Letter to the Editor

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Elrexfio™ (elranatamab-bcmm): The game-changer in treatment of multiple myeloma

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Abstract

Multiple myeloma is the second most common plasma cell malignancy, characterized by uncontrolled proliferation of plasma cells within the bone marrow. ELREXFIO™ (elranatamab-bcmm) is a recently FDA-approved drug for relapsed and refractory multiple myeloma. The progression of multiple myeloma involves interactions with various bone marrow cell types, and targeting this microenvironment has shown promising results in inhibiting its growth and osteolysis. ELREXFIO, a bispecific antibody targeting CD3 and BCMA, activates cytotoxic T-lymphocyte responses against BCMA-expressing myeloma cells. Clinical trials, such as MagnetisMM-3, demonstrated significant response rates and long-term tolerability. Its approval offers hope to multiple myeloma patients, especially those with relapsed or refractory cases, as innovative therapies like ELREXFIO continue to improve outcomes in this challenging malignancy.

Keywords

Multiple myeloma, elranatamab-bcmm, bispecific antibody, myeloma progression, immunotherapy

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Dear editor,

Multiple myeloma is the second most common plasma cell malignancy, marked by uncontrolled proliferation of clonal plasma cells within the bone marrow, and accounts for approximately 1% of all cancer cases and 10% of blood and bone marrow cancer.[1,2] Proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAb) are commonly used for the treatment of multiple myeloma but despite the approval of numerous therapeutic approaches for myeloma, it remains an incurable malignancy, affecting approximately 12,410 patients in the USA.[3] The Food and Drug Administration (FDA) has accelerated approved ELREXFIO™ (elranatamab-bcmm) for the treatment of relapsed and refractory multiple myeloma.[4]

Multiple myeloma is characterized by the dissemination of multiple tumor cells throughout the bone marrow. The pathogenesis of multiple myeloma (MM) involves a progressive transformation from monoclonal gammopathy of undetermined significance (MGUS) to smoldering myeloma and eventually to symptomatic myeloma, marked by bone marrow infiltration and osteolytic lesions. This process disrupts the delicate balance between bone-building osteoblastic and bone-resorbing osteoclastic activities, leading to net bone loss. MM-induced bone breakdown releases growth factors from the bone matrix, fueling tumor growth and further stimulating osteoclast activity in a self-reinforcing cycle. Multiple myeloma progression is influenced by mutational diversity, clonality, and local bone marrow changes including interactions with various cell types, such as osteoblasts, osteoclasts, mesenchymal stem

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cells, immune cells, and osteocytes, which play pivotal roles in Multiple myeloma progression. Targeting this microenvironment, rather than just the tumor cells, has proven effective in inhibiting Multiple Myeloma growth and osteolysis.[5]

Elrexfio (Elranatamab) is a promising therapeutic antibody designed to target multiple myeloma cells. It functions as a bispecific antibody, binding both to CD3 on T-cells and to B-cell maturation antigen (BCMA) on the surface of myeloma cells. By doing so, it initiates a process where T-cells are cross-linked with myeloma cells, leading to the activation of potent cytotoxic T-lymphocyte responses against BCMA-expressing myeloma cells. BCMA is known to activate various survival signaling pathways in malignant plasma B cells, including those involving NF-kappa B, STAT3, ERK1/2, and AKT/PI3K pathway. Since BCMA is often overexpressed in multiple myeloma cells, Elrexfio's mechanism of action exploits this by binding BCMA on plasma cells, plasmablasts, and multiple myeloma cells and CD3 on T-cells leading to cytolysis of the BCMA-expressing cells. Elrexfio activated T-cells, and caused pro-inflammatory cytokine release, ultimately contributing to the potential treatment of multiple myeloma.[6]

ELREXFIO's effectiveness as a sole treatment was examined in individuals with relapsed or refractory multiple myeloma through a clinical trial called MagnetisMM-3 (NCT04649359). The approval of ELREXFIO is grounded in data about response rates and the duration of these responses. In the Phase 2 MagnetisMM-3 study's cohort A, patients heavily treated for relapsed and refractory multiple myeloma (RRMM) received ELREXFIO as their initial BCMA-directed therapy, resulting in significant and meaningful responses. Among this subset, those who had undergone four or more previous treatments demonstrated a 58% response rate, with around 82% maintaining their response for at least 9 months. The median time to achieve the initial response was 1.2 months. ELREXFIO was introduced as the first BCMA-directed therapy in the US with a less frequent dosing regimen after 24 weeks of weekly treatment, potentially improving its long-term tolerability. Additionally, data from MagnetisMM-3 cohort B revealed a 33% response rate and an estimated 84% response continuation among patients who had undergone at least four prior treatment regimens.[4]

Elrexfio, while showing promising therapeutic applications, is associated with several notable adverse effects. The most frequently reported adverse reactions observed in patients undergoing treatment with Elrexfio include cytokine release syndrome (CRS), as well as fatigue, injection site reactions, diarrhea, upper respiratory tract infections, musculoskeletal pain, pneumonia, decreased appetite, rash, cough, nausea, and pyrexia (fever). Additionally, the drug may lead to Grade 3 to 4 laboratory abnormalities, characterized by decreased lymphocyte counts, decreased neutrophils, decreased hemoglobin levels, decreased white blood cell counts, and decreased platelet counts. Healthcare providers and patients must be aware of these potential adverse effects when considering the use of Elrexfio as part of their treatment regimen, and close monitoring is often necessary to manage these side effects effectively.[4]

This new FDA-approved drug brings hope to patients with multiple myeloma by offering a more effective and well-tolerated treatment option. Clinical trials have demonstrated impressive response rates and prolonged progression-free survival in patients treated with Elrexfio, particularly those who have previously experienced relapses or are resistant to existing therapies. The introduction of innovative therapies like Elrexfio represents a significant step forward in addressing this complex cancer. As research and development efforts continue, there is a growing potential to further enhance patient outcomes and improve the quality of life for those affected by multiple myeloma.

Author Contributions

Taruba Rais researched the literature. Taruba Rais and Afsheen Khan drafted the manuscript. Rumaisa Riaz revised it critically for important intellectual content. All authors approved final version of article to be published

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