



Multiple myeloma treatment in transplant-eligible patients

Dr Saeid Anvari
Hematologist and Medical oncologist
Guilan University of medical Sciences



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- ▶ Although in the past there were differences in the type of regimen used based on transplant eligibility, this is less of a factor now.
- ▶ Non-melphalan-containing regimens traditionally used in patients who are candidates for HCT are increasingly being used as the first choice in patients ineligible for HCT as well.
- ▶ The choice of initial therapy is influenced more by risk stratification.

- ▶ One of the first steps in evaluating newly diagnosed patients with MM is to determine whether they are candidates for high-dose therapy and transplant, based on age and comorbidities.
- ▶ It should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant. Therefore, referral to an HCT center to assess whether patient is eligible for HCT is important.

Risk stratification of myeloma

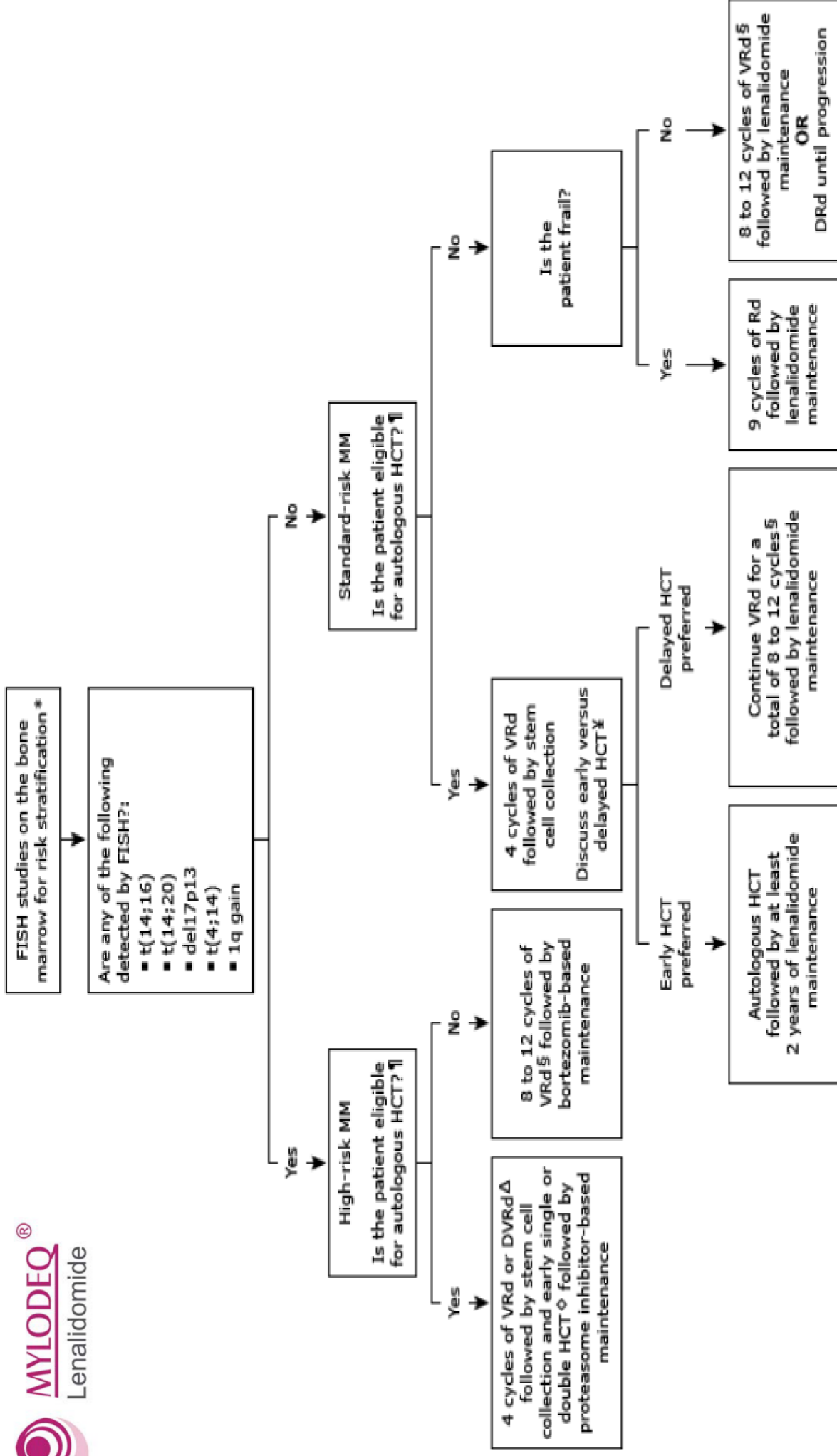
High risk	Standard risk
<ul style="list-style-type: none"> 17p13 deletion t(4;14) t(14;16) t(14;20) Gain 1q LDH ≥ 2 times institutional upper limit of normal Features of primary plasma cell leukemia* High-risk gene expression profiling signature[¶] 	<ul style="list-style-type: none"> All others including those with: <ul style="list-style-type: none"> Trisomies (hyperdiploidy) t(11;14) t(6;14)

