Volasertib in Cancer Therapy: From Mechanism to Clinical Potential

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Abstract

Volasertib is a second-generation, selective inhibitor of polo-like kinase 1 (PLK1), created for targeted therapy in cancer treatment, particularly acute myeloid leukemia (AML). PLK1 plays a crucial role in regulating mitosis and is often overexpressed in cancerous cells, which makes it a promising target for therapy. By inhibiting PLK1-mediated progression through mitosis, volasertib prompts G2/M cell-cycle arrest and leads to apoptosis. Preclinical studies showed significant antitumor effects, prompting further clinical investigations in both hematological and solid tumors. In AML, volasertib exhibited clinical effectiveness, particularly when paired with low-dose cytarabine in elderly or unfit patients; however, hematologic toxicity hindered its continued development. Despite some encouraging results in early-phase trials, phase III studies did not show a survival advantage, underlining the difficulties associated with using PLK1 inhibition as a standalone treatment. This review outlines the mechanism of action, clinical findings, limitations, and future outlook for volasertib, stressing the insights gained for developing next-generation PLK1 inhibitors in cancer therapy.

Keywords

- volasertib
- polo-like kinase 1
- acute myeloid leukemia
- cell-cycle arrest
- mitotic arrest
- targeted therapy

Introduction

Cancer arises when normal control of cell division is disrupted, leading to uncontrolled cell growth. Polo-like kinase 1 (PLK1) is a key regulator of mitosis and plays an essential role in processes such as spindle formation and chromosome segregation.[1] Overexpression of PLK1 has been reported in several malignancies, including acute myeloid leukemia (AML), where it is often associated with aggressive disease and poor prognosis.[1,2] These findings have made PLK1 an attractive target for anticancer drug development.

Volasertib (BI 6727) is a second-generation, selective PLK1 inhibitor developed to overcome the limitations of earlier PLK1-targeted agents.[3] By inhibiting PLK1 activity, volasertib disrupts mitotic progression, resulting in G2/M cell-cycle arrest and subsequent cancer cell death. Early preclinical and clinical studies demonstrated encouraging antitumor activity, particularly in AML. However, later clinical trials revealed dose-limiting hematologic toxicity and failed to show a clear survival benefit, which ultimately restricted its further clinical development.

Review Methodology

This narrative review was prepared by systematically searching electronic databases, including PubMed, Scopus, and Google Scholar, for relevant literature published up to October 2025. The search terms used included *"Volasertib," "polo-like kinase 1," "PLK1 inhibitor," "acute myeloid leukemia,"* and *"volasertib clinical trials."* Original research articles, review articles, and clinical trial reports published in the English language were considered. Studies focusing on the mechanism of action, preclinical evaluation, clinical development, therapeutic efficacy, and limitations of volasertib in cancer therapy

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were included. Reference lists of selected articles were also screened to identify additional relevant publications.

Discovery and Development

PLK1 gained attention as a potential anticancer target because of its essential role in cell division and its frequent overexpression in cancer cells. Early efforts to inhibit PLK1 led to the development of BI-2536, one of the first PLK1 inhibitors to be evaluated clinically.[4] Although BI-2536 demonstrated strong anticancer activity in preclinical studies, its clinical performance was limited due to modest therapeutic benefit and pharmacokinetic challenges, leading to discontinuation of its development after phase II trials.[3,4]

To address these limitations, volasertib (BI 6727) was developed as a second-generation PLK1 inhibitor with improved selectivity and better tissue distribution.[3] Preclinical studies showed that volasertib effectively inhibited mitosis and induced apoptosis in rapidly dividing cancer cells, including AML models.[3,5] These encouraging findings supported its advancement into clinical trials. Volasertib subsequently received orphan drug designation for the treatment of AML and progressed to phase III evaluation, particularly in elderly patients who were not suitable for intensive chemotherapy.[6,7] However, despite promising early-phase results, later clinical trials failed to demonstrate a clear survival benefit, which ultimately limited its further clinical development.[3]

Mechanism of Action

PLK1 is a key regulator of mitotic progression and plays an essential role in centrosome maturation, spindle assembly, chromosome segregation, and cytokinesis (►**Fig. 1**). In rapidly dividing cancer cells, PLK1 activity is often upregulated, making these cells highly dependent on PLK1 for successful cell division.[1,2] Inhibition of PLK1 therefore disrupts multiple stages of mitosis and ultimately leads to mitotic failure and cell death.

