Impact of new approaches to pharmacological management of patients with renal cell carcinoma: a population-based study of process and outcomes in The Netherlands

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The 1st main objective is to collect detailed quantitative data on the everyday management of mRCC in the Netherlands, the clinical outcome of this management, as well as the resulting quality of life and financial costs. Treatment selection for...

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

Summary

ID

NL-OMON35060

Source
ToetsingOnline

Brief title
Cost-effectiveness of targeted treatment of mRCC

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
kidney cancer, renal cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: ZonMW,Pfizer,Wyeth

Intervention

Keyword: Cost-effectiveness, Pharmacogenetics, Renal cell cancer, Targeted therapy

Outcome measures

Primary outcome

Choice of end points:

The clinical end points will be response rate, time to progression, progression free survival, and overall survival. Patient reported outcomes, such as side effects and quality of life, will also be included in the study. The end points for the economic evaluation will be: life years, quality adjusted life years, costs, progression-free life years, costs per life years gained, costs per QALYs gained and costs per progression free life years gained. The progression free life years are used as in this patient group, i.e. a situation with almost no cure perspective and then prolonging life without progression of disease is very relevant.

Effectiveness study

Effectiveness is defined in terms of life years, quality adjusted life years, progression free life years, and grade III/IV toxicity (e.g. leukopenia, anemia). For the calculation of QALYs, quality-weights (utilities) are assigned to each health state and multiplied with the number of years patients stayed in

a state, summed over all health states.

Cost study

The cost study will focus on the direct costs (cost of relapse treatment and cost of follow-up). Due to the poor prognosis of the patients the cost of production loss will be neglected. It will be investigated whether it is possible to include costs on informal care in this study. Informal care is a relevant issue in this patient group, but the patient questionnaires should not be too extensive (in order to receive a better response) This issue should be discussed with medical experts whether this is possible.If possible we will use the *Vragenlijst mantelzorg* in order to collect data on the time spent on informal care by carers. The cost analysis will ideally be based on the resource use of the individual patients in daily practice. Resource data from patients treated in daily practice will be collected in a number of hospitals (both academic and regional hospitals). Unit costs will be collected from official national reimbursement systems. Where necessary, costs of medications will be derived from the
Z-index. The costs of a hospital day, outpatient visits, day care treatment, general tests (such a laboratory testing, etc.) will be derived calculated by means of a cost price study. The base year for unit costs will be 2010. Costs will be expressed in Euros and discounted at a discount rate of 4% for costs and 1.5% for effects according to the Dutch pharmaco-economic guidelines.

Secondary outcome

We maken geen onderscheid tussen primaire en secundaire uitkomstparameters.

Study description

Background summary

For patients with (advanced) renal malignancies many randomized clinical trials (RCTs) of anticancer drug efficacy have been performed worldwide. Recent RCTs have shown promising results. Based on this, clinical guidelines are being developed to improve RCC treatment effectiveness in *routine* clinical practice. New drugs such as the tyrosine kinase inhibitors (TKI) sunitinib and sorafenib, the mammalian target of rapamycin (mTOR) inhibitor temsirolimus and the monoclonal antibody bevacizumab targeting the vascular endothelial growth factor (VEGF)) have become available for the treatment of patients with (advanced) renal carcinoma.
In the most general sense, sunitinib, bevacizumab combined with interferon-alpha (IFN), and temsirolimus led to increased progression-free survival of 2 to 6 months in RCTs. Sunitinib and the combination of bevacizumab yielded partial responses in approximately 30% of patients. Furthermore, sunitinib has been shown to improve overall survival. In a RCT, temsirolimus has also been shown to improve overall survival in patients with unfavorable prognostic features, while sorafenib doubles progression-free survival in patients pre-treated with cytokines, the old first-line standard. However the improved outcomes obtained by these novel drugs come at the expense of toxicity which is sometimes severe. Many patients (up to 67%) experience mild to severe toxicity. Furthermore, the costs of these compounds are considerable (approximately 3000-4000 Euro per month). To what extent these treatments lead to improved survival in daily clinical practice and with how much side effects is unclear. Empirical data on everyday clinical practice variation and its effects on disease outcome may lead to improvements of quality of care and even cost savings per life-year saved. Even in the absence of such data, it is very clear that there is a strong need for improved stratification of patients in order to come to tailored, individualized treatment of patients with better response rates, less toxicity and much more efficient drug use. Another issue is the patients* treatment location, i.e. in expert or normal community hospitals. Because a good prognostic classification is still not available, and treatments are rather complex and regularly result in severe toxicity, it is questionable whether these patients can be treated optimally outsideexpert centers.