The definition of high-risk disease continues to evolve based on available evidence. To risk-stratify myeloma patients at initial diagnosis we perform fluorescence in situ hybridization (FISH) studies on the bone marrow for t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), del17p13, gain 1q, and trisomies of odd numbered chromosomes.

LDH: lactate dehydrogenase.

* Defined by either ≥ 2000 plasma cells/microL of peripheral blood, or $\geq 20\%$ on a manual differential count.

¶ While patients with a high-risk signature on gene expression profiling are considered to have high-risk myeloma, this test is not recommended on a routine basis.





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- ▶ The NCCN Panel prefers 3-drug regimens as the standard for primary treatment of all patients who are transplant eligible. This is based on improved response rates, depth of response, and rates of progression-free survival (PFS) or OS seen with 3-drug regimens in clinical trials.
- ▶ The doublet regimens are no longer recommended for transplant candidates with the rationale that doublets would be recommended for patients who would not be considered for initial treatment with a three-drug regimen such as those not initially eligible for transplant

- ▲ For non-transplant patients, the 2- drug regimens are still listed as options with a note that a triplet regimen is the standard therapy but patients who cannot tolerate a 3- drug regimen due to poor performance status, can be started with a 2- drug regimen, and the third drug can be added if the performance status improves.

Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

- ▶ The preferred primary therapy options for patients who are HCT eligible include:
- ▶ bortezomib / lenalidomide / dexamethasone
- ▶ bortezomib / cyclophosphamide / dexamethasone



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Bortezomib, lenalidomide, dexamethasone (VRd)

- ▶ The combination of bortezomib, lenalidomide, and dexamethasone (VRd) is one of preferred treatment options for MM.
- ▶ Results from phase III SWOG S077 and ENDURANCE E1A11 trial suggest that VRd improves survival over that seen with lenalidomide plus dexamethasone (Rd), although at a cost of increased toxicity.
- ▶ The dosing schedule commonly used in practice is a modification of that used in clinical trials in order to reduce neurotoxicity and dexamethasone-related toxicity.



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- ▶ Subcutaneous administration is the preferred route for bortezomib.
- ▶ Major toxicities of VRd include peripheral neuropathy, transient cytopenias, fatigue, and gastrointestinal distress. Thromboprophylaxis and antiviral prophylaxis are required.
- ▶ Lenalidomide is teratogenic and there are emerging concerns regarding an increased risk of second primary malignancy. Patients with renal insufficiency experience more neutropenia with the use of lenalidomide.



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Bortezomib, cyclophosphamide, dexamethasone (VCd)

- ▶ Based on data from phase II EVOLUTION and German DSMM Xia studies, the combination of cyclophosphamide/bortezomib/dexamethasone to the list of primary treatment available for transplant candidates.
- ▶ This is a preferred option, especially in patients with acute renal insufficiency.
- ▶ Switching to bortezomib/lenalidomide/dexamethasone after renal function improves can consider .



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- ▶ The combination of bortezomib, cyclophosphamide, and dexamethasone (VCd, also called CyBorD) has demonstrated tolerability and efficacy in the management of patients with newly diagnosed MM.
- ▶ VCd is a reasonable alternative if VRd is not available and in patients presenting with acute renal failure.
- ▶ The dosing schedule for VCd typically used in practice is a modification of that used in clinical trials in order to reduce neurotoxicity and dexamethasone-related toxicity.

