Clinical Compendium:
A Critical Update on Therapy Selection, Sequencing, and Toxicity Management of Novel Therapies for Multiple Myeloma

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An Invitation from Sagar Lonial, MD

I want to encourage you to take a look at this activity for a number of reasons. First, we know that the field of myeloma therapy is rapidly evolving. All the way back to induction therapy where we know there are innovative approaches to not just triplet-based inductions, but potentially quad-based inductions and maximizing the benefit that patients get from standard consolidation and maintenance approaches by using anti-CD38 as part of our initial induction therapy.

We also know that there are strategies to maximize the benefit for patients with early relapse, making sure we take full advantage of all of the active regimens we have, focusing on triplet-based approaches, using or reusing drugs when appropriate, but not reusing drugs when we have other agents that may be able to take the place of those agents in the context of resistant disease. And finally, one of the most rapidly approaching and evolving areas in management of myeloma is the revolution of cell therapy with CAR T-cells as well as bispecifics or T-cell engagers. And this, to me, really represents the next foothold, if you will, of immune therapy in myeloma therapeutics that is going to move earlier and earlier in the disease course. Knowing how to manage it, how to expect it and when to use it really are key pieces of a successful patient experience and really improving outcomes for patients across the board.

So, please join us as we go through these cases that really illustrate how best to use the currently available drugs to maximize benefits for your patients.

Case 1: Epidemiology, Risk Stratification, Cytogenetics and Biomarkers

Question 1

A 61-year-old male is referred for evaluation by his primary care physician. The patient presented with a 1-month history of fatigue and lower back pain. The initial evaluation revealed anemia, hypercalcemia, diffuse osteopenia, and renal insufficiency. Further workup reveals IgG kappa multiple myeloma (MM) with an M-protein level of 2.74 g/dL. A bone marrow biopsy reveals 70% kappa restricted plasma cells. A FISH panel is negative for del(17p), t(4;14); and t(14;16).

Laboratory evaluation on referral shows:

- Hemoglobin 7.2 g/dL
- Serum creatinine: 1.4 mg/dL
- Calcium: 11.9 mg/dL
- Albumin: 3.2 g/dL
- Beta-2 microglobulin: 6.9 mg/L
- LDH: 390 U/L (reference range 100-240 U/L)

Which one of the following Revised International Staging System (R-ISS) stage and cytogenetic risk category applies to this patient?

a. R-ISS II; high-risk cytogenetics
b. R-ISS I; standard-risk cytogenetics
c. R-ISS III; high-risk cytogenetics
d. R-ISS III; standard-risk cytogenetics

Answer Rationale

The correct answer is D.

- This patient with IgG kappa multiple myeloma meets the criteria for R-ISS stage III with standard-risk cytogenetics.
- MM is a hematologic malignancy characterized by presence of abnormal clonal plasma cells in the bone marrow, with potential for uncontrolled growth causing destructive bone lesions, kidney injury, anemia, and hypercalcemia. Multiple myeloma is diagnosed in an estimated 34,920 people in the US and in approximately 588,161 people worldwide each year.[1]
- The International Staging System (ISS) is a simple risk stratification algorithm based on 2 parameters2
    - serum β2-microglobulin level reflects high tumor mass and reduced renal function
    - low serum albumin in MM is mainly caused by inflammatory cytokines

such as interleukin-6 secreted by the myeloma microenvironment

- The R-ISS uses ISS as well as cytogenetic abnormalities and baseline LDH for a more powerful prognostic tool.[1,2]
- For example, the R-ISS staging system is as follows:
    - Stage II: ISS stage 1 and standard-risk cytogenetics by FISH and serum LDH ≤ ULN
    - Stage II: Not R-ISS stage I or III
    - Stage III: ISS stage III and either high-risk cytogenetics by FISH or LDH > ULN
- Patients with R-ISS stage I, II, and III had 5-year OS rates of 82%, 62%, and 40%, respectively.[2]
- Standard-risk: No high-risk chromosomal abnormality. High-risk: Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)[2,3]

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Faculty Discussion

The answer to this question is D, R-ISS stage III with standard-risk cytogenetics. There are a number of different ways a patient can be defined as Revised International Staging System (R-ISS) stage III. Typically, high-risk diagnosis is made through the presence of high-risk genetics including the 17p deletion, 4;14 translocation or 14;16 translocation. However, there are subsets of patients that may have normal genetics, but at the same time functionally behave like a high-risk myeloma patient. And what has been determined in a number of large series of patients that go back 30 or 40 years is that having an elevated lactate dehydrogenase (LDH) puts one intrinsically in a higher risk category of multiple myeloma. And we know, if we look at nongenomic predictors of poor outcomes, presenting with an elevated LDH is one of the most powerful prognostic factors we see among laboratory data that occur when a patient is newly diagnosed with myeloma.

