Red cells or Red flags: Weighing the Risks of HIF Stabilizers in CKD and Hematologic Malignancies

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Introduction

Hypoxia-inducible factors (HIFs) play a central role in the cellular hypoxic response and regulation of erythropoiesis. HIF-prolyl hydroxylase inhibitors (HIF-PHIs), such as roxadustat and daprodustat, have emerged as useful oral therapies for anemia of chronic kidney disease (CKD) through the stabilization of HIF and activation of endogenous erythropoietin (EPO) production [1][2]. These medications represent a major advance in the treatment of renal anemia, particularly in dialysis-dependent or refractory patients to standard erythropoiesis-stimulating agents. However, the broader biological functions of the HIFs are a concern for their potential oncogenic activity, especially in hematologic malignancies.

Objectives

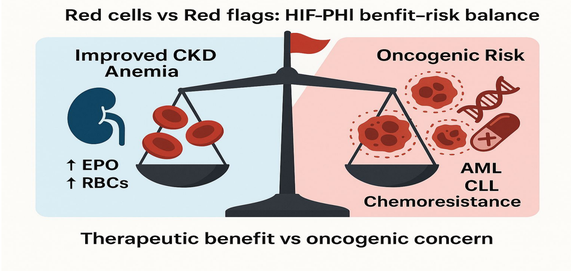
To explore the potential oncological risks associated with HIF-PHIs, particularly for hematologic malignancies.

Methods

A focused literature review (PubMed/Embase, 2010–2024) was performed using terms related to HIF, HIF-PHIs, CKD anemia, and hematologic malignancies. Key clinical trials, translational studies, and preclinical reports were reviewed for therapeutic efficacy and oncogenic risk.

Results

HIF-PHIs (roxadustat, daprodustat) improve anemia in CKD by stabilizing HIF and enhancing endogenous EPO. However, HIF-1a/2a overexpression in AML, CLL, and myeloma promotes proliferation, tumor–microenvironment interactions, and chemoresistance. Phase 3 trials reported efficacy in CKD but excluded cancer patients; long-term malignancy risk remains undefined.



Discussion

HIF-2a and HIF-1a are overexpressed in various hematologic malignancies including acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma. Their stabilization leads to metabolic reprogramming and proliferation under hypoxic bone marrow conditions. It has also shown to play a role in resistance to chemotherapy[3]. In CLL, HIF-1a promotes tumor cell interaction with the microenvironment, increasing survival signals[3]. Furthermore, preclinical studies have demonstrated that enforced HIF-1a expression in hematopoietic stem and progenitor cells can facilitate leukemogenesis and cause chemoresistance[4].Although phase 3 trials of large size involving HIF-PHIs have not indicated increased malignancy risk, these trials excluded patients with active or past cancers, so safety data are less broadly applicable[1]. Also, long-term monitoring data regarding cancer incidence in patients who received HIF-PHIs are scarce, and post-marketing surveillance is limited.

Conclusion

HIF-PHIs offer significant therapeutic benefit in CKD-associated anemia but are theoretically unsafe in the context of latent or active hematologic malignancy due to the oncogenic risk of chronic HIF activation. Careful patient selection, prolonged pharmacovigilance, and mechanistic research are required to minimize risks. Since the data and research in this context is limited, clinicians should be cautious in the use of HIF-PHIs in patients with active or history of hematologic cancer. Given the role of HIFs in tumor biology further research and surveillance in warranted in this direction.

References

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