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Aspects on optimisation of High Dose Methotrexate treatment in children with Acute Lymphoblastic Leukaemia

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Childhood Acute Lymphoblastic Leukaemia (ALL) has a unique place in the history of oncology, as it was the first cancer to be cured by drugs. It is therefore an important model upon which concepts of chemotherapy in other malignancies have been developed. Methotrexate is a major component of most contemporary childhood ALL treatment protocols.

The main objectives of this thesis were to investigate how methotrexate concentration time data from high dose methotrexate intravenous infusions relate to renal toxicity, to investigate how methotrexate concentrations in the cerebrospinal fluid are related to systemic levels and risk of a central nervous system (CNS) relapse, to build a population pharmacokinetic model from methotrexate concentration time data and assess how pharmacokinetic parameter predict relapse risk.

An increase in serum creatinine of more than 50% could identify individuals with a delayed elimination of methotrexate whereas markers of tubular function were not related to a delayed elimination of methotrexate. A relationship between cerebrospinal fluid (CSF) and systemic concentrations was described with statistics that handle both the inter- and intra patient variability. Applying this relationship to a larger population suggests that increased CSF methotrexate concentrations are related to a decreased risk of a CNS relapse. Using a population pharmacokinetic model body weight was found to give a better model fit to the data than body surface area. Thus, a dose calculated from body weight may result in more predictable methotrexate concentrations. Patients with an increased clearance and volume of distribution had an increased risk of relapse. Pharmacokinetic parameters adjusted for body weight were, however, not significantly correlated to relapse risk. This further indicates that body weight is a preferred anthropomorphic measurement for dose modification of high dose methotrexate intravenous infusions in childhood ALL.

The clinical value of these findings should be evaluated in prospective, controlled clinical trials before they are put into clinical practice.

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