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ORIGINAL PAPER

Pre-treatment global quality of health predicts progression free survival in metastatic kidney cancer patients treated with sorafenib or sunitinib

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Abstract
Purpose Our goal was to prospectively evaluate self-reported quality-of-life (QoL) during second-line therapy in 51 consecutive patients with cytokine-refractory kidney cancer treated with sorafenib or sunitinib.
Methods QoL was assessed by the EORTC QoL questionnaire QLQ-C30 at baseline and at weeks 4, 6, 10, 12 and 16.
Results Global QoL deteriorated significantly during the first 4 weeks of treatment ($P < 0.0001$). Patients experienced a reduction of their role, cognitive, and social function (all $P < 0.0001$). In addition, fatigue ($P < 0.0001$), nausea/vomiting ($P = 0.003$), and pain ($P < 0.0001$) as well as dyspnoea ($P < 0.0001$), insomnia ($P = 0.026$), appetite loss ($P = 0.013$), and diarrhoea ($P < 0.0001$) increased significantly. After 16 weeks, fatigue ($P < 0.0001$), pain ($P = 0.015$), appetite loss ($P = 0.002$) and diarrhoea ($P = 0.038$) were still influenced by the therapy, while all functional scales recovered. Global QoL at baseline was predictive of overall response ($P = 0.006$) and progression free survival (PFS) ($P < 0.0001$). A better physical function at baseline, a better ECOG performance status, and a low risk profile according to MSKCC risk groups correlated with a longer PFS (all $P < 0.0001$). No significant differences regarding QoL were found between sorafenib and sunitinib during the study period.
Conclusions Second-line therapy with sorafenib or sunitinib does not adversely affect patients global QoL after 16 weeks of treatment. Evaluation of baseline QoL can help to further stratify patients into risk groups predicting overall response and PFS.

Keywords Kidney cancer · Renal cell carcinoma · Sorafenib · Sunitinib · Quality of life

Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all malignant tumours in adults. In the United States the estimated incidence was 51.190 cases and 12.890 cancer-related deaths in 2007 (Jemal et al. 2007). Patients with untreated metastatic disease have an overall median survival of no more than 12 months and a 5-year survival of less than 10% (Atzpodien et al. 2003).

For patients with metastatic disease, radical nephrectomy followed by cytokine therapy had been the treatment of choice (Flanigan et al. 2001; Mickisch et al. 2001) until the tyrosine kinase inhibitor (TKI) sunitinib was approved for first-line treatment by the United States Food and Drug Administration (FDA) in February 2007. To date, only selected patients with metastatic RCC, revealing a low risk profile and a clear cell subtype histology should be recommended to immunotherapy after nephrectomy (Ljungberg et al. 2007; Motzer et al. 2002; Choueiri et al. 2008). When

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immunotherapy fails both TKIs sorafenib and sunitinib show antitumour efficacy for second-line treatment doubling the progression-free survival (PFS) compared to placebo (Motzer et al. 2006a, b; Escudier et al. 2007). However, second-line treatment with TKIs is regarded as a palliative therapy, such that tumour control and survival are not the only end points of successful care. Patients with advanced cancer require palliative care for relief of pain and for the resolution of emotional, social, psychological and spiritual problems. Quality of life (QoL) is now recognised as an end point, succeeding survival in importance.

For evaluation of the impact of palliative care, various outcome scales and systems have been developed in recent years. In 1986, the European Organization for Research and Treatment of Cancer (EORTC) study group developed a 30-item version of an integrated measurement system for evaluating the QoL of patients participating in international clinical trials (Aaronson et al. 1993). Today, the core QoL questionnaire QLQ-C30 is the most internationally recognised instrument for patients who self-report their health-related QoL in cancer research.

The purpose of our study was to evaluate changes in QoL during second-line treatment with sorafenib and sunitinib for advanced kidney cancer following the QLQ-C30 experienced by a homogenous cohort of 51 patients.

Patients and methods

Study design and treatment

Between July 2006 and January 2008, 51 consecutive patients who previously presented to our outpatient clinic for metastastic RCC and had refractory disease after one or more cycles of immunotherapy were treated with second-line treatment of either sorafenib or sunitinib. The baseline characteristics of the study population are summarised in Table 1.

