Maximally tolerated dose vs. metronomic chemotherapy using oral satraplatin in dogs

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Abstract

(Revised) Satraplatin is the first oral platinum chemotherapy drug used in cancer treatment. Oral chemotherapy for dogs has several advantages including ease of administration and peripheral vein sparing. Metronomic dosing provides frequent, low-dose, continuous chemotherapy, inhibiting angiogenesis and decreasing chemotherapy-related toxicity.

Our hypothesis is that satraplatin given metronomically to dogs with cancer will result in minimal toxicity. We evaluated satraplatin *in vitro* and *in vivo*. First, a maximally tolerated dosing (MTD) study was completed to determine a dose from which we would extrapolate our metronomic dose. Pharmacokinetic and toxicity assessment allowed modeling of the metronomic study. Second, D17 canine osteosarcoma cells were maintained in culture and exposed to conditions to mimic metronomic versus MTD dosing, at levels determined by pharmacokinetic evaluation of the dogs in the MTD study, and assessed by clonogenic survival. Finally, dogs will be enrolled in a metronomic dosing trial, receiving low daily doses of satraplatin continuously.

The MTD was determined to be 35 mg/m2/day satraplatin for 5 days, repeated every 3-4 weeks. The dose-limiting toxicity was myelosuppression. D17 cells were inhibited by exposure to clinically achievable concentrations of satraplatin. The metronomic trial is ongoing and dogs receive 5 mg/m2/day satraplatin continuously until progressive disease or exit from the study due to toxicity or voluntary withdrawal. Dogs are monitored with CBC, biochemical profile and urinalysis before treatment and on days 14, 28, 56, 84, and 112. The tumor will be reassessed every 3 months. Satraplatin capsules of 5mg, 2mg, and 1mg have been compounded for this trial.

Background

The difference in satraplatin from other platinum drugs like cisplatin and carboplatin comes from its structure. It is a Pt(IV) compound instead of a Pt(II) which modifies its DNA adduct profile causing it to be more lipophilic and stable in an aqueous environment. These properties allow oral administration.

Tumors resistant to other platinum drugs are not necessarily cross-resistant to satraplatin, making the drug attractive for refractory cancers.

Satraplatin has been shown to decrease stat3 signaling which is involved in angiogenesis, suggesting that this drug may be uniquely suited to metronomic, anti-angiogenic chemotherapy.

With metronomic chemotherapy, **our goal** is different from standard administration in that the endpoint is not rapid tumor regression, but a stabilization of tumor size with minimal toxic side effects. The principal target is the endothelial cell rather than the tumor itself. By using this approach, the animal may have increased survival time and a better quality of life during treatment.

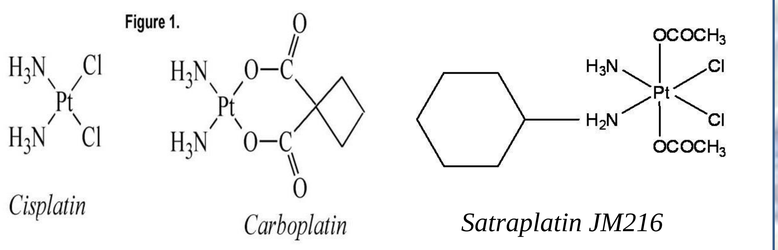


Figure 1: Chemical structures of cisplatin, carboplatin, and satraplatin.

Materials/Methods

In vivo:

MTD:

- Dogs with confirmed diagnosis of neoplasia enrolled in standard 3+3 phase 1 study for dose (de)escalation
- 21 dogs, mean 9 yrs old, various breeds, even distribution of sex
- Started at 50 mg/m^2/d x 5 days orally after 5 hr fast
- Toxicity graded according to VCOG-CTCAE.v1
- At MTD, additional dogs enrolled to evaluate for efficacy, if efficacy seen in at least one dog, then phase 2 study indicated.

Metronomic:

- A minimum of 10 tumor-bearing dogs recruited from the Veterinary Medical Teaching Hospital.
- Satraplatin capsules of 1mg, 2mg, and 5mg to be given at 5mg/m^2/day.
- Hematologic evaluation on days 14 and 28, then monthly.

In vitro:

- Canine osteosarcoma D17 cell line
- Plate 1: Maximally Tolerated Dose
  - Control, 140, and 280 ng/mL satraplatin for 4 hours
- Plate 2: Metronomic Dose
  - Control, 4.4, and 17.5 ng/mL satraplatin continuously

Figure 2: Splitting canine osteosarcoma D17 cells to prepare for liquid nitrogen freezing.

