EuroTARGET: European collaborative project on TArgeted therapy in Renal cell cancer: GEnetic and Tumour-related biomarkers for response and toxicity

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON34570

Source
ToetsingOnline

Brief title
EuroTARGET

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
metastatic renal cell cancer - metastatic kidney cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: EU;7e kaderprogramma

Intervention

Keyword: biomarker, metastatic renal cell cancer, response, targeted therapy

Outcome measures

Primary outcome

Therapy response:

- poor responders defined as: no response after initiation of treatment (i.e., continued progressive disease) evaluated by RECIST criteria (see http://www.recist.com/).

- good responders: best responders (evaluated by RECIST criteria) in the retrospective and prospective cohorts. I.e., we will select the most extreme cases for this evaluation.

Secondary outcome

Therapy toxicity according to Common Terminology Criteria for Adverse Events (CTCAE)

Study description

Background summary

With an estimated 3.2 million new cases and 1.7 million deaths each year, cancer remains an important public health problem in Europe for patients themselves, their family as well as health care systems across Europe. With the ageing of the European population these numbers are predicted to steadily increase until the 2040s, even if age-specific rates of cancer remain constant. In line with the Lisbon objectives of, amongst others, improvement of human health and quality of life, advancements in the field of medicine are needed to offer solutions for diseases which are currently untreatable. Also, advancements in personalised medicine are needed to improve therapeutic indices, avoid chronicity, prevent relapse, reduce adverse effects and permit

greater cost effectiveness. Definition of new validated risk stratification criteria to be used in personalized patient management, i.e. prediction of individual therapy response and resistance leading to optimal treatment outcome while reducing unnecessary drug use and expense, is therefore urgently needed.

Kidney cancer is the 10th most common cancer in the European Union. Each year more than 40,000 men and more than 24,000 women are newly diagnosed with the disease (European Cancer Observatory, 2009; Ferlay et al., 2007). More than 27,000 European Union men and women die from the disease each year. 90% of all kidney cancers are renal cell carcinomas (RCC). Survival of RCC has remained more or less stable during the last 20 years and is highly dependent on stage. Surgery is quite effective for localized disease, leading to 5-year relative survival rates of more than 70%. However, 20 to 30% of patients with primary RCC have metastasized disease at diagnosis and approximately 30% of the remaining patients develop metastases after surgery. For this group of patients, curative treatment is not possible and, until recently, 5-year relative survival was extremely poor: 5 to 10%. The poor survival rate reflected the limited treatment options for patients with metastatic RCC (mRCC).

Treatment options for mRCC have improved substantially in the past 5 years. Long mired in therapeutic nihilism because of chemotherapy resistance and modest effects of immunotherapy, suddenly multiple active agents with robust clinical effects are available for mRCC. Knowledge of underlying molecular characteristics identified the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathways as fundamental to the biology of RCC. This biologic insight provided a rationale for targeting these growth factor signaling pathways in RCC. Small molecules inhibitory against the tyrosine kinase portion of the intracellular receptor for VEGF (VEGFR) have undergone extensive clinical testing. Two of these drugs, sunitinib and sorafenib, are now widely used in clinical practice. These agents inhibit not only VEGFR but also a broad spectrum of related receptor tyrosine kinases (i.e. are more general tyrosine kinase inhibitors or TKIs). The agents also differ in the spectrum of inhibitory effects and potency against any single receptor. These and other targeted agents that are not (or not yet) as widely used as sunitinib and sorafenib have shown objective response rates up to 45% (sunitinib), twice as high as immunotherapy treatment. 70 to 75% of all patients experience some reduction in tumour burden and the median progression free survival and overall survival has increased with about 6 months to approximately 1.5 to 2 years. Thus, targeted therapy in mRCC can be considered a revolution after decades without any progress. Unfortunately, the treatment is expensive with costs of about ¤4,000 per month per patient (life-long) which means that the drugs are not available in a large part of the EU, particularly in the former Eastern-European countries.
Even though the new drugs are *targeted therapy*, aiming at specific pathways, not all patients show clinical benefit from therapy, and inherent or acquired resistance to the drugs poses a problem. Sequential therapy is therefore