Volasertib (BI 6727) is a selective, adenosine triphosphate–competitive inhibitor of PLK1 that exerts its antitumor effects primarily by blocking PLK1-mediated mitotic signaling.[3,5] Treatment with volasertib results in accumulation of cells in the G2/M phase of the cell cycle, indicating mitotic arrest (►**Fig. 2**). This arrest is followed by failure of proper chromosome alignment and spindle formation, leading to mitotic catastrophe and subsequent apoptosis.[5] Preclinical studies in AML cell lines have shown that volasertib induces a time- and dose-dependent increase in apoptotic cell death after prolonged mitotic arrest.[5]

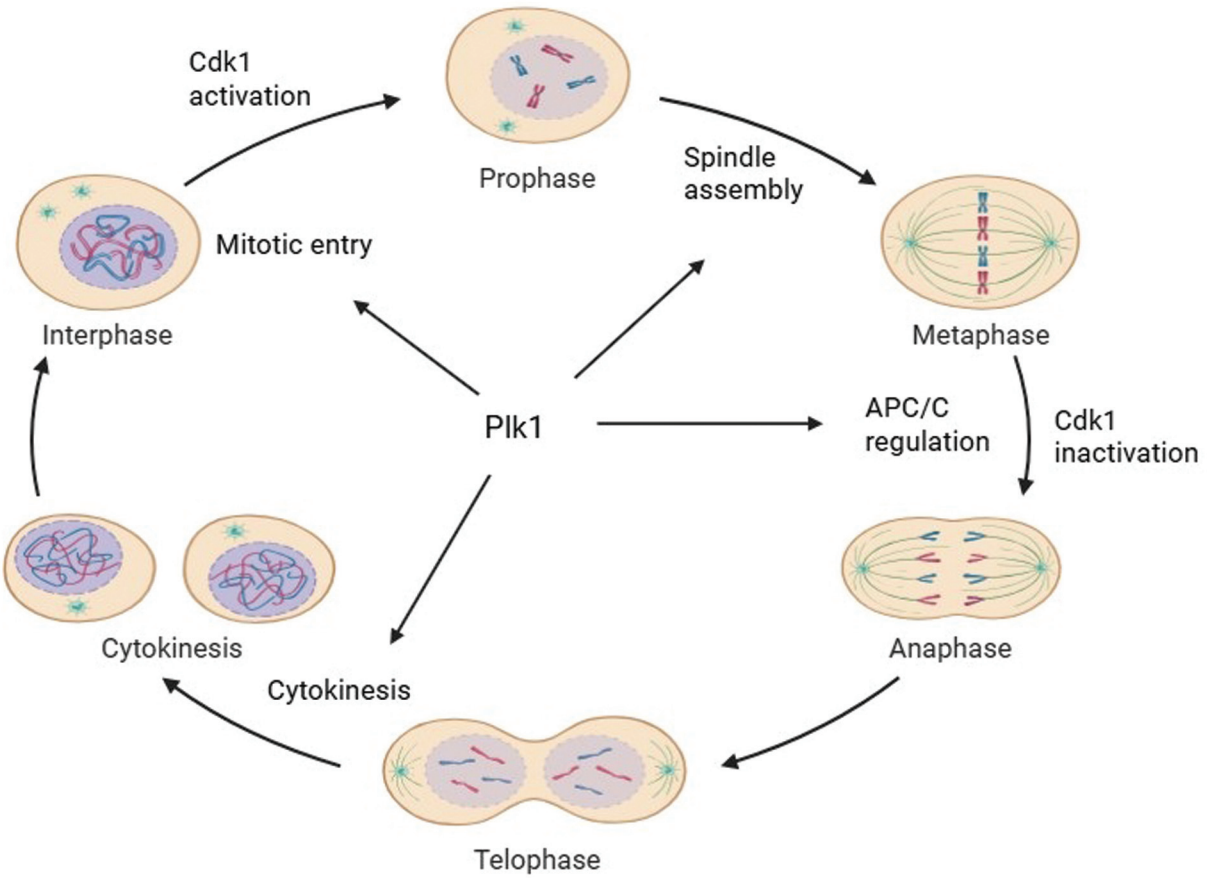

Fig. 1 Role of polo-like kinase 1 (PLK1) in the regulation of mitotic progression during the cell cycle. (This figure has been redrawn and created by the authors based on the conceptual framework described in Gjertsen and Schöffski (2015)[3].).

