



ABSTRACT

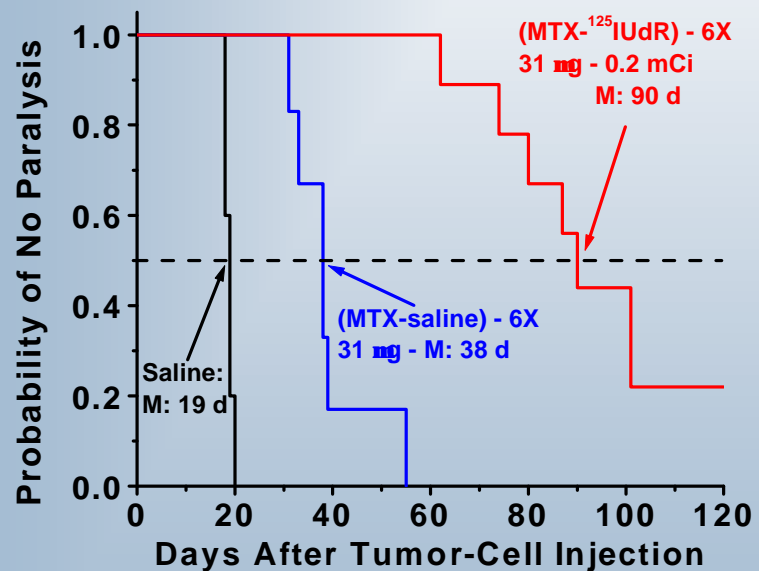
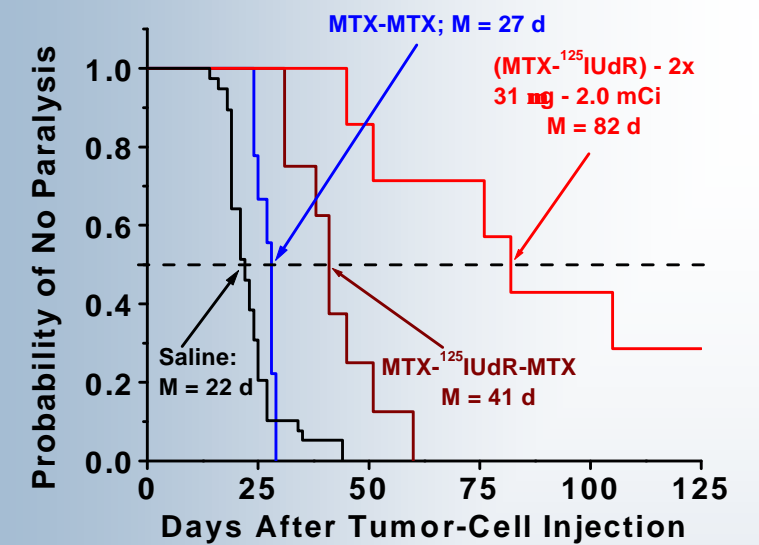
Methotrexate (MTX) is used clinically to treat neoplastic meningitis. This antimetabolite also enhances the *in-vitro* and *in-vivo* uptake of the thymidine analog 5-[¹²⁵I]iodo-2'-deoxyuridine (¹²⁵IUdR). We had previously demonstrated that the sequential administration of the maximum tolerated doses (MTD) of these two agents (MTX-¹²⁵IUdR) in rats bearing intrathecal (i.t.) TE-671 human rhabdomyosarcoma significantly augmented the therapeutic efficacy of this Auger-electron-emitting radiopharmaceutical. We have now assessed whether six cycles of MTX and ¹²⁵IUdR at 1/10th the MTD (i.e. 0.2 mCi) are therapeutically efficacious.

Nude rats were injected with TE-671 cells through an i.t.-placed catheter. Three days later, the animals were injected i.t. with (i) saline (daily, 4x, 6x, or 12x), (ii) 31 µg MTX (every other day, 2 or 6 x), and (iii) 31 µg MTX and 0.2 mCi or 2.0 mCi of ¹²⁵IUdR on alternating days (2x or 6 x). Probability of the onset of paralysis was determined as a function of time and the data were fitted to determine the medians (M) and statistical significance thereof.

The data show that (i) the injection of MTX leads to a modest increase in the onset of paralysis ($M_{2x} = 27$ d; $M_{6x} = 38$ d; vs saline = 19-22 d), (ii) the administration of 0.2 mCi of ¹²⁵IUdR is moderately more effective ($M_{3x} = 36$ d; $M_{6x} = 45$ d), (iii) the injection of 2 mCi of ¹²⁵IUdR results in a substantial delay in the onset of paralysis ($M_{2x} = 53$ d; $M_{3x} = 60$ d), (iv) the sequential administration of (MTX-¹²⁵IUdR)_{2x} (2 mCi) increases the therapeutic efficacy of ¹²⁵IUdR ($M_{2x} = 82$ d - 30% cure), and (v) the successive injection of (MTX-¹²⁵IUdR)_{6x} (0.2 mCi) is also quite effective in the therapy of this disease ($M_{6x} = 90$ d - 20% cures).

