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Satraplatin as an orally active Pt(IV) prodrug: mechanistic distinction from cisplatin and therapeutic prospects

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1. Abstract

Satraplatin (JM-216) is an orally administered platinum(IV) prodrug developed to address the clinical limitations of cisplatin, including intravenous delivery, dose-limiting toxicity, and resistance. Its octahedral geometry and axial ligands confer stability in the gastric environment, allowing for absorption via passive diffusion. Following cellular uptake, Satraplatin is reduced intracellularly to JM-118, a platinum(II) species capable of forming DNA crosslinks. These adducts are less readily recognised by mismatch repair and high-mobility group proteins, contributing to activity in cisplatin-resistant models. Reduced nephrotoxicity and neurotoxicity have also been reported in preclinical studies. Although regulatory approval has not been achieved, ongoing interest in orally active platinum agents suggests potential for future clinical development.

2. Introduction

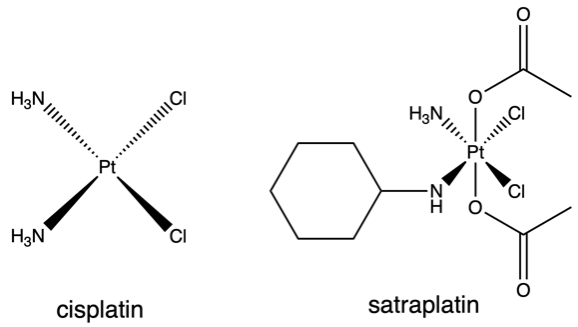
Platinum-based chemotherapeutics, notably cisplatin and carboplatin, remain widely used in the treatment of solid tumours, including testicular, ovarian, lung, and head and neck cancers. Their clinical activity arises from the formation of DNA crosslinks, which induce cell cycle arrest and apoptosis.[1] However, their use is limited by cumulative nephrotoxicity, neurotoxicity, and ototoxicity, and by the need for intravenous administration due to the instability of Pt(II) centres in acidic environments.[1,2]

Resistance further restricts their efficacy, often driven by enhanced DNA repair, increased expression of efflux transporters, and detoxification via intracellular thiols such as glutathione and metallothionein.[2,3] These limitations have prompted the development of next-generation platinum agents that retain anticancer activity while improving tolerability and delivery profiles.

Satraplatin (JM-216) is a rationally designed platinum(IV) prodrug with an improved pharmacological profile. Unlike cisplatin, satraplatin remains stable in gastric acid due to its octahedral Pt(IV) geometry and axial acetato ligands, which reduce ligand exchange and premature hydrolysis.[1,4] Following oral administration, it is absorbed via passive transcellular diffusion, enters systemic circulation intact, and is taken up into tumour cells.[4] The structural differences between cisplatin and satraplatin are illustrated in Figure 1.

Contrary to earlier assumptions of hepatic metabolism, satraplatin is now understood to undergo intracellular reduction within tumour cells, forming the active Pt(II) metabolite JM-118.[1] This process, along with systemic uptake and nuclear targeting, is described in more detail in Section 3 and conveyed in Figure 2.

Fig. 1 Chemical structures of cisplatin and satraplatin (JM-216). Satraplatin's Pt(IV) centre adopts an octahedral geometry with two axial acetato ligands, in contrast to the square planar Pt(II) configuration of cisplatin.



Satraplatin has demonstrated activity in preclinical models of prostate, lung, and breast cancers, and is associated with reduced nephrotoxicity and neurotoxicity compared to cisplatin.[4,6] Despite progression-free survival benefits observed in a Phase III trial for metastatic castration-resistant prostate cancer (CRPC), overall survival was not significantly improved, limiting its clinical approval.[2]

