HUMAN-MOUSE DOSIMETRY IN CLINICAL RADIOIMMUNOTHERAPY- SPECIAL EMPHASIS ON PEDIATRIC APPLICATIONS

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Monoclonal antibody ("MAB") has been developed for targeting secretory alpha-fetoprotein in hepatic tissue. We have used these MABs for radioimmunotherapy and dose planning of recurrent hepatoblastoma, a rare childhood malignancy This MAB has been labelled with In-111 and Y-90 for clinical purposes, and can be applied for diagnosis and therapy of liver neoplasms.

Physiology based pharmacokinetic (PBPK) modeling and simulation is a useful method for prediction of biodistribution of macromolecules, it can enhance our understanding of the underlying mechanisms and hence may help in rational design of diagnostic and therapeutic agents. Here we also discuss PBPK modeling and simulation of this MAB in mice without tumor and in a pediatric patient.

In the clinical study, radiopharmacokinetic parameters for this MAB (^{111}In-DOTA-hAFP31 IgG) were calculated after serial quantitative whole body scans in a child with hepatoblastoma. A 3-D dose planning computer program was used to calculate tumor doses for In-111 and Y-90, the active tumor was delineated on PET/CT images and tumor dose calculation was done based on the In-111-MAB SPECT data using dose point kernel approach both for In-111 and Y-90. The results were compared with MIRD doses obtained for organs in SPECT imaging field, i.e. bone marrow, heart, kidneys, liver, spleen, lungs. The simulated results were fitted to experimental time series data by varying parameters which were not fixed a priori.

From quantitative serial imaging based on 8 whole body images at 0-168 hrs using In-111-MAB, the half-lives of spleen, lungs, kidneys and whole body were 502 hrs, 230 hrs, 193 hrs and 490 hrs, respectively. The measured blood half-life was 132 hrs, after a total MAB dose of 50 mg and In-111 activity of 105 MBq. The presumed Y-90 dose based on this kinetic behavior was 43 MBq which should had given 0.3Gy bone marrow dose with assumption of bone marrow: blood ratio 0.4 for IgG. The calculated MIRD Y-90 doses were for cardiac wall 0.75 Gy, liver 0.62 Gy, spleen 0.51 Gy and bone marrow 0.053 Gy, and the effective whole body dose was 0.18 Gy, i.e. 4.23 mGy/MBq. The 3-D program demonstrated the mean doses in normal tissues as follows: heart 0.58 Gy, liver 0.48 Gy, spleen 0.37 Gy and bone marrow 0.34 Gy.

The actual liver tumor dose according to the 3-D calculations was in average 0.51 Gy with range of 0.22-0.96 Gy.

It was demonstrated that the PBPK model describes the main features of the pharmacokinetics of the studied systems. It was also shown that simulation can be used for evaluating the parameters of the system and scaling up the pharmacokinetics of MAB from mice to man.

As a conclusion, a ccording to the data, probably 5-6 fold activity could have been infused without limiting toxicity. Using current activity only minor change in the biomarker behavior was observed, but with higher activities the response could have been evaluated. This data demonstrates that radioimmunotherapy procedure may be applied in childhood solid tumors, if appropriate dosimetry software is available.

It was also concluded that the transvascular permeabilities are the most important parameters and more research is needed to enable prediction of permeabilities from molecular characteristics of macromolecules. It would also be necessary to understand better and describe with a more detailed model the microstructure of the tumor and to measure or predict the antigen concentration in tumor. Non-specific, non-saturable binding in other organs/tissues should be understood better and the kinetic constants of the binding should be measured experimentally.

Although the metabolism and clearance were neglected in this study they need to be included in more detailed studies. Also the intracellular trafficking of macromolecules, which was not included in this study, shall be included in the more accurate models.