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IMMUNOTHERAPY

Local chemotherapy synergizes with CTLA-4 inhibition

The availability of immune-checkpoint inhibition has dramatically improved the treatment of patients with advanced-stage melanoma; however, not all patients respond and, in particular, patients with a non-inflamed tumour microenvironment (TME) are particularly insensitive to this approach. Now, using a translational approach, researchers have demonstrated that promoting the development of an inflamed TME using local chemotherapy renders tumours more sensitive to cytotoxic T-lymphocyte protein 4 (CTLA-4) inhibition and improved upon historical response rates in a small cohort of patients.

Researchers injected mouse models of melanoma with a single dose of either an anti-CTLA-4 antibody alone or in combination with the alkylating agent melphalan. Mice that received the combination therapy had significantly improved overall survival, with tumour $CD8^+$ T cell: regulatory T (T_{reg}) cell ratios suggesting the development of a proinflammatory TME.

On the basis of these promising results, researchers explored the safety and efficacy of this combination in 26 patients with stage 3B–4 melanoma. All patients initially received melphalan plus dactinomycin delivered as an isolated limb infusion, followed by systemic administration of the anti-CTLA-4 antibody ipilimumab. 85% of patients had responded to treatment at 3 months, with a complete response rate of 62% and a partial response rate of 23%. The majority of patients (58%) had progression-free survival durations >1 year. Similar to mouse models, patients that responded to this approach had increased tumour T cell infiltration. Grade 3–4 adverse events were observed in 38% of patients, among which diarrhoea (in 12%), colitis (12%) and pruritus (8%) were the most prevalent.

These findings provide a proof-of-principle that combination with local chemotherapy can improve sensitivity to immune-checkpoint inhibition.

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ORIGINAL ARTICLE Ariyan, C. E. *et al.* Robust antitumor responses result from local chemotherapy and CTLA-4 blockade. *Cancer Immunol. Res.* https://doi.org/10.1158/2326-6066.CIR-17-0356 (2018)