be considered in those with PFS of at least 24 months following first transplant who achieve at least partial response to salvage therapy.

Non-transplant based options

The majority of relapsing patients will not be eligible for second transplant and should be considered for novel agent based regimens. Generally, triplet regimens are considered more efficacious than doublets, with a trade off of increased cost and toxicities. The choice of regimen will depend on number of factors including:

- Comorbidities such as renal impairment, cardiac disease, peripheral neuropathy, history of DVT

- Patient age, performance status, and frailty. Frail patients my benefit from reduced-dose regimens in order to avoid toxicity and preserve quality of life
- Prior treatment and drug sensitivities. The Alberta Health Services *Outpatient Cancer Drug Benefits Program* outlines the criteria for prescribing individual drugs and regimens, and should be considered when determining a treatment plan.
- Tolerance/side effects to prior therapies.

The majority of patients relapsing after first line therapy will have received and be refractory to lenalidomide, either as part of post transplant maintenance for transplant eligible patients, or as part of the Rd or DRd regimens for those who were initially transplant ineligible. A smaller number of patients will have received bortezomib based initial therapy and be bortezomib refractory, while patients rarely will be refractory to both lenalidomide and bortezomib at first relapse. Daratumumab has recently been approved as part of front line therapy for transplant ineligible patients, and has been used as past of clinical trials for this population for several years. A growing number of patients will have received and be refractory to daratumumab at first relapse. **Table 2** reviews currently available regimens for relapsed/refractory myeloma.

Lenalidomide based regimens

Thrombosis prophylaxis is required for all patients receiving a regimen containing lenalidomide or other Imids.

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

Patients who are lenalidomide sensitive or naïve:
Patients not previously treated with lenalidomide or who remain sensitive to lenalidomide, can be considered for treatment with lenalidomide and dexamethasone (RD)[8] alone or in combination with daratumumab (DRd)[9], or carfilzomib (KRd)[10]. Lenalidomide with ixazomib (IRd)[11] or elotuzumab (ERd)[12] are also options, however neither regimen is funded in Alberta. A summary of the efficacy of these agents is incorporated in **Table 3**. In general, triplet regimens are more effective than doublets, though with increased toxicity, and should be preferred over doublets in most patients who are not considered frail.

RD

Treatment with Rd was initially shown to have an overall response rate of 61% with a time to progression of 11.1 months and overall survival of 29.6mo when compared to dexamethasone alone[8]. However, when moved to earlier lines of therapy the PFS has been reported to be between 14 to 17 months[10],[11]. Neutropenia is frequently seen with lenalidomide, especially when used in combination regimens. Dose reductions and/or GCSF may be required. Because of the risk of thrombosis with lenalidomide and other proteasome inhibitors, all patients should be on prophylactic ASA or full dose anticoagulation.

Daratumumab+ lenalidomide + dexamethasone (DRd):

Triplet regimens that include Daratumumab have been shown to be effective for the treatment of relapsed myeloma. The DRd regimen has been shown to be superior to Rd alone. In the POLLUX[9] study, 569 patients with multiple myeloma relapsed after 1 – 3 prior regimens were randomized to daratumumab, lenalidomide, and dexamethasone (DRd) or to lenalidomide and dexamethasone (Rd) alone. 2 year PFS was 68.0% among DRd treated patients compared to 40% for those treated with Rd. Overall response rates were 92.9 versus 76.4%, and CR rates 51.2 versus 21.0%. Two year PFS for those relapsing after only one prior line was 70.3% for DRd versus 45% for Rd. For those treated after 2-3 prior lines of therapy, median progression free survival was 28.9 months (DRd) versus 15.7 months (Rd). Patients with high risk cytogenetics also benefited, with PFS of 22.6 months (DRd) versus 10.2 months (Rd), though these result were still inferior to those seen in standard risk patients treated with DRd for whom median PFS was not reached but 2 year PFS was 74.3%.

