Experience with sunitinib treatment of patients with metastatic renal cell carcinoma

PhD theses

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INTRODUCTION

The 80-90% of primary kidney tumors are renal cell carcinomas (RCCs) with the starting point in renal cortex. The most common histological type of RCC is clear-cell RCC (70% -80%). RCC is the most deadly urological malignancy and its incidence is still rising in Europe (doubling over the last 30 years). Worldwide, the incidence of RCC varies widely across regions, with the highest rates in Europe and North America. In 2010, 2735 new cases were reported in Hungary (1173 women and 1562 men) and 818 patients died of the disease. Unfortunately, one third of patients have visceral metastases at the time of diagnosis and half of these patients develop distant metastases. Treatment options for metastatic RCC (mRCC) cases were scarce until 2005.

The oral agent, sunitinib, is a multi-targeted receptor tyrosine kinase inhibitor including VEGF and PDGF receptors. The RCC was approved by the US FDA on January 26, 2006. Until recently, sunitinib was the gold standard of treatment for mRCC. It has been used first-line in 2007 and was used as the standard treatment for patients with advanced RCC classified as a good to moderate prognosis group under MSKCC.

Targeted biological agents are not free from side effects. Some side effects are not directly related to VEGF pathway inhibition (off-target side effects) such as fatigue / weakness, diarrhea, rash, stomatitis / mucositis, hand-foot syndrome (HFS), cardiotoxicity, hematological and liver toxicity. The direct onset VEGF inhibition (on-target side effects) include hypertension, bleeding, thromboembolic events, hypothyroidism, ulcers, kidney and pancreatic toxicity. Previous studies have shown that some of these side effects are predictive of the efficacy of sunitinib treatment.

According to the current practice the treatment is continued till progression or unacceptable toxicity. The clinical experience is that a significant proportion of

patients discontinue treatment temporarily on the basis of complete response (CR), stable disease (SD), recurring side effects, co-morbidities, or discretion.
It is still unclear whether continuous TKI treatment or discontinued therapy is safe without compromising the outcome. Some studies reported that the majority of patients who discontinued treatment had a favorable response if they restarted the treatment with the same TKI.
Despite the benefits of sunitinib, all patients develop resistance and eventually relapse. The mechanisms of resistance are diverse and multifactorial, and the exact pathway by which the tumor progresses during this particular VEGF-targeted therapy is unknown. Treatment guides recommend sequential therapy. After progression during one drug treatment, the use of another drug can control the disease and provide further clinical benefit. Patients with favourable biological background can be treated with several drug. The current long-term strategy for mRCC is to receive multiple sequential treatments with different agents, and a growing number of studies and case reports suggest that re-administering a specific drug may also be of therapeutic benefit. Among other settings, re-challenge of another TKI or the same TKI may be an option, as recommended by the ESMO Clinical Practice Guide, in cases where patients have already been treated with TKI or mTOR inhibitors. TKI re-challenge does not fit into the current and future treatment guidelines. Recent international recommendations suggest that sunitinib treatment is almost completely out of line due to new TKIs and, in particular, immunotherapeutic drugs. The use of TKI re-challenge is recommended in countries where the introduction of new treatment modalities is difficult due to financial considerations.

OBJECTIVES

1. To systematically analyze in a retrospective study the relationship between the efficacy of sunitinib treatment and adverse events in advanced RCC patients in case of:

- on-target side effects and
- off-target side effects, and
- the correlation between the number of adverse events and the outcome

2. To retrospectively study the outcome of sunitinib treatment in advanced RCC patients who have restarted sunitinib after at least 3 months of interruption in:

- a group of patients treated in our institution, and

based on a combination of case studies reported in the literature, and

- to compare the results of the above two groups.

3. To retrospectively evaluate the efficacy of sunitinib treatment in advanced RCC patients who received other targeted treatment (s) after first sunitinib treatment and then were rechallenged with sunitinib.

