Reactive to Inert: A Novel Way to Tackle Issues With Chemotherapy

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Clinically approved platinum anti-cancer drugs cisplatin, carboplatin and oxaliplatin suffer from two major drawbacks: (i) inherent and acquired chemo resistance, that leads to relapse of resistant tumour and (ii) dose limiting toxic side effects such as nephrotoxicity, neurotoxicity and myelosuppression.[1, 2] Reactivity of platinum (II) drugs correlate linearly to glutathione mediated resistance as well as adverse side effects due to their non-specific biomolecule binding.[3] To circumvent these issues, we hypothesized to design substitutionally inert platinum drugs with novel mechanism of action. As positively charged platinum complexes containing planar polypyridyl ligand are capable of binding to *ds*-DNA or proteins through intercalation, a small library of cyclometalated platinum(II) complexes were screened for anticancer properties and a novel lead molecule, compound **4**, was identified which is 25-fold more potent compared to cisplatin in human cervical cancer cell line. Owing to its inertness, the antiproliferative activity of **4** is independent of intracellular glutathione and has been found to overcome platinum resistance in ovarian, lung and prostate cancer cells. While cisplatin and oxaliplatin has plasma half-life of *ca.* 1.5 h, **4** remained unchanged in plasma over 24 h. The *in vivo* efficacy of **4** was confirmed in an A549 xenograft. Importantly, by evaluating the expression levels of inflammatory markers in kidney, we demonstrated that **4** is significantly less nephrotoxic than cisplatin. However, this 1st generation molecule suffers from limited solubility and no cancer targetability. Hence, there stands a need for further improvisation of the molecule to tune its pharmacokinetics. Attaching sugars to platinum drugs have been seen to increase solubility and impart cancer targetability without compromising its toxicity.[4] Thus, we hypothesized to design sugar conjugates of **4** which we speculate to address the aforementioned issues.

In the presentation, I will be discussing the above mentioned aspects in detail.

References

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