Abstract

Tumor diseases are severe problem worldwide with increasing number of patients suffering from various types of malignancies. Many of approved therapeutics cause serious side toxicities. Therefore, there are intensive efforts to improve cancer treatment protocols.

The aim of this study was to deplete regulatory T (T_{reg}) cells without affecting other immunocompetent cells playing a positive role in tumor eradication. T_{reg} cells were reported to hamper anti-tumor immunity and promote tumor growth and survival. Thus, their selective elimination could lead to induction of anti-tumor responses and tumor rejection if combined with chemotherapy with selected *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-bound drug conjugates.

Original approach was to deplete of T_{reg} cells without the use of anti-CD25 mAb that has been widely exploited for T_{reg} cell elimination; however, its long-term persistence in circulation together with inhibitory effect on activated effector cells ($CD25^+$) are its main disadvantages. Thus, T_{reg} cells were sensitized to cell cycle-specific cytostatic drugs via application of IL-2/anti-IL-2 JES6.1 mAb immunocomplexes that induce vigorous selective proliferation of this cell population. Subsequent application of cell cycle-specific cytostatics showed steep decrease of T_{reg} cell counts but the resulting level of T_{reg} cell numbers was similar to the steady-state level in naïve mice. Therefore, alternative protocol for T_{reg} cell elimination was employed. The approach is based on application of biotinylated anti-CD25 mAb for T_{reg} cell depletion and its subsequent elimination from circulation by HPMA copolymer-bound avidin. It appears to be promising, as it negates disadvantages of anti-CD25 mAb treatment.

Next, maximal tolerated dose of selected HPMA copolymer-bound drug conjugates was determined. These conjugates showed also potent anti-tumor activity indicating they could be used in further experiments combining T_{reg} cell depletion with chemotherapy.

Keywords: cancer, regulatory T cells, IL-2, immunocomplexes, cytostatic drugs, avidin, biotin, anti-CD25 mAb, HPMA copolymer-bound drugs, doxorubicin