Abstract

Cancer treatment with polymer-bound cytostatic drugs and its potentiation through immunomodulation

Poly[N-2-(hydroxypropyl)-methacrylamide] (PHPMA) is a synthetic water soluble and biocompatible polymer which can be used as a carrier of a cytostatic drug and an antibody as a targeting moiety. The antibody ensures the site-specific delivery of the conjugate. Nevertheless, even polymeric conjugates without any tumor-specific targeting moiety are passively accumulated within solid tumors via so called Enhanced Permeability and Retention (EPR) effect, in case that their molecular wight is at least 40 kDa. Antibody-targeted polymeric drugs have been shown previously to have a cytostatic activity *in vitro* and an antitumor activity *in vivo*. Since treatment of cancer diseases in practice is far from such ideal conditions and many tumors have no strictly specific marker suitable for targeted therapy, upgrading of the treatment efficacy represents the major challenge. One of the possible ways how to improve insufficient chemotherapy outcome can be using of a combination of polymer-bound cytostatic drug and potent immunomodulation able to induce a robust anti-cancer immune response.

In this study, we have used B cell leukemia BCL1 as an experimental tumor model. BCL1 cells express surface IgM with an unique idiotype which is thus a perfect tumor-specific target. BCL1-specific IgM idiotype can be recognized by monoclonal antibody (mAb) produced by B1 hybridoma. We used suboptimal treatment protocols combining B1 mAb-targeted polymeric drug with depletion of T regulatory cells or application of poly I:C. Immunocomplexes formed by murine IL-2 and anti-mouse IL-2 mAb S4B6 were previously reported to strongly stimulate expansion of $CD122^{hi}$ cell populations, namely $CD8^{+}$ memory T cells and NK cells, which are essential in anti-tumor immunity. Immunotherapy with IL-2 immunocomplexes can be further improved by co-injection of IL-12 which strongly increases an expression of molecules involved in T cell and NK cell effector functions. We tested whether this approach can potentiate the effect of a conjugate containing irrelevant human polyclonal antibody instead of specific B1 mAb.

While the suboptimal protocols using low doses of B1 mAb-targeted polymeric conjugate or using conjugate containing irrelevant antibody lead to only poor therapeutic efficacy, we were able to reach significantly better outcome when the immunomodulation was applied. Thus we suggest that immunomodulation represents a suitable improvement of polymeric drug-based therapy and consider the IL-2 immunocomplexes as a promising component of the advanced treatment schedules.

Keywords

malignant diseases, polymeric conjugate, PHPMA, doxorubicin, immunomodulation, interleukin-2, interleukin-12, $CD8^{+}$ T cells, NK cells, T regulatory cells

Klíčová slova

nádorová onemocnění, polymerní konjugát, PHPMA, doxorubicin, imunomodulace, interleukin-2, interleukin-12, $CD8^{+}$ T buňky, NK buňky, T regulační buňky