- best response and PFS for first and rechallenged sunitinib
- search for survival factors
- differences in side effects of the first and the re-challenged sunitinib

PATIENTS AND METHODS

Investigation of the relationship between treatment efficacy and adverse events

Between November 2005 and April 2014, a total of 448 advanced RCC patients were treated with sunitinib in the urooncological department. Of these, 274 patients were treated in first line setting. A systematic retrospective analysis was performed to assess the prognostic value of the most common adverse events. The data of efficacy and adverse events were obtained from the institute database. Clinicopathology, performance status, and risk classification were based on UICC TNM rank, Karnofsky index, and MSKCC risk categories. Sunitinib treatment was started at 50 mg/day with 4 weeks on and 2 weeks off treatment. Treatment continued for 6-week cycles until progression or unacceptable toxicity. Dose reductions (37.5 and then 25 mg/day) have occurred occasionally as a consequence of toxicities, but treatment interruption rarely occured. Patient follow-up included medical examination, routine laboratory testing (including thyroid function), chest X-ray, abdominal and / or chest CT. The adverse events were reported every six weeks according to NCI CTCAE 3.0 based on patient reports, physical examination, and laboratory tests. On-target adverse events include hypertension, hypothyroidism, renal toxicity, bleeding, thrombosis and ulcer, while off-target side effects include mucositis, diarrhea, vomiting, cardiotoxicity, hand-foot syndrome (HFS), skin rash and haematological toxicity. The best clinical response was assessed every three months according to RECIST 1.0 criteria. Patients had signed a consent for sunitinib treatment at the institute. The study was approved by the local Ethics Committee prior to data collection.

The primary objective is to establish a relationship between the occurrence of adverse events and efficacy [objective response rate (ORR), median

progression-free (mPFS) and overall survival mOS]. The association between clinical response and adverse events was evaluated by $\chi 2$ test. Survival was tested by Kaplan-Meier method and compared by log-rank test. Multivariate Cox regression was also used to examine the effect ofadverse events on survival. The hazard ratio (HR) and 95% confidence intervals (95% CI) were presented. Only those adverse events that were statistically significant for both mPFS and mOS were included in the multivariate analysis. Hepatic toxicity (elevated transaminase and bilirubin levels) was excluded, as the incidence of liver metastases (which may cause poor hepatic function) was significantly different in patients with and without hepatic toxicity (26% vs. 15%; $p = 0.045$). Gender, age ($\leq$ vs. 65 years), histology (light-cell RCC vs. other components), number of metastases (one vs. more), location of metastasis (lung vs. other), prognostic category (good vs. moderate), number of side effects (0-2 vs. 3-6), nephrectomy (yes vs. no), and second-line treatment (yes vs. no, OS only) were included in the multivariate Cox regression analysis. The log-likelihood ratio of multivariate regression was used to test the fit of the model with or without adverse events. If the bilateral p value was <0.05, then it was considered statistically significant. The following equation was used to determine the synergism of survival: $\beta = Dn - \Sigma Di$, where Dx = median survival at number x adverse events - median survival without adverse events, $n > 1$ and $\Sigma i = n$, [e.g. ß = mPFS5-mPFS0-(mPFS3-mPFS0 + mPFS1-mPFS0 mPFS1-mPFS0 +)]. If β is significantly greater than 0, the effect of adverse events on survival is synergistic. Taking all ß values into account, the p value (one-sided null hypothesis) was calculated by the one-sample t-test. All statistical tests were performed using NCSS software.

Investigation of the efficacy of restarted sunitinib treatment

Between January 2006 and March 2016, data from 556 mRCC patients receiving sunitinib in first- or second-line setting were retrospectively reviewed. Patients with SD or better response to sunitinib treatment were discontinued for any reason other than progressive disease. Only patients who continued (re-started) sunitinib treatment due to tumor progression that occurred during the therapeutic holiday (≥3 months) were included in the final analysis. Of the 556 mRCC patients who received first or second line sunitinib treatment, 38 met the criteria for analysis. Patients' medical records included demographics, tumor characteristics, previous treatments, progression time, and patient status at the end of follow-up. Patients were categorized according to MSKCC risk criteria. The tumor response was classified according to RECIST 1.1 guidelines. Tumor response was determined by CT scan every 2 cycles and side effects by NCI CTCAE (v. 3.0). The dose of orally administered sunitinib was 50 mg daily in 6-week cycles (4 weeks treatment on and 2 weeks off). The daily dose was reduced to 37.5 or 25 mg in case of serious adverse events. This study was approved by the ETT and the Ethics Committee of the institute.

