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Medizinische Fakultät Mannheim
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**Optimisation of Molecular Radiotherapy for Leukaemia Patients
using Physiologically Based Pharmacokinetic Models**

Autor: Christian Maaß
Institut / Klinik: Klinik für Strahlentherapie und Radioonkologie
Doktorvater: Prof. Dr. G. Glatting

Radioimmunotherapy (RIT) with ^{90}Y -labelled anti-CD66 antibody is used to selectively irradiate the red marrow (RM) before blood stem cell transplantation of acute leukemia patients. The activity to administer is calculated based on the estimation of time-integrated activity coefficients. These coefficients are determined prior to therapy using gamma camera and serum measurements after injection of ^{111}In -labelled anti-CD66 antibody and measure the accumulated amount of antibody per organ. Equal pre-therapeutic and therapeutic biodistributions are usually assumed to calculate these coefficients. However, additional measurements during therapy have shown that this assumption needs to be abandoned. Furthermore, an investigation using a simple compartmental model and pre-therapeutic and therapeutic serum data of ten patients showed that the biodistribution of fully, half- and non-immunoreactive antibody has to be modelled to accurately determine the time-integrated activity coefficients.

In the first part of this work, two physiologically based pharmacokinetic models differing in constraints for the estimation of the red bone marrow and serum antigen numbers were developed. Pre-therapeutic and therapeutic gamma-series and serum measurements of 27 patients were investigated individually. Submodels to account for alterations in immunoreactivity of administered radiolabelled anti-CD66 antibody were implemented. Model selection was performed based on the corrected Akaike Information Criterion. Time-integrated activity coefficients for the red bone marrow, liver, spleen, serum and whole body were estimated. For treatment planning, prediction of the therapeutic serum time-activity curve was evaluated by comparing the simulated (predicted) and measured time-integrated activity coefficients. Prediction accuracy could be improved using the developed model when compared to the former standard of using sums of exponential functions for individual dosimetry. In the second part of this work, further improvements of the model were investigated using population based parameters (Bayes statistics) and two different fitting algorithms. Therefore, biokinetic data of 26 patients were investigated. The ratio of circulating and granulocytic red bone marrow forms was explicitly fitted in the model showing a considerable alteration of the expression of CD66 cells on all granulocytic forms due to leukaemia.

The novel application of Bayes parameters in physiologically based pharmacokinetic modelling improved prediction accuracy of therapeutic serum time-activity curves considerably. Thus, integrating this knowledge about the investigated patient population will optimize individual treatment planning with ^{90}Y -labelled anti-CD66 antibody in radioimmunotherapy for leukaemia patients.