Abstract

Multidrug resistance (MDR) is a common cause of failure in chemotherapy for malignant diseases. Cancer cells develop MDR most often via the up-regulation of P-glycoprotein (P-gp) expression. P-gp is an efflux pump with broad specificity belonging to ATP-binding cassette (ABC) transporters which decreases the intracellular concentration of various drugs.

We designed polymeric conjugates based on an N-(2-hydroxypropyl)methacrylamide (HPMA) bearing a cytostatic drug and/or P-gp inhibitor and tested their cytostatic/cytotoxic activity in vitro and their therapeutic efficacy in vivo in MDR tumors. We demonstrated that HPMA copolymer conjugates bearing both the cytostatic drug (doxorubicin (Dox) or pirarubicin) and the P-gp inhibitor (derivative of reversin 121 (R121) or ritonavir) possess remarkable cytostatic and cytotoxic activity in MDR tumor cell lines in vitro and superior antitumor activity in vivo. Notably, the HPMA copolymer conjugate bearing both Dox and R121 showed significant antitumor activity in both P388/MDR and CT26 mouse tumor models and was capable to completely cure 6 out of 8 mice with established CT26 tumors.

We explored the potential of micelle-forming HPMA copolymer-poly(propylene oxide) (PPO) diblock bearing Dox to overcome MDR in vitro and in vivo. The HPMA copolymer-PPO diblock bearing Dox showed higher cytostatic and cytotoxic activity in vitro in comparison to the HPMA copolymer conjugate bearing Dox in MDR murine and human cancer cell lines. Moreover, the HPMA copolymer-PPO diblock bearing Dox showed higher antitumor activity and accumulation in mouse EL4 lymphoma in vivo in comparison to the HPMA conjugate bearing Dox.

Finally, we evaluated the potential of polymeric NO donors to improve the therapeutic activity of the HPMA copolymer conjugate bearing Dox through an increase of the enhanced permeability and retention effect. Polymeric NO donors were able to sensitize murine and human cell lines to the cytostatic activity of Dox in vitro and significantly improved the treatment of EL4 lymphoma-bearing mice with the HPMA copolymer conjugate bearing Dox in vivo.