Gemcitabine versus Modified Gemcitabine: A Review of Several Promising Chemical Modifications

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Résumé en anglais	Gemcitabine, an anticancer agent which acts against a wide range of solid tumors, is known to be rapidly deaminated in blood to the inactive metabolite 2′,2′-difluorodeoxyuridine and to be rapidly excreted by the urine. Moreover, many cancers develop resistance against this drug, such as loss of transporters and kinases responsible for the first phosphorylation step. To increase its therapeutic levels, gemcitabine is administered at high doses (1000 mg/m2) causing side effects (neutropenia, nausea, and so forth). To improve its metabolic stability and cytotoxic activity and to limit the phenomena of resistance many alternatives have emerged, such as the synthesis of prodrugs. Modifying an anticancer agent is not new; paclitaxel or ara-C has been subjected to such changes. This review summarizes the various chemical modifications that can be found in the 4-(N)- and 5′-positions of gemcitabine. They can provide (i) a protection against deamination, (ii) a better storage and (iii) a prolonged release in the cell, (iv) a possible use in the case of deoxycytidine kinase deficiency, and (v) transporter deficiency. These new gemcitabine-based sysems have the potential to improve the clinical outcome of a chemotherapy strategy.
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[5] http://dx.doi.org/10.1021/mp300370t