Pharmacogenetics and cost-effectiveness of systemic treatment in soft tissue sarcoma

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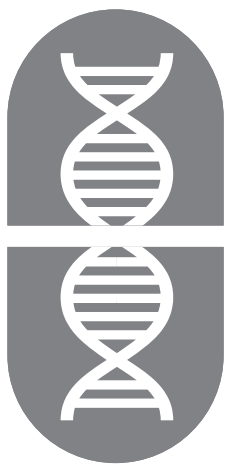
Summary and appendices

English summary
Nederlandse samenvatting
List of publications
Curriculum vitae
Dankwoord



English summary

This thesis on systemic treatment options in soft tissue sarcomas consists of two parts, as written in the general introduction in **chapter 1**. In part I, the pharmacogenetics of systemic gastro-intestinal stromal tumors (GIST) treatment is investigated. In part II the usage of trabectedin is soft tissue sarcomas (STS) in the Netherlands is studied.

Part I: Pharmacogenetics of systemic GIST-treatment

The development of the current systemic treatment of advanced GIST is described in **chapter 2**, with an emphasis on imatinib and sunitinib, the first and second line therapies, respectively. Also, after a description of the third line agent regorafenib, new drugs are highlighted. Those drugs may supplant an existing drug or may contribute to establish a fourth line of systemic therapy. In particular, DCC-2618 and BLU-285 hold promise, as these tyrosine kinase inhibitors are able to block kinase domains, regardless of a wide variety of possible mutations.

The core of this part of the thesis consists of three exploratory pharmacogenetic pathway analyses. DNA samples were obtained from a cohort of GIST patients from four referral center in the Netherlands. Single nucleotide polymorphisms (SNPs) were selected in genes related to pharmacokinetics and pharmacodynamics of imatinib or sunitinib. This was based on rational criteria including a minor allele frequency of 0.1 and a presumed functionality of the SNP. Together with clinical factors, these SNPs were then associated with the endpoints in each study.

The endpoints in **chapter 3** are the progression free survival (PFS) and overall survival (OS) of imatinib 400mg once daily as first line therapy in 227 patients with advanced GIST. This study in imatinib efficacy shows SNPs in angiogenesis related genes to be associated with worse PFS. These were the AA genotype in rs1570360 in *VEGFA* and the AA genotype in rs1870377 in *KDR* (also known as VEGFR2). The altered tumor microvasculature may affect imatinib function. In the pharmacokinetic pathway of imatinib, PFS was only associated with a T allele in rs4149117 in *SLCO1B3*, which encodes for a drug-influx transporter protein that has imatinib as a substrate. The other tested SNPs in the pharmacokinetic pathway (such as in *ABCB1*, *ABCG2*, *SLC22A1*, *SL22A5* or *CYP3A4*) were not associated with survival, possibly because the effects of these SNPs are absent or too small to detect. Synchronous metastases and *KIT* exon 9 mutations were also associated with worse PFS, whereas *KIT* exon 11 mutations led to longer PFS. The imatinib dosage of 400mg once daily is considered too low for patients with a *KIT* exon 9 mutation, but this was corrected for in the multivariate analysis. OS was not associated with any of the tested SNPs.

Sunitinib was the drug that was investigated in **chapter 4** , the second line therapy for advanced GIST. In 127 patients clinical factors and SNPs were associated with survival. The TT genotype in rs1056878 in *POR* was associated with PFS. This gene influences the activity of cytochrome P450 (CYP) metabolizing enzymes and thus could have an impact on sunitinib serum levels. OS was associated with a T allele in rs4149117 in *SLCO1B3,* and with the CCC-CCC alleles in a haploblock in *SLC22A5*, consisting of three rs2631367, rs2631370 and rs2631372. *SLC22A5* encodes for a drug influx transporter. The GC-GC alleles in a haploblock in *IL4R*, consisting of rs1801275 and rs1805015, for the IL4-receptor were also associated with OS. Synchronous metastases were associated with shorter survival, as was the case with imatinib efficacy. In contrast to the imatinib study, the primary etiologic GIST mutation was not associated with survival.

