

Recent Advances in the Treatment Of Newly Diagnosed Multiple Myeloma

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Abstract

Edward Libby, MD, and Josh Epworth, ARNP, interpreted data on current and novel treatments, discussed how to select initial therapy based on patient risk and in alignment with guidelines and best practices, and evaluated the use of minimal residual disease testing in patients with multiple myeloma.

Multiple myeloma is a malignancy characterized by clonal proliferation of terminally differentiated plasma cells within the bone marrow. While this leads to a host of different issues within the body, OS has steadily improved in recent years, and approximately 50% of patients are alive 5 years past diagnosis. “This is largely because of better identification and diagnosis, better methods of treatment, and improved symptom management,” said Josh Epworth, ARNP, of SCCA.

These topics were discussed at JADPRO Live 2019 by Mr. Epworth and Edward Libby, MD, Associate Professor of Medical Oncology at the University of Washington. Dr. Libby also previewed exciting new treatments that should be available to clinicians in the near future.

PRESENTATION

The subjective signs and symptoms at presentation are well known: bone

pain, frequent infections, fatigue, unintentional weight loss, foaming urine, and easy bruising and bleeding. This scenario should trigger an evaluation for hypercalcemia, elevated creatinine, anemia, pancytopenia, elevated serum protein levels, and bone fractures, lesions, or soft tissue masses.

“Multiple myeloma is a disease of peaks and valleys. We want to diagnose it early, before it causes damage, and we want to suppress the disease as best we can in those first two treatment cycles,” Mr. Epworth said. Nearly all patients respond to their treatment regimen, he said, but remissions do not last forever. The first two will be the longest, but as the disease evolves, these remissions become shorter and the cancer becomes more aggressive. It is important, therefore, to achieve a robust effect early. “And because this disease is a marathon,” he added, clinicians should consider how to best suppress the disease and evaluate the spectrum of treatments available.

In the diagnostic workup, the National Comprehensive Cancer Network (NCCN) Guidelines on imaging have been updated to recommend (1) whole-body low-dose high-speed CT, (2) PET-CT, or (3) bone marrow MRI (NCCN, 2019). In all cases, a number of lab tests are necessary, as is bone marrow biopsy for genetic and morphological testing.

The main biomarkers of myeloma are a spike in monoclonal protein (M-spike) and an asymmetry in free light chains. The former is identified by serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), and the latter by serum free light chains (SFLC). One or both of these markers are present in approximately 85% of patients; in the 15% of patients with no detectable M-spike, serum free light chains can be detected and are diagnostic. The M-spike, while a critical marker on the status of disease, is not currently considered diagnostic for the disease.

Discussing myeloma precursors, Mr. Epworth noted that monoclonal gammopathy of undetermined significance (MGUS) carries a risk of progression to myeloma of only 1% per year. Smoldering myeloma, on the other hand, progresses at a rate of 10% per year for the first 5 years and should be carefully monitored. He also noted that the CRAB criteria are no longer the only way to diagnose myeloma; a “myeloma-defining event” also qualifies (Table 1). “Myeloma-defining event

means there are some markers of an opening act to multiple myeloma, and if we don't act within a short period of time, we can expect to see damage,” he said. “Once we see CRAB criteria or a myeloma-defining event, that's the trigger to begin treatment. And once we start treating, we don't stop until we come to the end of the patient's life.”

STAGING AND INITIAL TREATMENT

Levels of beta-2 microglobulin, albumin, lactate dehydrogenase, and cytogenetics are informative as to disease stage, and they come together in the Revised International Staging System (R-ISS) to form prognosis, which differs greatly by stage. For example, R-ISS stage 1 patients have a median survival about 40 months longer than R-ISS stage 3 (Palumbo et al., 2015). “We have to take a more aggressive stance with high-risk cytogenetics, which are often found in stage 3 patients,” according to Mr. Epworth.

For initial treatment, triplets are now the standard of care, but regimens containing four drugs are being considered for upfront treatment. Lenalidomide/bortezomib/dexamethasone (RVd) on a 21-day cycle is the gold standard backbone. Common side effects of lenalidomide are fatigue, rash, and diarrhea; the main issue with bortezomib is peripheral neuropathy, although this is less common/severe with subcutaneous compared with intravenous administration. Following four to six cycles of RVd, the care team should consider whether to proceed with transplant, deferred transplant, or maintenance alone. Maintenance can consist of reduced-dose lenalidomide, reduced-frequency bortezomib with or without steroids. For patients with high cytogenetic risk factors, carfilzomib (KRd) on a 28-day cycle may be the preferred proteasome inhibitor. When patients have multiple comorbidities or advanced age and are transplant-ineligible, RVd “lite,” given on a 35-day cycle with a reduced dose of lenalidomide and a longer recovery period, helps maintain higher blood counts compared to RVd standard, Mr. Epworth said.

