ERA-Net EuroNanoMed JTC-3 2011
Transnational collaborative project

Title:
Chemo-hyperthermal Delivery - Combined chemo-hyperthermal control of hepatic tumors, based on microwave-activated subendothelial-targeted magnetic nano-assemblies
CheTherDel

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Background:
While resection is the main potentially curative tool in liver metastasis it is neither always possible nor easy to achieve R0 resections as in many circumstances multiple lesions are distributed in both liver lobes. An associated problem is related to liver reserve tissue after resection as well as potential recurrence and difficulties associate with sequential resections. An alternative approach is thermal complete destruction of tumoral tissue in tumor negative margins. Being a non-resectional technique the results are seldom verified as there is no surgical specimen and thermal destruction is only controlled by obtaining a sufficient volume of delivered heat. Such cure is the unusual result because tumoral destruction is seldom complete in the case of larger metastasis and the presence of non visible metastatic foci either in the vicinity of the lesion or elsewhere in the liver. Chemotherapy for metastatic liver diseases suffered a dramatic improvement over the last decades with new drugs being used and significant improvement of survival. However, there is a high degree of systemic toxicity and sometimes therapy has to be stopped due to major toxicity; in addition, there is significant limitation in quality of life during long term therapy. Delivering drugs and particles to target area, by use of customised nano-aggregates became recently an area of major interest, and it became especially important to create new preparations and systems for chemotherapy delivery, which increase the activity of known anti-cancer drugs and allow for more pronounced pharmacological effect.

Project aims
The main aim of the project is to synergistically combine nano-theranostics principles with targeted chemo-thermal-delivery, by use of customized microwave energy.
A common strategy to achieve active NPs retention in anti-tumor therapy is based on conferring them a ***selective high affinity binding to phenotypically altered neoplastic cells or tumoral subendothelial structures***, using ***monoclonal antibodies***. This approach is expected to co-

operate with the passive accumulation of NPs in the tumor mass, due to enhanced permeability retention effect.

The **first purpose** is to ***design and develop two classes of bio-compatible - targeted as further thermo-activable - nano-therapeutics***

1. Development of Nano-magnetic carrier particles (FeOx with different sizes) able to focalize microwave energy and generate upon irradiation local heat at tailored temperatures around 45C. These particles will be derivatized with monoclonal antibodies to inflamed endothelial surface antigens, and to sub-endothelial antigens
2. Development of Liposomes entrapping chemotherapeutics at physiological temperatures but releasing them at higher temperatures, as generated by microwave irraditon of previously entrapped nano-magnetic carrier particles.

The **second purpose** is to ***functionalise the nano-assemblies by focalized microwave irradiation in two stages, obtained through an apparatus that will be developed within the present network***:

1. The first irradiation, performed before nano-assemblies administration, is intended to sensitize the tumor by inducing a hyperthermic effect increasing blood supply and by enhancing endothelial damage/permeation and inflammatory activation: the procedure should allow an enhanced EPR effect and therefore an increased diffusion/retention of subendothelial structure-targeted NPs in the tumor
2. The second microwave irradiation will be performed after the injection in the hepatic artery and diffusion in the tumor of the activated nano-assemblies and to determine a strong, but localized and focalised, hyperthermic action. Nano-magnetic assemblies hyperthermia will accomplish the proposed ***chemo-thermal-delivery***

Innovation

The project focuses on the development of pharmaceutical nanocarriers. Diverse innovative nano-magnetic assemblies will be designed by modifying materials, size and surface properties and tested in hepatocytes from rats in cell culture for their general toxicity and their specific influence on the proteome. The project will combine nano-theranostics principles with targeted chemo-thermal-delivery, by use of customized microwave energy in a 2-stages therapy. The physico-chemical and toxicological data will be correlated with findings from the microwave targeting efficiency in-vivo in rats, to allow establishing a benefit-risk estimation for the various nano-assemblies tested in successive trials. Separately, the particles will be tested for their effect on human hepatocytes in cell culture in order to know whether correlations can be established that simplify a later screening.

Scientific Impact

A new concept of generating ***various types of self-assembling compounds for drug delivery,*** by rational approaches, customised design and synthesis of optimal products. Target driven synthesis of novel amphyphylic heterocycles, will result in elaboration of more efficient synthetic delivery systems. A better understanding of physicochemical mechanisms, lipoplex and polyplex structure, stability in serum and transport across cellular membranes should facilitate advances toward the rationalization and conception of new self-assembling compounds. As the structure, charge and formulation of nano-particles formed by these compounds has direct influence on the stability, better understanding of the influence of these factors on the efficiency of drug delivery is also beneficial.