Carfilzomib + lenalidomide + dexamethasone:

The combination of Carfilzomib, lenalidomide and dexamethasone (KRd) was shown to be superior than Rd in relapsed myeloma, with improvement in overall survival (48.3 versus 40.4 months), response rate (87.1% versus 66.7%), and PFS (26.1 months versus 16.6 months)[10, 13]. PFS and response rate, but not OS, were improved in those with high risk cytogenetics (PFS 23.1 versus 13.9 months, response rate 79.2 versus 59.6%)[14]. Carfilzomib given once weekly results in higher PFS but also more adverse events than twice weekly dosing[15]. There is no restriction on how carfilzomib based regimens are sequenced with anti-CD38 or pomalidomide based regimens

Lenalidomide Resistant

Bortezomib based regimens

Patients who are bortezomib sensitive or naïve:

Patients who remain sensitive to bortezomib can be considered for treatment with bortezomib and dexamethasone (Vd) with cyclophosphamide (CYBOR-D) or daratumumab (DVd)[16] , carfilzomib and dexamethasone (Kd)[17], or selinexor, bortezomib and dexamethasone (XVd)[45]. A summary of these regimens is incorporated into **table 4**.

Daratumumab + bortezomib + dexamethasone (DVd):
The CASTOR[16] study randomised 498 patients with myeloma relapsing after at least one prior therapy to receive daratumumab, bortezomib, and dexamethasone (DVd) or bortezomib and dexamethasone (Vd) alone. DVd significantly prolonged PFS versus Vd (median: 16.7 versus 7.1 months with 18-month PFS rates of 48.0% vs 7.9%). DVd significantly improved ORR (83.8% vs 63.2), stringent CR rate (8.8% vs2.6%), rates of CR or better (28.8% versus 9.8%), and VGPR or better (62.1% *versus* 29.1%) compared to Vd. Among patients who received DVd at first relapse PFS was significantly prolonged (median: not reached vs 7.9 months for Vd), with 18-month PFS of 68.0% versus 11.5%, respectively. DVd prolonged PFS among patients with 2 to 3 prior lines of therapy (median: 9.8 vs 6.3 months). high-risk (median: 11.2 vs 7.2 months) and standard-risk disease (median: 19.6 vs 7.0 months). ORRs were higher with DVd for both high-risk (81.8% vs 61.7%) and standard-risk (84.7% vss 64.1%) subgroups.

Carfilzomib and dexamethasone:
When compared to bortezomib and dexamethasone (Vd), Carfilzomib and dexamethasone (Kd) improved survival (47.6 versus 40.0 months)[18] and PFS (1.6 vs 9.4 months).

Selinexor, bortezomib, and dexamethasone:
The BOSTON[45] trial randomised 402 previously treated with one to three lines of therapy, including proteasome inhibitors, to receive selinexor (100 mg once per week), bortezomib (1·3 mg/m2 once per week), and dexamethasone (20 mg twice per week) (SVd), or bortezomib (1·3 mg/m2 twice per week for the first 24 weeks and once per week thereafter) and dexamethasone (20 mg four times per week for the first 24 weeks and twice per week thereafter)(Vd). After a median follow-up of 13·2 months for SVd and 16·5 months for Vd, median progression-free survival was 13·9 months for SVd and 9·5 months for Vd. SVd was associated with higher rates of thrombocytopenia, fatigue, anaemia, and nausea, which requires more supportive care when first initiating this regime. Peripheral neuropathy was more frequent with VD.

Isatuximab based regimens

Isatuximab + carfilzomib + dexamethasone:
The IKEMA[46] randomised 302 patients with relapsed or refractory myeloma and one to three previous lines of therapy to isatuximab plus carfilzomib-dexamethasone (IsaKd) or carfilzomib-dexamethasone (Kd). Isatuximab was given at a dose of 10 mg/kg intravenously weekly for the first 4 weeks, then every 2 weeks. Median progression-free survival was not reached in the isatuximab group compared with 19·15 months for Kd, (p=0·0007).

