MEDICAL MANAGEMENT OF METASTATIC RENAL CELL CARCINOMA, RETROSPECTIVE ANALYSIS OF REAL WORLD DATA SETTINGS

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BACKGROUND

Renal cell carcinoma is the most common type of kidney cancer in adults, responsible for approximately 80% of cases. [1] It is also known to be the most lethal of all the genitourinary tumors. About 70% of patients develop metastases during the course of their disease. A median survival time of 6-12 months and a 2-year survival rate of 10-20% have been estimated for patients with metastatic renal cell carcinoma (mRCC). [2]

Until late 2005, cytokine therapy with interleukin-2 (IL-2) or interferon-alpha (IFN-α) was the only treatment option for patients with mRCC and was associated with considerable toxicity[3, 4]. Since then, the ongoing introduction of molecular targeted therapies for mRCC has provided treatment options that are more efficacious and better tolerated than cytokine therapy. There are now five targeted agents, i.e. sorafenib, sunitinib, temsirolimus, bevacizumab (in combination with interferon) and everolimus that have been shown to improve the outcome in patients with mRCC. Clinical trials resulted a 5-6 months PFS with sorafenib and 11 months with sunitinib versus 4-5 months of interferon therapy. [5]

In Hungary until July 2010 interferon as a first line treatment, sunitinib and sorafenib as a second line treatment were available for mRCC patients. After July 2010 the financing protocol was changed and sunitinib became a first line and sorafenib remained a second line therapy. It is increasingly recognized that conclusions drawn from classical clinical trials are not always a useful aid for decision-making - assessing the value of a drug or technology requires an understanding of its impact on current management in a practical, real-life setting.

OBJECTIVES

The aim of this study was to explore and describe the real treatment effectiveness (PFS: progression free survival, OS: overall survival) in different treatment types of mRCC patients on a real-life data settings in Hungary.

METHODS

The analysis based on real life database of the National Health Insurance Fund and Administration (NHIFA). This official, national financing database chronologically includes all the reimbursed health resource utilisation (medicine, out- and inpatient services). It is a strongly validated and representative database, while includes almost the whole 10 million Hungarian population.

This retrospective analysis included data from January 2008 to July 2011. Subjects were enrolled with a diagnosis of mRCC (ICD-10 code: C64), with a relevant prescription (interferon, sunitinib, sorafenib) in the study period.

Patient data were analyzed by treatment types i.e.: interferon as a first line therapy, sorafenib as a second line therapy and sunitinib as a second line therapy till 01.06.2010, and thereafter as first line therapy.

OS and PFS were determined by descriptive statistical methods and Kaplan-Meier analysis. A hypothesis was made that PFS can be defined by therapy persistence. PFS was analyzed in two different approaches:

- Duration of treatment: duration between the first and last prescription was determined by treatment types, considering drug holidays and treatment interruptions. Before the end of the study period of three months new patients were censored.
- Kaplan-Meier analysis: the minimum continuous duration of treatment was analyzed with Kaplan-Meier survival analysis. In case of abeyance (because of other disease or side effect), the treatment periods were separated to different persistence curves.

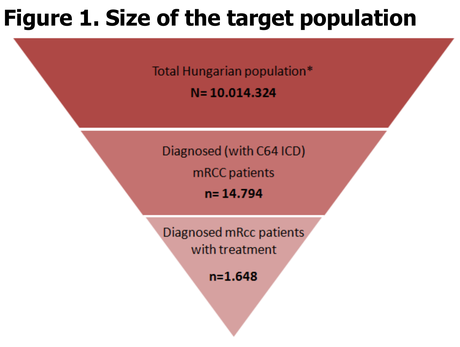
The OS (from the beginning of treatment to the death) was determined with Kaplan-Meier survival analysis.

This is an observational study for which the analysis was descriptive in nature, and a formal hypothesis was not tested. In general, data summaries were presented by treatment types. All statistical analysis was performed using R Statistical program. [6]

RESULTS

In Hungary there were 14.794 patients with a diagnosis of mRCC (with ICD-10 code C64) during the study period. 1.648 subjects (11.14%) were included in the analysis with relevant prescription.

