



Innovative and strategic materials against cancer: Preclinical researches on tumour accumulative novel sugar dendritic Gd-DTPA complex MRI contrast agents and IER5/Cdc25B targeted novel phospho sugar anti-tumour agents to innovate in cancer therapy

Mitsuji Yamashita

Shizuoka University, Japan

Abstract

Innovative and strategic materials against tumor cells to decrease sharply the number of dead people by tumors are desired eagerly. To innovate in medical technologies of diagnosis and cure for various kinds of tumors by novel medicinal materials, i.e., sugar dendritic Gd-DTPA complex MRI contrast agent (DEN-OH) and IER5/Cdc25B targeted novel phospho sugar antitumor agents (TBMPP) were prepared and evaluated in vitro and in vivo methods, and then these novel medicinal materials were revealed preclinically to have excellent characters against tumor cells. To innovate in the medical technologies, tumour accumulative sugar dendritic Gd-DTPA complex MRI contrast agent (DEN-OH) and IER5/Cdc25B targeted novel phospho sugar antitumor agents (TBMPP) were prepared and evaluated preclinically. These novel medicinal materials were revealed to exert excellent characteristics against tumour cells. DEN-OH was prepared by introduction of protected sugar dendritic parts to the ligand of diethylenetriamine pentaacetic acid (DTPA) and the successive complex formation with Gd (III) and hydrolysis. The prepared DEN-OH for MRI contrast agent with the less concentration (10% Gd concentration of Gd-DTPA complex) showed quite clearer images of quite early stage (ca. 1 mm size) cancer. To innovate in the medical technologies, tumour accumulative sugar dendritic Gd-DTPA complex MRI contrast agent (DEN-OH) and IER5/Cdc25B targeted novel phospho sugar antitumor agents (TBMPP) were prepared and evaluated preclinically. These novel medicinal materials were revealed to exert excellent characteristics against tumour cells. DEN-OH was prepared by introduction of protected sugar dendritic parts to the ligand of diethylenetriamine pentaacetic acid (DTPA) and the successive complex formation with Gd (III) and hydrolysis. The prepared DEN-OH for MRI contrast agent with the less concentration (10% Gd concentration of Gd-DTPA complex) showed quite clearer images of quite early stage (ca. 1 mm size) cancer (Figure 1). Phospho sugar derivatives were prepared by new synthetic pathway to construct the compound library. Deoxybromophospho sugar derivatives such as TBMPP (Tribromophospho sugar derivative) prepared from phospholene derivative were first found to exert quite strong and wide spectral antitumor activities by in vitro evaluation against various kinds of leukemia cells such as K562, U937, etc. cell lines as well as solid cancer cells. Mechanistic studies with TBMPP against leukemia cells by Western blotting showed that the phospho sugar enhanced the expression of IER5, suppressed the expression of Cdc25B against tumour cells selectively and specifically, and then induced apoptosis at the mitosis step of the tumour cell cycle. In vivo evaluation for TBMPP was successfully performed by using a nude mouse transplanted by K562 cells on the skin. Phospho sugar derivatives were prepared by new synthetic pathway to construct the compound library. Deoxybromophospho sugar derivatives such as TBMPP (Tribromophospho sugar derivative) prepared from phospholene derivative were first found to exert quite strong and wide spectral antitumor activities by in vitro evaluation against various kinds of leukemia cells such as K562, U937, etc. cell lines as well as solid cancer cells. Mechanistic studies with TBMPP against leukemia cells by Western blotting showed that the phospho sugar enhanced the expression of IER5, suppressed the expression of Cdc25B against tumour cells selectively and specifically, and then induced apoptosis at the mitosis step of the tumour cell cycle. In vivo evaluation for TBMPP was successfully performed by using a nude mouse transplanted by K562 cells on the skin. The main strategy to achieve a targeted CA relies on the optimization of each component, for example, the Gd³⁺ chelate unit, responsible for the imaging and the targeting moiety, responsible for the recognition of the desired biomarker. Several chelate scaffolds were reported and different conjugation strategies described.

Nevertheless, several parameters rule the final in vivo application of such contrast agents, making their translation to routine use in clinic application a demanding process. Such parameters include: the thermodynamic stability and kinetic inertness of the Gd³⁺ complex; its conjugation to a targeting unit (which should insure the maintenance of a good affinity and selectivity towards the desired target/biomarker); maximal relaxivity; optimal pharmacokinetic properties and good clearance, while guarantying an adequate imaging window; no in vivo toxicity and good solubility. Understanding how changes in the structure of the ligands can influence the main relaxometric parameters, together with the choice of a good target, enables the rational design of optimal contrast agents. The clinical translation of targeted contrast agents is indeed still scarce, with only few contrast agents reaching clinical trials phase.

Note: This work is partly presented at Joint Event on 12th International Conference on PHARMACEUTICAL CHEMISTRY & 2nd EUROPEAN PATHOLOGY CONGRESS during on May 20-21, 2019 held at Berlin, Germany