





Trilaciclib: A Novel Approach to Mitigate Chemotherapy-Induced Myelosuppression in Cancer Treatment

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Abstract

Trilaciclib, a novel cyclin-dependent kinase 4/6 inhibitor, has demonstrated the ability to protect bone marrow from chemotherapy toxicity, improving patients' quality of life (QoL). This review describes the mechanism of action, efficacy, and toxicity profile of trilaciclib. Trilaciclib halts retinoblastoma protein phosphorylation during the early G1 phase, preventing the transition from the G1/S phase and inducing the cell cycle arrest in the G1 phase, which protects the hematopoietic cell lineages. Trilaciclib is indicated by the United States Food and Drug Administration and National Comprehensive Cancer Network to decrease the incidence of chemotherapy-induced myelosuppression in adult patients before a platinum/etoposide or topotecan containing regimen for extensive stage small cell lung cancer. Its ease of administration as an intravenous infusion, given before starting chemotherapy, and the favorable side effect profile make it a better-tolerated drug, improving patient QoL.

Keywords

- ▶ trilaciclib
- ▶ neutropenia
- ▶ CDK 4/6 inhibitor
- ▶ chemotherapy-induced myelosuppression

Introduction

Myelosuppressive chemotherapeutic agents have an associated risk of chemotherapy-induced myelosuppression (CIM). Neutropenic complications include febrile neutropenia, prolonged hospitalization days, and increased mortality rates.¹ Granulocyte colony-stimulating factor (G-CSF) reduces these side effects and improves patient outcomes.² However, financial burden, side effects of G-CSF, including bone pain, administration after chemotherapy mostly in a home-based setting, multiple uses of injections, and continued vulnerability to infection after chemotherapy remain unmet needs.^{3–5} It is challenging to ensure the cold chain maintenance for the G-CSF injection and patient compliance in home-based settings, especially in the illiterate population. Trilaciclib, a novel cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, has shown promise in achieving this balance. Its ease of administration as an intravenous injection given just

before chemotherapy addresses the logistic issues associated with traditional G-CSF injections.

This review delves into trilaciclib's mechanism of action, preclinical and clinical studies, safety profile, and potential applications. By preserving bone marrow and immune cells during chemotherapy, trilaciclib minimizes myelosuppression impact and promotes a more efficient approach to treatment.

Discovery, Mechanism of Action, Pharmacokinetics, Indications, and Contraindications

Trilaciclib's development stemmed from advancements in understanding the role of CDK4/6 in cell cycle regulation and the need for improved strategies to protect patients from chemotherapy's myelosuppressive effects. G1 therapeutics spearheaded the drug's research and conducted a series of

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Table 1 Data for Trilaciclib

Study	Phase	Disease	Intervention	FN	Hospitalization Rate
NCT03041311 (2020)	2	ES-SCLC	Trilaciclib (240 mg/m ² OD DAY 1–3) before Carboplatin DAY 1 + Etoposide DAY 1–3 + Atezolizumab DAY 1 → Atezolizumab maintenance DAY 1 (CYCLE Q21D)	1.9%	3.8%
NCT02978716 (2019)	2	TNBC	Group 1: Gemcitabine + Carboplatin D1,8	3%	N/A
NCT02499770 (2019)	1b/ 2	ES-SCLC	Trilaciclib (200/240 mg/m ² OD DAY 1–3) before Carboplatin DAY 1 + Etoposide DAY 1–3	3%	N/A
NCT02514447 (2021)	1b/2a	ES-SCLC	Trilaciclib (240 mg/m OD D1–3) prior to (≤4h) Topotecan D1-5d Q21D	6.3%	9.4%

Abbreviations: ES-SCLC, extensive stage small cell lung cancer; FN, febrile neutropenia; Q21D, every 21 days; OD, once daily; N/A, Not Available.

