A multicenter validation study of genetic polymorphisms associated with toxicity and efficacy of sunitinib in patients with metastatic renal cell carcinoma

Meta H.M. Diekstra1, Jesse J. Swen1,2, Epi Boven2,3, D Castellano4,5, R. Ganapathi, Hans Gelderblom2,7, Ron H.J. Mathijssen2,9, Cristina Rodriguez-Antonio1,8, Jesús Garcia-Donas4,5,9, Brian I. Rini6, Henk-Jan Guchelaar1,2.

1. University of Leiden, Dept. of Clinical Pharmacy and Toxicology, Leiden, Netherlands; 2. Dutch SUTOX consortium, UU University Medical Center, Dept. of Medical Oncology, Amsterdam, The Netherlands; 3. Hospital Universitario 12 de Octubre, Oncology Department, Madrid, Spain; 4. Spanish Oncology Genitourinary Biobank Group (BDGUK); Madrid, Spain; 5. Cleveland Clinic Taussig Cancer Institute (CCF), Dept. of Solid Tumor Oncology, Cleveland, Ohio, USA; 6. Erasmus MC Cancer Institute, Dept. of Medical Oncology, Rotterdam, Netherlands; 7. Spanish National Cancer Research Centre (CSN), Endocrinology Department, Group, Madrid, Spain; 8. SOSI Center for Biomedical Research on Rare Diseases (CIBERER), Madrid, Spain; 9. Cancer Campus Comprehensive Cancer Center, Oncology Unit.

Introduction

- Sunitinib, used in the treatment of metastatic renal cell carcinoma (mRCC), is characterized by a wide inter-individual variability.
- For sunitinib, dose reductions are needed in 32% of patients due to toxicities.
- In our exploratory studies we have associated single nucleotide polymorphisms (SNPs) in candidate genes with efficacy and toxicity recordings.

Objectives

1. To test whether SNPs are potential predictive biomarkers and may enable individualized treatment regimens.

Methods

- Patients with clear cell mRCC receiving 50.0 mg, 37.5 mg or 25.0 mg sunitinib for at least 4 weeks in a 4-weeks-on,2-weeks-off schedule were enrolled from centers participating in the Dutch SUTOX consortium (five medical centers in the Netherlands, Spanish Oncology Genitourinary Biobank Group (BDGUK), medical centers around Spain (Spanish participating hospitals) and the Cleveland Clinic Taussig Cancer Institute in the USA (CCF)).

Results

- We validated 2 out of 22 previously reported polymorphisms associated with toxicity and efficacy of sunitinib in a large cohort of 333 mRCC patients: CYP3A5*1F is associated with dose reductions and CGT presence in the ABCB1 haplotype is associated with an improved PFS (Figure 1, Table 3).

Conclusions

The confirmation of previously reported associations between genetic polymorphisms in CYP3A4 and ABCB1 and sunitinib toxicity and efficacy respectively indicates these markers may play an important role in guiding sunitinib treatment.

References


Acknowledgments

This research is supported by Pfizer and Meta Bionik is supported by the European Research Council’s Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 294938.

Figure 2: Patients and SNPs

Figure 3: Possible explanations on observed associations between genetic polymorphisms in CYP3A4 and the ABCB1 on sunitinib treatment outcome.