After efficacy, in **chapter 5** the toxicity of imatinib was investigated. In this study the clinical endpoints were the need for imatinib dose reduction and cessation of therapy due to adverse events. Imatinib has a relatively mild toxicity profile, yet concurrent multiple adverse events can lead to a dose reduction. In 315 GIST patients who were treated with imatinib 400mg once daily in the neo-adjuvant, adjuvant or palliative stage, the dose was reduced in about ten percent of patients. Most of these dose reduction occurred early in treatment and older patients usually experienced more toxicity. The A allele in rs2231137 in *ABCG2* and the CC genotype in rs762551 in *CYP1A2* were associated with the need for dose reduction, even after correction for multiple testing of 36 SNPs. *ABCG2* encodes for a drug efflux transporter, that might be impaired by this SNP. This could result in increased intracellular imatinib levels and thus increased toxicity. The enzyme encoded for by *CYP1A2* is one of the cytochrome P450 metabolizing enzymes and has reduced activity if the tested SNP is present. This could lead to increased imatinib exposure. The well-known polymorphisms in *ABCB1* such as rs1045642, rs1128503 and rs2032582 were not associated with dose reduction. Cessation of imatinib due to adverse events was not associated with any of the tested SNPs, possibly due too few events of treatment cessation.

The last study in this part of thesis also was a pharmacogenetic study, but **chapter 6** has a different design in several aspects. First, although all patients received imatinib a number of patients did not have a GIST, but had chronic myeloid leukemia instead, a hematological malignancy that responds very well to imatinib therapy. Secondly, standardized imatinib trough levels were associated with SNPs in *CYP2C8* after patients had taken imatinib for at least one month. It was assumed that after this period CYP2C8 would become a more prominent metabolizer of imatinib due to auto-inhibition of CYP3A4. However, none of the tested SNPs in *CYP2C8* were associated with standardized imatinib trough levels.

Part II: Usage of trabectedin in STS

The development of trabectedin is described in **chapter 7**, especially its use in the treatment of advanced STS. The mechanism of action of trabectedin is highlighted, as is its efficacy in different types of STS. Clearly, trabectedin will incur most benefit in patients with a leiomyosarcoma or a liposarcoma, but in case of a synovial sarcoma trabectedin may also induce an anti-tumor effect. Toxicity is usually manageable, with fatigue, elevated transaminases and bone marrow depression the most frequent adverse events.

The cost-effectiveness of trabectedin versus ifosfamide monotherapy in the second line therapy of advanced STS was studied in **chapter 8**. The original idea was to compare trabectedin to best supportive care in this setting. However, the observational phase IV study performed to gather data to this end, resulted in patients choosing trabectedin so often, that only sufficient data was collected for the trabectedin arm. Therefore, previously published EORTC data on ifosfamide in this treatment setting was obtained and used for comparison. Data on quality of life during treatment was taken from the observational study and from literature. The use of health care recourses were scored in the study and cost were taken from public sources.

In this study in **chapter 8**, trabectedin was shown to be active in patients with leiomyosarcoma or a liposarcoma, the so-called L-sarcomas. In the survival analysis, the progression free survival for L-sarcoma patients was 2.5 months longer with trabectedin compared to ifosfamide. In the group of non-L-sarcomas patients, however, ifosfamide resulted in longer survival. All these differences were not statistically significant. In the cost-effectiveness analysis, the incremental cost-effectiveness ratio of trabectedin for L-sarcoma was € 80,000 per QALY gained. The difference in survival and the drug acquisition costs had the largest impact in this result. The costs per QALY are at the top end of what is currently acceptable in the Netherlands. In non-L-sarcoma patients ifosfamide was dominant, as it resulted in longer survival at lower costs.

A trabectedin specific adverse event was described in **chapter 9**, together with other vascular access related adverse events. The new adverse event was the development of a sterile inflammation along the catheter trajectory. This was observed in the LUMC after implantation of vascular access ports, but not in other centers using the same device. Placing the catheter deeper under the skin resolved the issue.

A general discussion in **chapter 10** concludes this thesis. Comments made regarding the pharmacogenetic pathway analyses in GIST patients include the exploratory character of these studies and the relatively large numbers of patients included. Also the retrospective nature of data collection was a significant factor and it precluded

the inclusion of tyrosine kinase inhibitor serum concentration measurement into the analyses. Obviously, the SNPs associated with survival or adverse events need to be validated before clinical usage. If that would succeed, these SNPs could help in establishing personalized medicine in GIST treatment, and thus improving patient´s quality of life. Comments regarding the cost-effectiveness analysis of trabectedin versus ifosfamide include the notion that trabectedin was active in L-sarcomas, according to EORTC criteria for STS. The cost per QALY gained is at the top end of the usually accepted amount. Nonetheless, as long as there is an unmet clinical need in patients with advanced STS, the cost- effectiveness of trabectedin may not be the decisive criterion whether or not to prescribe this drug, but the desire to provide the best possible medical care will be.