Combined strategy based on pre-activated analogs of oxazaphosphorines for increased therapeutic index and immune modulation

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Résumé en anglais	Oxazaphosphorines (Oxaza) represented by cyclophosphamide (CPA) and ifosfamide (IFO) are still the corner stone of several polychemotherapy protocols as they are widely indicated in the treatment of numerous cancer from soft tissue sarcomas to lymphomas and immune-related diseases. However, Oxaza are prodrugs requiring cytochrome (CYP) P450 bioactivation responsible of limiting adverse effects. In the case of IFO, bioactivation leads to a low release of 4-OH-IFO (10%), which generates the active nitrogen mustard displaying DNA cross-links. Associated toxicities of IFO due to acrolein, (urotoxicity) and to chloroacetaldehyde (neuro and nephrotoxicity) have been described. Thus, increasing IFO therapeutic index could be of major interest. To circumvent these toxicities, our team has designed new pre-activated IFO analogs to avoid CYP bioactivation (Skarbek et al J Med Chem 2015). Among these analogues some have the ability to self-assemble as nanoassemblies (NAs), the others can be encapsulated within nano-lipid capsules (NLCs). These new drug delivery systems (DDS) can take advantage of passive targeting, as stealthiness of these DDS can be provided by PEGylation by using Cholesterol-polyethylene glycol or the use of surfactant. These DDS can also be functionalized by appropriate monoclonal antibodies leading to multi stage DDS with active targeting properties. Regarding CPA, it has been shown and described in literature that low doses of CPA enhance the immunity by promoting differentiation of $CD4^+$ cell toward Th1. As IFO is isomeric form of CPA, it was assumed that IFO could also have such properties. Studies on immunocompetent MCA205 mouse model, an immunogenic fibrosarcoma mouse model, demonstrate a dose-dependent immunomodulation of IFO towards a modulation of the secretion of IFNy, IL-17A and IL-6 cytokines. The ongoing experiments on mouse model depleted in $CD4^+$ T cells and $CD8^+$ T cells show the antitumor efficacy of IFO 150mg/kg on these immune cells in tumor regression. Both strategies could lead to the design of nano-immuno-conjugates (NICs) which could benefit of the immunomodulatory effects of X-Oxaza combined to their antiproliferative properties targeted through immune checkpoint antibodies. These new functionalized DDS may provide a useful strategy to give specificity to active drugs used for many years in clinical practice. Both DDS could be grafted with mAbs which could lead to a new family of DDS aiming to combine antiproliferative and immunomodulatory properties for a dual antitumoral action Citation Format: Julia Delahousse, Charles Skarbek, Valentine Gauthier, M Desbois, Emilie Roger, C. Pioche-Durieu, M. Rivard, D. Desmaële, T. Martens, E. LeCam, Jean-Pierre Benoit, P. Couvreur, Nathalie Chaput-Gras, Angelo Paci. Combined strategy based on pre-activated analogs of oxazaphosphorines for increased therapeutic index and immune modulation [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017;77(13 Suppl):Abstract nr 2195. doi:10.1158/1538-7445.AM2017-2195
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