Oral platinum therapy: design evolution or dead end?

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

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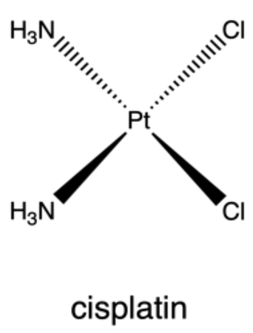
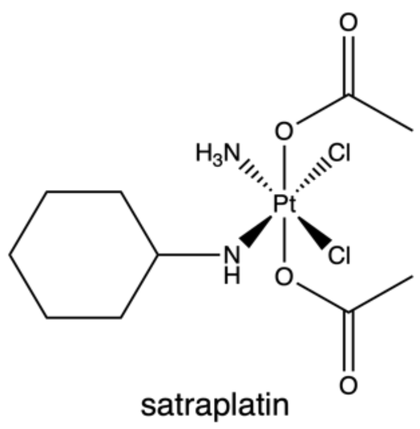
Introduction

Platinum-based like **cisplatin** remain widely used but are **limited by toxicity, IV-only delivery, and tumour resistance**.

Satraplatin (JM-216), a platinum(IV) prodrug, enables **oral dosing**, **improves tolerability**, **and bypasses resistance mechanisms**. It survives gastric conditions and passively diffuses into tumour cells, where it is reduced to its active Pt(II) form (JM-118).



cisplatin



satraplatin

Mechanism of Action

- Satraplatin's **octahedral Pt(IV) geometry** and axial acetate ligands provide **stability in gastric acid**.
- Lipophilic **axial ligands enable passive diffusion** into tumour cells.
- Inside the cytoplasm, **glutathione** and ascorbate **reduce Pt(IV) to Pt(II)**
- JM-118 forms **1,2-intrastrand crosslinks** between **guanine bases**, disrupting replication and transcription.
- These adducts are **poorly recognised by MMR and HMG-domain** proteins, helping bypass resistance mechanisms seen with cisplatin.

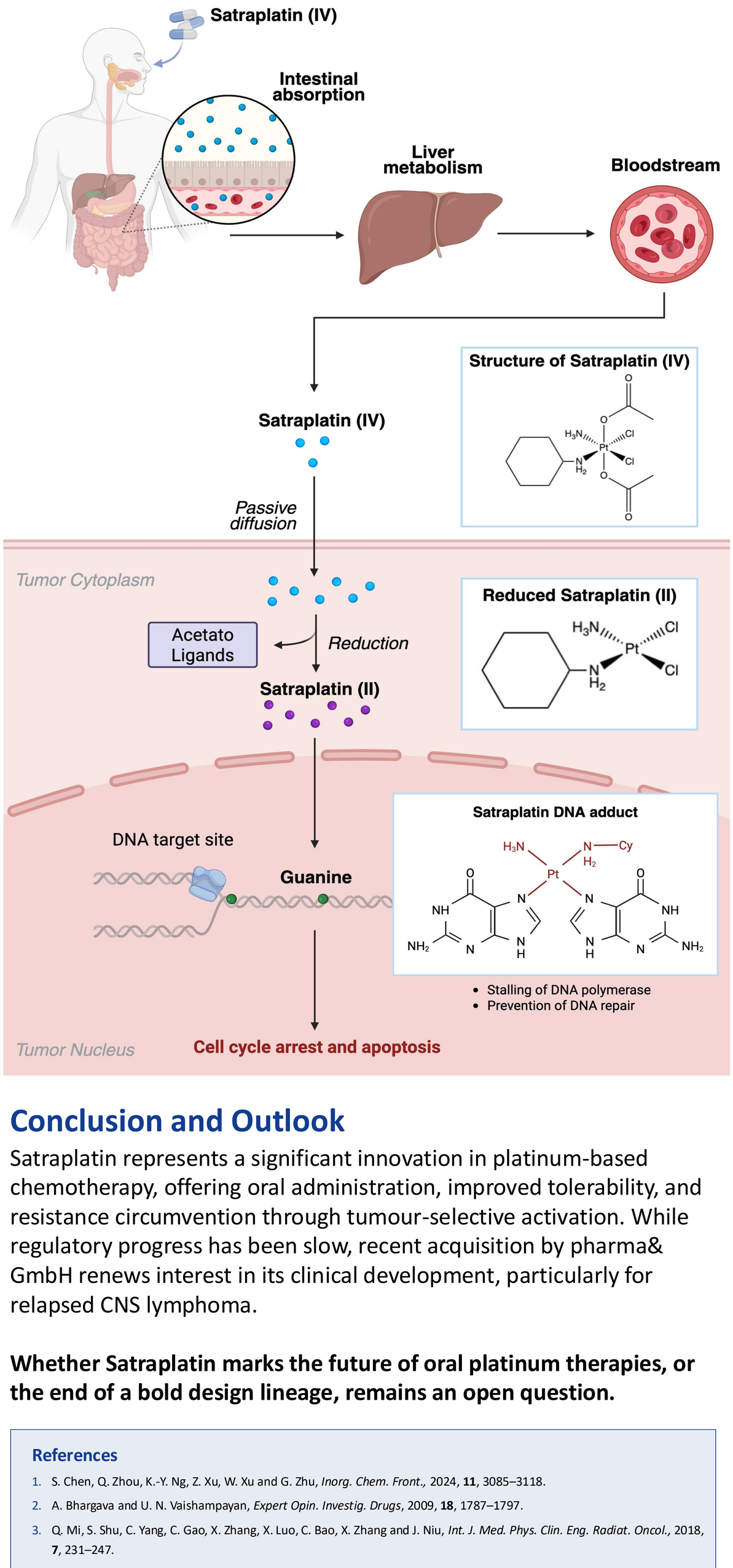
Toxicity and Clinical Context

Satraplatin degree of **toxicity is significantly lower** than of other compounds such as cisplatin. It avoids the sharp plasma peaks associated with IV dosing, offering improved tolerability in outpatient settings. Satraplatin's design allows it target tumour cells more selectively, the design keeps in inert, and allows to exploit passive diffusion.

Toxicity Feature	Cisplatin	Satraplatin
Nephrotoxicity	Common, dose-limiting	Rare
Neurotoxicity	Frequent	Mild/Occasional
Ototoxicity	Moderate to severe	Minimal to none
GI toxicity	Severe	Mild-moderate
Hematologic toxicity	Mild	Moderate and common

Clinical trials in metastatic castration-resistant prostate cancer (CRPC) showed **improved progression-free survival**, though **no overall survival benefit.**

Majority of toxicity features are lighter than other platinum compounds however it is important to note that Satraplatins Hematologic toxicity is by far the strongest. Satraplatin's strong dose-limiting toxicity is bone marrow suppression.



Conclusion and Outlook

Satraplatin represents a significant innovation in platinum-based chemotherapy, offering oral administration, improved tolerability, and resistance circumvention through tumour-selective activation. While regulatory progress has been slow, recent acquisition by pharma& GmbH renews interest in its clinical development, particularly for relapsed CNS lymphoma.

Whether Satraplatin marks the future of oral platinum therapies, or the end of a bold design lineage, remains an open question.

References

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