We conclude that the intrathecal injection of MTX-¹²⁵IUdR at 1/10th the MTD is therapeutically quite efficacious and can cure rats bearing i.t. tumors.

RESULTS



- MTX alone leads to a modest increase in the onset of paralysis
- The successive injection of MTX-¹²⁵IUdR at their respective MTDs enhances the therapeutic efficacy of ¹²⁵IUdR and can cure rats bearing i.t. tumor
- Six successive administrations of MTX-¹²⁵IUdR at 1/10th the MTD (0.2 mCi) are therapeutically as effective as two injections of MTX-¹²⁵IUdR at the MTD (2 mCi)

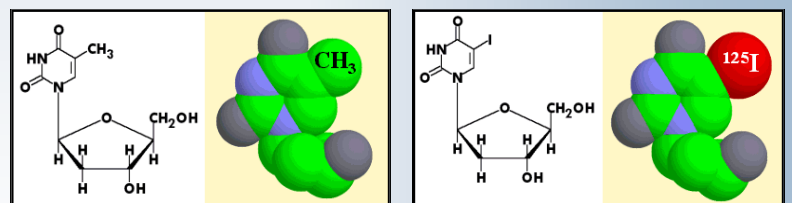
INTRODUCTION

Neoplastic Meningitis

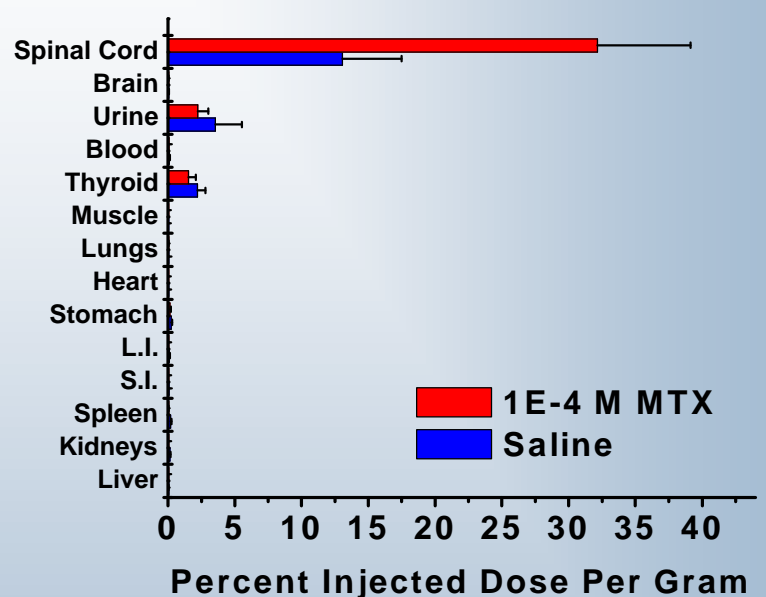
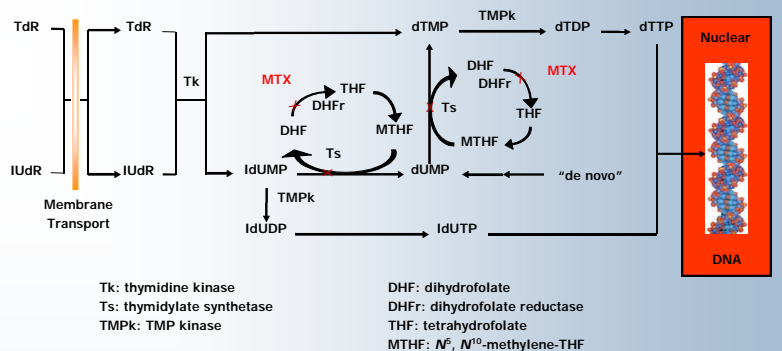
- Tumor cells confined to the leptomeninges and Subarachnoid space
- Incidence increasing, in part as a result of improved therapy for systemic malignancies (e.g. leukemia, non-Hodgkin's lymphoma, breast and lung adenocarcinomas and melanomas)
- Prognosis: poor, *median survival 4-6 weeks*
- Following treatment (radiation, MTX, cytosine arabinoside, thiotepa): *median survival 6-7 months*

Decay of ¹²⁵I

- ~21 electrons with energies from 15 eV to 24 keV
- Most electrons travel 1-2 nm
- Energy deposited per unit volume decreases 100-fold at ~4 nm from ¹²⁵I decay site
- 1 decay = >1 DSB in DNA (chromatin)



¹²⁵IUdR/TdR METABOLISM



- Biodistribution of ¹²⁵IUdR following i.t. administration in rats bearing i.t. tumors is highly favorable
- ¹²⁵IUdR uptake by i.t. TE-671 tumor is enhanced by co-administration of MTX