Tesevatinib monotherapy efficacy against GBM12 is robust in vitro but relatively modest in the intracranial GBM12 model, despite excellent brain penetration

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Abstract

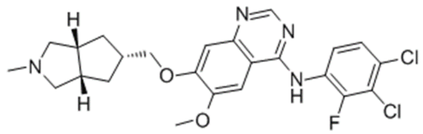
BACKGROUND: Tesevatinib (TES) is a potent brain penetrant EGFR/VEGFR2 inhibitor. This study evaluated TES monotherapy efficacy in a wildtype EGFR overexpressing, patient-derived xenograft (PDX) glioblastoma model (GBM12) and the influence of efflux transport and tissue binding on TES distribution to the brain.

METHODS: In vitro TES efficacy was evaluated in a GBM12 primary neurosphere assay. In vivo efficacy was assessed using athymic nude mice bearing either intracranial or flank GBM12 tumors, treated with TES 70 mg/kg PO d1-5 q7 days. Non-tumor bearing FVB mice (wild-type (WT) and Mdr1a/b(-/-)Bcrp(-/-) (TKO) knockouts) were dosed once with TES 70 mg/kg PO to assess plasma and brain disposition. Steady-state TES brain/plasma ratios were evaluated using osmotic minipumps. TES binding to plasma and brain was assessed by rapid equilibrium dialysis.

RESULTS: GBM12 neurosphere counts were reduced by 81% and 97% with TES 100 nmol/L (49 ng/ml) and 300 nmol/L, respectively. TES efficacy in both intracranial (median survival increased from 22 to 30 days, p =0.019) and flank GBM12 models (time to predefined tumor volume increased from 13 to 22 days, p =0.001) was observed but was less pronounced than the in vitro models. Two-hour brain and plasma concentrations were 0.72 µg/g and 1.33 µg/ml in WT mice (ratio = 0.53), and 10.03 µg/g and 2.03 µg/ml in TKO mice (ratio = 5.73). At steady-state, brain and plasma concentrations were 1.54 µg/g and 1.10 µg/ml in WT mice (ratio = 1.44), and 27.35 µg/g and 1.13 µg/ml in TKO mice (ratio = 24.37). TES fraction unbound was 0.2% in brain and 1% in plasma.

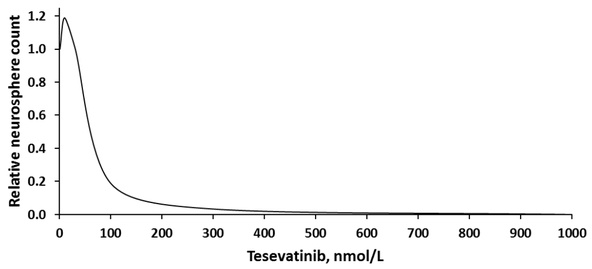
CONCLUSION: TES monotherapy efficacy against GBM12 is robust in vitro but relatively modest in the intracranial GBM12 model, despite excellent brain penetration. Pharmacodynamic experiments and survival studies in other PDX GBM models are in progress to investigate this phenomenon further.

Background



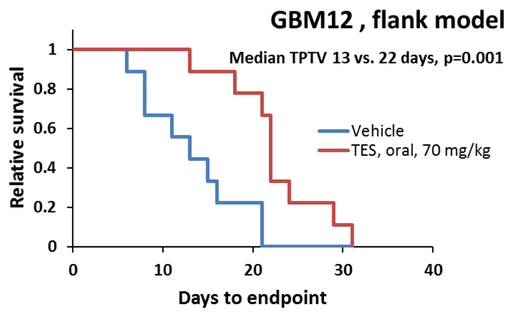
- Tesevatinib (TES) is a mult-targeted tyrosine kinase inhibitor
- EGFR IC_{50} = 0.3 nmol/L
- VEGFR-2 IC_{50} = 1.5 nmol/L
- EGFR and VEGFR-2 amplification is common in gliomas, and play roles in gliomagenesis
- We investigated the efficacy of TES monotherapy in a wildtype EGFR overexpressing, patient-derived xenograft (PDX) glioblastoma model (GBM12)
- We also investigated the influence of efflux transport and tissue binding on TES distribution to the brain

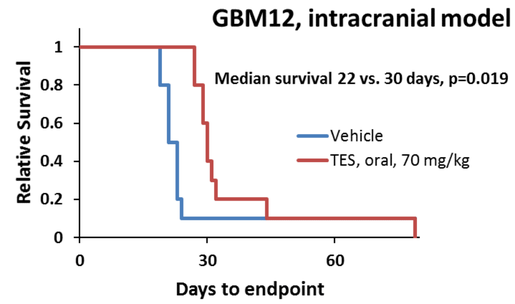
In vitro efficacy in PDX GBM12



PDX GBM12 cells were plated in stem cell media and treated with TES 0-1000 nmol/L for three weeks. Neurosphere counts were determined manually and compared.