Eligible patients were at least 18-years-of-age and had metastatic RCC confirmed by histology that had progressed despite previous cytokine therapy. Additional eligibility criteria were a performance status of 0–2 on the basis of the Eastern Cooperative Oncology Group (ECOG) criteria; a life expectancy of at least 12 weeks; and adequate bone marrow, haematologic, liver, pancreatic, renal and cardiac function. Patients were stratified into risk groups according to MSKCC criteria (Motzer et al. 2004) (Table 1). Patients were excluded, when any significant cardiac event had occurred within the previous 12 months, and when left ventricular ejection fraction was not determined as normal by echocardiogram or multigated acquisition scan. All patients gave their informed consent before participating in this study. In case of progression they did not have to complete further questionnaires.

Table 1 Baseline characteristics and treatment responses of patients

Characteristics	Sorafenib ($n = 30$)	Sunitinib ($n = 21$)
Gender		
Male	20	13
Female	10	8
Median age	63	61
ECOG performance status no./(%)		
0	16/(53.3)	12/(57.1)
1	13/(43.4)	8/(38.1)
2	1/(3.3)	1/(4.8)
Prior cytokine therapy no./(%)		
1	11/(36.7)	9/(42.9)
2	6/(20.0)	4/(19.0)
>2	13/(43.3)	8/(38.1)
Metastatic sites no./(%)		
1	6/(20.0)	3/(14.3)
2	7/(23.3)	6/(28.6)
>2	17/(56.7)	12/(57.1)
Prior nephrectomy no./(%)		
Yes	28/(93.3)	20/(95.2)
No	2/(6.7)	1/(4.8)
Histologic subtype no./(%)		
Clear cell	28/(93.3)	20/(95.2)
Other	2/(6.7)	1/(4.8)
MSKCC prognostic risk factors no./(%)		
Low	10/(33.3)	6/(28.6)
Intermediate	8/(26.7)	8/(38.1)
Poor	9/(30.0)	4/(19.0)
Missing data	3/(10.0)	3/(14.3)
Best treatment response no./(%)		
CR	0/(0)	0/(0)
PR	4/(13.3)	6/(28.6)
SD	18/(60.0)	12/(57.1)
PD	8/(26.7)	3/(14.3)

MSKCC Memorial Sloan–Kettering Cancer Center (low Karnofsky performace status (<80%), low haemoglobin (males: <14 g/dl, females: <12.0 g/dl), high corrected serum calcium (>10 mg/dl), *low* 0, *intermediate* 1, *poor* 2-3 risk factors)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

According to recently published data (Escudier et al. 2007), patients received continuous treatment with oral sorafenib at a dose of 400 mg twice daily in 6-week cycles. Sunitinib was administered at 50 mg once daily without regard to meals in repeated 6-week cycles of daily therapy for 4 weeks, followed by 2 weeks off the treatment (Motzer et al. 2006b). Doses were delayed or reduced if patients had clinically significant haematologic or other adverse events that were considered to be related to the TKIs.

Assessment of response

Response to therapy was evaluated according to RECIST-criteria on intent-to-treat basis every 6 weeks. Best treatment responses of each patient in both treatment groups are shown in Table 1.

QLQ-C30 questionnaire

Patients responded to all questions without help and/or influence. Among the 30 items, 28 are scored from 1 to 4 with a lower score representing a better quality of life.

The questionnaire permits the grouping of individual items into five functional scales (physical, role, emotional, cognitive, and social), a global-quality-of-health scale, three symptom scales (fatigue, nausea/vomiting, and pain), and a number of physical symptoms (dyspnoea, insomnia, appetite loss, constipation, diarrhoea), as well as the financial impact of the disease and treatment.

As published elsewhere, the raw EORTC QLQ-C30 scores were transformed to scales of 0–100 (Atzpodien et al. 2003). For the five functional scales, items responses were recoded, such that a higher score represents a better level of functioning. For the symptom-oriented scales, a higher score corresponds to a higher level of symptoms. A mean change in scores of 5–10 has been found to represent "a little" subjective change to patients, whereas a change of 10–20 represents a moderate change (Osoba et al. 1998). Therefore, a difference of 10 points or greater may be regarded as clinically significant.

Each patient completed the questionnaire initially before treatment (baseline) and again at weeks 4, 6, 10, 12 and 16.