Table 2 Ongoing Clinical Trials

Study	Phase	Disease	Drugs	Status
PRESERVE 1 (NCT04607668)	3	m CRC	FOLFOXIRI / Bevacizumab + Trilaciclib V/s Placebo	Ended (placebo outperformed trilaciclib)
PRESERVE 2 (NCT04799249)	3	m TNBC	Gemcitabine / Carboplatin + Trilaciclib V/s Placebo	Active
PRESERVE 3 (NCT04887831)	2	Advanced / metastatic bladder cancer	Chemotherapy and/or Trilaciclib Followed By Avelumab	Active
PRESERVE4 (NCT04863248)	2	NSCLC	Docetaxel + Trilaciclib Vs Placebo	Terminated
NCT04902885	3	ES SCLC	Carboplatin / Etoposide Or Topotecan + Trilaciclib V/s Placebo	Recruitment completed

Abbreviations: ES SCLC, extensive stage small cell lung cancer; FOLFOXIRI, folinic acid, 5- fluorouracil, oxaliplatin and irinotecan; m CRC, metastatic colorectal cancer; m TNBC, metastatic triple negative breast cancer; NSCLC, non small cell lung cancer.

pivotal trials. This led to its emergence as a promising myelopreservation agent in cancer therapy.

Trilaciclib (G1T28) selectively inhibits CDK4/6, crucial cell cycle regulators. This action halts retinoblastoma protein phosphorylation during the early G1 phase, preventing transition from the G1/S phase and inducing cell cycle arrest in the G1 phase. This protects the hematopoietic cell lineages (red blood cells [RBCs], platelets, neutrophils, and lymphocytes) from the cytotoxic effects of chemotherapy. Additionally, trilaciclib triggers apoptosis and inhibits the proliferation of tumor cells overexpressing CDK4/6. Moreover, for patients with CDK4/6-independent tumor cells, the drug protects against CIM. This safeguarding mechanism reduces myelosuppression and heightens immune responses during cancer treatment.⁶

Trilaciclib has an average terminal half-life of approximately 14 hours, primarily eliminated through the fecal route, with a minor contribution via the renal route. No dose adjustments are required according to differences in age, sex, or hepatic or renal function.

Trilaciclib is indicated by the United States Food and Drug Administration to decrease the incidence of CIM in adult patients before a platinum/etoposide or topotecan-containing regimen for extensive stage small cell lung cancer (ES-SCLC). National Comprehensive Cancer Network recommends trilaciclib as an option for decreasing the incidence of CIM in ES-SCLC. It is contraindicated in patients with a

history of severe hypersensitivity to the drug. Ongoing research aims to explore its application in various cancer types and treatment regimens. Additionally, investigations are underway to evaluate its use in hematopoietic stem cell transplantation and radiation therapy.

Pivotal Trials

The pre-existing data for Trilaciclib and the various ongoing trials are provided in ►Table 1 and ►Table 2. Trilaciclib has been shown to have benefits beyond preventing neutropenia and protecting other hematopoietic lineages such as RBCs and platelets. Trilaciclib can reduce the incidence of grade 4 neutropenia, grade ¾ anemia, thrombocytopenia, RBC transfusions, and erythropoiesis-stimulating agent administration. Additionally, trilaciclib has been shown to improve the quality of life (QoL). However, it is essential to note that these benefits may be tumor or chemotherapy-specific.^{7,8}

Dosage and Administration

The recommended dose of trilaciclib is 240 mg/m² per dose. It is administered as a 30-minute intravenous infusion. It should be given 4 hours before starting chemotherapy. At most, the interval between two consecutive day doses should be 28 hours.

Safety Profile

Trilaciclib has demonstrated a favorable safety profile in clinical trials. Common side effects reported were mild and transient, including fatigue (9.5%), nausea (7.8%), anemia (5.9%), and infusion-related reactions (5.9%). The low incidence of severe adverse events suggests its potential for broad clinical use.⁹

Conclusion

In conclusion, trilaciclib can safeguard bone marrow cell lineages during chemotherapy, minimizing myelosuppression and enhancing immune responses, thus holding promise in improving patient outcomes. Trilaciclib offers hope for better patient compliance and QoL with its ease of use and favorable safety profile. Trilaciclib's potential applications in other cancer types and its role in hematopoietic stem cell transplantation and radiation therapy can improve cancer care in the future.

Note

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The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Patient Consent

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Conflict of Interest

None declared.

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