Antiangiogenesis agent minocycline as adjuvant therapy to oral temozolomide and radiotherapy in intracranial 9L gliosarcoma

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Introduction

In addition to being commonly used as antibiotics, tetracyclines have also been demonstrated to be potent inhibitors of tumor angiogenesis (1). In this study, we evaluate the effectiveness of minocycline, a semisynthetic tetracycline, as adjuvant therapy to two common methods of treating glioblastoma: oral temozolomide and radiotherapy (2).

Recently, the DNA-alkylating agent temolozomide has become one of the mainstays of treating glioblastoma (2). We previously demonstrated that intracranial minocycline combined with the alkylating agent BCNU extended survival beyond either one alone (3,4). In this study, we re-evaluate whether intracranial minocycline also potentiates the effects of temolozomide.

Currently, it is unclear whether antiangiogensis agents delivered systemically are synergistic with radiation when treating intracranial tumors (5). We hypothesize the blood-brain barrier is one obstacle inhibiting their action. In contrast to these previous studies, we deliver minocycline intracranially using drug-impregnated wafers and then irradiate the rats.

Methods

We assessed the effects of minocycline-impregnated wafers combined with either alkylating agents or radiation on glioma in rats. Forty-eight rats were divided into 5 groups: no treatment, minocycline, temozolomide, minocycline+temozolomide, radiation, and minocycline+radiation. All rats were implanted with intracranial 9L gliosarcoma on day 0. On day 5, animals received a controlled-release polymer containing minocycline and/or radiotherapy (20Gy). Temozolomide (100-mg/rat) was administered orally on days 5-9. Survival was the primary endpoint.

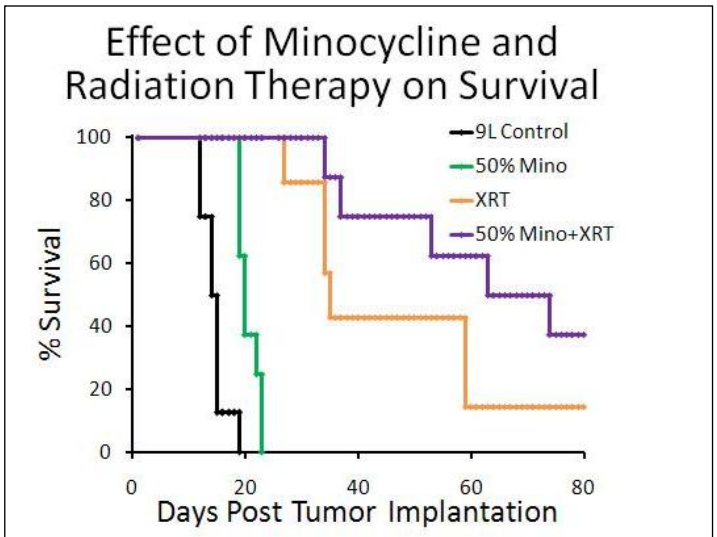

Figure 2. Effect of Minocycline and Radiation Therapy on Survival. Control animals had median survival of 15 days, while oral temozolomide had median survival of 19 (p=0.002) days. Radiation alone increased median survival to 35 (p<0.001) days, while the combination of radiation and intracranial minocycline increased survival to 68 (p<0.001) days.

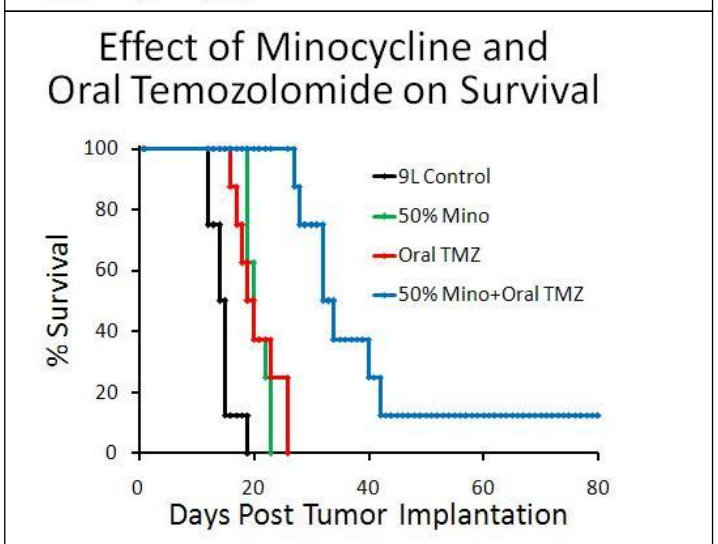

Figure 1. Effect of Minocycline and Oral Temozolomide on Survival. Control animals had median survival of 15 days, while oral temozolomide and intracranial minocycline had median survivals of 19 (p=0.002) and 20 (p=0.003) days, respectively. The combination of the two agents increased survival by 127% with a median survival of 32 days (p<0.001).

Results

Control animals had median survival of 15 days, while oral temozolomide and intracranial minocycline had median survivals of 19 (p=0.002) and 20 (p=0.003) days, respectively. The combination of the two agents increased survival by 127% with a median survival of 32 days (p<0.001). Radiation alone increased median survival to 35 (p<0.001) days, while the combination of radiation and intracranial minocycline increased survival to 68 (p<0.001) days.

Conclusions

Our results show that minocycline delivered intracranially is statistically synergistic with oral temozolomide. Furthermore, the results suggest that antiangiogenic agents delivered intracranially may be an effective way to improve radiation treatment for brain cancers.

Learning Objectives

The reader will learn that minocycline, when delivered intracranially, may potentiate the effects of systemic temolozomide and radiotherapy in a rodent gliosarcoma model.

References

1.Tamargo, R.; Bok, R.; Brem, H., Angiogenesis Inhibition by Minocycline. Cancer Research 1991, 51, (671), 672-675.

2.Stupp, R.; Mason, W.; van den Bent, M., et al., Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. NEJM 2005, 352, 987-996.

3.Weingart, J.; Sipos, E.; Brem, H., The role of minocycline in the treatment of intracranial 9L glioma. J Neurosurg 1995, 82, 635-640.

4.Frazier, J.; Wang, P.; Case, D., et al., Local delivery of minocycline and systemic BCNU have synergistic activity in the treatment of intracranial glioma. J Neurooncol. 2003, 64, (3), 203-209.

5.Norden, A.; Drappatz, J.; Wen, P., Antiangiogenic therapies for high-grade glioma. Nature Reviews Neurology 2009, 5, 610-620.