Important information to obtain at baseline include: albumin, beta-2 microglobulin, fluorescence in situ hybridization (FISH) testing, and serum LDH in order to do appropriate work-up for staging and risk assessment for a newly diagnosed myeloma patient.

Question 2

A 61-year-old male is referred for evaluation by his primary care physician. The patient presented with a 1-month history of fatigue and lower back pain. The initial evaluation revealed anemia, hypercalcemia, diffuse osteopenia, and renal insufficiency. Further workup reveals IgG kappa multiple myeloma (MM) with an M-protein level of 2.74 g/dL. A bone marrow biopsy reveals 70% kappa restricted plasma cells. A FISH panel is negative for del(17p), t(4;14); and t(14;16).

Which one of the following statements about response to treatment and prognosis in patients with multiple myeloma is true?

a. MM is considered curable with first-line therapy.
b. In patients who respond to first-line therapy, relapse invariably occurs.
c. Patients whose disease recurs after first-line therapy do not respond to salvage therapy.
d. Patients whose disease is refractory to a proteasome inhibitor (PI) and an immunomodulator (Imid) have a median overall survival of 29 months.

Answer Rationale

The correct answer is B.

- Although current treatments are highly effective in producing deep remissions, MM invariably relapses, requiring frequent therapeutic intervention to maintain disease control.[1]

- As MM relapses, it becomes increasingly refractory to the currently available drugs resulting in ever shorter remissions, with the vast majority of patients eventually succumbing to complications of relapsed, refractory disease.[1]
- Unmet needs include: the choice of the optimal strategy at diagnosis and at relapse, the scarcity of trials addressing important questions, such as the integration of the first salvage regimen into the assessment of front-line therapies to define optimal treatment sequencing, and the limited amount of data available on the efficacy of the different approved regimens in specific patient populations (refractory disease vs relapse after a treatment-free interval, biochemical vs symptomatic relapse, relapse after 1 previous line of therapy vs advanced disease, high-risk vs standard-risk cytogenetic profiles, and those with extramedullary disease).[2]
- Patients with myeloma refractory to a proteasome inhibitor (PI) and an immunomodulator (IMid) have a median overall survival of 9 months.[1]

References

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Faculty Discussion

This is an unfortunate reality of where we are in multiple myeloma in 2023. While certainly our group and others have survival curves of patients after induction therapy who have done remarkably well, we know that given long enough follow-up, most patients myeloma will ultimately relapse. There have been a number of improvements in overall survival based on approval of new drugs and this is particularly important because, for instance, back in 2000, 2001, when I first started working in the field of myeloma, the expected median overall survival was only 2 to 3 years. Fast forward to 2022 and the most recent publication of the bortezomib, lenalidomide, dexamethasone (RVD) 1000 series, the median expected overall survival for myeloma patients is greater than 10 years. In fact, if you're a standard-risk patient, it's greater than 14 years with a median not yet reached.

Despite these outstanding improvements in overall survival, patients do go through multiple lines of therapy, are exposed to different agents, and need to continue to have access to new drugs to respond in a meaningful way and we hope, ultimately, eliminate the myeloma clone in totality.

Question 3

A 61-year-old male is referred to you from his primary care office for fatigue and lower back pain. A diagnostic workup reveals IgG kappa MM with an M-protein level of 2.74 g/dL. A bone marrow biopsy reveals 70% kappa restricted plasma cells. He has standard risk cytogenetics with R-ISS III disease.

Labs on diagnosis

- Hemoglobin 7.2 g/dL
- Serum creatinine: 1.1 mg/dL
- CrCl: ~ 80 mL/min
- Calcium: 8.9 mg/dL
- Albumin: 3.2 g/dL
- Beta-2 microglobulin: 6.9 mg/L
- LDH: 390 U/L

Social history

- 32-year marriage with 2 grown children
- No history of substance or alcohol abuse
- Currently employed full time as high school teacher

Which one of the following regimens would be the most effective induction therapy for this patient?

a. Cyclophosphamide, bortezomib, dexamethasone (CyBorD)
b. Daratumumab, lenalidomide, dexamethasone (DRd)
c. Daratumumab, lenalidomide, bortezomib, dexamethasone (DRVd)

d. Lenalidomide, bortezomib, dexamethasone (RVd)

Answer Rationale

The correct answer is C.

