Insight in disease and drug interactions, with treatment optimisation of patients with cancer

Valorisation

In this thesis several real-life studies based on patients with type 2 diabetes mellitus (T2DM) using anti-hyperglycaemic agents and patients with cancer using anticancer agents, are presented. Both cancer and T2DM are among the most frequently diagnosed diseases worldwide, whose incidence is only increasing. Both diseases are a major threat to human health, affecting burden of morbidity and leading to mortality in millions of people worldwide. Of the 56.9 million deaths worldwide in 2016, respectively 9.0 and 1.6 million were attributed to the death of people from cancer and T2DM[1]. Cancer is characterised by an uncontrolled division of cells which can invade local tissue and metastasize to other organs. T2DM is a chronic disease characterised by high blood glucose levels. Patients with cancer often also suffer from other comorbidities, including T2DM. It is known that about 8-18% of patients with cancer also have T2DM[2]. This thesis provides value for society by gaining real-life insight in 1) safety of the use of anti-hyperglycaemic agents, 2) effectiveness and implementation of anticancer agents, and 3) treatment optimisation of patients with cancer.

In the first part of this thesis, the association between the use of biguanides and the risk of colorectal cancer and the use of incretin-based therapies and the risk of pancreatic cancer was investigated. We found no beneficial effect for the use of biguanides and the risk of colorectal cancer in T2DM patients[3]. In addition, we found no increased risk of pancreatic cancer with the use of incretin agents in T2DM patients[4]. Last, both studies showed that T2DM itself seemed to be associated with an increased risk of colorectal and pancreatic cancer[3,4]. These findings are of societal benefit. First, the finding that our study and others did not show any beneficial effects of biguanide use with the risk of colorectal cancer, supports no need to further investigate this potential inverse association in randomized controlled trials (RCTs). Given that RCTs are expensive and potentially not that effective in investigating (very) rare adverse events that take longer than one year to develop[5], this study may help to save society both costs and valuable time. In addition, participants of RCTs will not unnecessarily need to be exposed to biguanides. Second, it is valuable for society to learn that the use of incretin agents is not associated with pancreatic cancer. The initial concern of the risk of pancreatic cancer with the use of incretin agents was based on histological findings in human pancreata and spontaneous reports in an adverse event database[6,7]. The European Medicines Agency (EMA) published an assessment report regarding the safety of glucagon-like peptide-1 (GLP-1) based therapies in 2013, stating that large observational studies with minimal residual confounding are needed to investigate this association[8]. To date, our study is one of the largest observational studies that has investigated this association. Residual confounding was minimal as we were able to statistically adjust our analysis for important confounders such as body mass index (BMI), alcohol use and glycosylated hemoglobin type A1c (HbA1c) value. Thus, the findings from our study provide important reassurance to society that incretin agents

can probably be safely used as second-line treatment in T2DM patients, including those at high risk of pancreatic cancer. This reassurance is especially valuable given that pancreatic cancer is one of the most lethal worldwide with 5-year survival rates of stage IV exocrine pancreatic cancer of about 1%[9]. Third, both studies provide evidence that the disease T2DM itself may be associated with a risk of cancer. There are several explanations for the increased risk of cancer in patients with T2DM. The explanations include pathophysiological mechanisms, such as hyperglycemia, hyperinsulinemia or chronic inflammation, and shared risk factors, such as obesity, low physical activity, alcohol consumption or smoking[10]. As a consequence, both patients at risk of T2DM and cancer are likely to benefit from changing an unhealthy lifestyle into a healthy lifestyle[10]. This learns us that health care should probably focus more on prevention.