As far as medications, one of the latest “game changers” in myeloma is the monoclonal antibody daratumumab. Daratumumab is being combined with an ever-growing list of agents. The quadruplet of daratumumab/bortezomib/melphalan/

Table 1. Criteria for Diagnosis of Multiple Myeloma

CRAB Criteria

≥ 10% clonal cells in bone marrow or biopsy proven plasmacytoma PLUS one or more of the following creates a diagnosis of multiple myeloma

- Ca: 1 mg/dL over ULN or > 11 mg/dL
- Cr: > 2 mg/dL or CrCl < 40 mL/min
- Hgb: > 2 g/dL below LLN or < 10 g/dL
- Bone lesions (Y/N)

Or

Myeloma-Defining Events

Any one of the following creates a diagnosis of multiple myeloma

- BM biopsy > 60% (Y/N)
- Involved vs. uninvolved free light chain ratio ≥ 100:1 (Y/N)
- 1 focal lesion by MRI ≥ 5 mm (Y/N)

Note. Ca = calcium; ULN = upper limit of normal; Cr = creatinine; CrCl = creatinine clearance; Hgb = hemoglobin; LLN = lower limit of normal; BM = bone marrow. Information from Rajkumar et al. (2018).

prednisone is an option for transplant-ineligible patients and is being considered as an option in upfront therapy for transplant-eligible patients. “We’re seeing a good effect against the disease and good tolerability,” he noted.

The main issue in treating with daratumumab is its 50% rate of infusion reactions during the first two infusions. At least for the first two to four doses, infusions should be done at a center with experience in managing this side effect, he advised.

Autologous stem cell transplant, however, remains the goal for most patients whenever possible. “Currently, transplant has the best chance at suppressing the disease. It’s well tolerated and gives a good quality of life once patients move through the first post-transplant period. We tell most of our patients to plan on undergoing a transplant,” he said.

Dr. Libby noted that he now treats some patients up to around age 80. “Older patients can successfully get a stem cell transplant. Their risk of dying from a transplant is not dramatically higher,” he said. Renal dysfunction is also no longer a contraindication; 20% to 30% of his transplant patients have significant kidney damage from their disease but safely undergo transplant (as do some patients on dialysis), he said.

“So when considering stem cell transplant, know that it is still an option in the older patient and in the patient with renal dysfunction, but *not* in the patient who is fragile and frail, even if they are 55 years old,” he said. While stem cell transplant remains a “key” backbone therapy, he acknowledged “it’s no longer the only thing we have. Now it’s one of many very good treatments.”

MANAGING SIDE EFFECTS: FOCUS ON BONE

Side effects of multiple myeloma are most commonly related to bone disease, hypercalcemia, pain, anemia, coagulation/thrombosis, and infection (Table 2). Addressing issues of bone disease is especially important, as the risk of pathologic fractures is a concern. For patients receiving bisphosphonate therapy like zoledronic acid, monitoring for osteonecrosis of the jaw should be performed. Consultations with the dental team have made clear that cleanings, root canals, and crowns do not put patients at risk, but extractions (which engage the jaw bone) do, Mr. Epworth said.

Table 2. Managing Side Effects in Multiple Myeloma

Bone disease
<ul style="list-style-type: none"> • Strengthening <ul style="list-style-type: none"> » Zoledronic acid » Pamidronate » Denosumab • Assessments <ul style="list-style-type: none"> » Dental exam (monitor for ONJ) • Orthopedic consult <ul style="list-style-type: none"> » Impending or actual bone fractures » Spinal cord compression » Vertebral column instability
Hypercalcemia
<ul style="list-style-type: none"> • Hydration • Bisphosphonates
Pain
<ul style="list-style-type: none"> • Short/long-acting opioids • Radiation
Anemia
<ul style="list-style-type: none"> • Transfusions • Erythropoietin
Coagulation/thrombosis
<ul style="list-style-type: none"> • ASA (81-325 mg) • DOAC
Peripheral neuropathy
<ul style="list-style-type: none"> • Monitor, dose change
Infection
<ul style="list-style-type: none"> • Monitoring of CBC with neutrophils • Review infection risk reduction • Test for hepatitis B prior to start of daratumumab • Herpes zoster prophylaxis with use of proteasome inhibitor or daratumumab/elotuzumab • Re-vaccinate ASCT 6-12 months post-transplant
<i>Note.</i> ONJ = osteonecrosis of the jaw; ASA = acetylsalicylic acid; DOAC = direct oral anticoagulant; CBC = complete blood count; ASCT = autologous stem cell transplant.

Mr. Epworth added that collaboration with orthopedic surgeons (who can insert rods to support bones, when necessary) and radiation therapists (who can reduce tumor burden and treat painful lesions) can be helpful.