Study objective

The 1st main objective is to collect detailed quantitative data on the everyday management of mRCC in the Netherlands, the clinical outcome of this management, as well as the resulting quality of life and financial costs. Treatment selection for mRCC patients is mainly based on routine assessment of classical parameters: tumor histopathology and prognostic features. Determination of the

patients* and tumors* molecular makeup and activity of kinase cell signaling pathways before initiation of targeted treatment is likely to improve prognostic stratification of patients. The 2nd main objective is therefore to identify prognostic groups of mRCC patients based on classical ánd non-classical parameters in order to achieve a more tailored approach thereby avoiding toxicities and extremely expensive treatment in patients who don*t benefit from it. The specific aims are:
- To assess the approximate absolute and relative number of mRCC patients per year in the Netherlands who have an indication for treatment with targeted agents.
- To identify patient, tumor, and treating physician related determinants of prescription of these drugs.
- To assess progression-free-survival (PFS) and overall survival (OS) after treatment with these drugs in everyday clinical practice.
- To assess the probability, type and severity of side effects of these drugs.
- To assess the impact of treatment with targeted agents on quality of life.
- To build a population-based germline DNA biobank of RCC patients to facilitate pharmacogenomics research (in some university centers, such biobanks for pharmacogenetics research are already being created; an additional aim of the current proposal is to arrive at a concerted action for such biobanks)
- To genotype responding and non-responding patients for all genes that are known to be involved in the different pathways which are involved in targeted therapies (in collaboration with ongoing activities in academic centers).
- To get insight in the effectiveness of new targeted treatments, as compared to the efficacy as reported from the clinical
trials.
- To get insight in the cost-effectiveness of new targeted treatments, as compared to the efficacy as stated in the clinical trials.
- To investigate the possibility to build a frozen-tissue biobank of RCC tumors through the Dutch pathology Departments.

Study design

In this project we will collect and analyze population-based data regarding clinical management, clinical outcome, quality of life, results of prognostic parameters and new (costly) treatments of mRCC. In addition, we will collect blood samples from RCC patients, isolate the DNA and genotype the DNA of patients treated with targeted therapies for the VEGF and mTOR pathways and correlate the findings with response and toxicity to treatment. Through this, we will improve the suboptimal classical prognostic assessment of patients with mRCC.

Study population

Prospective study

The challenge of the project will be the recruitment of patients very early

after their diagnosis. The reason for the necessity to recruit them early has to do with the poor prognosis of mRCC patients and with the desire to collect QoL data and symptom, co-morbidity and side effects questionnaires related to the primary treatment. Because the cancer registry has a delay of about 6 months before patients are registered, it is not possible to recruit all patients through the cancer registry. Because 17% of all patients have no histological confirmation [3] and this is the group that consists of patients with metastasized tumors it is also not possible to use the pathology registry (PALGA) as the only source of identification. For that reason, the following recruitment scheme will be followed:
1. The study will be explained to and consent requested from all medical oncologists and urologists in the hospitals of the 4 comprehensive cancer centers.
2. Cancer registry personnel will visit the hospitals weekly and (with the help of hospital personnel) select all new patients in the hospital information system with a medical oncology Diagnosis Treatment Code (DBC) 83400 (*nierkanker*) or a urology DBC 10 (*(bij)niertumor*).
3. Eligibility for the study (patients with renal cancer of any stage) will be verified through contacts with the treating physician.
4. Patients will be invited for the study by the cancer registry departments of the 4 comprehensive cancer centers in the name of the treating physician. Hospitalized patients will be invited by the treating physicians themselves. Written informed consent will be requested.
5. In case of informed consent, symptom and QoL questionnaires will be sent to the patient.
6. Also, 2 plastic EDTA tubes will be sent to the patient in postal packages. It will be requested to take these tubes to their treating physician at the next visit and ask the physician for a blood draw. After that, the blood can be sent by normal mail to the Urology Research Laboratory of the Radboud University Nijmegen Medical Center.
7. Cancer registry personnel collect extensive clinical data from the medical files in addition to the routinely collected data. Specific emphasis will be given to prognostic parameters that are part of the Memorial Sloan Kettering Cancer Center score. A slightly modified version of the widely used Charlson co-morbidity index will be used for recording co-morbidity. Follow-up data will be collected with emphasis on response, recurrence, late effects of treatment and survival.
This routine has been proven feasible within the EU 6th framework program Polygene. In this project IKO has collected questionnaire data, clinical info and germline DNA from more than 5000 patients in the last 2 years (e,g, Kiemeney et al, 2008). Through the recruitment in the 4 CCC areas covering 55% of the hospitals in the Netherlands and a total catchment population of 9 million, approximately 800 new patients with renal cancer can be identified each year. With a recruitment period of 2 years, 1600 patients. We aim at recruiting at least 1000 of them. From these 1000 patients, basic clinical data and questionnaires will be collected. More detailed information will be collected from the group of primary mRCC patients. The size of the latter group