- Until recently, triplet induction therapy with lenalidomide, bortezomib, and dexamethasone (RVd), followed by high-dose chemotherapy and stem cell transplantation, and maintenance chemotherapy, was the standard of care for patients newly diagnosed with MM with standard risk cytogenetics who are transplant-eligible.[1,2]
- Quadruplet induction therapy with addition of **daratumumab** to lenalidomide, bortezomib, and dexamethasone (DRVd) has demonstrated deeper responses, higher rates of minimal residual disease (MRD) negativity, and improved progression-free survival (PFS) when compared with standard triplet induction therapy (RVd) in patients newly diagnosed with MM with standard risk cytogenetics who are transplant-eligible.[2]
- Quadruplet induction therapy with addition of **isatuximab** to lenalidomide, bortezomib, and dexamethasone (IsaRVd) has also shown higher rates of MRD negativity compared with standard triplet induction therapy (RVd) in patients newly diagnosed with MM who are transplant-eligible.[3]
- The NCCN guidelines support use of the DRVd quadruplet as primary therapy for patients with MM who are transplant-eligible.[4]
- PERSEUS is an ongoing phase 3 study investigating PFS and overall survival (OS) in patients treated with subcutaneous daratumumab+RVd vs RVd to confirm improved survival outcomes seen in the phase 2 GRIFFIN trial.[5]
- The strategy for maintenance therapy may differ depending on induction regimen and cytogenetic risk profile (Rev vs. Dara-Rev vs. Rev/PI)[1,2,4]

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Faculty Discussion

When we think about modern induction therapy, there are 2 big competitors in terms of the most commonly used regimen in the United States. RVd has been the standard regimen for a long period of time, but many large academic groups, including ours, have supplemented RVd with the addition of dara, based on the Griffin study. The Griffin study was a very nice example of a randomized phase 2 that was powered for response rate, but now at 3- and 4-years' follow-up, the progression-free survival with the addition of dara to induction therapy is actually better than patients who did not receive daratumumab as part of their initial induction therapy.

There are other large, randomized, phase 3 trials that are going to more fully assess this, including the PERSEUS study, a randomized, phase 3 trial that has completed enrollment. We're going to have to wait for

data maturation to really understand whether or not the addition of daratumumab in this phase 3 trial demonstrates longer progression-free survival in addition to higher overall response rates and a higher MRD-negativity rate earlier on. But certainly many folks are using daratumumab as part of the initial induction therapy, although not yet adopting it in the maintenance form. And this, to me, is really important as we think about how to manage relapsed myeloma and particularly waiting for phase 3 data supporting the use of daratumumab over no daratumumab in a maintenance setting when a patient received daratumumab as part of their initial induction therapy.

Question 4

A 61-year-old male is referred to you from his primary care office for fatigue and lower back pain. A diagnostic workup reveals IgG kappa MM with an M-protein level of 2.74 g/dL. A bone marrow biopsy reveals 70% kappa restricted plasma cells. He has standard risk cytogenetics with R-ISS III disease. Discussion with the patient reveals that he lacks family and social support and has no caregiver.

Which one of the following regimens would be most appropriate if this patient were not eligible for stem cell transplantation?

a. Daratumumab, lenalidomide, dexamethasone (DRd)
b. Cyclophosphamide, bortezomib, dexamethasone (CyBorD)
c. Lenalidomide and dexamethasone (Rd)
d. Bortezomib and dexamethasone (Vd)

Answer Rationale

The correct answer is A.

- Triplet induction therapy with DRd has shown improved PFS and OS when compared with Rd in patients newly diagnosed with MM who are transplant-ineligible[1]
- Daratumumab added to bortezomib, melphalan, and dexamethasone also showed an increase in OS in patients newly diagnosed with MM who are transplant-ineligible[2]
- Overall, daratumumab-based regimens have set new PFS and OS benchmarks for transplantation-ineligible patients with newly diagnosed MM1,[2]

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Faculty Discussion

This is a really important case of an older, frailer patient who we know perhaps should be treated somewhat differently, particularly given he does not have the caregiver or potential support a patient needs to undergo transplant. In this context, for a nontransplant-eligible patient, the randomized, phase 3 MAIA data really do support the use of DRd, based on a head-to-head comparison of DRd vs lenalidomide and dexamethasone alone. We know, bortezomib and dexamethasone, one of the other options, simply doesn't have the progression-free survival advantage we see with lenalidomide/dexamethasone or with DRd. VCd or cyclophosphamide in combination with bortezomib and dexamethasone has not been shown in a randomized, head-to-head study to be superior to either lenalidomide /dexamethasone or RVd as part of induction therapy.

What we know from the MAIA study is that the median progression-free survival is somewhere between 4 and 5 years for the average frail patient receiving DRd as initial induction therapy. DRd is a relatively safe option, and given the limitation on caregivers, represents a great option for a patient who perhaps is living on their own and who you want to minimize potential toxicity and side effects to maximize long-term treatment benefit and remission in a case like this.

Key Concepts

As we wrap up this module, it is very clear that risk assessment and choice of induction therapy are rapidly evolving in the context of newly diagnosed multiple myeloma. It is important to perform appropriate staging and risk assessment so that you and the patient can have reasonable predictions of their outcomes, both in the short term and in the long term. More importantly, choosing the optimal induction therapy likely has a significant impact on long-term outcomes and most recent trials are suggesting the addition of daratumumab to standard triplet IMiD/PI induction deepens the response and increases the fraction of MRD-negative patients earlier on. More importantly, the use of anti-CD38-based induction therapy does have a significant benefit, even for the frail patient who may not necessarily be transplant-eligible and should be strongly considered as a front-line treatment option for those patients as well.

