

Perspective

In the pursuit of a new route on acute myeloid leukemia treatment

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Abstract

Acute myeloid leukaemia (AML) is the forefront disorder of the bone marrow among others that disrupt the normal production of blood cells and platelets. The bone marrow microenvironment or the bone marrow niche (BM niche) that orchestrates the proliferation and survival of Leukaemic stem cells (LSC) is the reason for relapse after complete remission and also chemotherapy drug resistance. As for most cancers oxidative phosphorylation, a fundamental mitochondrial process of energy production, is under focus for the treatment of AML and a novel strategy of targeting heat shock proteins appears as a promising route for further research.

Introduction

Acute myeloid leukemia is a diverse set of leukemia's that develops when haematopoietic precursors undergo clonal transformations as a result of chromosomal rearrangements and several gene alterations [1]. It contributes to 1.9% of all cancer deaths, an estimated new cases of more than 20,000 in 2021 and a 30% five-year relative survival rate from 2012-2018 in the United States of America [2].

(<https://seer.cancer.gov/statfacts/html/amyl.html>).

Since there are currently few effective treatment options for AML, which is still mainly incurable, it is crucial to find promising pharmacological approaches. AML treatments are essential for frontline, relapsed/refractory AML as well as for cases of drug resistance. Many therapeutic approaches and medicines are being developed in an effort to increase survival because of the weak response to current medications and the associated adverse effects they present with. Future research on Oxidative phosphorylation (OXPHOS) inhibitors should outline the best treatment plans and drug combinations either for AML management that promote or at the very least work well with anticancer immune responses.

The most popular treatment for non-acute promyelocytic leukemia disease is the well-known 7+3 induction chemotherapy, consisting of three days of anthracyclines (often Daunorubicin) followed by a continuous infusion of a pyrimidine analogue for example with cytarabine for seven days [1]. Hematopoietic stem cell transplantation (HSCT) alone or with a moderate to a high dose of Cytarabine that

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is administered as a combination therapy post-complete remission (CR) [3]. Relapse in AML and refractory AML are unavoidable obstacles even after treatment. It is not assured for those patients who have achieved CR, a significant proportion of them still experience a relapse. A variety of factors, including disordered regulation of the signaling pathways related to DNA damage response sensing, genetic abnormalities in cell cycle control genes, modifications to cell death processes of apoptosis and autophagy, transformed anti-cancer drug delivery, and unidentified mechanisms, contribute to AML relapse [4]. Another significant reason for relapse is the unsuccessful treatment options available for the destruction of the leukemic stem cell (LSC) population [5]. AML is considered when cytogenetic and molecular aberrations present an actionable target in AML, targeted therapy is viewed as the next paradigm shift in the field of medicine and personalized medicine becomes an emerging strategy for managing AML cases.

The Food and Drug Administration (FDA) of the United States of America has recently approved several new treatments for AML that are all targeted therapies as listed in Table 1.

Arriving at the molecular aspect of understanding AML condition, the bone marrow microenvironment manages the

Table 1: List of some FDA-approved treatments for Acute Myeloid Leukaemia [1,6,7].

FDA approved drug	Type
Glasdegib	Smoothened (SMO) inhibitor
Midostaurin	FLT3 inhibitor
Gilteritinib	FLT3 inhibitor
CPX-351	Liposomal cytarabine and daunorubicin that is in a fixed 5:1 molar ratio
Venetoclax	B-cell lymphoma 2 (BCL-2) inhibitor
Gemtuzumab-Ozogamicin	Anti-CD33 monoclonal antibody conjugated with calicheamicin
Ivosidenib	Isocitrate Dehydrogenase 1 (IDH1) inhibitor
Enasidenib	Isocitrate Dehydrogenase 2 (IDH2) inhibitor
CC-486	Oral azacitidine hypomethylating agent
Oral Decitabine-cedaruzidine	Oral hypomethylating agent

growth and persistence of LSCs [8]. The BM niche features a sinusoidal blood supply, various lineages of haematopoietic and mesenchymal cells, the bone extracellular matrix, and the bone marrow stroma. Under normal conditions, resident bone cells (osteoblasts, osteoclasts, and osteocytes) interact with other cell types such as platelets, myeloid and immune cells, haematopoietic and endothelial cells from the bone marrow, and bone marrow-derived mesenchymal stem cells, in a coordinated manner [9]. The bone marrow niche has been implicated in the development and maintenance of AML, as well as in the drug resistance of the leukemic stem cell population promoting their survival, among other mechanisms that give rise to the resistance of chemotherapy or targeted inhibitors [6,10].

Recent research has demonstrated that the activation of bone marrow stromal cells increases the number of mitochondria in AML cells and AML blast cells, which favours oxidative phosphorylation (OXPHOS) [11]. They are vulnerable to oxidative stress because the activity and reserve capacity of their electron transport chain (ETC) complex I, III, IV, and V do not rise concurrently. Consequently, inducing oxidative stress and cell death in AML cells by increasing the electron flow across the respiratory chain [12]. Moreover, OXPHOS suppression results in cell arrest, death, and differentiation because energy and macromolecules are depleted [13]. Targeting the OXPHOS chain with possible metabolic vulnerability is an effective method for AML because it has been discovered that inhibiting OXPHOS cannot increase glycolysis in AML and stem cells [14]. AML chemoresistance is predicted by a rise in mitochondrial population, mitochondrial membrane potential, and OXPHOS, while the OXPHOS inhibition can reestablish chemotherapy sensitivity [15].

Reprogramming metabolic energy generation prompts the onset of cellular dysfunction and stress conditions. Heat shock transcription factor 1 (HSF1) increases the generation of heat shock proteins (HSPs), shielding cells against proteotoxic stress brought on by misfolded proteins, and plays a role in the oncogenesis and metastasis of a variety of cancers [16]. There has not been much research explicitly evaluating the function and mode of action of HSF1 in the transformed BM niche and its interactions in the AML stem cells. HSF1

is essential for LSC self-renewal and it is not necessary for normal hematopoiesis. In part, HSF1 regulates genes involved in the maintenance of LSC, like the ETC complex II-mediated OXPHOS to manage LSC self-renewal. It is agreeable that they believed in directly targeting HSF1 to be a more desirable option since it simultaneously inhibits a variety of HSF1-dependent oncogenic signaling, survival, and metastatic programmes, as well as protein chaperone expression and LSC OXPHOS activity [16].

Conclusion

AML being incurable drives medical practitioners and researchers to persistently search for the optimal treatment and therapy with the best results. Although complex, through rigorous research our understanding of its complexities has brought about opportunities to explore and discover novel targets and strategies in AML management and treatment. Following the strategy of targeting HSF1 and heat shock protein production is a novel approach to treating AML and many other cancers with a promising result. Thus, research on this topic is desirable for taking a step further in understanding the BM niche, the extent of the role played by OXPHOS in AML, HSF1 interactions, and ultimately closer to finding the optimal treatment for AML.

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