Isatuximab + pomalidomide + dexamethasone:
The ICARIA-MM[47]trial randomised 307 patients with relapsed and refractory multiple myeloma who had received at least two previous lines of treatment, including lenalidomide and a proteasome

inhibitor, to either isatuximab, pomalidomide and dexamethasone 40 mg (IsaPD), or Pd. At a median follow-up of 11·6 months, median progression-free survival was 11·5 for IPd versus 6·5 months for Pd. After 35·3 months, median overall survival was 24·6 for IsaPd and 17·7 months for Pd[48].

Pomalidomide:
For patients who are considered refractory to lenalidomide and proteasome inhibitors (velcade and/or carfilzomib) treatment with a pomalidomide and dexamethasone (Pd)[19], with or without an additional active agent, should be considered. Options for a third active agent include: cyclophosphamide[20], velcade[21], daratumumab[22], and Isatuximab (IPd)[23]. A summary of these trials is included in **table 5**.

Other agents:
In addition to the above, several new Health Canada approved agents have shown efficacy in multiple myeloma, either alone or in combination regimens (elotuzumab, ixazomib, belantamab) but are currently not funded in Alberta (**Table 5**).

Venetoclax is a BCL-2 inhibitor currently approved for the treatment of CLL. In combination with dexamethasone it has shown modest activity in relapsed/refractory myeloma(ORR 21%) but higher response rates in those with t(11;14) (ORR 40%, VGPR 27%)[24]. Response rates are higher when used in combination with bortezomib and dexamethasone (ORR 67%, VGPR 42%, median TTP 9.5 months).[25]
Venetoclax is currently not approved for treatment of myeloma and not funded in Alberta.

Belantamab mafodotin is a immunoconjugate targeting BCMA. The DREAMM-2 study of patients with relapsed multiple myeloma and three or more lines of therapy gave either 2.5 mg/kg or 3.4 mg/kg of belantamab every 3 weeks. Overall response rates of 31-34% were seen[50]. Median estimated duration of response, OS, and PFS were 11.0 months, 13.7 months, and 2.8 months, respectively[51].
Belantamab is currently not funded in Alberta.

Two CAR-T cell products have been approved by Health Canada. Idecabtagene vicleucel (ide-cel) has yet to receive CADTh endorsement or reimbursement by provinces. Ciltacabtagene autoleucel (cilta-cel)has been recommended by CADTH but is not currently funded in Alberta.
Cilta-cel, a chimeric antigen receptor T-cell therapy targeting BCMA was studied in relapsed myeloma patients who had received 3 or more previous lines of therapy or were double-refractory to a proteasome inhibitor and an immunomodulatory drug, and had received a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody[52]. 97/113 enrolled patients were able to receive the product. Overall response rate was 97%, and 82% achieved stringent complete response. The 27-month PFS and OS rates were 54.9% and 70.4%, respectively. Cytokine release syndrome occurred in 95% of patients (4% grade 3 or 4and resolved in all except one grade 5 CRS event. CAR T-cell neurotoxicity occurred in 21% (9% were grade 3 or 4).
CAR-T cell therapy for myeloma is currently not funded in Alberta.

Bispecific T-cell engager (BiTE) antibodies can simultaneously bind to two different epitopes, one on tumor-specific T cells, and a specific antigen on myeloma cells, which leads to T-cell dependent destruction of myeloma cells. Several products are in development however none are currently funded in Alberta. Among 165 patients who received Teclistamab, for example, there was an ORR of 63% with 39% CR. PFS 11.3 months and OS 18.3 months[53].