Figure 1. Size of the target population



*in 2010 from source of Hungarian Central Statistical Office

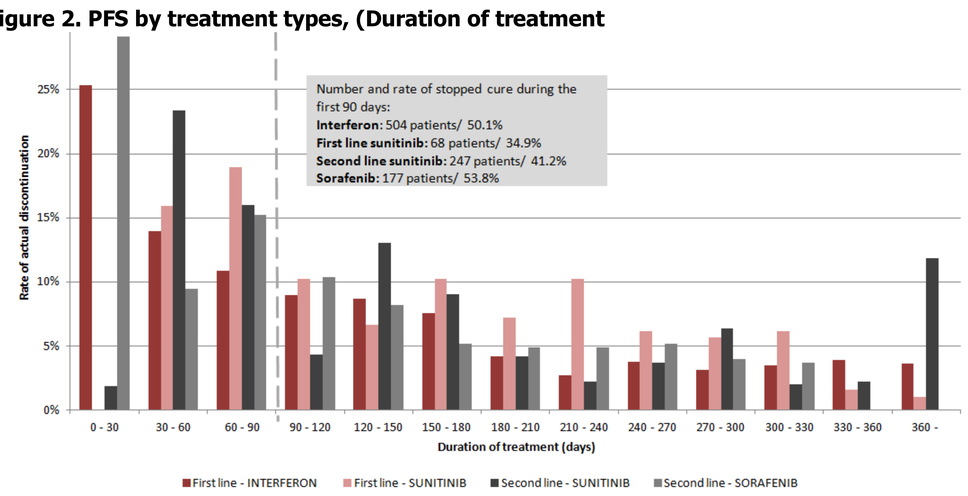
In the study period 1.098 mRCC patients (66.6%) were treated with interferon and 271 (16.4%) with sunitinib as a first line therapy. 529 (32.1%) patients with sunitinib and 409 (24,8%) patients with sorafenib were detected as second line therapy.

Table 1. Patient number by treatment types

Treatment types	Number of patients	Rate
Patients with first line interferon	1 098	66.6%
Patients with first line sunitinib	271	16.4%
Patients with second line sunitinib	529	32.1%
Patients with second line sorafenib	409	24.8%

PFS was found in the 60-90 days interval by interferon and sorafenib and in the 120-150 days interval by sunitinib by the median treatment duration approach. A large number of patients (35-54%) stopped them cure during the first 90 day period and it was found by every treatment types. Figure 2. shows the actual discontinuation rate at each time period.

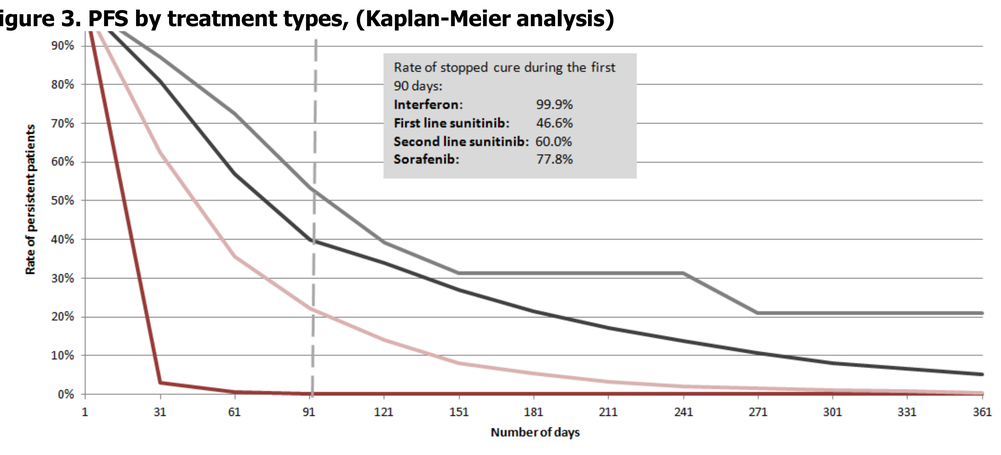
Figure 2. PFS by treatment types, (Duration of treatment



PFS was found in the 1-30 days interval by interferon, in the 90-120 days interval by first line sunitinib, 60-90 days interval by second line sunitinib, and in the 30-60 days interval by sorafenib by Kaplan-Meier analysis at Figure 3. There were a higher number of patients (47-99%) who stopped them cure during the first 90 day period and it was found by every treatment types, because this approach identifies shorter treatment interruptions as the end of cure.

Results demonstrated that interferon therapy has only a per protocol practice, before patients receive newly targeted therapies. Examination of PFS curves showed an advantage of sunitinib first and second line therapies versus sorafenib. The median PFS by both approaches is similar. As the Kaplan-Meier method can take into account some types of censored data (different starting point of treatment or length of follow-up period by patients), it can given better estimate of PFS in a longer follow-up period (longer than 6 months).

Figure 3. PFS by treatment types, (Kaplan-Meier analysis)



CONCLUSIONS

This study found that in Hungary generally just a small portion of patients are on the relevant treatments (35-54% discontinued the therapy) after a three months period. Interferon therapy has only a per protocol practice before newly targeted therapies and a shorter PFS were realised than in the clinical studies (1.5-3 months vs. 6-11 months). Examination of PFS curves showed that there is an advantage of first line sunitinib than second line therapies, and second line sunitinib has an advantage versus sorafenib. Difference between therapies in OS couldn't be experienced due to the short study period..

Finally, these findings suggested that besides newly targeted therapies a shorter PFS and similar OS results were observed in real life data settings compare to published sources. Further extension of the analysis and research is needed to better understand of discontinuation and statistically confirm our findings.

LIMITATIONS

The main purpose of the NHIFA registry is the administration of financed health services by public services. For that reason disease specific parameters (e.g. laboratory values, tumour size, etc.) are not fully taken into account which is the main limitation of the study.

As the duration of treatment as an approach of PFS takes no count of the censored time horizon and the different starting points of treatment by patients, it can be used with strong limitation for the estimate of PFS.

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