The primary objectives were the clinical response and progression-free survival (PFS) for initial and restarted sunitinib treatment. The secondary objective was the overall survival (OS). Adverse events were reported as reported in our previously study. PFS was calculated from the start of sunitinib treatment until disease progression, death for any cause, or end of follow-up. OS was calculated from the start of the initial sunitinib treatment until death or end of follow-up. Multivariate logistic regression was used to find predictive markers of response. Multivariate Cox regression analysis was performed to find independent variables of survival. Correlation analysis was used to exclude correlation between variables (multicollinearity). NCSS statistical software was used for all statistical analyzes.

Investigation of the efficacy of re-challenged sunitinib treatment

This retrospective study was conducted at our institute between March 2010 and April 2018. 21 cases met the criteria for analysis. Patients with confirmed mRCC (any histology) who were previously treated with sunitinib in first- or second line until progression, then received another TKI and/or mTOR inhibitor and after progression re-challenged sunitinib. Data of both sunitinib treatments and of the intermediate therapies were taken into account. The best response, PFS, adverse events, and OS were also recorded. Tumors were evaluated using RECIST version 1.1 and treatment-related adverse events were assessed according to NCI CTCEA version 5.0.

PFS was calculated from the start of treatment until progression according to RECIST. OS refers to the time from first sunitinib treatment until death or end of follow-up. Kaplan-Meier methodology was used for survival curves,. Independent markers of survival, if any, were analyzed by multivariate Cox regression. $P < 0.05$ was the statistical significance level. NCSS software was used for all statistical evaluations.

RESULTS

Investigation of the relationship between treatment efficacy and adverse events

The median duration of treatment of patients was 50 weeks (1-343 weeks). Seventy-six (27%) patients required dose reduction because of adverse events. Relative dose intensity (RDI) was 90-99% in 13 (17%), 80-89% in 36 (47%), 70-79% in 14 (18%), 60-69% 5 (7%) and 50-59% in 8 (11%) patients. At the end of the follow-up period, 65 patients were still being treated, and in others, sunitinib was discontinued because of disease progression (n=185, 68%) or because of intolerable toxicity (n=24, 8%). During the median follow-up of 32 months (95% CI 26-37) the mPFS and mOS were 9 (95% CI 7-10) and 19 (95% CI 15-23) months, respectively.

The relationship between treatment efficacy and adverse events was only investigated for adverse events (to any degree) with a frequency >10%.

The analyses have shown that patients with hypertension, HFS, hypothyroidism, skin toxicity, diarrhea or leucopenia were significantly more likely to respond to treatment and to survive longer. The presence or absence of mucositis had a neutral effect on survival, while anemia and hepatic impairment were inversely related to survival.

A synergistic effect of 6 adverse reactions (hypertension, diarrhea, HFS, hypothyroidism, skin toxicity and leukopenia) on survival (mPFS and mOS) was observed: for mPFS, ß=12.2 (95% CI 7.3-17.1), $p<0.001$; and for mOS, ß=24.5 (15.6-33.4), $p <0.001$. Synergism was also present in the subgroups showing only on-target or only off-target side effects.

The greatest difference in survival was observed when the 6 selected adverse events were divided into two groups (dichotomized) (0-2 vs. 3-6 adverse events), so this variable was used for multivariate analysis.

Surprisingly, there was no difference in survival in patients suffering from only on-target or only off-target adverse events. Patients with both on-target and off-target toxicities had the longest survival.

The degree of adverse events was also investigated, but regardless of the number of adverse events, the more severe degree did not affect survival.