Other Recommended Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

Carfilzomib, lenalidomide, dexamethasone (KRd)

- ▶ The results of the phase III ENDURANCE trial showed similar PFS with carfilzomib/lenalidomide/dexamethasone versus bortezomib/lenalidomide/dexamethasone. However, high risk patients were not included.
- ▶ Carfilzomib/lenalidomide/dexamethasone was associated with less neuropathy but more dyspnea, hypertension, heart failure, and acute kidney injury compared with bortezomib/lenalidomide/dexamethasone.



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- ▲ The most common toxicities with carfilzomib are fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia.
- ▲ Infusion can be associated with a hypersensitivity reaction immediately following or up to 24 hours after the administration.

Daratumumab/Lenalidomide/Bortezomib/Dexamethasone

- ▶ The benefit of adding a fourth drug for the primary treatment transplant eligible patients is emerging.
- ▶ In the GRIFFIN trial, transplant-eligible patients with MM (n= 207) were randomized to daratumumab or bortezomib/lenalidomide/dexamethasone or bortezomib/lenalidomide/dexamethasone followed by autologous HCT plus consolidation and maintenance.
- ▶ The rate of stringent complete response rate after autologous HCT and consolidation with 4-drug regimen was 42% versus 32% with the 3-drug regimen.



- ▶ Follow-up after median of 22 months showed further improved sCR rates for the daratumumab-containing 4 drug regimen (62.6% vs 45.4%; $P = .0177$).
- ▶ Although the hematological toxicities were higher with the 4-drug regimen, no major safety concerns were reported in the study.
- ▶ The NCCN Panel has included
- ▶ daratumumab/lenalidomide/bortezomib/dexamethasone as an option for primary treatment of transplant-eligible patients with MM.

Ixazomib, lenalidomide, dexamethasone (IRd)

- ▶ A phase III trial (TOURMALINE-MM2) evaluated the addition of ixazomib to lenalidomide and dexamethasone versus lenalidomide/dexamethasone plus placebo in newly diagnosed MM patients not eligible for autologous stem cell transplant. The results showed higher CR with the addition of ixazomib (26% vs. 14%).
- ▶ This trial did not meet its pre-specified primary endpoint of improved PFS as the data failed to meet the threshold for statistical significance.

- Based on the above data and pending publication of the phase III TOURMALINE trial, the NCCN Panel has included ixazomib/lenalidomide/dexamethasone as an option (category 2B) for treatment of patients with newly diagnosed MM.

Regimens Useful In Certain Circumstances for Newly Diagnosed Transplant Candidates



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Bortezomib/Doxorubicin/Dexamethasone

- ▶ The updated results from the HOVON-65/GMMG-HD4 group phase III trial of newly diagnosed patients with stage II/III MM demonstrated high response rates after primary therapy with bortezomib/doxorubicin/dexamethasone versus vincristine/doxorubicin/dexamethasone (VAD), and this superior response rate (CR + near CR was 31% vs. 15%; $P < .001$) was maintained even after HCT with significantly higher ORR.

- Based on data from the HOVON-65/GMMG-HD4 trial and the uniform consensus among the NCCN Multiple Myeloma Panel members, bortezomib/doxorubicin/dexamethasone is a category 1 option for primary therapy for transplant-eligible patients with MM.

Carfilzomib/Cyclophosphamide/Dexamethasone

- ▶ A phase 1b study, CHAMPION-2 evaluated the safety and tolerability of twice-weekly carfilzomib (3 different doses) in combination with cyclophosphamide and dexamethasone for the treatment of newly diagnosed MM patients.
- ▶ This study found that 56 mg/m² carfilzomib combined with weekly cyclophosphamide and dexamethasone was effective and with manageable toxicity.

- ▲ The NCCN Panel has included
- ▲ carfilzomib/cyclophosphamide/dexamethasone for both transplant and non-transplant settings as an option useful in certain circumstances such as those with renal insufficiency and/or peripheral neuropathy.