Case 2: 2nd Line Treatment Considerations

Question 1

A 57-year-old male is evaluated in myeloma clinic. The patient was diagnosed with IgG lambda MM and achieved a very good partial response (VGPR) after induction with lenalidomide, bortezomib, dexamethasone (RVd), autologous stem cell transplant (ASCT), and lenalidomide maintenance. His ASCT was 14 months ago. Current laboratory evaluation shows progression of MM.

Labs on progression

- Hemoglobin 10.2 g/dL
- Serum creatinine: 1.2 mg/dL
- M-protein: 1.7 g/dL

Cytogenetics

- t(4;14)

Past medical history

- IgG lambda MM
- Osteoarthritis

Which of the following regimens would be most appropriate for this patient experiencing an early first relapse?

a. Pomalidomide, dexamethasone (Pd)
b. Carfilzomib, dexamethasone (Kd)
c. Daratumumab, lenalidomide, dexamethasone (DRd)
d. Isatuximab, carfilzomib, dexamethasone (IsaKd)

Answer Rationale

The correct answer is D.

- Isatuximab added to carfilzomib and dexamethasone (IsaKd) showed an increase in PFS vs Kd (not reached vs 19.1 months) in patients diagnosed with MM previously exposed/refractory to lenalidomide and experiencing early relapse. [1,2,4]
- Other options include: [2,3,4]
    - DPd: median PFS not reached (POM MM 014 phase 2 trial)[2]
    - DKd vs Kd: median PFS= not reached vs 15.8 months[2]
    - PVd vs Vd: median PFS= 11.2 vs 7.1 months[2]
    - DVd vs Vd: median PFS= 16.7 vs 7.2 months[2]
    - KPd: median follow-up of 16.3 months, PFS = 18 months (EMN011/HO114 trial)[2]
- If the patient's myeloma was not refractory to lenalidomide, options include: DRd, KRd, DVd, Kd, DKd, IsaKd, IRd, Elo-Rd, or PVd[2,3,4]

References

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Faculty Discussion

The answer to this question is D, isatuximab, carfilzomib, and dexamethasone. There are a couple of important features here that I think are worth discussing. The first is that this patient not only has known 4;14 translocation, but also has functional high-risk multiple myeloma. This patient received a standard IMiD/PI induction therapy, transplant, and lenalidomide maintenance and had what I would consider relatively quick relapse of their disease. Among the choices available in this question, the doublets of Pd or Kd are probably suboptimal, given that doublets are not really optimal choices in the context of first relapse.

The use of DRd is suboptimal because the patient has progressed on lenalidomide maintenance. So, in this context, the use of an anti-CD38 antibody, in combination with carfilzomib and dexamethasone, clearly represents the optimal choice and is an option that I would choose in this situation as well, knowing the proteasome inhibitors, particularly the more potent proteasome inhibitor, such as carfilzomib, is highly active in the 4;14 subset of patients. And that really does make the use of an anti-CD38 antibody, in partnership with carfilzomib and dexamethasone, the optimal answer in a functional and genetically high-risk patient with early relapse, following what I would consider as very appropriate induction and consolidation therapy.

Question 2

A 57-year-old male with a past medical history significant for IgG lambda MM who achieved very good partial response (VGPR) following first-line induction with RVd, autologous stem cell transplant (ASCT), and lenalidomide maintenance. His ASCT was 14 months ago. He presents to myeloma clinic with labs indicating progression of MM.

Labs on progression

- Hemoglobin 10.2 g/dL
- Serum creatinine: 1.2 mg/dL
- M-protein: 1.7 g/dL

Cytogenetics

- t(4;14)

Past medical history

- IgG lambda MM

Which one of the following therapies would be most appropriate if this patient had been exposed to an anti-CD38 monoclonal antibody as part of induction therapy?

a. Re-treatment with an anti-CD38 based therapy
b. Bortezomib, dexamethasone (Vd)
c. Pomalidomide, bortezomib, dexamethasone (PVd)
d. Pomalidomide, dexamethasone (Pd)

Answer Rationale

The correct answer is A.

- Currently, there are limited data available for treatment options for patients who progress on anti-CD38 antibodies, however re-treatment with an anti-CD38 antibody may be an option with overall response rates (ORR) ranging between 41%-55% in patients with myeloma refractory to daratumumab and/or pomalidomide[1,2]
- The washout period between re-treatment may be important to consider to allow for the expansion of a myeloma cell clone with high CD38 expression[2]
- Several small retrospective studies have demonstrated responses using isatuximab-based combinations for patients with multiple myeloma who have been exposed to daratumumab[3,4]

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Faculty Discussion

The answer to this question is A, retreatment with an anti-CD38-based therapy. This is pretty much the same case as we saw a moment ago except that this patient received quadruplet therapy, including an anti-CD38 antibody as part of their initial induction therapy. I think one of the real advantages, even in a high-risk patient like this, of using daratumumab as part of initial induction therapy, but not using it in the maintenance setting, is having it available for treatment at a patient's first relapse. And so, in this context, I would use an anti-CD38 antibody and combine it with carfilzomib and dexamethasone as we saw in the previous version of this case, because this is a high-risk patient, and I would not have hesitation retreating with an anti-CD38 antibody.

