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International Conference and Exhibition on
Pediatric Oncology and Clinical Pediatrics
August 11-13, 2016 Toronto, Canada

Individualized treatment with an optimal risk-benefit in children using pharmacokinetic-pharmacodynamic modeling in pediatric diseases and solid tumors

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The dose of drugs in pediatrics is routinely calculated in an empirical manner using information from adult-studies with either body surface area (BSA), bodyweight based dosing or allometric scaling, even though most developmental changes in the pharmacokinetics (PK) and pharmacodynamics (PD) are non-linear dynamic processes. The design of dosing regimens for the treatment of solid tumors in children is further complicated by the interplay between the tumor and the tumor environment. Historically, understanding such concentration-outcome relationships in children has been a challenge, due to limitations on blood volumes, invasive tumor biopsies, ethical considerations, bioanalytical sensitivity and PK modeling methodologies. However, our studies with busulfan, carboplatin and veliparib are an example that these barriers can be overcome. In a large, multicenter study we associated intravenous busulfan plasma concentrations with clinical outcomes in 674 children/young adults between 0.1-30.4 years undergoing hematopoetic cell transplantation (HCT). The relationship between body weight and clearance was characterized using an allometric equation with a scaling exponent that changed with body weight from 1.2 in neonates to 0.55 in young adults. The primary outcome of event-free survival (EFS) evaluated using a polynomial function was associated with busulfan exposure. The optimal busulfan area-under-the-cure (AUC) of 78-101 mg*h/L showed 81% EFS at 2 years compared to 66.1% in the low (<78 mg*h/L) and 49.5% in the high (>101 mg*h/L) busulfan AUC group (P=0.024) for both malignant and non-malignant indications. With the clinical adoption of model-based dosing and this new therapeutic goal in European Bone Marrow Transplant (EBMT) guidelines and several study protocols at the University of California San Francisco, this work is directly helping to improve the standard-of-care and outcomes for pediatric patients receiving busulfan undergoing HCT. Drug exposure is often assumed to be relatively homogenous across target tissues, with the penetration of busulfan into the bone marrow niche a representative example. However, our preclinical research of carboplatin and the Poly(ADP-ribose) polymerase inhibitor (PARPi) veliparib demonstrates that the distribution of drug in the tumor can be highly variable and was poorly correlated with either dose or plasma concentrations. In patients Carboplatin-adducts (its covalent binding to nuclear DNA) showed a higher correlation with hematologic toxicity than carboplatin concentrations in plasma. In these studies we demonstrated that two techniques: Matrix Assisted Laser Desorption/Ionization (MALDI-MSI) and inductively coupled plasma mass spectrometry (ICP-MS) can be used to assess the distribution of small molecule-based drugs in core needle biopsies. With these techniques it is now feasible to study the concentration-response at the pharmacological target site of solid tumors in children.

Biography

Imke H Bartelink completed her PharmD and PhD from the Utrecht Medical Center in Utrecht, the Netherlands and Post-doctoral studies in Integrative Pharmacology from the University of California, San Francisco (UCSF). Currently, she has Clinical Pharmacology Fellowship at UCSF. She published more than 20 papers in high impact peer reviewed journals in the areas of pharmacokinetics, pharmacodynamics and biomarkers of response.

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