3. Mechanism of Action

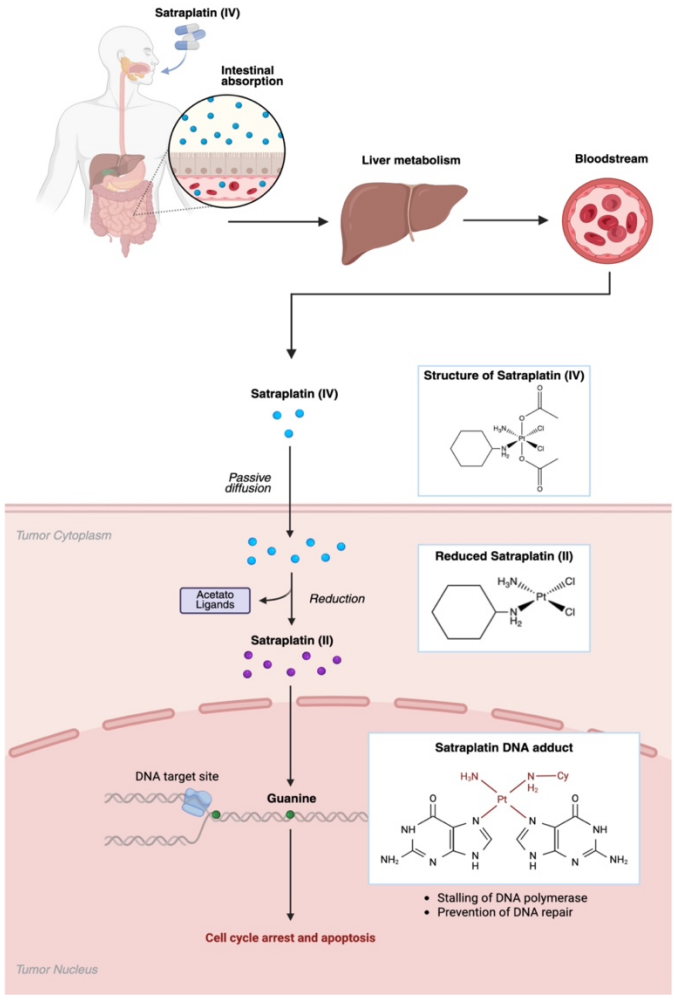
Following oral administration and systemic distribution, satraplatin reaches tumour cells and enters via passive diffusion, driven by its enhanced lipophilicity. Within the cytoplasm, intracellular reductants such as glutathione and ascorbate reduce the Pt(IV) centre to form JM-118, the active Pt(II) species. [1] This transformation shifts the

coordination geometry from octahedral to square planar, allowing the compound to bind DNA.

JM-118 preferentially forms 1,2-intrastrand crosslinks between adjacent guanine bases. These adducts induce structural distortion of the DNA helix, which disrupts replication fork progression and transcriptional machinery, ultimately triggering cell cycle arrest and apoptosis. Notably, these lesions are poorly recognised by mismatch repair (MMR) proteins and high-mobility group (HMG) domain factors, contributing to Satraplatin's retained activity in cisplatin-resistant cancers. [2,7]

This mechanism circumvents common resistance pathways such as increased DNA repair efficiency and enhanced Pt(II) efflux. In vitro and in vivo studies have shown that JM-118 exhibits a unique adduct recognition profile and reduced susceptibility to glutathione-mediated detoxification compared to cisplatin. [3]

Fig. 2 Proposed mechanism of satraplatin activation and DNA targeting. Following oral absorption and systemic distribution, satraplatin enters tumour cells via passive diffusion. Inside the reductive intracellular environment, it is converted to JM-118, a Pt(II) species that binds to DNA, disrupts replication and transcription, ultimately inducing apoptosis.



4. Toxicity and Clinical Context

Satraplatin exhibits a notably improved toxicity profile when compared to intravenous platinum agents such as cisplatin, as shown in Table 1. Reduced rates of nephrotoxicity and neurotoxicity have been reported in both preclinical models and clinical trials.[4,6] As an orally administered drug, Satraplatin avoids the sharp plasma peaks associated with IV dosing, contributing to better tolerability.

Table 1 Comparison of major toxicity features of cisplatin and Satraplatin, based on published preclinical and clinical data

Toxicity Feature	Cisplatin	Satraplatin
Nephrotoxicity	Common, dose-limiting	Rare
Neurotoxicity	Frequent	Mild/Occasional
Ototoxicity	Moderate to severe	Minimal
Nausea/Vomiting	Severe	Mild-moderate

During a Phase III trial in metastatic castration-resistant prostate cancer (CRPC), patients receiving Satraplatin experienced improved progression-free survival, although overall survival was not significantly improved from the control.[2] Nevertheless, the treatment was well tolerated, and adverse events typically associated with cisplatin- such as renal impairment, peripheral neuropathy, and the need for intensive hydration- were much less frequent.

5. Conclusion and Outlook

Satraplatin represents a promising evolution in platinum-based chemotherapy, combining oral administration, tumour-selective activation, and reduced toxicity. While clinical progress has been limited by regulatory hurdles, its unique mechanism and favourable side-effect profile continue to offer value in resistant and hard-to-treat cancers. Its combination of practicality, selectivity, and reduced toxicity continues to position Satraplatin as a model for future Pt(IV) drug design.

In 2024, pharma& acquired global rights to Satraplatin, with plans to investigate its potential in relapsed central nervous system lymphoma.[8] As interest in oral platinum therapeutics grows, Satraplatin may yet see renewed clinical relevance.

Whether Satraplatin represents a blueprint for future oral platinum therapies, or the end of a design lineage remains an open question. Its story highlights both the promise and the persistent challenges in bringing orally active metal-based drugs to clinical reality.

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