Next to safety, we assessed the effectiveness of targeted oncologic therapies in real-life populations of patients with cancer. We determined the median progression-free survival (PFS) of patients with advanced breast cancer treated with exemestane plus everolimus and of patients with metastatic *BRAF* V600 mutated melanoma treated with vemurafenib. We found that the real-life PFS was slightly shorter as seen in the RCTs, 6.3 months versus 7.8 months for the patients treated with exemestane plus everolimus[11,12], and 6.0 months versus 6.9 months for the patients treated with vemurafenib[13,14]. This information may help us to inform patients making treatment decisions. What is more, we found a large difference in median PFS of patients with advanced breast cancer treated with exemestane plus everolimus per type of hospital, which was respectively 8.5 months, 4.2 months and 5.5 months for the patients treated in academic, teaching and non-teaching hospitals[11]. The borderline significantly difference in median PFS between hospital types was possibly the result of a different assessment approach in the first 12-week treatment period[11]. The transparency on the variation in outcome by type of hospital may help to improve the quality of health care, as there is a willingness to share best practices, treatment protocols and treatment experiences. The OncoZON (Comprehensive Cancer Network Southeast Netherlands) initiative, which started in 2010, is a good example, where knowledge on best practices in oncological health care is optimally shared. The results from the presented regional real-life studies will be used to improve health care of future patients overall and more specifically in the OncoZON region.

Besides determining the real-life safety and effectiveness of (anticancer) treatment options, we have also investigated methods to measure and potentially optimize the safety and effectiveness of anticancer agents[15,16]. Currently, patients with cancer are increasingly being treated with fixed-dosed anticancer agents that are given orally. Yet, the oral administration route may result in large inter-individual variability in pharmacokinetics and introduces the risk for treatment adherence risks[17], potentially resulting in less optimal treatment outcomes. Therapeutic drug monitoring (TDM) of anticancer agents has the potential to individualize the dose and thereby potentially optimize treatment outcomes. This thesis includes two studies that describe the

development of a bioanalytical method together with the analytical and clinical validation of a DBS method to quantify everolimus in patients with cancer[15,16]. The results of these studies showed that the everolimus DBS sampling method in patients with cancer had a sufficient analytical and clinical validity[15,16], thereby for the first time ever enabling the possibility to perform everolimus DBS sampling in patients with cancer. The benefit for society may especially be present to early recognise patients with cancer that are over- or underexposed and deserve a dose adaption especially to avoid everolimus induced toxicity.

Further, the development and validation of this DBS sampling method also facilitates the miniaturisation of blood collection, since it only requires a blood spotting volume of 30 µL[18]. This, in addition to the ability to have patients perform DBS sampling themselves at their homes and sent the samples to the laboratory by regular mail for analysis, potentially eases the use of TDM in oncology[18]. One of the future improvements may be to use DBS sampling to determine all routine health (check-up) parameters along with the (trough) concentration of an anticancer agent, enabling the early detection of deviations or abnormalities. An effective clinical tool may be used to interpret the analysis results and provide the patient and physician with an individual (dosing) advice. Although these ideas are currently both analytically and technologically challenging, it may be achievable when collaborating with the right professionals with the desired expertise.

Last, this thesis consists of real-life (cohort) studies, which are of benefit to society as they provide insight in new, real-life evidence. Real-life evidence cannot be provided by RCTs, as these use well-regulated and controlled settings. Thus, real-life studies are necessary to translate data from RCTs to real-life patients and this thesis has contributed to that. Yet, given that the importance of real-life studies is very clear, it is remarkable that the digital collection and storage of real-life data is not yet available. Data from electronic patient files are not in a standard fashion recorded and also not transferred to a central database. For that reason data in registries, such as the SOutheast Netherlands Advanced BReast cancer (SONABRE) registry, are manually and retrospectively collected by data clerks. The SONABRE registry is quite unique, also showing that it is not easy to build a database on patients with distant recurrence of cancer which is currently not captured in national cancer registries. One of the future improvements should therefore be the collection of relevant real-life data in a consistent, structured and digital (automated) way. By doing so, the SONABRE registry and comparable initiatives can be extended to other regions in the Netherlands and abroad. Further, it should become easier to link data from different databases. Data linkage is not only an important tool to provide complementary information from one data source that will not be captured in the other, but also to enable identifying and reducing potential misclassification. It may therefore be one step forward to link the real-life data from the studies in this thesis to another large health care database.

In conclusion, this thesis provides essential real-life insight in safety and effectiveness of antidiabetic and anticancer agents in patients with T2DM and cancer. The safety and effectiveness of targeted anticancer agents may be improved by using DBS sampling, which enables to measure drug exposure in routine care to optimise dosing. We hope that the results from this thesis will help stimulate to perform more real-life studies and to generate more real-life evidence. It is only by collaboration of multiple professionals and physicians that we can provide the best possible health care to all real-life patients, regardless of their comorbidities, or type of hospital they are treated in.

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