INTRATUMORAL DNA-BASED GENE TRANSFER AS AN EFFICIENT DELIVERY APPROACH TO COMBINE CHECKPOINT-INHIBITING ANTIBODIES WITH INTERLEUKIN 12

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Background Checkpoint inhibitors have demonstrated clinical benefit for several types of cancer, but still a large proportion of patients do not respond to treatment. To improve response rates, many combination therapies are currently under clinical evaluation. One such example is the combination of anti-PD-1 monoclonal antibodies with intratumoral gene transfer of plasmid-based interleukin 12 (IL-12). Local expression of the cytokine IL-12 has been shown to increase immune cell infiltration in cold tumors, which can make them more responsive to anti-PD-1 antibodies. The current study evaluates the efficacy of simultaneous delivery of checkpoint-inhibiting antibodies and IL-12 by intratumoral gene transfer. We recently demonstrated that intratumoral delivery of plasmid-based checkpoint inhibitors yielded systemic anti-tumor responses in a mouse tumor model, with only limited systemic antibody exposure and therefore improved biosafety.

Methods C57Bl/6J mice bearing a subcutaneous syngeneic MC38 tumor received a single intratumoral injection of plasmid DNA followed by in vivo electroporation. DNA-based IL-12 (p(IL-12), 2.5 μg) was administered alone or in combination with a DNA-based anti-PD-1 antibody (p(aPD-1), 60 μg) and/or DNA-based anti-CTLA-4 antibody (p(aCTLA-4), 60 μg). Abscopal effects were studied in mice bearing two contralateral tumors, of which only one received therapy.

Results The combined intratumoral delivery of p(IL-12) and p(aPD-1) resulted in 10% complete responders, in contrast to no complete tumor regressions with each individual treatment. Yet, differences in tumor growth or survival did not reach statistical significance between these groups. To improve anti-tumor efficacy, the combined gene transfer was expanded with a second DNA-based checkpoint inhibitor, p(aCTLA-4). While intratumoral delivery of this triple combination also led to 10% complete regressions, the response did result in significant tumor growth delay compared to p(IL-12) alone (p<0.05) and the combination of both checkpoint inhibitors (p<0.01). Moreover, in a dual MC38 tumor model, the triple combination enabled significant abscopal effects compared to untreated mice (p<0.01), which was not the case for the other treatments.

Conclusions This study demonstrates that intratumoral DNA-based gene transfer can be applied to efficiently combine different immunotherapeutics. This approach allows simplification of the treatment schedule, addresses the complex production of conventional protein-based therapeutics, and enables local drug expression, thereby minimizing systemic exposure and subsequent adverse events. Ongoing studies focus on the further validation of combined intratumoral delivery of plasmid-based checkpoint inhibitors and IL-12, by investigating the effect on tumor-infiltrating and peripheral immune cells as well as through evaluation of the triple combination in other tumor models.

Ethics Approval This study was approved by the KU Leuven Animal Ethics Committee, approval number P130/2017.

REFERENCES