Evaluation of Interleukin-2 Neurovascular Toxicity Using DCE-MRI

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Introduction

Interleukin-2 (IL-2) is a cytokine that can produce durable complete remissions in a small percentage (5%) of patients with metastatic renal carcinoma and melanoma. One of the dose-limiting side effects of IL-2 is neuropsychiatric toxicity [1]. The pathophysiology of neuropsychiatric toxicity is not well understood, due to difficulties in performing imaging studies in critically ill patients during peak levels of side effects. It has been hypothesized that neuropsychiatric toxicity is due to vascular leak and brain edema. Our lab has developed a murine model of IL-2 treatment that closely mimics human cardiovascular toxicity. Using this murine model, dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) was employed to evaluate the effects of IL-2 on mouse brain blood vasculature and its permeability to small molecules.

Materials and Methods

MRI studies were performed on a Bruker 7T/20 scanner using a 3.5cm ID quadrature transceiver coil and a 7cm ID unshielded gradient. A total of 5 female, age matched C3H/HeN mice were scanned before and after 4 days of IL-2 treatment (150,000IU i.p., b.i.d). Ketamine-anesthetized mice underwent tail vein catheterization and injection of 0.1mmole/kg dose of gadobenate dimeglumine (MultiHance®; Bracco). DCE-MRI was performed using 2D-FLASH (TE /TR=3.1/93.5ms, flip angel=30º, FOV=2x2cm, matrix=128x128, ST=1mm, number of slices=11, TA=9sec, number of repetitions=54). Region of interests were drawn manually on the matched mouse's brain images using Osirix. Customized MATLAB programs were used to calculate signal intensities. We averaged the left and right maxillary arteries to derive the arterial input function. A two-compartment model was used to calculate fractional plasma volume (f^{PV}), endothelium transfer coefficient (K^{PS}), and permeability surface area product (PS) [2, 3]. We compared f^{PV}, K^{PS}, and PS of pre-IL2 with those of post-IL2 treated mice. Statistical analysis was performed using student 2-tailed paired t-test.

Results and Discussion

IL-2 treatment resulted in an increase in f^{PV} in the brain (Fig. 1A). The average of f^{PV} after IL-2 treatment (3.05±1.25%) was increased about 2-fold of f^{PV} pre-treatment (1.55±0.48%; p-value=0.03). These data suggest that IL-2 induces vasodilation in the blood brain vasculature. Furthermore, IL-2 also significantly doubled K^{PS} values in the brain (pre-IL2=0.20±0.09, post-IL2=0.43±0.12, p-value=0.008), indicating that IL-2 causes increased small molecule diffusion from the brain vasculature (Fig. 1B). Consistently, IL-2 increased the volume of the contrast agent taken up by the brain, as shown by the PS values (Fig. 1C; pre-IL2=0.30±0.11, post-IL2=1.28±0.49, p-value=0.008). These data suggest that mice receiving IL-2 immunotherapy experience vasodilation and brain vascular leak that may contribute to the development of neuropsychiatric toxicity.

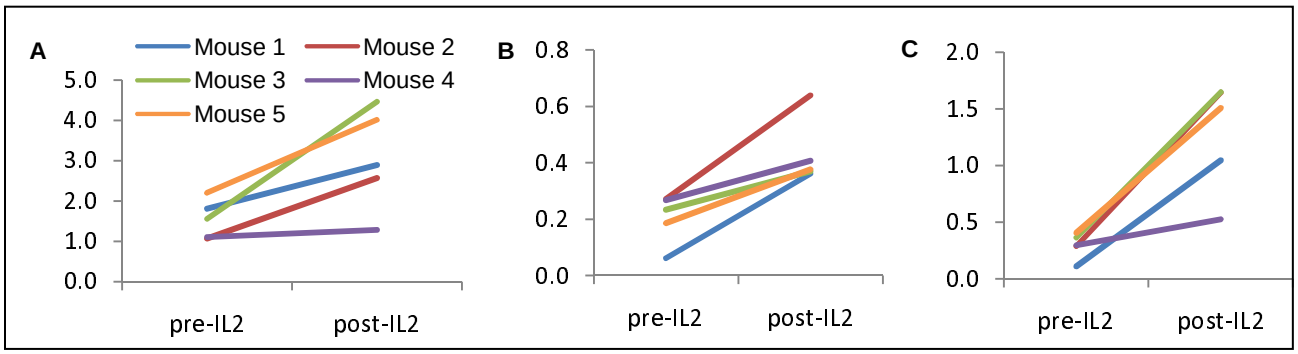

Figure 1. Individual mouse's values of f^{PV} (A), K^{PS} (B), and PS (C) before and after IL-2 treatment.

Conclusion

DCE-MRI results showed that IL-2 causes an average 2-fold increase in both f^{PV} and K^{PS} in the brains of the mice, indicating vasodilation and increase in the blood brain barrier permeability. These changes may contribute to IL-2 induced neuropsychiatric toxicity experienced by cancer patients receiving IL-2 therapy.

References

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