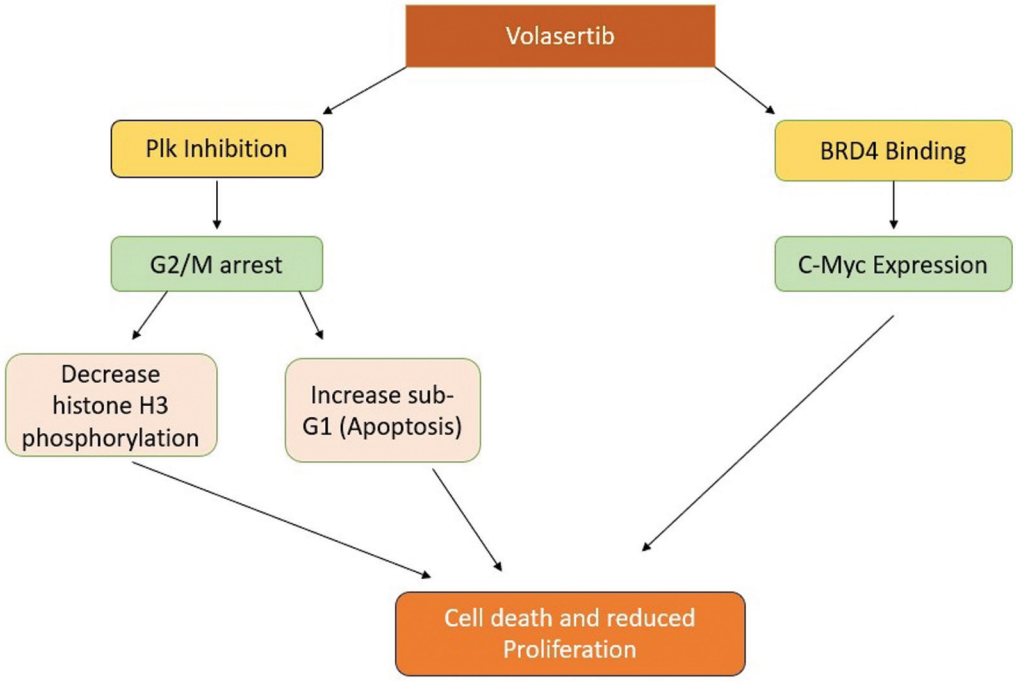

Fig. 2 Mechanism of action of volasertib showing PLK1 inhibition–mediated G2/M cell-cycle arrest leading to apoptosis and reduced tumor cell proliferation. (Figure created by the authors.)

In addition to PLK1 inhibition, volasertib has been reported to exhibit weak binding to bromodomain-containing protein 4 (BRD4); however, this interaction occurs at much higher concentrations than those required for PLK1 inhibition and is unlikely to represent its primary mechanism of action.[5] Overall, the antitumor activity of volasertib is mainly attributed to disruption of PLK1-driven mitotic processes, resulting in reduced cellular proliferation and induction of apoptosis in cancer cells. This mechanism forms the biological basis for its evaluation in hematologic malignancies, particularly AML.

Clinical Evidence of Volasertib in Acute Myeloid Leukemia

AML is an aggressive hematologic malignancy, and treatment options are limited for elderly patients or those who are not suitable for intensive chemotherapy. PLK1 is frequently overexpressed in AML cells and plays a critical role in mitotic progression, making it a rational therapeutic target.[2,8] Based on this rationale, volasertib was extensively evaluated in AML.

Preclinical studies demonstrated that volasertib induced G2/M cell-cycle arrest and apoptosis in AML cell lines, supporting its progression into clinical trials.[5] Early phase I studies established its safety profile and identified hematologic toxicities, including neutropenia and thrombocytopenia, as the main dose-limiting adverse effects.[6] Despite these toxicities, evidence of antileukemic activity was observed. Phase II clinical trials further evaluated volasertib as monotherapy and in combination with low-dose cytarabine in older, unfit patients with newly diagnosed AML. These studies reported higher remission rates and improved event-free survival with the combination regimen compared with low-dose cytarabine alone.[6,7] Encouraged by these findings, volasertib advanced to phase III evaluation.

However, subsequent phase III trials failed to demonstrate a significant overall survival benefit, and increased hematologic toxicity limited its clinical utility.[7] Consequently, further development of volasertib in AML was largely discontinued. Nevertheless, these studies provided important insights into the potential and limitations of PLK1 inhibition as a therapeutic strategy in AML.