Table 1. Studies of Salvage ASCT for Relapsed Myeloma

	#	# Of prior lines	Median PFS ASCT #1	TRM %	ORR (%)	OS (mo)	PFS (mo)	PFS by initial remission (mo)	Comment
Chow et al[26]	30	2 (15) 3 (13) 4+ (2)	30.2	3		45	22	<18 = 4.2 18-36=13.8 >36 = 49.1	
Lemieux et al[27]	81	1-2+ (26% >2)	40 (10-152)	0	93	48	18 (2-64)	<24 = 9 >24 = 18	
Jimenez-Zepeda[28]	81	Median =1	39 (9-100)	2.6	97	60% (3 Yr)	76% (3yr)	<24 = 9 >24 = 17	
Cook et al[29]	89	1	32 (1-149)	1	83	80% (3yr)	19	<24 = 11 >24 = 24	
Grovdal et al[30]	111	1	29		92	48	18	>12 = 28	
Garderet[31]	482	1+	24	4	93	33	13	<18 18-36 HR=.62 >36 HR =.35	2nd ASCT after prior Tandem
Garderet[31]	88	2+	11 after ASCT #2	7	86	15	8		3rd ASCT
Singh Abbi[32]	75	1 (1-4)	22 (3-136)	5	77	23	10		
Sellner[6]	200	2 (1-8)	64	3	80	15	42		Predictors of response: PFS to initial ASCT, response to salvage, LDH, ISS
Gossi[33]	61	1	29 (3-187)	0	70	129	23	<18 = 24 >18 = 30	Longer PFS (41 vs 26 mo) with len maintenance
Gimsing[34]	53	1	25	0	96	48	19	<12 = 10 >12 = 24	

Table 2: Available Regimens for Relapsed Myeloma[a]

Regimen	Drugs	Funded in Alberta	Available SAP[e]	Anti-CD38 Naive	Anti-CD38 Refractory	Lenalidomide Refractory	Bortezomib Refractory
DRD	Daratumumab/lenalidomide/ dexamethasone	Yes	n/a	Yes	No	No	Yes
DVD	Daratumumab/bortezomib/ dexamethasone	Yes	n/a	Yes	No	Yes	No
ISA-Kd	Isatuximab/carfilzomib/ dexamethasone	Yes	Yes	Yes	No	Yes	Yes
ISA-Pd	Isatuximab/pomalidomide/dexamethasone	Yes	Yes	Yes	No	Yes	Yes
KRD	Carfilzomib/lenalidomide/ dexamethasone	Yes	n/a	Yes	Yes	No	Yes
KCd	Carfilzomib/cyclophosphamide/ dexamethasone	Yes	n/a	Yes	Yes	Yes	Yes
KD	Carfilzomib/ dexamethasone	Yes	n/a	Yes	Yes	Yes	Yes
SVd	Selinexor/bortezomib/dexamethasone	Yes	Yes	Yes	Yes	Yes	No
RD	Lenalidomide/dexamethasone	Yes	n/a	Yes	Yes	No	Yes
CYBORD	Cyclophosphamide/bortezomib/dexamethasone	Yes	n/a	Yes	Yes	Yes	No
Pom/dex	Pomalidomide/dexamethasone	Yes	n/a	Yes	Yes	Yes	Yes
PCP	Pomalidomide/cyclophosphamide/prednisone	Yes	n/a	Yes	Yes	Yes	Yes
PVd[c]	Pomalidomide/bortezomib/dexamethsone	Yes	n/a	Yes	Yes	Yes	No
Elo[b] - Rd	Elotuzumab/lenalidomide/dexamethasone	No	?	Yes	Yes	No	Yes
IRD[b]	Ixazomib/lenalidomide/dexamethasone	No	Yes	Yes	Yes	No	Yes
DPd[b]	Daratumumab/pomalidomide/ dexamethasone	No	No	Yes	No	Yes	Yes
Dara/dex[d]	Daratumumab/ dexamethasone[d]	No	No	Yes	No	Yes	Yes
Bel[b]	Belantamab Mafodotin	No	Yes	No	Yes	Yes	Yes
Ven[b]	Venetoclax	No	No?	Yes	Yes	Yes	Yes

Currently not funded in Alberta

a. See Alberta Health Services Cancer Drug Benefit Program prescribing criteria
b. Currently not funded by AHS
c. PVd combination is currently not funded by AHS. Director's privileges required
d. Daratumumab as a single agent or with dexamethasone is currently not funded by AHS
e. Subject to change