becoming routine practice. With an increasing number of compounds becoming available, however, choice of compounds and sequence is becoming extraordinary challenging. In addition to the highly variable clinical response to the targeted treatments, toxicity, experienced by a substantial number of patients, is highly variable and frequently necessitates dose reduction or even cessation of therapy. Unfortunately, both response and toxicity are not predictable in the individual patient. Therefore drug choice, dose and sequence are highly empirical. The fundamental question facing the medical oncologist caring for a mRCC patient is how to consider the available agents and data to formulate an evidence-based individualized treatment approach (Rini, 2009). Until now, treatment choice in mRCC is determined by clinical parameters such as the patient*s performance status, serum biochemical measurements, and morphological / histological features of the tumour. Based on these parameters, patients are stratified into a good, intermediate or poor risk group. Treatment choice is partly based on this risk grouping. Although this risk grouping has clear prognostic value, also among patients on targeted treatment (Heng et al., 2009), it is very clear that the grouping is far from optimal: the agents lead to different clinical effects in different patients. Research is therefore ongoing to find markers with better predictive ability for drug response, both with regard to efficacy and toxicity in individual patients. On the patient level, treatment response and toxicity are (partly) derivatives of underlying interpatient genetic variability. The discipline of pharmacogenetics that evaluates germline genetic markers in candidate drug metabolizing or drug target genes (e.g., van Erp et al., 2009) is still in its infancy. In most cases, studies are small, focus on only a few markers in only a few candidate genes, and lack an independent replication to validate the results. On the tumour level, research mainly focuses on gene expression differences (e.g., Zhao et al., 2006) or specific gene mutations in tumours that show differences in response. But here again, studies are usually small and lack independent replications. In addition, integrated approaches which are envisioned to identify new and better predictive markers by combining different types of information from different research platforms and clinical determinants are lacking. To boost the identification of predictive markers we propose the application, integration, and validation of high-throughput platforms aimed at host as well as tumour related markers in an unprecedented scale.

Study objective

This project aims to identify and characterize host and tumour related biomarkers and to predict responders and/or adverse responders from non-responders for targeted therapy in mRCC. Our overall concept is to focus on germline genome and tumour transcriptome, methylome and kinome-related biomarkers using an hypothesis-free and integrative approach and to evaluate promising findings via replication as well as functional assays.

The specific objectives are:

• To create a standardized European clinical databank and bio-repository (germline DNA of all patients and serum and frozen tumour tissue of a subgroup) of a large series of patients with mRCC treated with different agents;
• To identify genetic markers for treatment response and toxicity by performing a high-resolution germline whole-genome profiling in patients treated with sunitinib or sorafenib, the most commonly used drugs at this moment;
• To identify exon and microRNA expression markers for treatment response and toxicity by gene expression profiling of tumours from patients with and without a good response to these drugs;
• To identify kinase activity profiles related to TKI response;
• To identify promoter hypermethylation markers TKI response;
• To identify the resulting protein profiles corresponding to genomic, epigenetic and expression alterations related to TKI response;
• To replicate all identified markers in independent patient series;
• To study the functional relevance of replicated markers/networks in vitro by knock-out and knock-in transfection experiments;
• To identify differentially expressed proteins before and after knock-down/ upregulation of genes of interest;
• To identify plasma drug and metabolite levels as a phenotype of response to sunitinib;
• To explore the possibility of individualizing dosage regimens by integrating plasma biomarker level-time profiles into pharmacokinetics / pharmacodynamics models for sunitinib as a model drug;
• To conduct integrated bioinformatical analyses of the results obtained by all different approaches in order to maximize the probability to find new markers and to understand the interrelatedness between them;
• To construct new risk stratification criteria to be used for personalized mRCC patient management;
• To disseminate the new knowledge to medical oncologists, urologists and the scientific community.

Study design

The project will be based on a design that makes it possible to:
1. Identify new markers for response (efficacy and toxicity) to TKI treatment in a discovery phase.
2. Use the same blood samples and tumour tissue on different platforms so that an optimal integration of different types of data can take place, leading to a maximal yield.
3. Replicate the identified markers in a validation phase.
4. Build on the possibility of future extensions of the project with a focus on other agents.

