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Original Research

Genetic polymorphisms in angiogenesis-related genes are associated with worse progression-free survival of patients with advanced gastrointestinal stromal tumours treated with imatinib

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Abstract ***Background:*** Imatinib 400 mg per day is first-line therapy for patients with gastrointestinal stromal tumours (GISTs). Although clinical benefit is high, progression-free survival (PFS) is variable. This study explores the relationship of single nucleotide polymorphisms (SNPs) in genes related to imatinib pharmacokinetics and pharmacodynamics and PFS in imatinib-treated patients with advanced GIST.

Methods: In 227 patients a pharmacogenetic pathway analysis was performed. Genotype data from 36 SNPs in 18 genes were tested in univariate analyses to investigate their relationship with PFS. Genetic variables which showed a trend ($p < 0.1$) were tested in a multivariate model, in which each singular SNP was added to clinicopathological factors.

Results: In univariate analyses, PFS was associated with synchronous metastases ($p = 0.0008$) and the mutational status ($p = 0.004$). Associations with rs1870377 in *KDR* (additive model, $p = 0.0009$), rs1570360 in *VEGFA* (additive model, $p = 0.053$) and rs4149117 in *SLCO1B3*

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(mutant dominant model, 0.027) were also found. In the multivariate model, significant associations and trends with shorter PFS were found for synchronous metastases (HR 1.94, p = 0.002), *KIT* exon 9 mutation (HR 2.45, p = 0.002) and the SNPs rs1870377 (AA genotype, HR 2.61, p = 0.015), rs1570360 (AA genotype, HR 2.02, p = 0.037) and rs4149117 (T allele, HR 0.62, p = 0.083).

Conclusion: In addition to *KIT* exon 9 mutation and synchronous metastases, SNPs in *KDR*, *VEGFA* and *SLCO1B3* appear to be associated with PFS in patients with advanced GIST receiving 400-mg imatinib. If validated, specific SNPs may serve as predictive biomarkers to identify patients with an increased risk for progressive disease during imatinib therapy.

1. Introduction

Imatinib mesylate (Gleevec®, Glivec®) is first-line therapy for chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GISTs) [1,2]. It has revolutionised the treatment of both malignancies by achieving significant survival benefit with limited toxicity [3]. Clinical response to this oral tyrosine kinase inhibitor (TKI) is determined by somatic mutations, as well as by germline genetic variations [4,5]. Single nucleotide polymorphisms (SNPs) are the most common germline genetic variations. SNPs can have various functional effects, ranging from silent mutations to affecting gene expression and enzyme function. The pharmacokinetics and pharmacodynamics of imatinib may be changed in patients carrying SNPs in genes encoding for enzymes and target proteins involved in imatinib pharmacology.

GIST is a mesenchymal tumour of the digestive tract, often caused by gain-of-function mutations in the genes encoding for KIT or PDGFR-α [6–8]. *KIT* mutations are routinely screened in GIST to predict imatinib efficacy which is dependent on the location of the *KIT* mutation [4]. Disease progression has also been associated with clinical factors, such as the location of the primary tumour [9,10].

In CML treatment, complete cytogenetic response to imatinib has been associated with SNPs in genes encoding for enzymes which have a role in imatinib metabolism. Also, polymorphisms in the genes encoding for the efflux transporter ABCG2 (rs2231137) and for the influx transporter SLC22A1 (rs683369) have been associated with poor response and progression to advanced disease, respectively [5]. In 54 patients with advanced GIST who were treated with imatinib, associations have been reported for SNPs in *SLC22A4* (rs1050152) and *SLC22A5* (rs2631367 and rs2631372) and time to progression [11]. Since this report, no similar studies have been published. A review highlighting SNPs found in relation to imatinib in CML and GIST has been published elsewhere [12].

This study aims to investigate the relationship of genetic variants in genes encoding proteins involved in the pharmacokinetics and pharmacodynamics of imatinib and efficacy in patients with locally advanced and metastatic GIST.

2. Methods

2.1. Patients

For this exploratory retrospective study, GIST patients were included who had been treated in four Dutch referral centres. All patients had a histologically proven GIST and documented non-curative disease, being either non-resectable locally advanced or metastatic disease at the time of start of imatinib. Patients started imatinib therapy in a dose of 400 mg once daily between January 2001 and May 2013 and follow-up lasted until July 2014. All patients had to be treated until the first treatment evaluation, with the exception of patients with clinical progression before this moment. Patients with *KIT* exon 9 mutation were retained in the analysis despite having received imatinib in a 400 mg daily dose, as the objective of the study was to test the pharmacogenetic effects of 400 mg daily, and a dose of 800 mg daily will induce more toxicity. Furthermore, it is common practice in the Netherlands to start with imatinib 400 mg daily in case of a *KIT* exon 9 mutation if the tumour load is low and a patient is asymptomatic, and only escalate to 800 mg in case of progressive disease.

DNA was obtained from residual blood samples or, in the Erasmus MC Cancer Institute, after specific informed consent was obtained. Samples were stored at −20 °C until genotyping. In one location, serum of these samples was stored. If a residual blood or serum sample was not available, DNA was obtained from residual formalin-fixated paraffin-embedded (FFPE) specimen. All samples were anonymised by a third party and the Code for Proper Secondary Use of Human Tissue was adhered to (www.federa.org/codes-conduct) [13].

2.2. SNP selection

SNPs in genes related to imatinib pharmacokinetics and pharmacodynamics were selected using a pathway