will be approximately 300. At least 100 additional primary non-mRCC will develop metastasized disease during the duration ofthe study. Therefore, ~400 patients with an indication for targeted therapies will be included.

Retrospective study

Retrospectively, all patients diagnosed with mRCC in the hospitals of the 4 CCCs since January 2008 will be selected from the cancer registry. Since that date, treatment with targeted drugs has been routinely recorded in the cancer registry and can be used as a stratification parameter for the comparison of patient and tumor characteristics between treatment groups. mRCC patients treated in the four regions will be stratified according to MSKCC prognostic parameters in order to investigate the correlation between therapy outcome and good/intermediate/poor risk score patients in relation to the specific drug. To obtainsufficiently detailed information, patient files will be screened to collect this information in a uniform manner. Furthermore, toxicity profiles will be collected retrospectively. This analysis will provide the necessary background information to investigate the correlation between these parameters and treatment outcome in The Netherlands.

Genomic DNA data.
As stated before, in the prospective study, patients will be requested to donate a blood sample for genetic analyses of drug pathways. The blood samples will be sent by normal mail to Radboud University Nijmegen Medical Center (RUNMC) for analysis. Isolated DNA will be arrayed on custom-made (Illumina Goldengate platform) SNP arrays, interrogating kinome-related pathways. Covered target genes will include known TKI targets and off-targets. Pharmacogenomic profiles will be compared with toxicity profiles to determine any correlative.

Frozen tissue samples
One of the goals of this project is to build a tissue biobank of patients with renal cancer. We attempt to do this by initiating discussions among pathologists, medical oncologists and urologists about the necessity of such a biobank for future mechanistic studies into targeted drug response.

Cost-effectiveness analyses
This study will include all patients with renal cancer but has a focus on patients with advanced and/or metastatic renal cell cancer (Stage IV or recurrent disease). Cost-effectiveness will be assessed for the whole patient group. Furthermore, specific sub-analyses will be performed focusing on the hospital drugs temsirolimus and bevacuzimab. Temsirolimus is registered for patients with advanced and/or metastatic renal cell cancer with a poor prognosis (defined as Karnofsky performance status of60%-70%, among other clinical measures such as more than one metastatic organ site, less than 1 year from time of initial RCC diagnosis to treatment). To assess the cost-effectiveness of temsirolimus the focus will lie on mRCC with poor prognosis. Bevacuzimab in combination with IFN-alpha is registered as

first-line treatment in patients with mRCC. To assess the cost-effectiveness of bevacuzimab the focus will lie on first line mRCC.

Study comparator:
The comparators will be interferon alpha and/or other drugs used in daily practice.

Study burden and risks

Niet van toepassing

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult patients with newly diagnosed kidney cancer

Exclusion criteria

Age => 18

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-03-2011
Enrollment:	1000
Type:	Actual

Ethics review

Approved WMO

Date:	26-05-2010
Application type:	First submission
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	NL31710.091.10