Evidence in Solid Tumors and Pediatric Malignancies

In addition to AML, volasertib has been evaluated in several solid tumors and pediatric malignancies, although clinical evidence in these settings remains limited. Preclinical studies demonstrated antitumor activity of volasertib in breast, lung, and colorectal cancer models, primarily through induction of mitotic arrest and enhanced sensitivity to radiotherapy.[5,9,10] In solid tumor clinical trials, volasertib showed modest activity, with stable disease being the most common outcome.[6,11]

Volasertib has also been investigated in pediatric cancers, including relapsed leukemia and advanced solid tumors. Phase I studies identified similar dose-limiting hematologic toxicities as seen in adults, while clinical responses were limited mainly to disease stabilization.[12,13] Overall, although volasertib demonstrated biological activity in these malignancies, its clinical benefit outside AML was modest, and further development in these indications was not pursued.

Comparison with Other Polo-Like Kinase Inhibitors

PLK1 plays a central role in cell-cycle regulation and has therefore been explored as a therapeutic target in cancer treatment.[8,14,15] Several PLK inhibitors have entered clinical development, among which volasertib, rigosertib, and onvansertib have received the greatest attention, particularly in hematologic malignancies such as AML.[3,6] Volasertib and onvansertib directly inhibit PLK1, resulting in mitotic arrest and apoptosis in rapidly dividing cancer cells, whereas rigosertib acts indirectly by interfering with RAS-related signaling pathways that influence PLK1 activity.[16]

Although volasertib demonstrated strong preclinical and early clinical activity, its clinical utility was limited by dose-dependent hematologic toxicity, including neutropenia and thrombocytopenia.[6,7] In contrast, onvansertib is a newer and more selective PLK1 inhibitor with a shorter half-life and has shown a relatively improved safety profile in early-phase clinical studies.[17,18] Rigosertib exhibits broader pathway inhibition but appears to have lower specificity for PLK1. Overall, while volasertib was instrumental in validating PLK1 as a therapeutic target, current research is focused on developing newer PLK1 inhibitors that offer improved tolerability while maintaining antitumor efficacy.

Combination Strategies and Safety Considerations

Combination approaches were explored to enhance the antitumor activity of volasertib and overcome the limitations observed with monotherapy. Preclinical and early clinical studies showed that combining volasertib with agents such as low-dose cytarabine or other targeted therapies could improve antileukemic activity by enhancing mitotic stress and apoptosis.[6,7] However, these combinations were also associated with increased hematologic toxicity, particularly neutropenia and thrombocytopenia, which remained the major dose-limiting adverse effects.[6,11] Overall, while combination strategies showed biological and early clinical promise, safety concerns limited their broader clinical application and contributed to the discontinuation of further development of volasertib.

Limitations of Volasertib Development

Despite encouraging preclinical findings and early clinical activity, the development of volasertib faced several important limitations. The most significant challenge was dose-limiting hematologic toxicity, including neutropenia and thrombocytopenia, which reduced its tolerability, particularly in elderly and frail patients.[6,7] In addition, phase III clinical trials failed to demonstrate a clear overall survival benefit, limiting its clinical value.[7] These factors, combined with the narrow therapeutic window of PLK1 inhibition, ultimately led to the discontinuation of further clinical development of volasertib as a therapeutic agent.

Future Perspectives for Polo-Like Kinase Inhibition

Although the clinical development of volasertib was limited, inhibition of PLK1 remains a relevant therapeutic strategy in cancer.[19] The experience gained from volasertib has highlighted the importance of patient selection, dosing strategies, and toxicity management when targeting mitotic kinases.[3,17] Future research is increasingly focused on developing newer PLK1 inhibitors with improved selectivity and more favorable safety profiles, such as onvansertib.[17,18] In addition, combination approaches guided by molecular biomarkers may help identify patient populations most likely to benefit from PLK1 inhibition. Advances in understanding PLK1 biology and its interaction with other oncogenic pathways may also support rational combination strategies and reduce toxicity.[20] Overall, the lessons learned from volasertib continue to inform the development of next-generation PLK1-targeted therapies in oncology.[21]

Conclusion

Volasertib emerged as a promising PLK1 inhibitor with strong biological rationale and encouraging early clinical activity, particularly in AML. However, dose-limiting hematologic toxicity and the absence of a clear survival benefit in later-stage trials restricted its clinical development. Despite these limitations, volasertib played an important role in validating PLK1 as a therapeutic target. The insights gained from its development continue to guide the design of safer and more effective next-generation PLK1 inhibitors in oncology.

Authors' Contributions

A.L. and S.L. contributed to the concept and design of the study and were involved in manuscript preparation. V.P., S.Z., and R.W. conducted the literature search. All authors participated in manuscript editing and review and approved the final version of the article.

Conflict of Interest

None declared.

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