Recent therapeutic advancements in early relapsed/refractory (R/R) multiple myeloma (MM) have led to several clinical trials and U.S. Food & Drug Administration (FDA) approvals. Although patient outcomes have improved due to the adoption of immunomodulatory drugs, proteasome inhibitors, and novel agents, the natural history of the disease predicts relapses will occur, necessitating subsequent lines of therapy. With the increasing use of frontline agents, such as lenalidomide (Revlimid) and bortezomib (Velcade), there is an emerging need for novel drug combinations with different mechanisms of action for relapsed/refractory disease where three-drug regimens are preferable.

Relapse is defined as progression off therapy, whereas refractory disease refers to progression on treatment in patients who have achieved at least a minor response or progression within 60 days of their last line of treatment. The latter population defines a higher-risk patient population with unmet needs. The advanced practitioner (AP) should be cognizant of emerging and complex treatment modalities to improve patient education, adverse event (AE) management, and patient outcomes.

**POMALIDOMIDE**

Several promising agents have shown meaningful activity in clinical trials for R/R MM patients. The OPTIMISM trial showed the addition of pomalidomide (Pomalyst) to bortezomib and dexamethasone improved progression-free survival (PFS) in a population that included lenalidomide-refractory patients (Richardson et al., 2019). Overall response rates (ORR) were 82% when pomalidomide was added to bortezomib + dexamethasone vs. 50% with bortezomib + dexamethasone in a patient population having received at least three prior regimens. Very good partial responses (VGPR) were 37% vs. 14% for the pomalidomide-containing arm. As with all bortezomib-containing regimens, the AP should educate and monitor patients for peripheral neuropathy, gastrointestinal effects, and administer prophylactic treatment against varicella zoster viral reactivation.

**ISATUXIMAB**

Another promising agent in the R/R MM population is isatuximab (Sarclisa). This anti-CD38 monoclonal antibody showed a significant PFS benefit when combined with pomalidomide and dexamethasone in patients having received at
least two prior lines of therapy, including patients refractory to lenalidomide and a proteasome inhibitor (Attal et al., 2019). Adverse events included infusion-related reactions (38%), upper respiratory infections (43%), and diarrhea (26%).

**Key Points**
- Advanced practitioners should stay current on emerging treatment modalities in relapsed/refractory multiple myeloma.
- They are in a pivotal position to manage toxicities from these drug combinations.
- Advanced practitioners should be aware of exacerbating underlying conditions in elderly patients.

**BELANTAMAB**
The antibody-drug conjugate belantamab (Blenrep) targets B-cell maturation antigen on malignant plasma cells. When combined with bortezomib and dexamethasone, it produced an ORR of 78%, with a VGPR of 50% (Nooka et al., 2020). Reported AEs included infusion-related reactions and corneal events of keratopathy, blurred vision, and dry eye. Keratopathy may be managed with dose modifications. The FDA has required a Risk Evaluation and Mitigation Strategy program due to ocular toxicity, with ophthalmic exams at baseline prior to each dose and promptly with worsening of symptoms.

**VENETOCLAX**
Venetoclax (Venclexta), a BCL2 inhibitor that induces apoptosis in MM cells, has demonstrated efficacy in combination with bortezomib and dexamethasone (Kumar et al., 2020). The greatest PFS benefit was seen in MM patients harboring t(11;14), which expresses high levels of BCL2. These data demonstrate that a more individualized approach may be pursued based on cytogenetics.

Venetoclax is generally well tolerated, with the most common AEs being mild gastrointestinal symptoms of nausea (37%) and diarrhea (15%), and grade 3 to 4 neutropenia (21%), thrombocytopenia (15%), and anemia (16%). Although the addition of venetoclax significantly improved PFS, there was an increased mortality as compared with the placebo arm, which is under further analysis.

**The Advanced Practitioner Perspective**
Earlier use of novel agents portends that R/R disease is becoming more prevalent and challenging. Therapy for R/R disease is becoming more complex as three-drug combinations are preferable. As APs, we are in a pivotal position to educate patients on their disease in addition to monitoring and managing toxicities from complex treatment algorithms. Increasing AEs may occur due to the multitude of on- and off-target effects of different signaling pathways targeted by such novel agents. In the case of R/R disease, therapy is indefinite, thus increasing exposure time to AEs and financial toxicities. Advanced practitioners must also be cognizant of potentially exacerbating underlying comorbid conditions in our elderly and often frail patient population that may be intolerant to drug combinations.

**Disclosure**
Dr. Nodzon has consulted for AbbVie, AstraZeneca, and Genentech.

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