Penelope: Tissue Penetration of Gemcitabine Phosphate Metabolites Following TAR-200 Administration vs Standard Intravesical Instillation in Minipigs

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Key Takeaway

TAR-200 improves delivery of active gemcitabine metabolites to the bladder compared with traditional intravesical delivery

Conclusions

Traditional intravesical delivery of gemcitabine has a limited therapeutic window due to the 2-hour indwelling time and the short half-life of active metabolites

TAR-200 led to persistent tissue penetration of active gemcitabine metabolites across bladder layers for the full indwelling period (as studied up to 96 hours in minipig model)

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Poster

Supplementary material

https://www.congresshub.com/Oncology/SUO2024/TAR-200/Daneshmand-Penelope

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Disclosures

Siamak Daneshmand is a consultant with BMS, CG Oncology, Ferring, Immunitybio, Johnson and Johnson, Janssen, Pacific Edge, Pfizer, Photocure, Protara, Urogen, Vesica Health.

Introduction

- Gemcitabine has been used for many years as an intravesical instillation to treat non-muscle invasive bladder cancer (NMIBC); however, its short half-life (<3h) limits tissue exposure[1]
- TAR-200 is a novel intravesical targeted releasing system (TRS) designed to deliver local sustained release of gemcitabine within the bladder offering the potential for deep-tissue penetration over time **(Figure 1)**
- Project Penelope was designed to compare the penetration, tissue distribution and retention of gemcitabine (dFdC) and its active metabolites, diphosphate and triphosphate of dFdC (dFdCDP, dFdCTP), between TAR-200 and traditional intravesical instillation methods

Figure 1: TAR-200

Methods

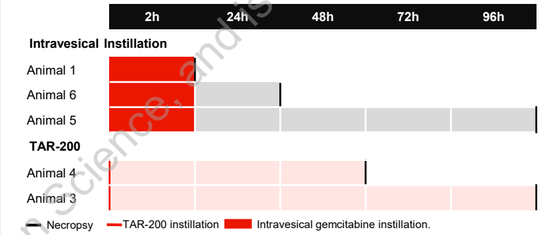
Study Design

- Five minipigs were treated with either traditional gemcitabine instillation (3 pigs) or TAR-200 (2 pigs) to assess penetration of active gemcitabine metabolites across different tissues of the bladder wall over a period of 96 hours

Intravesical Instillation

- A 50 mL solution containing 2 g free base-equivalent of gemcitabine HCl (dissolved in saline at 40 mg/mL) was prepared
- Each of 3 minipigs received a 2-hour intravesical instillation via a Foley balloon catheter (**Figure 2**)
- After the 2-hour exposure, the catheter was removed, and animals 5 and 6 were allowed to recover from the procedure and anesthesia; animal 1 was sacrificed immediately after the 2-hour instillation
- Tissues were collected at necropsy at different time intervals post gemcitabine delivery
  - Animal 1: Sacrificed immediately post 2h instillation
  - Animal 6: Sacrificed 24h after instillation
  - Animal 5: Sacrificed 96h after instillation

Figure 2: Time schedule for intravesical infusion and for placement and collection of a TAR-200 device in minipigs



TAR-200 Delivery

- The TAR-200 intravesical delivery system contained 225 mg free base-equivalent of gemcitabine (wall thickness: 0.2 mm)
- TAR-200 was inserted directly into the bladder of each of 2 minipigs and remained in place for the duration of the study until necropsy
- Tissues were collected at necropsy at different time intervals post insertion
  - Animal 4: Sacrificed 48h after TAR-200 insertion
  - Animal 3: Sacrificed 96h after TAR-200 insertion

Sample Collection

- Samples (~0.2 g) from the dome, left and right lateral wall, and trigone were collected, cut into smaller pieces, and snap frozen in liquid nitrogen
- Urothelium and lamina propria were separated from the muscle layer in subsamples of the dome, left/right lateral wall, and trigone and measured separately
- Frozen samples were transferred into pre-cooled 7 mL Precellys tubes with 1200 µL EDTA-EGTA 20 mM solution added and then homogenized in Precellys-Cryolys Evolution for 2 x 20 seconds at 8700 rpm (4°C) using 2.6- and 4-mm zirconium beads
- After homogenization, 2800 µL of methanol was added, and homogenization repeated (2 x 20 seconds at 8700 rpm). Samples were stored at -80°C

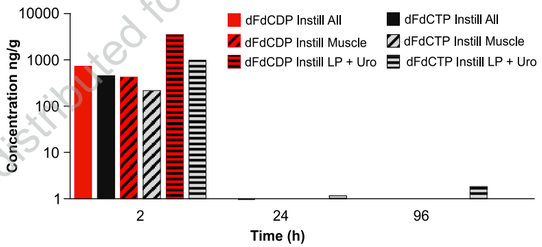
Sample Processing and Analysis

- Samples were analysed by LC-MS/MS for gemcitabine (dFdC) and its metabolites (dFdCDP, dFdCTP)

Results

- Results are reported as the mean of the four tissue samples collected (dome, left and right lateral wall, trigone). Results from the total tissue sample or by tissue type (urothelium/lamina propria and muscle wall) are reported separately

Figure 3: Mean dFdCDP and dFdCTP concentrations in bladder tissue layers following gemcitabine delivery by intravesical instillation



dFdCDP, diphosphate of dFdC; dFdCTP, triphosphate of dFdC; LP, Lamina propria; Uro, Urothelium.

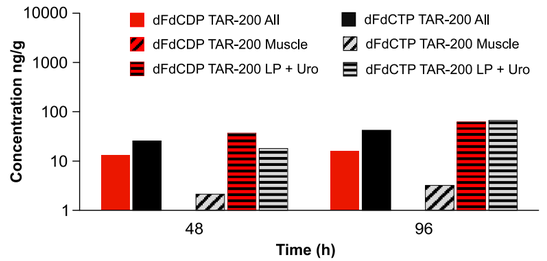
Intravesical Instillation

- After 2 hours, elevated concentrations of dFdCDP and dFdCTP were observed across bladder layers — urothelium/lamina propria, and muscle
- Due to short indwelling time and short half-life of gemcitabine, active metabolites were almost undetectable by 24 hours **(Figure 3)**

TAR-200

- With TAR-200, gemcitabine metabolites dFdCDP and dFdCTP were detected in all bladder tissue layers throughout the 48-hour and 96-hour indwelling period
- Active metabolite concentrations were higher in the urothelium and lamina propria compared to the muscle, but were sustained in both tissue samples for up to 96-hours
- Active metabolite concentrations were lower compared to levels detected following 2h gemcitabine instillation. However, concentrations of active metabolites were sustained across bladder tissues up to 96h **(Figure 4)**

Figure 4: Mean dFdCDP and dFdCTP concentrations in bladder tissue layers following gemcitabine delivery by TAR-200



dFdCDP, diphosphate of dFdC; dFdCTP, triphosphate of dFdC; LP, Lamina propria; Uro, Urothelium.

- Results confirmed that TAR-200 maintained persistent tissue penetration of active gemcitabine metabolites, particularly in the urothelium and lamina propria, where concentrations were sustained for up to 96-hours post insertion

References

1. Goldberg IP, et al. *Arch Pharmacol Ther.* 2022;4(1):13-22.

Urothelial Cancer

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