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Ixazomib/cyclophosphamide/dexamethasone

- ▶ A multicenter, phase 2 trial investigated the efficacy and toxicity of ixazomib, cyclophosphamide and low-dose dexamethasone as induction, followed by single-agent ixazomib maintenance, in elderly, transplant-ineligible newly diagnosed patients.
- ▶ The ORR after initial therapy with ixazomib/cyclophosphamide/dexamethasone was 73%. After a median follow-up of 26.1 months, the PFS was 23.5 months.

- ▲ NCCN Panel has included
- ▲ ixazomib/cyclophosphamide/dexamethasone for both transplant and non-transplant settings as options useful in certain circumstances such as those with renal insufficiency and/or peripheral neuropathy.

Bortezomib/Thalidomide/Dexamethasone

- ▶ The phase III IFM 2013-04 trial is evaluating 4 cycles of CyBorD versus 4 cycles of bortezomib/thalidomide/dexamethasone as induction therapy before autologous HCT in patients with newly diagnosed MM.
- ▶ The hematologic toxicity was greater in the CyBorD arm; however, higher rates of peripheral neuropathy were reported in the bortezomib/thalidomide/dexamethasone arm.
- ▶ No significant difference in OS was observed in any of the trials with bortezomib/thalidomide/dexamethasone.

- ▶ Bortezomib / thalidomide / dexamethasone is listed as a primary treatment option (category 1) under the category “useful in certain circumstances.”



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Cyclophosphamide/Lenalidomide/Dexamethasone

- ▶ The Myeloma XI trial compared responses to cyclophosphamide/ lenalidomide/dexamethasone with cyclophosphamide/thalidomide/ dexamethasone. The preliminary results reported that the combination of lenalidomide/cyclophosphamide/dexamethasone is effective and has a good safety profile in patients of all ages.
- ▶ The NCCN Panel include
- ▶ cyclophosphamide/lenalidomide/dexamethasone as a primary therapy option for transplant-eligible patients with MM under the category “useful in certain circumstances” (category 2A).



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Daratumumab/Bortezomib/Thalidomide/Dexamethasone

- ▶ In the CASSIOPEIA trial, patients with newly diagnosed MM (n=1085) were first randomly assigned to receive induction with four cycles of bortezomib/thalidomide/dexamethasone with or without daratumumab, followed by autologous HCT plus two cycles of consolidation with the induction regimen.
- ▶ At day 100 after transplantation, the daratumumab arm reported deeper response rates (CR or better of 39% vs. 26%). Addition of daratumumab increased neutropenia (28% vs 15%), lymphopenia (17% vs 10%). Infusion reactions to daratumumab (mostly mild) were reported in 35%.



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- ▶ The NCCN Panel has included
- ▶ Daratumumab/bortezomib/thalidomide/dexamethasone as a primary therapy option for transplant-eligible patients with MM under the category “useful in certain circumstances” (category 2A) based on the results of CASSIOPEIA trial and FDA approval for this indication.



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Daratumumab/Cyclophosphamide/Bortezomib/ Dexamethasone

- ▶ Patients with newly diagnosed MM ($n=87$) and patients with relapsed MM ($n=14$) received daratumumab, /bortezomib/cyclophosphamide/dexamethasone. In newly diagnosed patients, after 4 cycles of induction therapy, VGPR or better was seen in 44.2% and the ORR was observed was 79.1%.
- ▶ At the time of clinical cut-off, the 12-month OS rate was 98.8% (95% CI, 92.0–99.8%). Efficacy was also observed in patients with relapsed MM.

- ▶ Based on the above results, NCCN Panel has included
- ▶ Daratumumab/bortezomib/thalidomide/dexamethasone for newly diagnosed patients with MM (transplant eligible and ineligible patients) as an option useful in certain circumstances.

Bortezomib, Dexamethasone, Thalidomide, Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide (VTD-PACE)

- ▶ The total therapy 3 (TT3) trial evaluated induction therapy with the multiagent regimen, VTD-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) prior to highdose melphalan-based tandem auto-transplants and later as consolidation therapy.
- ▶ This regimen is a potent combination of newer agents as well as traditional chemotherapy agents.

- ▲ This regimen is listed under the category “useful in certain circumstances.” According to the NCCN Panel, VTD-PACE could be an option for newly diagnosed patients presenting with high-risk and aggressive extramedullary disease or plasma cell leukemia.

Thanks for Your Attention



