Abstract

Conjugation of anticancer drugs to biocompatible water soluble polymers is an attractive approach to improve the drug’s blood solubility and stability, tumour targeting properties and antitumour efficiency, while at the same time reduced the drug’s non specific tissue toxicity. This study sought to investigate the outcome of applying the polymer drug conjugation strategy to the water soluble anticancer antimetabolite nucleoside analogues. Typically, the changes that might be brought to the chemical properties, aqueous and plasma stabilities, and the antitumour efficiency of the drugs of this class upon conjugation of the drug to the water soluble biopolymers were of interest to be looked into. In the study, the antimetabolite nucleoside analogue gemcitabine was chosen to be the model drug, whereby a novel polymer-drug conjugate derivative for gemcitabine, that is poly-L-glutamic acid - gemcitabine (PG-G) was synthesized, chemically characterized and tested against its parent drug gemcitabine using in vitro and in vivo breast cancer models. Compare to its parent drug gemcitabine (G), the novel PG-G possess extensive plasma stability, (with in vitro plasma degradation half life that is 8 x longer than that of G), reduce in vitro cytotoxicity against cancer cells but was capable to exert superior antitumour activity potentially via enhanced permeability - retention (EPR) effect in the in vivo test using 4T1 mouse breast tumour model. At the same time, the acute and chronic toxicity of the PG-G were found to be tolerable, the in vivo plasma elimination half life of the PG-G was found to be 2.5 times longer at equivalent gemcitabine intravenous dose and the PG-G body distribution was significantly different to that of the gemcitabine. The improvement of gemcitabine’s plasma stability and anti breast tumour efficiency through the polymer-drug conjugation strategy has not only demonstrated the potential benefits and the possibility of applying the same strategy to the rest of the members of the water soluble
antimetabolite nucleoside analogue drug class, but again indicated the usefulness and
the need to conjugate the presently available water soluble anticancer drugs to the
biopolymer, in order to reduce non-specific toxicity and enhance the anticancer
efficiency of these drugs.
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