frontiers | Frontiers in Hematology

TYPE Editorial
PUBLISHED 24 January 2025
DOI 10.3389/frhem.2025.1548984

OPEN ACCESS

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RECEIVED 20 December 2024
ACCEPTED 02 January 2025
PUBLISHED 24 January 2025

CITATION
Cardoso BA and Neparidze N (2025) Editorial: Two decades of targeted therapies in hematology: new targets and novel combinations.
Front. Hematol. 4:1548984.
doi: 10.3389/frhem.2025.1548984

Editorial: Two decades of targeted therapies in hematology: new targets and novel combinations

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KEYWORDS

CCUS, bone marrow, hematological malignancies, Bcl-2 inhibition, CAR T-cell therapy, multiple myeloma

Editorial on the Research Topic
Two decades of targeted therapies in hematology: new targets and novel combinations

1 Introduction

The introduction of targeted therapies in the clinical practice of hematological malignancies, firstly in chronic myeloid leukemia (CML) with the paradigm of developing drugs based upon the molecular pathogenesis of the disease, is a groundbreaking development and marked a complete revolution in the medical community. Hematopoiesis is a complex homeostatic process that, when deregulated, can result in different pathologies. Extensive research over the years in understanding such processes has significantly impacted patient welfare. Nonetheless, several conditions still lack appropriate therapeutic options to improve patient prognosis. Etiopathogenesis for most hematological malignancies remains poorly understood, and preventive strategies are lacking for the precursor conditions, such as clonal cytopenia of undetermined significance (CCUS) and monoclonal gammopathies.

This Research Topic aimed to organize and discuss preclinical and clinical studies of novel therapeutic strategies and possible drug combinations for hematological malignancies. The contributing articles expanded this initial objective into other crucial areas covering disease biology and precursor conditions.

2 Clonal cytopenia of undetermined significance

Taborda et al. wrote a review manuscript describing the importance of discriminating CCUS as an independent hematological entity from clonal hematopoiesis of indetermined potential (CHIP) (1). As the authors discuss in the article, CHIP is defined as a condition characterized by the acquisition of somatic mutations commonly found in myeloid

malignancies with a variant allele fraction (VAF) of ≥2% in the absence of hematological malignancy or unexplained cytopenia, and when such cytopenia is persistent, it is classified as CCUS. The incidence of CCUS is approximately 30% in patients who do not meet the criteria for myelodysplastic syndromes (MDS) (2). The CCUS mutational landscape overlaps CHIP and MDS and includes genes commonly mutated in myeloid neoplasms (*TET2*, *DNMT3A*, *ASXL1*, and others). Increased understanding of clonality (through genome-wide association studies) led to the development of risk stratification tools to assess the likelihood of progression to myeloid neoplasms. Finally, the authors also discuss potential therapeutic targets that are currently being tested in the context of CCUS; these include epigenetic regulators (*TET2* and *IDH1/2*) and deregulated inflammation signaling.

3 Bone marrow microenvironment

Hematopoiesis is the complex process that gives rise to all the blood cellular lineage cells (3). This complex process occurs in a particular microenvironment, and when disrupted, allows for leukemic transformation and proliferation. The bone marrow comprises different cellular components that modulate and regulate hematopoiesis, and understanding these interactions is essential for developing effective therapies. In the review by Semedo et al., the authors suggest that successful treatment of leukemia may require strategies that simultaneously target leukemic cells and the supportive microenvironment—the dual targeting approach. This targeting approach could improve patient outcomes and reduce the likelihood of resistance to therapies. To illustrate their claims, the authors provide a comprehensive and detailed overview of all the clinical studies using therapeutic strategies targeting leukemic cells and the bone marrow microenvironment.

4 Targeting Bcl-2 in hematological malignancies

Wei and Konopleva provided a comprehensive overview of the role of Bcl-2 inhibitors in hematological malignancies, highlighting their potential, challenges, and the need for personalized treatment approaches in blood cancers. The Bcl-2 protein is a crucial regulator of apoptosis and is often upregulated in blood cancers, which makes them an attractive target in cancer research (4, 5). Venetoclax is the first FDA-approved Bcl-2 inhibitor to treat malignancies where this antiapoptotic protein is aberrantly overexpressed (6). The authors discuss the clinical applications of venetoclax in several conditions, particularly in chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML), and cast the outcomes of clinical trials that demonstrate their efficacy and safety profile. Furthermore, the article also discusses future directions in developing Bcl-2 inhibitors and combination therapies, resistance mechanisms, and the need for personalized treatment approaches.

5 CAR T-cell therapy in B-cell acute lymphoblastic leukemia

Phillips et al. conducted a retrospective review of 31 B-cell acute lymphoblastic leukemia (B-ALL) patients who received anti-CD19 CAR T-cell therapy (Tisagenlecleucel) (7, 8). The authors analyzed clinical data (response, survival rates, and remission duration) from relapsed or refractory B-ALL patients treated with anti-CD19 CAR T-cell therapy without prior hematopoietic stem cell transplantation (HSCT). Notably, the results suggest that in a significant proportion (12/31) of relapsed/refractory B-ALL patients, anti-CD19 CAR T-cell therapy is sufficient to induce long-term remissions without the need for further therapy and also delay the HSCT procedure in this difficult-to-treat group of patients. The authors discuss the importance of careful assessment and clinical judgment to determine the best clinical protocol for each patient since not all patients will benefit from a high-risk procedure such as HSCT.

6 Novel treatment combinations in refractory Multiple Myeloma

Abdallah et al. presented the results of the CheckMate 039 clinical trial. This is a multicentric (seven centers involved), randomized phase I/II clinical trial that tested the combination of nivolumab (checkpoint inhibitor) and daratumumab (anti-CD38) in patients with relapsed/refractory multiple myeloma (RRMM). The MM outcomes have improved over the years with the introduction of immunomodulatory agents, proteasome inhibitors (PIs), and monoclonal antibodies (mAbs) (9). This study evaluated the nivolumab–daratumumab combination in MM patients' safety, tolerability, and efficacy. Despite the small patient sample, this combination was safe and demonstrated encouraging efficacy signals, particularly in achieving high response rates. The findings are notable and challenge the hematology community to reexamine and reconsider the significance of a PD-1 checkpoint pathway in myeloma. These encouraging results suggest that combining immune checkpoint inhibitors with monoclonal antibodies may represent a promising strategy to improve outcomes for patients with RRMM, addressing a critical need in this patient population where a clinically unmet need remains.

7 Conclusions

In conclusion, even though the articles that compose this Research Topic extend beyond the intended original scope, they provide not only original data on therapeutic targeting of hematological malignancies but also essential reflections on the targets and strategies that the scientific research community should consider to develop effective therapies for such patients. Notably,

with the introduction of cutting-edge diagnostic tools such as next-generation sequencing and single-cell sequencing, a conscious effort should be put in place to provide personalized and effective treatment for patients with hematological malignancies.

Author contributions

BC: Supervision, Writing – original draft, Writing – review & editing, Conceptualization. NN: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Centro de Investigação Interdisciplinar em Saúde (CIIS) and Faculdade de Medicina da Universidade Católica Portuguesa (FM-UCP) internal funding, and Fundação para a Ciência e a Tecnologia (FCT) within the project UIDP/04279/2020.

Acknowledgments

We want to thank our funding agencies and the organizations that have provided financial support for this research.

Conflict of interest

NN has received research funding from GSK and Janssen.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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