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Targeted Therapy in Multiple Myeloma: Focus on BCL-2 and MCL-1 Inhibition

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Introduction

Multiple myeloma is a malignant hematological disorder characterized by the clonal proliferation of abnormal plasma cells within the bone marrow. Despite significant advancements in treatment, including the use of proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies, multiple myeloma remains largely incurable, with most patients eventually relapsing after initial response to therapy. The relapsing and remitting nature of the disease reflects its complex genetic and molecular landscape, as well as the emergence of resistant subclones over time. As the understanding of the molecular biology of multiple myeloma has deepened, novel therapeutic strategies have emerged that specifically target the survival pathways exploited by malignant plasma cells. Among these, the inhibition of pro-survival proteins such as B cell lymphoma 2 and myeloid cell leukemia sequence 1 has garnered significant attention as a promising approach to selectively induce apoptosis in myeloma cells and overcome drug resistance [1].

Description

B cell lymphoma 2 and myeloid cell leukemia sequence 1 are members of the B cell lymphoma 2 family of proteins, which regulate the intrinsic pathway of apoptosis. This family comprises both pro-apoptotic and anti-apoptotic members that interact with each other to determine a cell's fate. In normal physiology, a balance between these opposing forces ensures proper cell turnover and survival. However, in multiple myeloma, this balance is often disrupted in favor of anti-apoptotic signaling, allowing malignant cells to evade programmed cell death and persist despite therapeutic interventions. The overexpression of anti-apoptotic proteins such as B cell lymphoma 2 and myeloid cell leukemia sequence 1 contributes to the pathogenesis of the disease and correlates with poor prognosis and treatment resistance [2]. The rationale for targeting B cell lymphoma 2 in multiple myeloma is supported by preclinical studies demonstrating that a subset of myeloma cells, particularly those harboring specific genetic features such as translocations involving the cyclin D1 gene, are highly dependent on B cell lymphoma 2 for survival. This dependency creates a therapeutic vulnerability that can be exploited using selective inhibitors of B cell lymphoma 2 [3]. These agents mimic the activity of pro-apoptotic proteins, binding to the hydrophobic groove of B cell lymphoma 2 and displacing pro-apoptotic factors, thereby triggering the mitochondrial pathway of apoptosis. In clinical trials, selective inhibition of B cell lymphoma 2 has shown remarkable activity in patients with multiple myeloma, particularly those with the aforementioned genetic translocation. Deep and durable responses have been observed, including in patients with relapsed or refractory disease who have exhausted other treatment options [4].

However, the effectiveness of B cell lymphoma 2 inhibition appears to be limited to a specific subset of patients, underscoring the need for careful biomarker-driven patient selection. Gene expression profiling and functional assays that measure mitochondrial priming have been used to identify patients most likely to benefit from this approach. Moreover, the development of resistance to B cell lymphoma 2 inhibition, through upregulation of compensatory anti-apoptotic proteins such as myeloid cell leukemia sequence 1, presents a significant clinical challenge. This has led to the hypothesis that simultaneous targeting of multiple anti-apoptotic proteins may be necessary to achieve more comprehensive and durable responses [5].

Conclusion

In conclusion, the targeted inhibition of B cell lymphoma 2 and myeloid cell leukemia sequence 1 represents a significant advancement in the treatment of multiple myeloma, offering new hope for patients with relapsed or refractory disease and those who fail conventional therapies. These anti-apoptotic proteins play a critical role in myeloma cell survival and represent therapeutic vulnerabilities that can be exploited with selective inhibitors. While B cell lymphoma 2 inhibition has demonstrated compelling efficacy in genetically defined subgroups, myeloid cell leukemia sequence 1 inhibition has broader applicability across the disease spectrum. The future of this approach lies in the integration of biomarker-driven strategies, combination therapies, and continued efforts to overcome resistance. As clinical trials progress and real-world experience accumulates, the inhibition of B cell lymphoma 2 and myeloid cell leukemia sequence 1 is poised to become a key component of personalized therapy in multiple myeloma, contributing to improved survival and better quality of life for patients affected by this complex malignancy.

Acknowledgement

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Conflict of Interest

None.

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