The other choices here, including bortezomib and dexamethasone as a doublet, is suboptimal. Pomalidomide/dexamethasone as a doublet is suboptimal and pomalidomide/bortezomib and dexamethasone, as in the OPTIMISM study, is another suboptimal treatment, because retreatment with bortezomib in the relapse setting, after bortezomib as part of the initial induction, I think is fraught with a much higher risk of neuropathy. It's a tougher drug to give in that context when a patient has received bortezomib as part of their initial induction and the progression-free survival is not as good as one would like, as you see, for instance, in the CD38s combined with carfilzomib, whether it's isatuximab or daratumumab.

Key Concepts

When we talk about key concepts from case study 2, there are a couple. The first is you should think about treatments that really optimize the patient based on what they are resistant to at the time of first relapse. For most patients in 2023, they're not going to be resistant to an anti-CD38-based approach and so using an anti-CD38 and either partnering it with a proteasome inhibitor, such as carfilzomib or an IMiD, such as pomalidomide, really represent the 2 main choices of appropriate triplets in the management of patients with early relapse.

Furthermore, exposure to an anti-CD38 as part of the initial induction therapy, but not in the maintenance therapy, does not eliminate the power that anti-CD38-directed therapy can bring in the context of early relapse. And I certainly have no hesitation retreating with an anti-CD38 as long as the patient is not resistant to anti-CD38 through the context of continuous therapy. And that certainly is a model that our program and my patients really take full advantage of to make sure we've maximized the benefit of an anti-CD38 antibody, both up-front and in the early relapse setting.

Case 3: Multi-Class Refractory MM

Question 1

A 74-year-old female with a history of lambda light chain MM that has relapsed after multiple lines of therapy presents to myeloma clinic. She has new laboratory findings indicating progression of her disease. She is not interested in pursuing CAR T-cell therapy.

Labs on progression

- Hemoglobin 9.2 g/dL
- Serum creatinine: 1.3 mg/dL
- M-protein: 1.4 g/dL

Treatment history

- June 2017: Lenalidomide, bortezomib, dexamethasone (RVd) x 4 cycles
- Nov 2017: ASCT with lenalidomide maintenance
- Oct 2020: progression treated with daratumumab, bortezomib, dexamethasone (DVd)
- Nov 2021: progression treated with carfilzomib, pomalidomide, dexamethasone (KPd)

- Dec 2022: progression treated with dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP)
- February 2023: new progression

What is of the following therapies would be most appropriate for this patient?

a. aBortezomib, dexamethasone, cisplatin, doxorubicin, cisplatin, etoposide (Vd-PACE)
b. Re-treatment with KPd
c. Teclistamab-cqyv
d. Ciltacabtagene autoleucel

Answer Rationale

The correct answer is C.

- The outcome is very poor for patients whose multiple myeloma has become refractory to proteasome inhibitors, immunomodulatory agents, and anti-CD38 antibodies, with 1 study showing these patients have a median overall survival of only 5-6 months.[1]
- Teclistamab, a B-cell maturation antigen (BMCA) targeting bispecific T-cell engager, showed an ORR of 63% in patients who had relapsed/refractory MM after multiple lines of therapy. VGPR and CR were seen in 58.8% and 39.4% of patients, respectively. MRD negativity occurred in 26.7% of patients.[2]
- Ongoing clinical trials are investigating bispecific antibodies (bsAbs) in earlier lines of therapy, in combination with other agents, and with novel surface targets.[3-7]
- BMCA targeting CAR T-cell therapy also offers promising ORR, PFS, and OS rates in patients with MM who have relapsed/refractory disease after multiple lines of therapy. Access to care remains a challenge as CAR T is only available at large tertiary medical centers and manufacturing slots are limited.[8]
- The combination of twice weekly selinexor and dexamethasone also has shown responses in heavily pretreated patients with 39% of patients achieving a minimal response or better.[9]

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Faculty Discussion

The answer to this question is C, teclistamab. This is really an important situation that is arising more and more frequently now where patients are going through all the available treatment options, particularly using proteasome inhibitors, IMiDs, and anti-CD38 antibodies. And in this case, even the use of combination chemotherapy, such as dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP). We know that not all patients want to go to a tertiary center to get access to a CAR T-cell, and in this particular case, the patient has said they don't want to do that. This leaves us with an option like teclistamab which is clearly a very active way to target BCMA in the context of relapsed and refractory disease and represents an option with a much shorter hospitalization and with an easier safety profile perhaps than what we see with a CAR T-cell therapy. In many cases, teclistamab does not require travel or relocation to a tertiary referral center for the first 4 weeks, like patients receiving CAR T-cell therapy.

