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preclinical evidence and early clinical studies suggest that the combination of pd-1 blockade and radiotherapy might be beneficial for some tumors. however, it remains unclear whether and to what extent the combination has a synergistic effect or a potentiated effect on the anti-tumor immunity and other mechanisms. in mouse tumor models, combined pd-1 blockade and radiotherapy by intratumoral injection of anti-pd-1 antibody and/or fractionated radiotherapy demonstrated a potentiated therapeutic effect compared to single treatment in terms of prolonged os. the optimal dose of rt in combination with pd-1 blockade and the time sequence have been studied using different antibodies. in a mouse model of hep3b tumors, the anti-pd-1 antibody alone at a maximal tolerated dose (mtd) of 20 mg/kg has no anti-tumor activity, whereas anti-pd-1 therapy at 25 or 30 mg/kg was immunogenic, leading to prolonged tumor-specific cd8+ t cell responses and improved survival in the mice [142]. in a mouse tumor model of b16-f10 cells, anti-pd-1 antibody when given by subcutaneous injection at a mtd of 100 μg was ineffective, but 100 μg of anti-pd-1 antibody given by intraperitoneal injection resulted in a prolonged survival in the mice [143]. the dose-response effect of pd-1 blockade has also been studied in combination with rt by intratumoral injection of anti-pd-1 antibody. in a mouse model of b16 melanoma, the combination of anti-pd-1 antibody and hypofractionated x-ray rt up to 6gy induced a potentiated effect in terms of prolonged os and improved tumor-specific immunity [144]. the results from clinical studies are in line with those from preclinical studies in that inhibition of pd-1 was more effective when administered with fractionated rt than with a single dose. in a phase i dose escalation study of anti-pd-l1 antibody (nct00752093), different dose levels (0.1, 0.3, 1 and 3 mg/kg) of anti-pd-l1 antibody with or without radiation were given in combination to 12 patients with locally advanced or metastatic head and neck squamous cell carcinoma (hnscc). the combination of anti-pd-l1 antibody with radiation showed a significant pfs benefit compared to radiation alone (median pfs 12.6 versus 1.4 months) in the four patients who received >0.3 mg/kg of pd-l1 antibody, suggesting a ‘synergistic’ effect of pd-1/pd-l1 blockade in hnscc.

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