In vivo efficacy in PDX GBM12

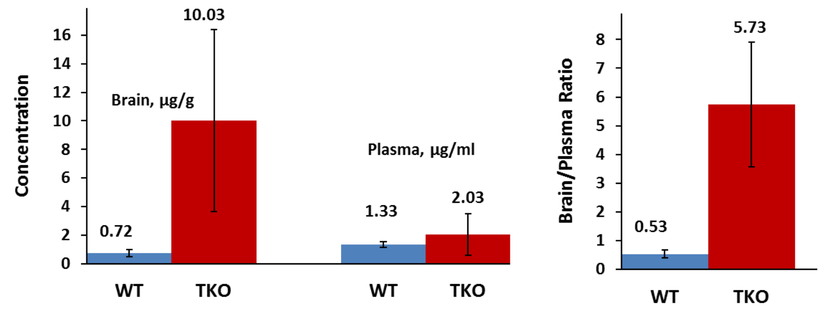




Athymic nude mice bearing either flank or intracranial GBM12 tumors were treated with TES 70 mg/kg PO d1-5 q7 days

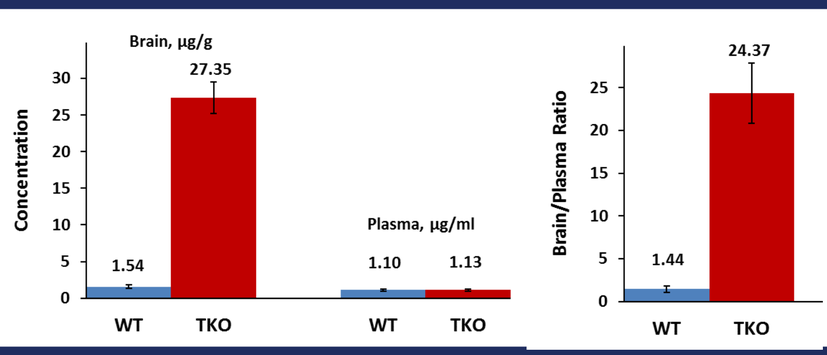
TPTV = Time to predefined tumor volume

TES pharmacokinetics in Mdr1a/b$^{(-/-)}$Bcrp$^{(-/-)}$, 2 hour timepoint



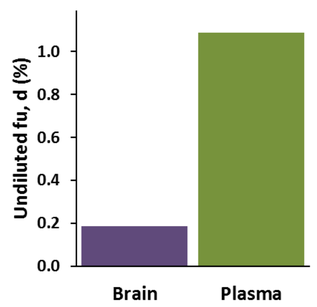
Non-tumor bearing FVB mice (wild-type (WT) and Mdr1a/b(-/-)Bcrp(-/-) (TKO) knockouts) were dosed once with TES 70 mg/kg PO. Plasma and brain were harvested after 2 hours to assess plasma and brain disposition.

TES pharmacokinetics in Mdr1a/b$^{(-/-)}$Bcrp$^{(-/-)}$, steady-state



Non-tumor bearing FVB mice (wild-type (WT) and Mdr1a/b(-/-)Bcrp(-/-) (TKO) knockouts) were dosed with TES using osmotic minipumps implanted intraperitoneally. Plasma and brain were harvested to assess plasma and brain disposition.

TES binding to brain and plasma



TES binding to plasma and brain was assessed by rapid equilibrium dialysis over 4 hours.

Conclusions

- TES monotherapy efficacy against GBM12 is robust in vitro
- TES monotherapy efficacy is relatively modest in the intracranial GBM12 model, despite excellent brain penetration.
- TES is highly bound in the brain (99.8%)
- Pharmacodynamic experiments are in progress to investigate this phenomenon further.