Teclistamab is highly effective with a very high overall response rate in this refractory patient population with a median duration of remission that is over a year, a median progression-free survival of close to a year, and adverse events including cytokine release syndrome (CRS) and neurologic toxicities, such as immune effector-associated neurotoxicity syndrome (ICANS), being 1 grade lower than what we see with a CAR T-cells, making this kind of treatment available and easier for patients closer to home. I do think it is important to make sure infection prophylaxis is managed appropriately for patients that are getting teclistamab, as this does represent one of the longer-term potential negative effects associated with infusion of a BCMA-directed bispecific antibody. When taking that into account, the efficacy and safety data is really overwhelming for this kind of an approach and represents a great option for patients who are unwilling to travel and have received most of the major classes of drugs and have exhausted options at that time.

Question 2

A 74-year-old female with a history of lambda light chain MM that has relapsed after multiple lines of therapy presents to myeloma clinic. She has new laboratory findings indicating progression of her disease. She is not interested in pursuing CAR T-cell therapy. A FISH panel reveals t(11;14).

Labs on progression

- Hemoglobin 9.2 g/dL
- Serum creatinine: 1.3 mg/dL
- M-protein: 1.4 g/dL
-

Treatment history

- June 2017: Lenalidomide, bortezomib, dexamethasone (RVd) x 4 cycles
- Nov 2017: ASCT with lenalidomide maintenance
- Oct 2020: progression treated with daratumumab, bortezomib, dexamethasone (DVd)
- Nov 2021: progression treated with carfilzomib, pomalidomide, dexamethasone (KPd)
- Dec 2022: progression treated with dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP)
- February 2023: new progression

Which of the following therapies would be most appropriate for this patient?

a. Bortezomib and dexamethasone (Vd)
b. Venetoclax and dexamethasone (VenDex)
c. Re-treatment with KPd
d. Continue more cycles of DCEP chemotherap**y**

Answer Rationale

The correct answer is B.

- Venetoclax and dexamethasone showed an overall response rate of 48% in patients diagnosed with MM with t(11;14) who were experiencing relapse after a median of 5 prior lines of therapy. [1,2]
- Higher BCL-2 levels were found in patients who a achieved a response.[1]
- Because of the potential for benefit in patients with high BCL-2 expression, ongoing trials will

focus on PCR-based assays to identify BCL-2 expression that might be predictive of response to venetoclax.[1,3]

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Key Concepts

- Key concept #1 – Patients with triple-class refractory disease have poor outcomes, necessitating development of novel agents with novel targets.
- Key concept #2 – CAR T-cell therapy, bispecific antibodies, selinexor, and venetoclax represent novel agents that may be utilized in later lines of therapy for patients with relapsed/refractory disease.

Faculty Discussion

The answer to this question is B, venetoclax and dexamethasone. This is a really interesting case because the presence of the 11;14 translocation in this patient is something that identifies them as one of a phenotypically different group of myeloma patients. We know that these patients seem to have gained less benefit from standard novel therapies, such as proteasome inhibitors and immunomodulatory drugs. They do gain some benefit from anti-CD38 antibodies, but they are uniquely sensitive to venetoclax, a BCL-2-targeted drug, that is active in chronic lymphocytic leukemia (CLL), and seems to have unique activity in the 11;14 subset of patients.

The use of venetoclax and dexamethasone was identified in a phase 1 study where the patients that got the best benefit from venetoclax were the 11;14 subset. This was then validated with a venetoclax/dexamethasone phase 2 trial that was published by my colleagues, Shaji Kumar and Jonathan Kauffman, and demonstrated again a very high overall response rate, even in triple-class refractory multiple myeloma. This is a safe and effective treatment, does not have tumor lysis as a significant potential toxicity in this context as we see in CLL or other lymphomas and, more importantly, is an easy oral treatment option for many of these patients.

Other treatment options may also be considered but require retreatment with drugs the patient has already been exposed to and, more importantly, the use of venetoclax/dexamethasone in the 11;14 subset really represents the closest example of precision medicine in myeloma and it's something I'm trying to employ earlier and earlier in the treatment course. Even in the context of first relapse, I'm considering whether I'm going to treat them with venetoclax-based therapy, whether it's using bortezomib as a partner, carfilzomib as a partner, or daratumumab as a partner, based on phase 2 and hopefully emerging randomized phase 3 data.

Key Concepts

As we think about key concepts from this case, it is important to recognize that patients with triple-class refractory myeloma clearly have suboptimal outcomes and how they're going to do is really dependent on access to new treatments. There's a big discussion in the community about CAR T-cells vs bispecifics and how to choose one or the other. I find that often patients make that decision. They either do or don't want a CAR T-cell. They either do or don't want a bispecific. And, certainly, access represents an important part of that equation.

