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Immunomodulatory Agents and Proteasome Inhibitors in the Treatment of Multiple Myeloma

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Objective: *To review the current evidence on the use of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) in the treatment of multiple myeloma (MM).*

Data Sources: *Journal articles, research reports, state of the science papers, and clinical guidelines.*

Conclusion: *There has been a tremendous increase of new agents to treat multiple myeloma in the last 15 years. The IMiDs and PIs remain essential components of many anti-myeloma regimens.*

Implications for Nursing Practice: *With these advances in the therapeutic landscape, knowledge of these drugs, side effects and nursing implications are essential to improve outcomes. Patient education is also of vital importance in achieving optimal responses to treatment.*

Key Words: *multiple myeloma, immunomodulatory drugs, proteasome inhibitors, treatment, side effects.*

Although multiple myeloma (MM) is an incurable disease, significant treatment advances have changed the landscape of the disease. Since the approval of immunomodulatory agents (IMiDs) and proteasome inhibitors (PI), survival has significantly improved. The history of MM began in the 1850s when MM was first diagnosed and named, but it was not until the 1960s that melphalan and prednisone were used with limited success in controlling the disease.[1,2] Autologous stem cell transplant offered another avenue of treatment in the 1990s with an improvement in overall survival (3–5 years) compared to those who received standard therapy.[3]

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TABLE 1.
Immunomodulatory agents and proteasome inhibitors

Immunomodulatory agents	Proteasome inhibitors
Thalidomide (PO)	Bortezomib (IV/SC)
Lenalidomide (PO)	Carfilzomib (IV)
Pomalidomide (PO)	Ixazomib (PO)

Abbreviations: PO, oral; IV, intravenous; SC, subcutaneous.

In 1999, thalidomide became the first novel therapy to be approved by the US Food and Drug Administration (FDA) for MM.[4] Bortezomib (Velcade, Millenium Pharmaceuticals, Cambridge, MA) was FDA-approved in 2003 and provided tremendous hope and an additional therapeutic option for patients with MM.[5] In 2005 lenalidomide (Revlimid, Celegene Corporation, Summit, NJ) was approved for the second-line treatment of MM patients and from this emerged a sea of possibilities for the MM patient in regards to treatment.[6] Carfilzomib (Kyprolis, Amgen Pharmaceuticals, Thousand Oaks, CA), a second-generation PI, was FDA-approved in July 2012 and pomalidomide (Pomalyst, Celegene Corporation, Summit, NJ), a third-generation IMiD, was approved in February 2013.[7] In December 2015, an oral PI, ixazomib (Ninlaro, Millenium Pharmaceuticals, Cambridge, MA), was approved.[8]

The 5-year overall survival from 1998–2002 was 38.2% and after FDA approval of thalidomide, bortezomib, and lenalidomide, it rose to 40.3%.[9,10] While treatment options for MM are rapidly changing, the management objectives are threefold: rapid disease control to reverse complications, extending disease control and survival, and maintaining quality of life.[9] Improved treatments have provided a number of options, as well as the opportunity to individualize treatment strategies. There are numerous possibilities for patients with MM to reach a clinically meaningful response, improved survival, and enhanced quality of life. The aim of this article is to present information about IMiD and PI mechanisms of action, clinical trial data, side effects, and management strategies to control the side effects of PI and IMiDs (Table 1).

Immunomodulatory Drugs

MM is a malignancy involving plasma cells and is characterized by a clonal proliferation in the bone marrow, lytic bone lesions, renal insufficiency, immunodeficiencies, and monoclonal proteins detected in the blood and/or urine.[11] IMiDs target plasma cells in the bone marrow microenvironment by inhibiting tumor necrosis factor-alpha (TNF-α) and angiogenesis.[12]

The interaction of MM and IMiDs is complicated but well documented.[12,13] It is thought that IMiDs inhibit the interaction of MM cellular growth. Cellular growth is enhanced when MM cells are in contact with the bone marrow microenvironment and this environment creates a comfortable setting for MM cells to prosper further by generating cellular survival, migration, and drug resistance. This situation sets off a cascade of activation such as nuclear factor-κB (NF-κB) in both the myeloma cells and bone marrow stromal cells (BMSCs) and results in the production of several myeloma growth factors, which ultimately leads to disease progression. These growth factors include interleukin-6 (IL-6), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF).[12,14]

The IMiDs both directly and indirectly lead to myeloma cell death.[12,13,15,16] They indirectly effect myeloma cells through modifications within the bone marrow microenvironment. The IMiDs interfere with the expression of adhesion molecules, osteoclasts, angiogenesis, downregulation of transcription factor PU.1, and T-regulatory cells. Furthermore, they inhibit the production of TNF-α, IL-1, IL-6, and IL-12 from peripheral blood mononuclear cells. Both IL-6 and TNF-α stimulate myeloma cell growth, so inhibition of these cytokines decreases myeloma cell growth and survival. Additionally, all of the IMiDs are considered to have anti-angiogenic properties through their inhibition of VEGF. The IMiDs also have an effect on the immune system by stimulating production of CD4 and CD8 T cells, as well as IL-2 and interferon-gamma. The increased production of IL-2 and interferon-gamma enhances antibody-dependent cellular cytotoxicity (ADCC) and stimulates natural killer (NK) cell proliferation, as well as NK cell cytotoxicity.[12,13,15,16] Lenalidomide and pomalidomide both have direct apoptotic effects through the activation Caspase 8 leading to G0/G1 cell cycle arrest.[16]

Thalidomide

Thalidomide was FDA-approved in the 1950s by a German pharmaceutical company as a non-addictive, non-barbiturate sedative. As the drug was used, it became associated with its anti-emetic capabilities and was used in 46 countries for pregnancy induced nausea and vomiting. The drug was marketed extensively until 1961 when it was pulled from