The effect of gender, age, histology, prognostic index, number of metastases, nephrectomy, number of adverse events and second line treatment (OS only) was examined by multivariate analysis. RDI was excluded from this analysis because there was a significant associated with the number of adverse events. In addition to the prognostic index, the number of adverse events was found to be an independent predictor of PFS and OS. Multiple adverse events (3-6 vs. 0-2) are the strongest predictive marker for longer survival: mPFS: 24 (95% CI 16-24) vs. 5 (95% CI 4-5) months and mOS: 51 (95% CI 32-69) vs. 9 (95% CI 7-10) months ($p<0.001$ for both mPFS and mOS). The log-likelihood ratio test resulted a $p<0.001$ (for both mPFS and mOS) when the multivariate Cox regression model included or not the number of adverse events.

Investigation of the efficacy of restarted sunitinib treatment

Patient characteristics were typical of the mRCC population: male majority (n=29) and median age 63.5 years (range 38-92) at initiation of sunitinib initial treatment. All patients have previously been nephrectomized.

The histologic diagnosis was either clear cell (n=33) or mixed (predominantly clear cell) (n=5) RCC. According to MSKCC 21 patients had good, while 17 had a moderate risk. Almost all patients were asynchronous metastatic. The most common localization of metastases was the lung (n=30) and the mediastinal lymph nodes (n=9).

Twenty-one patients who had not received systemic treatment prior to sunitinib treatment, cytokine (interferon ± IL-2) therapy was primarily administered to 15

patients, one patient was on cytokine+chemotherapy, and another patient on first line sorafenib. The most common reasons for discontinuation of sunitinib treatment were adverse events (n=15) and patient decision (n=14). The median PFS for initial sunitinib treatment was 21 (95% CI 18-27) months.

The sunitinib treatment holiday lasted for median 7 months (range 3-41 months). During the treatment holiday, 5 patients underwent metastaticectomy and one of them received radiotherapy, which was applied in another 2 cases, as well. Completely new metastatic localization was found in 11 patients. In all cases, sunitinib treatment was restarted as the disease progressed. The median duration of restarted sunitinib was 11.5 (range 1-48) months. At the end of follow-up (March 31, 2016), 5 patients were still on sunitinib treatment. The best response of restarted sunitinib therapy was 1 CR (3%) and 14 PR (37%), while 19 patients (50%) had stable disease (SD) and 4 (11%) had disease progression.

During the follow-up period 31 patients developed tumor progression and nearly 3/4 of them (23 patients) died. In 12 cases, new metastasis localization appeared during the restarted treatment. At a median follow-up of 76 months, median PFS for restarted sunitinib was 14 (95% CI 10-18) months and the median OS was 61 (56-80) months calculated from the start of first sunitinib treatment.

There was no statistical difference between the adverse events of the first and restarted treatment. The accumulation of adverse events was present in the majority of patients with 4 or more adverse reactions (n=29), but only in 2 cases with 2 different grade 3-4 toxicities.

For the PFS of first sunitinib gender, age, prognostic index, histology, metastatic synchronicity, multiple metastasis, lung metastasis, prior immunotherapy, sunitinib dose reduction, and the best clinical response was analyzed by Kaplan Meier method and log rank test.

Older age (≥63 years), synchronous metastasis, lack of previous immunotherapy, and PR resulted in statistically significantly shorter PFS. Only

parameters that had a significant effect on univariate survival were considered for multivariate analysis. Multivariate Cox regression analysis showed that older age, synchronous metastasis, PR vs. SD (or CR) has been shown to be an independent factor in shorter PFS.

Kaplan Meier method and log rank test was applied for the PFS of restarted sunitinib including the following variables: gender, age, histology, metastatic synchronicity, multiple metastasis, lung metastasis, previous immunotherapy, new metastatic localization, treatment during treatment holiday, duration of treatment holiday, duration of initial sunitinib treatment, toxicity at treatment interruption, dose reduction of restarted sunitinib, and best response of restarted treatment. Only the objective response influenced PFS on restarted sunitinib. Based on the results of multivariate logistic regression, none of the parameters significantly influenced the response. Similarly, OS was not influenced by any of the parameters when it was evaluated by multivariate Cox regression.