The pivotal part of the project will be WP1 in which patients with mRCC will be recruited in (parts of) The Netherlands, The United Kingdom, Germany, Austria, Switzerland, Iceland and Romania. A standardized protocol and web-based Case Record Forms to be used by all participants will guarantee consistency of data

collection procedures. The clinical data at baseline and follow-up will be maintained in a secure database under the control of one of the participants. Blood samples will be collected from all patients and shipped to the central biorepository in Nijmegen, the Netherlands. Frozen tumour tissue will be collected from as many patients as possible and sent to the central biorepository. The central biorepository will distribute samples to the different participants for biomarker identification in the discovery phase and biomarker replication and validation in the validation phase. We will use the following platforms to identify new biomarkers:
1. A whole-genome genotyping of 600 patients (150 with a good response to sunitinib, 150 with a poor response to sunitinib; 150 with a good response to sorafenib, 150 with a poor response to sorafenib) in the discovery phase and again of 500 patients in the validation phase. In both phases, we will use Illumina HumanOmni1*QuadBeadChips because this allows a combined analysis of both phases at limited additional costs in comparison with a smaller-scale replication of only the top hits from the discovery phase. (WP2)
2. We will conduct gene expression profiling on the exon-level (geneChip® human exon 1.0ST Array, Affymetrix) and on the microRNA level (GeneChip® miRNA Array, Affymetrix) on RNA isolated from frozen tumour tissue of 120 patients (30 with a good response to sunitinib, 30 with a poor response to sunitinib; 30 with a good response to sorafenib, 30 with a poor response to sorafenib). The results will be replicated on another 120 patients. (WP3)
3. Extracts from the same tumours will be used for kinase activity profiling. The functional readout will be combined with pharmacological studies in which other kinase inhibitors will be assessed for their potency of inhibiting kinase activities extracted from the tumours and reference cell lines or xenograft tissue. An assay will be developed for on-chip analysis of tumour biopsies by ex-vivo incubation of extracts with drug for monitoring on-target (efficacy) and off-target (toxicity) kinase activities. (WP4)
4. Again, the same tumour tissue will be used for the identification and characterization of DNA methylation biomarkers using the Infinium HumanMethylation27 BeadChip for a whole-genome interrogation of differentially methylated regions. In the replication phase, the selected top differentially methylated genes will be analyzed by ultra deep bisulfite sequencing in order to test the sensitivity of the proposed DNA methylation biomarkers. (WP5)
5. We will link PK/PD models and integrate the pharmacokinetic, biomarker and clinical data and thereby develop predictive models for response and toxicity in mRCC patients ultimately leading to individualized prediction of drug doses and therapy response. (WP7)
6. All generated data from the profiling studies will be transferred and kept in DiseaseMiner, a highly scalable, multi-user, rich client platform (RCP) based on multi-tiered architecture, optimized for large number of clinical samples as well as the extremely high volume of marker data that are currently produced by modern chip technology. (WP8)
7. Integrative analyses will take place of all the different data types generated within this project, with and without external data sources, to increase insight into molecular pathways and, ultimately, to be able to predict

response to therapy based on a fusion of all the measured high-throughput datasets: clinical, SNP, mRNA expression, miRNA expression, kinase activity and methylation status. (WP9)
8. Functional confirmation studies will take place focusing on selected candidate genes/networks identified in the previous profiling studies and integrative analyses. (WP6)
9. Finally, based on the results of the project, a web-based treatment algorithm will be developed to guide treatment selection in clinical practice: the *Predicted Response and Toxicity Calculator*. (WP9)
The biorepository of mRCC will be unique for Europe and an extremely valuable resource for future studies on prognostic and predictive markers.

Study burden and risks

The burden and risk (vena punction) of participation is negligible.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Postbus 9101
6500 HB Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Postbus 9101
6500 HB Nijmegen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Adult patients with metastatic kidney cancer

Exclusion criteria

Unable to read and understand the informed consent forms
Age under 18

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-08-2011
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO

Date:	23-05-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	26-04-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-07-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-12-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL34272.091.10