Statistical analyses

All data were analysed according to the guidelines of the EORTC and their questionnaire QLQ-C30. Beyond descriptive statistical analyses, the following nonparametric significance tests were applied. Intra-individual differences in QoL during treatment were assessed with the paired Wilcoxon test. The association of QoL with treatment response was analysed by means of the Kruskal–Wallis test. Differences between the treatment groups for sorafenib and sunitinib were assessed with the Mann–Whitney *U* test. For evaluation of PFS, patients were subdivided into two groups according to median QoL at baseline. The respective survival distributions were estimated according to Kaplan–Meier and the log-rank test was used to compare the survival curves.

All statistical analyses are intended to be explorative and not confirmative. No adjustment for multiple testing was carried out. *P* values were considered statistically significant in case of $P < 0.05$. For statistical analysis, SPSS for Windows (Version 15.0) and R (Version 2.6.0) were used.

Results

QoL during treatment

Baseline questionnaire compliance was 100%. During follow-up, compliance remained above 90%. The reasons for missing questionnaires were either related to administrative errors or because patients did not respond to the questionnaire within the allowed time frame.

Severe drug-related adverse events led to a reduction or interruption of doses in 10 (19.6%) cases; 7 (13.7%) patients had to do so during the first 4 weeks of treatment, and 3 (5.9%) patients between weeks 4 and 16. The most common adverse events of any grade according to Common Terminology Criteria for Adverse Events (CTCAE) (Trotti et al. 2003) during the first 4 weeks were fatigue (47.1%), diarrhoea (49.0%), and hypertension (31.4%); and between weeks 4 and 16 rash (43.1%), hand-food-skin reaction (41.2%), diarrhoea and nausea (both 39.2%).

Figure 1 demonstrates that patients mean pre-treatment global quality of health deteriorated significantly from 60 (baseline) to 39 (week 4) ($P < 0.0001$). At week 6 it significantly increased to 54 ($P = 0.001$) and persisted on constant levels at weeks 10 (46), 12 (52) and 16 (52), respectively. Neither the ECOG performance status, nor the MSKCC criteria had a significant impact on patients QoL at baseline. Patients in the sorafenib group had a mean global quality of health of 56 at baseline versus 67 for sunitinib. Hence, sunitinib patients had a clinically evident better global quality of health at baseline (>10 vs. sorafenib), albeit not statistically significant. Similarly for sorafenib and sunitinib, global quality of health decreased severely at week 4 (from 56 to 33 for sorafenib vs. 67 to 47 for sunitinib; both $P < 0.0001$) with no significant difference in deterioration between the TKIs. Subsequently global quality of health increased and lasted on a higher level at weeks 6 (57 for sorafenib vs. 50 for sunitinib), 10 (44 vs. 49), 12 (51 vs. 53)

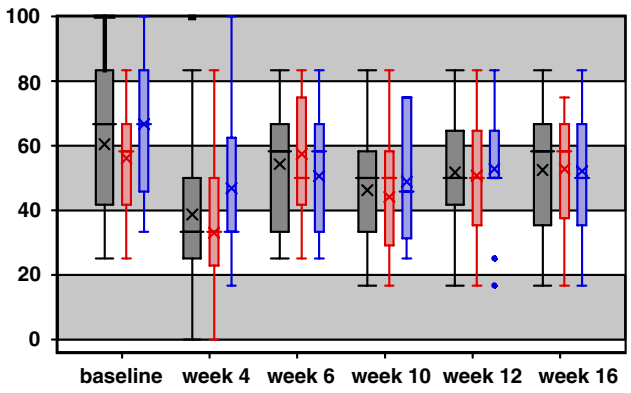

Fig. 1 Global quality of health during treatment [all patients *left boxplot*, sorafenib *center boxplot*, sunitinib *right boxplot*; (*cross*) mean value, (*horizontal line*) median]

and 16 (53 vs. 52) (Fig. 1). After 16 weeks of therapy neither functional scales, nor symptom scales, physical symptoms, nor the financial impact differed between both treatment groups in a clinically significant manner.

When we evaluated all patients without subdividing for sorafenib or sunitinib, a significant decline of 10 and more was found at week 4 compared to baseline for 3 functional scales: role function (from 54 to 31), cognitive function (from 73 to 59) and social function (from 55 to 34) (all $P < 0.0001$). At week 16, distinctions of all functional scales were less than 10 and were no longer clinically significant compared to baseline (Table 2).