Investigation of the efficacy of re-challenged sunitinib treatment

According to the type of treatment administered between the two sunitinib treatments three subgroups can be defined (TKI (n=7); mTOR inhibitor (n=8) or both (n=6)). It was demonstrated that the OS (from the start of the first sunitinib) was in correlation with the duration of the first sunitinib treatment, regardless of the type of systemic treatment given between the two sunitinib treatments. Between the sunitinib treatments the mTOR inhibitors (n=14) were given longer than the TKI (n=13) (mean 9.2 vs. 5.7 months / patient), although this comparison was not the aim of this study.

The best response during the first sunitinib treatment was 38% objective response (OR) and 86% clinical benefit (CB). The median PFS for the first sunitinib treatment was 22 (95% CI 17-26) months.

Dose reduction due to side effects was required in one third of patients. The initial dose of sunitinib was 50 mg, except for one patient who received 25 mg, The dose was reduced to 37.5 mg in 6 patients and to 25 mg in 2 patients.

Multivariate Cox analysis showed that dose reduction (hazard ratio (HR) =0.17; 95% CI 0.04-0.78; p=0.022) and previous cytokine treatment (HR = 0.29; 0.09-0.95; p=0.042) were independent markers of longer PFS of first sunitinib treatment.

In all cases, sunitinib was re-challenged due to progression. OR and CB were 19% and 76% for the re-challenged sunitinib, respectively. The median PFS for re-challenged sunitinib was 14 (6-20) months. Three patients required a dose reduction (25 mg) during re-challenged sunitinib.

Multivariate Cox analysis revealed no independent marker for the re-challenged sunitinib.

There was no statistically significant difference in toxicities between the first and the re-challenged sunitinib.

With a median follow-up of 146 months, the median OS (from the start of first sunitinib) was 67 (95% CI 46-74) months. The median OS considered from the nephrectomy was 111 (61-122) months.

Multivariate Cox regression showed that younger age (≤ 56 years) at the start of first sunitinib (HR=0.24; 0.07-0.79; p=0.019) and longer (>2 years) first sunitinib treatment (HR=0.28; 0.09-0.93; p=0.038) were independent markers of longer OS. At the end of the follow-up period, 3 patients were alive and one of them was still receiving sunitinib.

CONCLUSIONS

Investigation of the relationship between treatment efficacy and adverse events

Results of this study provide evidence for the synergistically enhanced efficacy of sunitinib treatment in patients who present multiple adverse events irrespective of their on- or off-target type. These adverse events are diagnosed routinely and their coexistence helps physicians to predict which group of patients would benefit the most from first-line sunitinib treatment. Therefore, the presence of multiple adverse events can be considered a powerful predictive marker of first-line sunitinib treatment in advanced RCC, however, further evidence and prospective validation is required to meet the criteria of a predictive biomarker.

Investigation of the efficacy of restarted sunitinib treatment

In conclusion, based on our results and on combined case reports from the literature sunitinib treatment could be interrupted when clinically warranted, but cessation should be approached with caution in older patients or patients having synchronous metastases at diagnosis or presenting partial response as best response of baseline Su treatment. Results of an ongoing prospective trial (STAR) probably will give a better approach with new aspects to be used in the routine practice.

Investigation of the efficacy of rechallenged sunitinib treatment

Sunitinib can be rechallenged after different targeted treatments, and its efficacy does not depends on the type of treatment(s) applied between the first and rechallenged sunitinib exposures. Re-applying sunitinib does not need further caution from oncologists because there were no differences between the pattern

of adverse events related to the first and rechallenged sunitinib treatment. The overall survival of patients with mRCC is markedly influenced by the duration of first sunitinib treatment.

Finally, we fully agree with the statement of Porta et al.[1] that "although many agents are presently available from second line on, in countries where treatment options are still limited, sunitinib rechallenge could still represent a reasonable treatment option" for patients with mRCC.

Further investigation is needed into how the recently approved immunotherapy modifies patients' outcome in sequential use and the rechallenge of sunitinib treatment in mRCC.

[1] Porta C. et al. J Clin Oncol 35(15 suppl):e16081, 2017

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