With new agents such as bispecific antibodies, venetoclax for the 11;14 subset of patients, and selinexor-based combinations, we clearly have new drugs and new targets that I think are really important for the triple-class refractory patient population and that are changing the natural history of the triple-class refractory patient population as well.

Case 4: Management of Adverse Effects of Novel Therapies

Question 1

A 53-year-old female with a history of MM that has been treated with 4 lines of therapy is evaluated in myeloma clinic. Laboratory results indicate disease progression. Treatment with selinexor and dexamethasone is being considered.

Which of the following adverse effects of selinexor should be explained to the patient?

a. Hair loss
b. Weight gain
c. Insomnia
d. Severe nausea

Answer Rationale

The correct answer is D.

- Selinexor, a selective inhibitor of nuclear export, is associated with multiple adverse effects including nausea, vomiting, thrombocytopenia, neutropenia, anorexia/weight loss, fatigue, diarrhea, hyponatremia, and neurotoxicity.[1,2]
- The 5HT-3 antagonist ondansetron should be scheduled 1-hour before each selinexor dose and used as needed thereafter. Olanzapine and/or an NK-1 antagonist may also be used for emesis prevention. Nausea is worst during the first 8 weeks of treatment and antiemetics may be reduced thereafter if nausea abates.[1]
- Other supportive care such as intravenous hydration, thrombopoietin (TPO) agonists, platelet transfusions, G-CSF, loperamide, and/or methylphenidate may be utilized to manage other adverse events associated with selinexor.[1]
- Once weekly dosing of selinexor has also been studied and may be better tolerated than traditional twice-weekly dosing regimens.[3,4]

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Faculty Discussion

When we talk about the use of selinexor-based combinations in the management of patients with relapsed and refractory multiple myeloma, it's clear from the adverse event profile of selinexor, whether given at full dose or even at a lower dose in partnership with either pomalidomide, bortezomib or carfilzomib, that GI toxicity clearly represents a significant effect that should be addressed early on, preemptively, rather than being reactionary when a patient develops severe nausea. Hair loss is not a significant issue. Weight gain is not a significant issue and insomnia is not a significant issue with the use of selinexor in salvage therapy. Nausea and GI symptoms, such as anorexia and weight loss, are probably larger ones, and so managing that with preemptive anti-emetics, as well as IV hydration and salt repletion, represent important therapeutic strategies when treating a patient with selinexor-based salvage therapy.

Question 2

A 53-year-old female with a past medical history significant for MM that has been treated with 4 lines of therapy presents to clinic with labs indicating new MM progression.

Past medical history

- Hyperlipidemia
- Hypertension

Current medications

- Pravastatin 40 mg daily
- Lisinopril 20 mg daily

The patient received selinexor-based therapy, and 16 months later the disease has progressed. Treatment with a B-cell maturation antigen (BCMA) targeting therapy--either chimeric antigen receptor (CAR) T-cell therapy or teclistamab, is being considered for the patient.

Which one of the following adverse effects is most closely associated with the BCMA targeting therapies?

a. Hypertension
b. Hair loss
c. Corneal keratopathy
d. Cytokine release syndrome

Answer Rationale

The correct answer is D.

- The BCMA targeting therapies ciltacabtagene autoleucel (cilta-cel), idecabtagene vicleucel (ide-cel), and teclistamab are commonly associated with the cytokine release syndrome (CRS), along with infections, and neurotoxicity.[1-3]
- Any grade CRS occurred in 95%, 84%, and 72% of patients receiving cilta-cel, ide-cel, and teclistamab, respectively. Grade 3+ CRS was more common with CAR T-cell therapy vs teclistamab (4% & 5% vs 0.6%).[1-3]
- CRS management involves use of supportive care including oxygen, hydration, tocilizumab, anakinra, and corticosteroids.[1-3]
- Teclistamab is initiated using a step-up dosing schema to reduce CRS and neurotoxicity.1
- Any grade neurotoxicity occurred in 21%, 18%, and 14.5% of patients receiving cilta-cel, ide-cel, and teclistamab, respectively. Grade 3+ neurotoxicity was more common with CAR T-cell therapy vs teclistamab (9% & 3% vs 0.6%).[1-3]
- Neurotoxicity management involves use of corticosteroids, tocilizumab, anakinra, and levetiracetam.[1-3]
- Any grade infection occurred in 95%, 84%, and 72% of patients receiving cilta-cel, ide-cel, and teclistamab, respectively. Grade 3+ CRS was more common with CAR T-cell therapy vs teclistamab (4% & 5% vs 0.6%).[1-3]
- Early and prolonged cytopenias are common after BCMA directed CAR T-cell therapy and approximately half the patients in the KarMMA-1 trial experienced prolonged grade ≥ 3 neutropenia, anemia, and thrombocytopenia for at least a month after infusion despite treatment with granulocyte colony stimulating factors (G-CSF), erythrocyte stimulating agents (ESA), and thrombopoietin agonists (TPO).[3,4]
- Cytopenia and infection management may include use of transfusions, IVIG, prophylactic antivirals, antimicrobials and antifungals, G-CSF, TPO mimetics, stem cell boosts, and post CAR T reimmunizations.[4,5]