Results

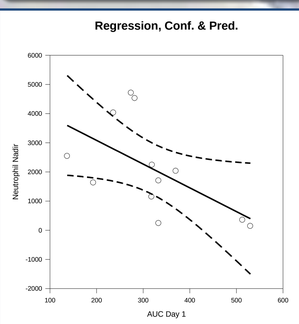


Figure 3: AUC correlated inversely with nadir (lowest) neutrophil count

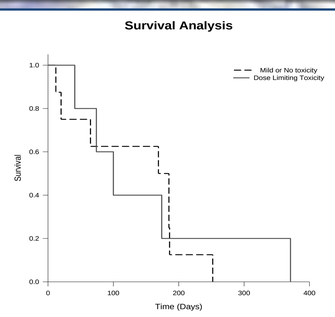


Figure 4: Toxicity had no effect on survival time by KM analysis

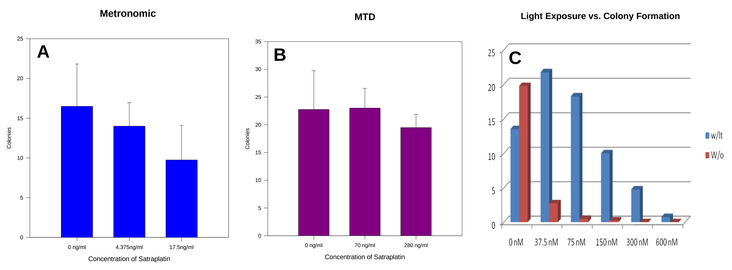


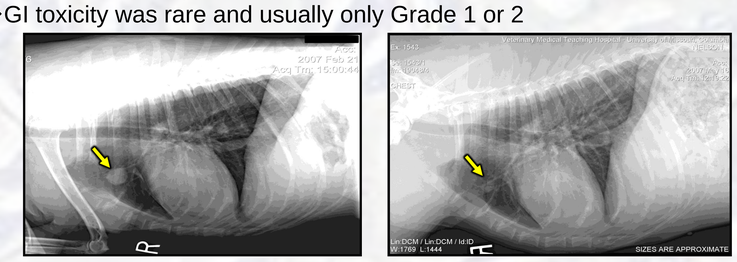
Figure 5: A. Metronomic (blue) inhibited colonies whereas **B.** MTD (pink) did not. **C.** Light exposure decreased efficacy (blue=with light, red=without light)

Results (cont.)

In vivo:

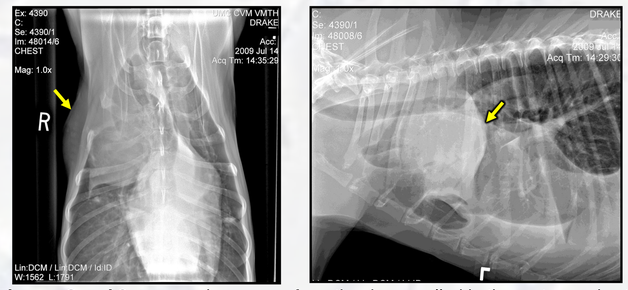
MTD:

- 21 dogs treated, 63 cycles, 14 dogs with PK
- Recommended dose= 35mg/m^2/day for 5 days
- Dose limiting toxicity was neutropenia (n=6, corr. w/AUC fig.3)
- Neutrophil nadir (2089/ul day 16), platelet nadir (95K day 14)
- GI toxicity was rare and usually only Grade 1 or 2



Figures 6 and 7: Regression of lung nodule in a dog treated with 30mg/m2/day x5 days repeated every 3-4 weeks for a total of 4 cycles. The radiograph on the left is before MTD satraplatin, the radiograph on the right is after MTD satraplatin.

Metronomic: Currently one dog with a hemangiosarcoma is enrolled in the trial. The 14 day CBC results show normal neutrophils and slightly decreased platelets, with no reported problems.



Figures 8 and 9: Hemangiosarcoma from the dog enrolled in the metronomic study.

In vitro:

- Dose-dependant inhibition of clonogenic survival was seen
- Metronomic levels resulted in fewer colonies than MTD

Conclusion

MTD: The drug was well tolerated with good quality of life of the animal. Efficacy may be comparable to other platinum drugs.

Metronomic: Currently one patient enrolled in the trial and plan to have a minimum of 10 dogs to complete the study.

In vitro: Satraplatin is highly light-sensitive. Duration of drug exposure may be more important than concentration.

Future Directions

- Complete metronomic clinical trial
- Satraplatin as a radiosensitizer
- Satraplatin in cats
- Investigate STAT3 inhibition by satraplatin

Acknowledgements

Student supported by Merck-Merial. Drug provided by GPC Biotech, Inc. Special thanks to Mary Cockrell for assistance with cell culture, and to Dr. Armando Villamil for statistical support.