Intra-Arterial Gemcitabine vs IV Gemcitabine: Pharmacokinetic Sub-study of the TIGeR-PaC Phase 3 Clinical Trial

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BACKGROUND

Localized dual-balloon catheter-mediated intra-arterial delivery of gemcitabine (**IAG**) into tumors/tissue:

- May lead to decreased systemic drug concentration and associated side effects compared to intravenous delivery of gemcitabine (**IVG**)
- Can lead to higher local drug potency[1]

This approach is currently being tested with locally advanced pancreatic cancer (**LAPC**) patients in TIGeR-PaC, a contemporary Phase 3 clinical trial. Herein, we report the results of a 16-patient pharmacokinetic (**PK**) analysis sub-study within TIGeR-PaC.

METHODS

COHORT

The planned TIGER-PAC 16-patient PK analysis sub-study was completed in August 2024. In this sub-study, collected blood samples were analyzed for systemic gemcitabine exposure (Area Under the Curve [**AUC**]) and peak plasma gemcitabine level ($\mathbf{C_{max}}$). Six study sites participated in this sub-study.

IAG/IVG TREATMENT

Gemcitabine was delivered per the following rate and duration:

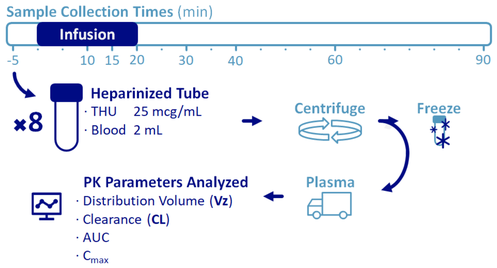
IAG	IVG
1000 mg/m^2	1000 mg/m^2
20 minutes	30 minutes

Collection times included baseline, 10m, 15m, 20m, 30m, 40m, 60m, and 90m for IAG, and 10m, 15m, 20m, 30m, 40m, 50m, 70m, and 100m for IVG after the start of infusion.

SAMPLE PROCESSING & ANALYSIS

Collected blood samples were processed and analyzed at the SKCCC core lab at Johns Hopkins University.

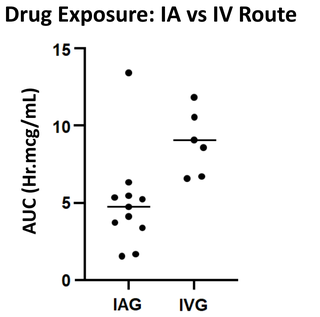
The data were quality controlled for administration and sample collection and were analyzed using standard software.



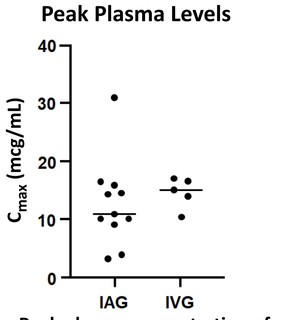
RESULTS

Of the 16 total patients in this sub-study, 11 patients received IAG, and 5 patients received IVG.

The results for AUC and C_{max} are as follows:



Impact of route of administration on systemic drug exposure

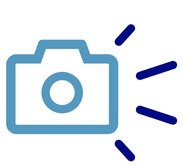


Peak plasma concentration of gemcitabine (20 min IA infusion vs 30 min IV infusion)

In terms of systemic drug exposure, IAG was associated with a significant reduction in AUC (mean, 4.99 hr · mcg/mL [SE, ± 0.96]) vs IVG administration (mean, 8.93 hr · mcg/mL [SE, ± 1.0]) (*P* = 0.026).

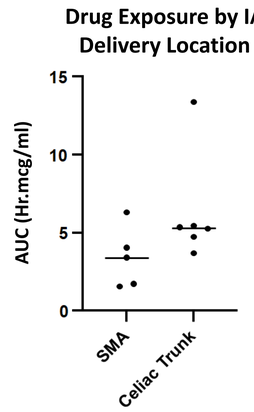
Peak plasma gemcitabine concentrations were also lower with IAG (mean C_{max}, 12.9 mcg/mL [SE, ± 2.4]) vs IVG (14.6 mcg/mL [SE, ± 1.2]) despite a 50% higher drug concentration during IAG infusion (1000 mg/m^2 over 20 minutes for IAG vs 30 minutes for IVG).

[1]Farsad K, et al. Double-balloon catheter-mediated transarterial chemotherapy delivery in a swine model: A mechanism recruiting the vasa vasorum for localized therapies. *J Vasc Intervent Radiol*. 2024; 35:1043-1048. https://doi.org/10.1016/j.jvir.2024.03.016



Among patients in the IAG group, we also examined the impact of IA delivery location (superior mesenteric artery [**SMA**] vs celiac trunk) on systemic drug exposure.

A significant difference in AUC was not observed for IA gemcitabine delivery via the SMA vs the celiac trunk.



CONCLUSIONS

Localized and targeted intra-arterial delivery of gemcitabine in patients with LAPC demonstrates a PK profile that may improve both clinical efficacy and the side effect profile of gemcitabine in this setting.

The Phase 3 TIGeR-PaC study, currently enrolling, aims to determine the impact of this approach on overall survival in patients with LAPC.

FUTURE DIRECTIONS

IAG may be better tolerated than IVG with less systemic drug exposure due to local metabolism prior to systemic exposure. This hypothesis is being assessed formally as a secondary endpoint of the Phase 3 TIGeR-PaC clinical trial by assessing quality of life and use of medications to overcome myelosuppression side effects associated with chemotherapy administration.