MEASURING SUCCESSFUL TREATMENT

Determining the response to disease is initially done with blood tests alone and can include M-spike (SPEP) and/or SFLC. Additional tests like bone marrow biopsies and imaging can give a more in-depth assessment of response to treatment.

A partial response to treatment is defined as $\geq 50\%$ reduction of serum M-protein plus reduction in 24-hour urinary M-protein by $\geq 90\%$ or < 200 mg/24 hours; if the disease is marked by free

light chains, only a $\geq 50\%$ decrease in the difference between involved and uninvolved free light chains is required. “I would like to see this after two to three cycles of chemotherapy, to know the patient is responding well to treatment and we can continue it. If you only see a 10% to 20% fall, you need to think about changing the treatment,” he said. “But a 50% reduction is not the goal. We want a deeper remission.”

A very good partial response (VGPR) is $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg/24 hours. “When we see this, we start to feel pretty confident the drugs are working well and the patient is on the right track,” he said. “The markers reflect what’s going on in the bone marrow. If they are coming down, almost certainly the cells in the bone marrow are dying and there are fewer cancerous cells producing abnormal proteins.”

A complete response is indicated by complete disappearance of M-protein spike or free light chains (or plasmacytoma) and $< 5\%$ plasma cells in bone marrow, he continued, noting that patients can have both M-protein spike and free light chains, but providers should pick one to monitor. The deeper the response, the longer the remission. While complete response used to be the goal, a stringent complete response is a step beyond: not only has all evidence of disease been eradicated from the blood and urine, but the bone marrow shows no abnormal plasma cells by flow cytometry. “This is my goal for my patients,” Dr. Libby said.

Minimal Residual Disease Negativity

However, an even deeper level of response is now recognized: minimal residual disease (MRD) negativity. Flow cytometry can now detect abnormal cells at a sensitivity of 10^{-5} to 10^{-6} and next-generation sequencing can detect one in 1,000,000. Studies have consistently shown that patients who achieve MRD negativity can have better outcomes.

“Depth of response matters,” Dr. Libby emphasized. “MRD negativity has become a new target in multiple myeloma...It’s probably going to be our new goal when we’re treating multiple myeloma: not just to get a complete remission, but to get a patient to be MRD-negative, which means the patient may have a fairly long remis-

sion. Perhaps we can even start to achieve cures in some of these people.” MRD is a useful measure in clinical trials, and while it can be ordered in clinical practice, it is not yet clear how it should be applied, he added.

TREATMENT IN THE FORESEEABLE FUTURE

Three new agents in development are generating much excitement. Belantamab mafodotin contains a monoclonal antibody targeting B-cell maturation antigen (BCMA), which most myeloma cells express. Belantamab has generated response rates of 60% in heavily pretreated relapsed/refractory disease and 30% in penta-refractory patients (including daratumumab). Main adverse events with belantamab are thrombocytopenia and keratitis.

“This is very, very exciting. It’s the kind of data that were presented for daratumumab to become approved,” he noted. Patients in the daratumumab trials had also failed all effective treatments, yet daratumumab worked in 30% of them. Belantamab could be approved within months.

Bispecific T-cell engagers, i.e., BiTE antibodies, are early in development for myeloma, but one, blinatumomab, is already approved for acute lymphoblastic leukemia. BiTEs are composed of two single-chain antibodies with different targets, which attach to the myeloma cell (the target) and pull T cells into the area to engage and kill the myeloma cell. “This is a very exciting form of therapy,” he said. “We are hopeful it will be brought to reality in multiple myeloma.”

Finally, CAR T-cell therapy is in development for myeloma by many different companies, with at least one product expected to become approved in 2020. “While the process of treating with CAR T-cell therapy is cumbersome, once you infuse the genetically modified cells back into the patient, the response rates in myeloma are jaw dropping. The patient may be dying from the large burden of disease, but 1 week later you cannot find a single cell,” Dr. Libby said. “The biggest issue has been that CAR T cells don’t last, and remissions have been limited to about 1 year, but it’s still early in the game. We will figure this out.”

In a small but pivotal study of 33 very heavily pretreated patients, the response rate was 85%, with 45% being complete responses (Raje et al.,

2019). Median progression-free survival was 11.8 months. Cytokine release syndrome occurred in 75%, but all but 6% were grades 1 and 2. Neurologic toxicity occurred but was mainly low grade, although one patient had a reversible grade 4 neurologic event.

Next-generation immunomodulatory drugs include iberdomide, a cereblon E3 ligase modulator. In a phase 1b/2a study, approximately 30% of patients responded after becoming refractory to daratumumab and pomalidomide (Lonial et al., 2019). ●

Disclosure

Dr. Libby and Mr. Epworth have no conflicts of interest to disclose.

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