Convection enhanced delivery of EGFR-targeting antibody drug conjugates: Sercurvatulatine tamine and Depatux-M in glioblastoma patient derived xenografts

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ABSTRACT

BACKGROUND
EGFR-targeted antibody-drug conjugates (ADCs) show promise as a novel treatment in a subset of glioblastoma (GBM). Two EGFR-targeting ADCs include first generation Depatux-M with an anti-EGFR toxin monomethoxypolyethylene glycol (mPEG) linker and Sercurvatulatine tamine (Ser-T), with a DNA cleaving agent pegylated polyboronic acid dimethyl ester (PBD) toxin. Due to their large molecular weight, poor drug distribution across the blood brain barrier significantly limits the efficacy in EGFR-amplified GBM. We studied whether convection enhanced delivery (CED) can be used to safely infuse these two EGFR-targeted ADCs in patient derived xenografts (PDX) models of EGFR-amplified GBM.

METHODS
The efficacy of Depatux-M and Ser-T was evaluated in vitro and in vivo in two EGFR-amplified PDXs (GBM10 and GBM108). Immunofluorescence staining was used to evaluate drug distribution along with pharmacodynamics of the ADCs. CED was performed by stereotactic placement of an infusion catheter within the orthotopically implanted xenograft. Immunohistochemistry was used to explore mechanisms of normal cell toxicity.

RESULTS
Despite potent activity and impressive bystander killing in vitro, systemic administration of either ADC conferred minimal extension in survival for either GBM10 or GBM108. In contrast, CED significantly enhanced ADC delivery to tumor and peri-tumoral regions and extended survival. Dose-finding studies in orthotopic GBM108 identified 2 μg Ser-T and 80 μg Depatux-M as safe and effective associated with extended survival prolongation (~300 days and 95 days, respectively). Four Ser-T infusions every 21 days controlled tumor growth but was associated with lethal toxicity approximately 7 days after the final infusion. Limiting dosing to two infusions in GBM108 provided profound treatment survival extension of over 200 days. In contrast, four Depatux-M CED infusions were well tolerated and significantly extended survival in both GBM108 (%98 days) and GBM108 (%120 days). In a toxicity analysis, Ser-T treated in 100 nmol of the indicated drugs were collected and added 1:1 to existing media of SVG-A cultures. Cytotoxicity was calculated after 7 days.

SYSTEMIC DOSING EFFICACY

Conclusions
Depatux-M is well tolerated when infused into normal brain and results in extended survival in orthotopic GBM PDXs. In contrast, Ser-T, with a distinct PBD toxin, had a much narrower therapeutic window when delivered by CED.

REFERENCES

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Figure 7: MALDI: Mice with established GBM tumors were dosed as indicated AbbV5 (60 mg CED), AbbV5- MBAF (60 μg CED) and Depatux-M (5 mg/kg IP or 60 μg CED) and were processed 24 hrs later for H&E staining. MALDI MSI ion images reflect the spatial distribution of the CED-MMAF fragment used for quantitation. <LOD is below limit of detection.

CONCLUSIONS

- Circumventing the BBB through CED increases delivery and efficacy of brain impermeable drugs like Depatux-M and Ser-T.
- Tat-like non-specific cytotoxic effects against both proliferating and quiescent cells which may contribute to the significant toxicity.
- Toxicity seen with Abb5-tatrine suggest linker cleavage and brain microenvironment by hydrolytic enzymes, such as carboxylesterase 1.
- Non-specific activity of Abb5-MMAF likely reflects non-specific endocytosis or tat toxicity via Fo\_ receptor.

CONCLUSIONS

- CED infusion of ADCs provides robust and sustained distribution throughout the tumor and surrounding normal brain tissue.
- Depatux-M has much wider therapeutic window which further preclinical and possible clinical development of CED infusion.