Preclinical evaluation of targeted radionuclide therapy combined with immune checkpoint inhibition

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Abstract

Introduction: Immune checkpoint inhibition (ICI) has substantially changed cancer treatment, but (long-lasting) responses remain absent in the majority of patients. Critical determinants for successful ICI treatment are high tumour mutational burden and pre-existing tumour infiltrating lymphocytes (TIL). Ionizing radiation can trigger inflammatory signaling that increases TIL and can give rise to mutations that can be recognized by T-cells. We are employing mouse models to evaluate therapeutic action of targeted radionuclide therapy (TRT) and combined TRT+ICI therapy.

Methods: Renca cells, transfected with human CAIX, were injected S.C. in Balb/C mice. Tumour-bearing mice received lutetium-177-labeled CAIX-specific antibody 177Lu-hG250 (i.v.) followed by ex vivo biodistribution study. Additionally, tumour growth inhibition and survival were determined upon injection of (1) 12, 18, or 24 MBq 177Lu-hG250 monotherapy, (2) ICI consisting of anti-PD-1 + anti-CTLA-4, (3) a combination of 18 MBq 177Lu-hG250 and ICI, (4) vehicle. Mean tumor volume (MTV) of each tumour growth curve was determined. Mice that had complete regressions were re-challenged with tumour cells.

Results: Tumour uptake of 177Lu-hG250 was 32±9% ID/g in Renca-CAIX and IHC confirmed CAIX expression. Furthermore, Renca-CAIX tumours showed high expression of PD-L1 and few CD8+ TIL. Compared to non-treated animals (MTV=449±204 mm3), 18 and 24 MBq 177Lu-hG250 monotherapy and TRT+ICI combination therapy significantly inhibited Renca-CAIX tumour growth (MTV=202±201 mm3, $p<0.001$, MTV=95±78 mm3, $p<0.0001$ and MTV=66±64 mm3, $p<0.0001$ respectively). Additionally, these treatments significantly prolonged survival compared to non-treated animals ($p<0.01$, $p<0.001$, and $p<0.005$ respectively). Complete tumour regression was observed in 50%, 40%, and 57% of the mice, respectively. Re-challenge of these animals with tumour cells resulted in 100% rejection of Renca-CAIX in all groups. In the TRT+ICI combination therapy group, 100% of parental Renca tumours were also rejected, whereas 40% and 75% were rejected in 18 and 24 MBq TRT monotherapy groups, respectively.

Conclusion: TRT with 177Lu-hG250 as well as its combination with ICI was therapeutically efficacious. Re-challenge experiments suggest the induction of tumour-specific T cell responses following TRT.