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Efficacy of Mcl-1 inhibitors in multiple myeloma cells resistant to bortezomib

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Abstract

Multiple myeloma (MM) is a type of cancer that affects plasma B cells. Patients with MM often experience frequent relapses and can develop resistance to drugs. As a medical researcher, it is important to understand the role of Mcl-1 in preventing intrinsic apoptosis and drug resistance. Mcl-1 belongs to the anti-apoptotic subgroup of Bcl-2 family proteins and plays a crucial role in these processes. Mcl-1 has a short half-life due to degradation via ubiquitin-proteasome system. Extracellular signaling, such as IL-6, significantly increases Mcl-1 transcription (2.3).

Introduction

The American Cancer Society estimates in the year 2024 that 12,540 multiple myeloma patients will die and almost 36 thousand new cases will be diagnosed within the United States. MM disease progression and acquired resistance to therapeutic agents is related to Mcl-1 overexpression (1, 2, 4).

The Bcl-2 family subgroup of antiapoptotic proteins includes Mcl-1, Bcl-2, Bcl-xL, and Bcl-W. These proteins sequester Bak and Bax indirectly and inhibit BH-3 activators (Bcl-2 protein part of the proapoptotic subgroup). Pro-survival proteins therefore prevent mitochondrial pore formation which would result in cell death (3).

Results

Development of BTZ resistance MM cell lines.

Mcl-1 overexpressed in BTZ-R cells, despite treatment with inhibitors.

Conclusion and Future Directions

The BTZ-R MM cells exhibited a significant upregulation of Mcl-1. The Mcl-1 inhibitors S63845, AZ5991, and U661013 showed no effectiveness in BTZ-resistant MM cell lines.

Cells resistant to BTZ also showed the presence of Bcl-2. Furthermore, the administration of Mcl-1 inhibitors did not yield any impact on Bcl-2 expression. This implies that Bcl-2 does indeed contribute to resistance, alongside Mcl-1. Therefore, inhibiting Bcl-2 is necessary to prevent any potential resistance.

In BTZ-resistant cells, Mcl-1 inhibitors demonstrated a higher IC50 compared to sensitive cell lines.

Our next step is in vitro testing to determine the best inhibitor among the three. These inhibitors will also be tested in drug-resistant MM cells like Lenalidomide-R and Veneclaxic-R.

Further investigation is needed to understand how acquired BTZ resistance can bypass the actions of Mcl-1 inhibitors.

References


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