Investigating Glycosylation Inhibition in Chronic Myeloid Leukemia: A Literature Review

Massachusetts College of Pharmacy and Health Sciences

Norymar Ayala, Zein Dib, Najlaa Alsini, Binyaz Ilavia and Robert Campbell, PhD

Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, Worcester, MA

INTRODUCTION

- Background: Chronic Myeloid Leukemia (CML) is a hematopoietic stem cell disorder caused by a chromosomal translocation that produces the Bcr-Abl fusion protein (Philadelphia chromosome). This fusion protein stimulates the excessive growth of granulocytic lineage cells, resulting in the chronic phase of CML, which eventually advances to the more severe blast crisis[1]. Glycosylation is the process of attaching sugar molecules to proteins and lipids on the cell membrane, forming a protective glycocalyx. This thick and complex covering blocks medication penetration, decreasing the efficiency of cancer-targeting treatment medicines[2]. Furthermore, the variety of glycosylation patterns among CML can be a barrier to medication delivery techniques, necessitating novel ways to overcome this barrier.
- Hypothesis: MUC1 presents a barrier to the efficacy of drug delivery in CML. Inhibiting O-glycosylation in CML cells will enhance drug uptake and improve therapeutic outcomes.

OBJECTIVE

- This study aims to identify clinical databases that can be utilized to:
  1) Understand the role of glycosylation as a potential barrier to drug delivery.
  2) Explore the use of glycosylation inhibitors in the treatment of CML.
  3) Identify strategies to overcome the barrier of glycosylation in drug delivery for CML.

METHODS

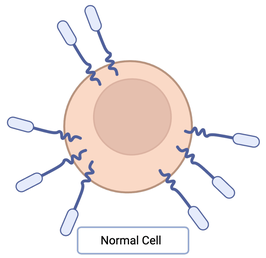
- A comprehensive exploration of the literature was conducted to assess the impact of various glycosylation inhibitors. The search encompassed clinically relevant articles from PubMed database. Specifically, articles focusing on glycosylation inhibitor drugs applied to CML were assessed and screened for exclusion and inclusion in the review.

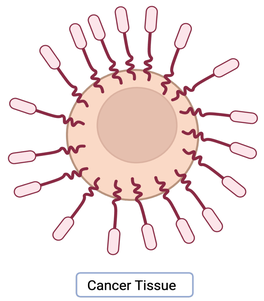
PubMed database (1946-February 29, 2024) was searched using the keywords "CML" "Glycosylation" and "Inhibitors" using the Boolean operator "AND" resulting in 21 articles

Articles that reported on, O-glycosylation as a barrier for drug delivery and inhibited its expression were of the greatest interest.

Articles that included results regarding the K562 (CML) cell line were evaluated and considered for further review.

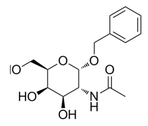
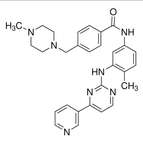
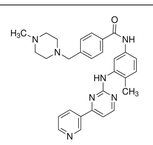
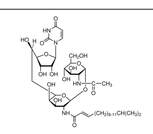
FIGURES



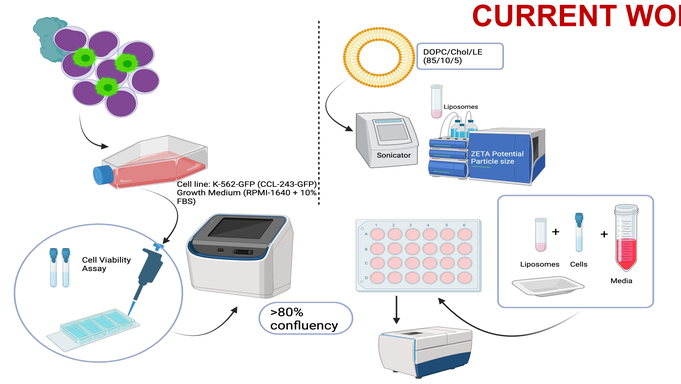


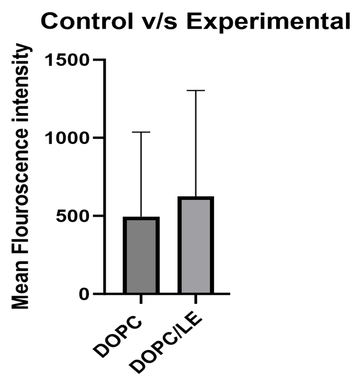
- In normal cells, glycosylation is tightly regulated and ensures proper protein folding, stability, and cell signaling. However, in CML cells, aberrant glycosylation patterns are often observed, which can affect cell adhesion, migration, and immune recognition. These abnormal glycosylation patterns in CML cells contribute to the cancer's progression and resistance to therapy[2]. Consequently, targeting glycosylation pathways is being explored as a potential therapeutic approach for CML.

