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Intratumoral Administration of Ultra High-Concentration Nitric Oxide (UNO) is more Efficacious than Anti-PD1 Therapy in 4T1 Tumor-Bearing Mice

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Background

For the majority of metastatic triple-negative breast cancer (mTNBC) patients, chemotherapy is the standard first-line treatment, however, outcomes in this population are poor. A monoclonal antibody against the immune checkpoint inhibitor anti–programmed death 1 (PD-1) also has antitumor activity in patients with mTNBC.

Previously, we reported that delivering ultra-high concentrations of nitric oxide (UNO) to mouse colon tumors stimulated innate and adaptive immune responses leading to the rejection of secondarily-induced tumors. Moreover, adding an anti-PD-1 antibody to UNO treatment resulted in primary tumor regression in 53% of the mice, the rejection of a distant tumors in all mice, and prolonged survival compared to control and anti-PD-1 arms.

In this *in vivo* study, we investigated the ability of UNO to improve the efficacy of anti-PD-1 antibody treatment in the aggressive mouse breast cancer model, 4T1.

Methods

We tested two treatment protocols: 4T1 mice tumors were treated with either a single dose of UNO and anti-PD-1 or a repeated dose of UNO and anti-PD-1. In the single dose design, 4T1 tumors were treated with a single administration of UNO combined with Anti-PD1 administration starting one day after UNO treatment (n=9-10 mice per group). In the repeated dosing design, 4T1 tumors were treated with UNO twice combined with Anti-PD-1 administration starting on the first UNO treatment day (n=8 mice per group).

- UNO treatment regimen: 50,000 ppm, 10 minutes, flow rate ~0.2 liters per minute
- Anti-PD1 treatment regimen: 10 mg/kg antibody was administered every 3 days for a total of 5 treatments.

Results – UNO Single Dose

The primary tumors of 4T1 tumor-bearing mice were 13.2% smaller in the combined single-dose UNO group compared to anti-PD-1 alone 15 days post-UNO treatment.

Results – UNO Repeated Dosing

The primary tumors of 4T1 tumor-bearing mice were 25.2% smaller in the combined repeated dose UNO group compared to the anti-PD-1 alone group 16 days after the first UNO treatment.

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Conclusion

Treating 4T1 tumors with single and repeated doses of UNO improved outcomes compared to anti-PD-1 alone. This suggests that local short-term treatment with UNO can serve as a treatment option for cancer patients with tumors that are not amenable to immune checkpoint inhibitor treatment.