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Faculty Discussion

When we think about BCMA-targeted therapy with either a CAR T-cell or a bispecific T-cell engager, cytokine release syndrome or CRS represents one of the more common adverse events we see. In many ways, CRS is a sign that the drugs are working, that they're being effective, because what we're seeing is a very vigorous T-cell mediated immune response targeting the tumor cells. As those T-cells grow and expand, interleukin-6 (IL-6) is secreted and can induce a response associated not just with high and persistent fevers, but with hypotension that often may require volume replacement, pressor support, or in some cases, even intensive care support as well.

In myeloma, we're fortunate that the severity of CRS with CAR T-cells is, on average, a grade less than what's seen with CD-19-directed CAR T-cells in acute lymphoblastic leukemia (ALL) or diffuse large B-cell lymphoma. On average, CRS tends to be grade 1 or 2, or rarely grade 3. I've not seen a grade 4 case of CRS in my experience to date. It does happen, but it's reported relatively rarely.

At the same time, when we think about bispecifics, I think about them as being, on average, a grade lower than what we see with BCMA-directed CAR T-cells in myeloma. So again, mostly grade 1 with a little bit of grade 2, rarely grade 3, and I've not seen a grade 4 with a bispecific-targeted BCMA at this point. And so I think it's important to recognize these are common adverse events for using T-cells to kill multiple myeloma cells. Their severity and grade are different than what we see with CD-19-directed therapy and can be managed with either tocilizumab, observation and supportive care, or corticosteroids, depending upon the severity and the rapidity of the CRS course in this context.

In addition to CRS, we also see ICANS or neurologic toxicity that can manifest in a number of different ways. Again, when we think about BCMA-directed CAR T-cells, on average, I think of ICANS being one grade less than what we see with CD-19-directed neurologic toxicity, and with the bispecifics, I think about it as one grade less than what we see with BCMA-directed CAR T-cells. These can be mitigated by limiting the severity of CRS as often CRS is a harbinger of potential neurotoxicity, but, more importantly, the use of corticosteroids is employed more commonly in the management of neurologic toxicity. It does tend to occur a little bit later in the disease course and, for instance, with ciltacabtagene autoleucel (cilta-cel) as 1 of the CAR T-cell products that are available, we do see a Parkinsonian-type issue that occurs in less than 5% of patients and can occur beyond day 30 after infusion of the CAR T-cell.

These are things to be aware of and know that they need to be managed aggressively. CAR T-cell infusion centers will typically be on the lookout for neurologic toxicity with mini-mental state exams done every shift, as well as handwriting exams.

Finally, the last adverse events to be aware of in the context of BCMA-directed either CAR T-cells or bispecifics are infectious complications. This is a bigger issue for the bispecifics than it is for the CAR T-cells because CAR T-cells have somewhat of a limited duration therapy, meaning that somewhere around 6 months after the infusion, the suppression of the immune system seems to wind down a little bit, whereas with a bispecific, immune suppression lasts longer because patients are being administered a bispecific for a longer period of time.

In this context, monthly IVIG infusions are really very important. Antibiotic prophylaxis is important if they become neutropenic. The use of growth colony stimulating factor (G-CSF) to try and keep the counts up is also really important. Surveillance and viral serologies are recommended by a number of groups, as well, particularly focusing on cytomegalovirus (CMV) reactivation, and if patients develop cytopenias it may be a consequence of CRS or the CAR T-cell or it may be infectious in nature. And the best example I can give is a patient at day 30 who lost their counts and it turns out it was all related to CMV. So, unusual infections are things that one should be aware of with BCMA-directed therapy, particularly highly potent BCMA-directed therapy such as CAR T-cells or bispecifics.

Key Concepts

When we think about key concepts for case 4, there are a number that are really important in terms of managing adverse events and maximizing the potential benefit that patients can get from therapy. For instance, with selinexor, being focused on some of the GI toxicities preemptively is more effective than reacting to it once a patient already develops nausea and vomiting, anorexia,

and/or weakness. When thinking about venetoclax, tumor lysis syndrome really is not a major issue in myeloma in the 11;14 subset, like it is in lymphomas or CLL. Being aware of appropriate modifications of drugs and doses based on adverse events and being able to anticipate CRS, neurotoxicity, and infectious complications for patients getting BCMA-directed therapy really represents important prevention strategies to maximize the benefit a patient gets from these highly effective therapies.

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