Depletion of central memory CD8$^+$T cells might impede the antitumor therapeutic effect of Mogamulizumab

Highlights

- **In a phase I study (NCT01929486) with an anti-CCR4 monoclonal antibody (mogamulizumab) in solid tumors to deplete regulatory T cells that suppress immune responses, limited anti-tumor activity was observed despite a decrease of Treg cells in peripheral blood.**
- **Comprehensive immune-monitoring revealed that patients who achieved long-term survival with mogamulizumab treatment possessed high levels of central memory CD8$^+$ T cells, which are reportedly important for anti-tumor immune responses.**
- **Modulating the dose of mogamulizumab could enhance the anti-tumor immune response through selective depletion of Treg cells that highly expressed CCR4 while preserving central memory CD8$^+$ T cells, leading to therapeutic response.**
- **Reducing the dosage of reagent could improve the specificity of target cells and lead to a better therapeutic effect, which is an important finding when considering the optimal dosage of cancer immunotherapy.**

Summary

Regulatory T (Treg) cells are important negative regulators of immune homeostasis, but in cancers they prevent the anti-tumor immune response. As they harbor high expression levels of the chemokine receptor CCR4, their targeting by the anti-CCR4 monoclonal antibody mogamulizumab holds therapeutic promise. Here, we investigated mogamulizumab with solid cancer patients in phase 1b clinical trial based on the predominant detection of CCR4-expressing effector Treg (eTreg) cells in tumors. While eTreg cells in peripheral blood were significantly decreased after mogamulizumab administration in all patients, clinical responses were hardly detected. Comprehensive immune-monitoring revealed that concomitant reduction of central memory CD8$^+$ T cells with CCR4 expression, that reportedly play important roles in antitumor activity. This reduction was subsided in long survivors in whom central memory CD8$^+$ T cells possessed lower CCR4 expression and/or NK cells exhibited an exhausted phenotype. Thus, excess doses of mogamulizumab harboring enhanced antibody-dependent cellular cytotoxicity could unexpectedly deplete central memory CD8$^+$ T cells with CCR4 expression. We therefore need to carefully determine the optimal dose of mogamulizumab for successful clinical application as cancer immunotherapy to avoid unexpected depletion of effector components.

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