Table 3

Regimen	# Of prior lines	ORR (%)	PFS (mo)	OS (mo)	HR for progression
Rd[8]	>1	61	11.1	N/A	N/A
DRd v Rd (POLLUX)[9]	>1	92.9	44.5 v 17.5	NR	0.37
KRd v Rd (ASPIRE)[10]	1-3	87.1	26.1 v 16.6	48.3 v 40.4	0.69
IRd* v Rd (TOURMALINE)[11]	1-3	78	20.6 v 14.7	NR	0.74
ERd* v Rd (ELOQUENT-2)[12]	>1	79	19.4 v 14.9	N/A	0.7

*Currently not funded in Alberta

Table 4

Regimen	# of prior lines	ORR (%)	PFS (mo)	OS (mo)	HR for progression
Kd vs Vd (ENDEAVOUR)[17, 18]	1-3	54	17.6 v 9.4	47.6 v 40.0	0.53
DVd vs Vd (CASTOR)[16]	>3	82.9	16.7 v 7.1	NR	0.31

Table 5

Regimen	ORR (%)	PFS (mo)
Pd[19]	31	4.0
PCp[20]	N/A	10.4
PVd[21]*	82.2	11.2
DPd[22]*	60	8.8
IPd[23]	60	11.5

*Currently not funded in Alberta

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Appendix A: Regimens

XPV, Isa Kd. Isa PD,

RD
28 day cycle

- Lenalidomide 25mg orally daily for 21 days
- Dexamethasone 40 mg orally every 7 days

DRD
28 day cycle

- Lenalidomide 25mg orally daily for 21 days
- Dexamethasone 40 mg orally every 7 days
- Daratumumab 1800mg SC weekly for cycles 1-2, then every two weeks for cycles 3-6, then every 4 weeks

KRD
28 day cycle

- Carfilzomib 20 mg/m^2 on days 1 and 2 of cycle one then 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16 during cycles one to 12 and on days 1, 2, 15, and 16 in cycles 13 to 18.
- Lenalidomide 25mg orally daily for 21 days until progression
- Dexamethasone 40 mg orally every 7 days until progression

VD

- Bortezomib 1.5mg/m^2 subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

CYBOR-D

- Cyclophosphamide 300mg/m^2 orally weekly for 4 weeks
- Bortezomib 1.5mg/m^2 subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.
- 9-12 cycles followed by maintenance bortezomib (1.3mg/m^2 every 2 weeks for 2 years).

DVd

8 – 21 day cycles of :

- bortezomib 1.3 mg/m2 subcutaneously on Days 1, 4, 8, 11
- dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, 12
- daratumumab 1800 mg SC once weekly in Cycles 1-3, Day 1 of Cycles 4-8

Followed by daratumumab every 4 weeks until disease progression

Kd low dose

- Carfilzomib 20 mg/m² on days 1 and 2 of cycle 1 then 27 mg/m² on days 1, 2, 8, 9, 15, and 16 of each cycle
- dexamethasone 20 mg oral on days 1, 2, 8, 9, 15, 16, 22, and 23 (or 40mg weekly)
- 28-day cycles repeated until disease progression

Kd high dose

- Carfilzomib 20 mg/m² on days 1 and 2 of cycle 1 then 56 mg/m² on days 1, 2, 8, 9, 15, and 16 of each cycle
- dexamethasone 20 mg oral on days 1, 2, 8, 9, 15, 16, 22, and 23 (or 40mg weekly)
- 28-day cycles repeated until disease progression

Kd weekly

- carfilzomib 20 mg/m² on days 1 of cycle 1 then 70 mg/m² on days 1, 8, and 15 of each cycle
- dexamethasone 40 mg oral on days 1, 8, 15, and 22
- 28-day cycles repeated until disease progression

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

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

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*Working group lead

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