FINDING

Structure	Agent	MOA	Type/Cell Line	Availability	Refs.
	Benzyl 2-acetamido-2-deoxy-α-D-galactopyranoside (Benzyl-α-GalNAc)	A competitive inhibitor of Galβ1-3GalNAc α2,3-sialyltransferase, which is responsible for transferring sialic acid residues to oligosaccharide chains on glycoproteins.	Caco-2	$160 per 25 mg (Sigma Aldrich)	[3,4]
	GO-201, GO-203 (Cell-Penetrating Peptide)	Inhibits MUC1-C oligomerization, Downregulate BCR-ABL expression and inhibits cell growth	KU812, K562	GO-201: $200.50 per 1 mg. GO-203: $178.16 per 2 mg (Sigma Aldrich)	[6,7,8]
	Imatinib (tyrosine-Kinase) inhibitor	Targets and inhibits the activity of BCR-ABL tyrosine kinase which is responsible for the uncontrolled growth of CML cells.	K562	$84.90 per 25 mg (Sigma Aldrich)	[9,10]
	Tunicamycin (N-glycosylation inhibitor)	Inhibits the first step of glycosylation by blocking the transfer of Di and Tri saccharides to N-Linked Glycoprotein	K562, KCL-22, LAMA-84	$290 per 10 mg (Sigma Aldrich)	[11,12]

CURRENT WORK





DISCUSSION

- Our review of glycosylation in chronic myeloid leukemia (CML) highlights the critical role of this process in influencing drug therapies. Specifically, the presence of O-glycans on the cell surface can hinder drug penetration. Targeting glycosylation pathways, such as inhibiting specific enzymes, could disrupt this protective effect and enhance drug penetration. Notable inhibitors examined in this study include benzyl-α-GalNAc, GO-201, GO-203, imatinib, and tunicamycin. Integrating glycosylation inhibitors with existing therapies like imatinib could enhance drug efficacy and overcome resistance mechanisms. These inhibitors show promise in preclinical and clinical settings, and their exploration in clinical trials could have significant clinical relevance for CML patients.

CLINICAL RELEVANCE

- CML is a hematological malignancy that originates in the blood-forming cells of the bone marrow and spreads to the blood. CML constitutes approximately 20% of leukemia found in adults. Investigating the functional significance of glycoproteins in drug therapy, particularly the extracellular-bound MUC-1 of CML cells, could give rise to the development of novel therapeutic approaches for the treatment of CML.

REFERENCES

1. American Cancer Society. (2024). Chronic Myeloid Leukemia. Retrieved from https://www.cancer.org/cancer/types/chronic-myeloid-leukemia/references.html.
2. Leukemia Cells by a ROS-Mediated Mechanism. Genes Cancer. Jan 2011;2(1):56-64 doi:10.1177/1947601911405044
3. Byrd JC, Dahiya R, Huang J, Kim YS. Inhibition of mucin synthesis by benzyl-alpha-GalNAc in KATO III gastric cancer and Caco-2 colon cancer cells. *Eur J Cancer*. 1995;31A(9):1498-1505. doi:10.1016/0959-8049(95)00248-h
4. Sigma-Aldrich. Brefeldin A from Eupenicillium brefeldianum. Available at: https://www.sigmaaldrich.com/US/en/product/sigma/b4894?icid=sharepdp-clipboard-copy-productdetailpage
5. Akotiah A, Walker D, Boddie S, Campbell RB. Drug Targeting and Therapeutic Management of Chronic Myeloid Leukemia: Conventional and Nanotherapeutic Drug Options. Anticancer Agents Med Chem. 2022;22(17):2933-2941. doi:10.2174/1871520622666220426104631
6. Kawano T, Ito M, Raina D, et al. MUC1 oncoprotein regulates Bcr-Abl stability and pathogenesis in chronic myelogenous leukemia cells. Cancer Res. 2007;67(24):11576-11584. doi:10.1158/0008-5472.CAN-07-2756
7. Yin L, Kufe D. MUC1-C Oncoprotein Blocks Terminal Differentiation of Chronic Myelogenous Leukemia Cells by a ROS-Mediated Mechanism. Genes Cancer. 2011;2(1):56-64. doi:10.1177/1947601911405044
8. Yin L, Ahmad R, Kosugi M, et al. Terminal differentiation of chronic myelogenous leukemia cells is induced by targeting of the MUC1-C oncoprotein. Cancer Biol Ther. Sep 1 2010;10(5):483-91. doi:10.4161/cbt.10.5.12584
9. https://www.sigmaaldrich.com/US/en/product/aldrich/cds022173?icid=sharepdp-clipboard-copy-productdetailpage
10. Sun QC, Liu MB, Shen HJ, et al. Inhibition by imatinib of expression of O-glycan-related glycosyltransferases and tumor-associated carbohydrate antigens in the K562 human leukemia cell line. Asian Pac J Cancer Prev. 2013;14(4):2447-2451. doi:10.7314/APJCP.2013.14.4.2447
11. Gahmberg CG, Jokinen M, Karhi KK, Andersson LC. Effect of tunicamycin on the biosynthesis of the major human red cell sialoglycoprotein, glycophorin A, in the leukemia cell line K562. J Biol Chem. 1980;255(5):2169-2175.
12. Sigma-Aldrich. Tunicamycin from Streptomyces sp., ≥95% (HPLC). Product number T7765. Sigma-Aldrich website. Available at: https://www.sigmaaldrich.com/US/en/product/sigma/t7765?icid=sharepdp-clipboard-copy-productdetailpage.
13. Alkholief M, Campbell RB. Investigating the role of mucin in the delivery of nanoparticles to cellular models of human cancer disease: an in vitro study. Nanomedicine. 2016;12(5):1291-1302. doi:10.1016/j.nano.2016.01.007

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