

SUMMARY

Annually around 650 children are diagnosed with cancer in the Netherlands. Over the past 25 years, the survival rate of childhood cancer has steadily improved. Nowadays eight of every ten children who are diagnosed with cancer will survive more than five years beyond their diagnosis and the majority of them will become long-term survivors. This success has led to a stronger emphasis on other outcome measures besides survival, such as disease- and treatment-related adverse effects. The kidneys play a central role in the treatment for cancer as many drugs are cleared by the kidneys. Moreover, nephrotoxicity is an important adverse effect of treatment for childhood cancer and may lead to irreversible damage. Proactive monitoring of renal function may facilitate timely preventive or remedial intervention. This is of particular importance when carboplatin, a chemotherapeutic drug that is both nephrotoxic and cleared by the kidneys, is administered. Precise carboplatin dosing based on renal function results in more controlled drug exposure and less toxicity. The aim of this thesis was to gain insight into the assessment of renal function in children with cancer, both for toxicity monitoring and carboplatin dosing.

The background of this thesis is addressed in **Chapter 1**: childhood cancer; renal (late) effects of treatment for childhood cancer; monitoring of renal function in childhood; carboplatin-based therapy and population pharmacokinetics to optimize drug dosing. In the first part of this thesis we focus on assessment of renal function during childhood, in particular in children with a malignancy.

In **Chapter 2** we summarize the different methods available to the pediatrician to determine the glomerular filtration rate (GFR) in children. We discuss the advantages and disadvantages of creatinine, the most widely used endogenous renal function marker and cystatin C, a promising alternative endogenous filtration marker. We emphasize the limitations of relying on serum concentrations of endogenous renal function markers alone and recommend to estimate GFR instead, using equations developed for children. With the most commonly used estimating equation by Schwartz et al., GFR can be calculated from the patient's height and serum creatinine concentration. The mandatory height information precludes automatic reporting of estimated GFR in children.

We therefore externally validated two height-independent GFR estimating equations in a cohort of children with known GFR in **Chapter 3**. The equation by Pottel et al. demonstrated similar diagnostic accuracy as the Schwartz equation and could be used in situations when the patient's height is unknown. Furthermore, this equation allows automatic reporting of estimated eGFR by the laboratory. This would be a step forward in pediatric clinical care where physicians often still rely on endogenous markers alone.

It has become evident that equations based on cystatin C or a combination of cystatin C and creatinine are superior in children, particularly those with reduced muscle mass. However, cystatin C has not yet gained widespread use, mainly because of the lack of assay standardiza-

tion and the use of different assay calibrators. The recent introduction of a certified reference material enables production of cystatin C assays with good inter-assay agreement. This may allow the development of uniform cystatin C-based estimating equations. The results of the first study in which an assay-independent cystatin C-based estimating equation that can be used in children as well as in adults are presented in **Chapter 4**. We used the certified reference material with some further assay adjustments and developed an equation based on cystatin C and age, the CAPA equation. This simple GFR estimating equation, without terms for sex and race, had sufficient overall accuracy. Its diagnostic performance was comparable to that of the widely used cystatin C-based CKD-EPI equation, which was also developed using standardized cystatin C. Not only can the CAPA equation be used both in children and adults, it also allows automatic reporting of estimated GFR by the laboratory in children since it does not rely on anthropometric data.

Chapter 5 provides evidence that cystatin C-based GFR estimating equations are better suited for children with cancer. The use of estimated GFR based on creatinine in these patients resulted in overestimation of measured GFR, which was not observed with estimated GFR based on cystatin C, nor in controls. Furthermore, the use of cystatin C-based estimated GFR results in more accurate detection of mildly impaired renal function in children treated for cancer than creatinine-based estimated GFR.

The results of the survey in **Chapter 6** quantify the high degree of variability in protocol-based recommendations for renal function monitoring and dose modifications seen across clinical studies for children with cancer. The variability occurred in all aspects of renal function assessment that can impact patient care and outcome, including the frequency of monitoring, renal function thresholds for dose modification, the magnitude of dose modification and recommendations to omit or substitute drugs. In some protocols recommended renal function measures are even inappropriate given the chemotherapy prescribed. This variability is unwanted from a clinical and research perspective and calls for a standardized approach, utilizing existing evidence to drive such standards.

The second part of this thesis is based on a prospective observational pharmacokinetic study in 30 children receiving carboplatin-based chemotherapy. The results of the external validation of the Newell dosing formula using different endogenous renal function markers are presented in **Chapter 7**. The use of cystatin C-based estimated GFR in the Newell dosing formula proved to be more accurate than estimated GFR based on serum creatinine. The use of the latter resulted in significant overestimation of carboplatin clearance with the risk of overdosing and toxicity.

To further optimize dosing of carboplatin in children, we performed a population pharmacokinetic analysis studying covariates that influence carboplatin clearance. The results of this analysis are discussed in **Chapter 8**. The most important predictors of carboplatin clearance were measures related to body size: age, height, and body weight. Serum cystatin C, in contrast to serum creatinine, was the only measure of renal function that significantly

influenced carboplatin clearance. We developed and internally validated a simple model based on body weight and cystatin C that can be used for carboplatin dosing in children. This model proved to be accurate and robust and reduced the between-subject variability in carboplatin clearance by 92%, stressing the need for an individualized renal function-guided dosing approach in children.

Chapter 9 addresses the importance of controlling carboplatin exposure. We demonstrated that flat dosing based on body surface area or body weight results in highly variable and often imprecise drug exposure, emphasizing the importance of renal function-based dosing.

Finally, in **Chapter 10** a general discussion with a reflection on the findings described in this thesis, the implications for clinical practice and directions for future research are presented. In short, future pediatric clinical studies should contain appropriate, standardized and evidence-based recommendations for renal toxicity monitoring and dose modifications. Reliance solely on serum concentrations of endogenous markers should be abandoned and recommendations in protocols should include the use of GFR estimating equations. Furthermore, considering the toxicity profile and factors that impact carboplatin clearance, justifies a personalized, renal function-based dosing approach of this drug, using a gold standard GFR measurement or cystatin C.