Revolutionary Immunotherapy for Merkel Cell Carcinoma: Retifanlimab-Dlwr (Zynyz) Receives FDA Approval

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Abstract

Approval of Retifanlimab-dlwr (brand name Zynyz) represents a significant breakthrough in the field of dermatology, providing a promising treatment option for patients diagnosed with this highly aggressive and rare form of Merkel Cell Carcinoma (MCC). Traditionally, treatment options for MCC have been limited, with surgery, radiation, and chemotherapy are the mainstays.

Retifanlimab-dlwr debut will mark a milestone in the treatment of MCC. Clinical trials have shown impressive results, with a significant number of patients experiencing durable responses to the therapy. Retifanlimab-dlwr is a monoclonal antibody that targets the programmed cell death protein 1 (PD-1), which is expressed on immune cells and helps to reactivate the body's immune response against cancer cells.

The impending use of Retifanlimab-dlwr not only provides a groundbreaking treatment option for MCC but also paves the way for further advancements in immunotherapy and personalized medicine.

Keywords: *Immunotherapy, merkel cell carcinoma, retifanlimab-dlwr, skin cancer.*

INTRODUCTION

Intravenous Retifanlimab-dlwr (Zynyz) treatment for adult patients with metastatic or recurrent locally advanced Merkel cell cancer (MCC) was approved by the US Food and Drug Administration (FDA) on March 22, 2023, based on clinical trials [1].

Merkel cell cancer (MCC) is a rare neuroendocrine skin malignancy with trabecular growth. Merkel cell cancer (MCC) has a significant possibility of lymphatic metastasis and is typically observed in elderly white people with only sporadic cases reported before the age of 50 [2]. MCC often develops as a single, quickly expanding, irregular, red cutaneous or subcutaneous tumour on the head, neck, and, less frequently, the limbs and buttocks. Population groups at risk are elderly, previous history of cutaneous and haematological malignancies and those with impaired immune systems [3].

Merkel cell cancer MCC can begin as a result of DNA damage caused by UV brought on repeated sunlight exposure or the genome of the Merkel cell polyomavirus (MCPyV). UV exposure may contribute to viral carcinogenesis by impairing local immunity. Antigen-presenting dendritic cells undergo functional changes and the expression of inflammatory mediators as a result of UV radiation, which sets off a series of events that affect immunological sensitivity. Merkel cell precursors, pre-B cells, pro-B cells, dermal fibroblasts, epidermal stem cells, or hair follicle stem cells in Merkel cell cancer MCC. Normal Merkel cells are not the source of MCC because they are terminally differentiated and do not undergo cell division [4].

Damaged Merkel cells originate from early B-cells (lymphocytes), as evidenced by their cellular structure, a clonal immunoglobulin chain rearrangement and the expression of early B-cell markers and biopsy of the tumor serves as the primary tests. This exhibits pathophysiology that is typical with Merkel cell carcinoma. Thyroid transcription factor (TTF1), which is frequently negative, and cytokeratin-20 (CK20), which is positive in up to 95% of tumors, make immunohistochemistry effective. Merkel cell polyomavirus (MCPyV) is found in 80% of the Merkel cell carcinomas [5]. Retifanlimab provides opportunity to healthcare professionals for first-line therapy of Merkel cell carcinoma. This drug can produce a positive response in patients with the localized and metastatic disease, which has significant mortality rates.

EXISTING TREATMENTS

Treating MCC is the most difficult of all the dermatological malignancies. Combining surgical excision, chemotherapy, radiotherapy, immunotherapy and immune checkpoint inhibitors may aid to some degree to regress the size of the tumor and delay the course of the illness. Primary Merkel cell cancer is mostly treated surgically. In particular case for the larger lesions (> 2 cm), the primary location may be treated with radiation onwards. Disease is better controlled locally and regionally with radiation therapy and has high long-term survival rate. Surgical removal of the pertinent lymph node is another option or radioactively treated as a preventative precaution. Systemic chemotherapy may also be used in some circumstances. Merkel cell cancer is exceedingly hazardous and has a very poor prognosis when it has spread to a distant place. The goal of

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treating any metastatic disease is to enhance quality of life. Radiation therapy and systemic chemotherapy may be used as a kind of treatment in specific circumstances.

The immune system uses checkpoint proteins to prevent itself from attacking normal cells which are called the immune checkpoint inhibitors. These are medications that either block PD-1 is a checkpoint protein found on T cells, which are immune cells andthe protein PD-L1 is also found on some cancerous and normal cells. They are able to halt this binding and strengthen the body's defences against cancerous cells. Checkpoint inhibitors like Avelumab (Bavencio), which targets PD-L1, can be used to treat MCC. Nivolumab (Opdivo), pembrolizumab (Keytruda), and retifanlimab (Zynyz), which block PD-1 [6].

RETIFANLIMAB

Retifanlimab is a monoclonal antibody that prevents the activity of programmed death receptor-1 (PD-1). A unique humanized monoclonal antibody potential immune checkpoint inhibitory and anti-cancer effects that is aimed targeting the human cell surface receptor PD-1 that regulates negative immunity. Retifanlimab-dlwr binds to PD-1 and its downstream signaling pathways after injection, inhibiting them. This may restore immunological function by triggering the immune system's cell-mediated defenses against the transmembrane immunoglobulin superfamily (IgSF) protein PD-1 operates as an immunological checkpoint that inhibits T-cell activation and effector function when activated by its ligands, programmed cell death ligand 1 (PD-L1) or 2 (PD-L2). This function is crucial for tumor immunity evasion [7].

The PODIUM-201 trial, which enrolled 65 patients with metastatic or recurrent locally advanced MCC who had not previously received comprehensive treatment for a severe illness, assessed for the safety and effectiveness of retifanlimab-dlwr. Retifanlimab-dlwr 500 mg were given intravenously over30 minutes every four weeks until the disease progressed, or up to 24 months [8]. The median response time for patients who received the drug ranged from 1.1 months to over 24.9 months. About 76 percent of the population remained responsive for at least six months, and 62 percent remained responsive for at least twelve months [9]. The most significant adverse events (AEs) were pneumonitis, arrhythmia, and tiredness, muscles and skeletal pain, pruritus, diarrhoea, rash, pyrexia, and nausea were noted [10].

CONCLUSION

On a final note, with the approval of, Retifanlimab-dlwr (Zynyz), now an alternative therapeutic option for the treatment of Merkel Cell Carcinoma. Clinically trials with Retifanlimab-dlwr have shown outstanding results in the treatment of patients with dose given of 00 mg administered intravenously over 30 minutes every 4 weeks. However, it is still a new drug and more research is required to examine the drug's effectiveness, safety as well as long term effects to acquire the best possible outcome for patients with merkel cell carcinoma (MCC).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nimra Ahmed Khan and Zaib Un Nisa Mughal. The conceptualization was done by Nimra Ahmed Khan and Ayesha Zahid Malik. The first draft of the manuscript was written by Nimra Ahmed Khan and Zaib Un Nisa Mughal and all authors commented on previous versions of the manuscript. The editing and revisions were performed by Ayesha Zahid Malik and the final draft was written by Nimra Ahmed Khan. All authors read and agreed to the final version of the manuscript.

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