All symptom scales as well as the physical symptoms dyspnoea, insomnia, appetite loss, and diarrhoea; but not constipation significantly increased ($\geq$10) at week 4 compared to baseline (all $P \leq 0.026$) (Table 2). After 16 weeks of treatment, fatigue (from 45 to 61; $P < 0.0001$), pain (from 28 to 45; $P = 0.015$), appetite loss (from 25 to 38; $P = 0.002$) and diarrhoea (from 22 to 32; $P = 0.038$) were still impaired; while dyspnoea, insomnia, constipation and financial problems were no longer significantly influenced by the therapy. Although nausea/vomiting had higher scores ($P = 0.002$) at week 16, the increase compared to baseline was less than 10 (from 13 to 17) and therefore clinically insignificant (Table 2).

QoL and response rates

Of the 31 patients treated with sorafenib, 4 (13.3%) had a partial response (PR), 18 (60.0) had a stable disease (SD) as the best treatment response and 8 (26.7) were progressive. In the sunitinib group, 6 (28.6) patients achieved a PR, while 12 (57.1) were stable, and 3 (14.3) had a progressive disease (PD) (Table 1). There was no significant difference between both treatment groups regarding overall response.

The global quality of health at baseline was predictive of tumour response ($P = 0.006$) (Fig. 2). This difference was even more distinct, when we excluded patients with SD, but compared partial responders to PD patients ($P = 0.001$). Especially physical (PR, 97 vs. PD, 87; $P = 0.001$) and social functioning (72 vs. 50; $P = 0.038$) had higher scores at baseline in the first subgroup. On the other hand, fatigue (32 vs. 48; $P = 0.02$) and pain (11 vs. 35; $P = 0.016$) as well as appetite loss (15 vs. 61; $P = 0.004$) were found more commonly in patients before they started treatment and subsequently were more likely to progress during their course of disease. Regarding the association of global quality of health at baseline with the overall response, no differences could be found between sorafenib and sunitinib.

QoL and PFS

The median PFS for all patients was 6.2 months. No significant differences were found between sorafenib and suniti-

Table 2 QLQ-C30 QoL questionnaire-specific functional scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain), physical symptoms (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), and the financial impact during therapy

Variable	Physical function	Role function	Emotional function	Cognitive function	Social function	Fatigue	Nausea/ vomiting	Pain	Dyspnoea	Insomnia	Appetite loss	Constipation	Diarrhoea	Financial problems
Baseline	89	54	55	73	55	45	13	28	34	42	25	24	22	37
Week 4	82	31	46	59	34	62	23	48	46	55	40	25	51	44
P value*	<0.0001	<0.0001	0.003	<0.0001	<0.0001	<0.0001	0.003	<0.0001	<0.0001	0.026	0.013	0.903	<0.0001	0.014
Week 6	88	61	56	66	42	60	26	37	29	44	27	20	52	42
Week 10	85	39	40	58	28	72	14	55	27	59	49	21	70	40
Week 12	90	67	54	65	41	58	47	44	40	54	21	24	32	47
Week 16	87	65	52	65	50	61	17	45	32	49	38	25	32	49
P value**	0.101	0.083	0.485	0.446	0.881	<0.0001	0.002	0.015	0.658	0.315	0.002	0.745	0.038	0.447

* Week 4 compared to baseline

** Week 16 compared to baseline

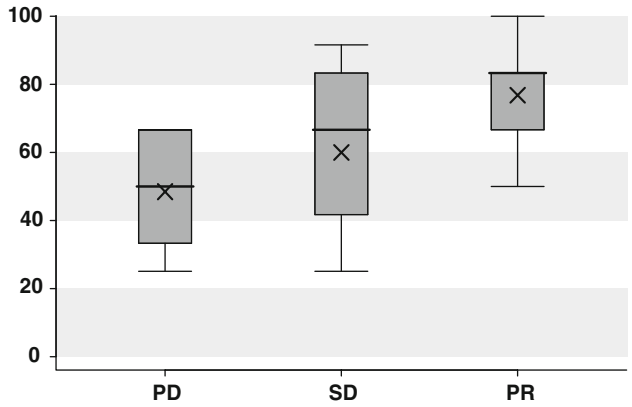

Fig. 2 Global quality of life at baseline assigned to treatment response (*PD* progressive disease, *SD* stable disease, *PR* partial response; (*cross*) mean value, (*horizontal line*) median)

nib. Patients with a better global quality of health at baseline (>median) had a significantly longer median PFS compared to patients with a lower score (≤median) (11.0 vs. 5.9 months; $P = 0.002$) (Fig. 3). Patients with a better physical function at baseline (11.0 vs. 5.5 months; $P < 0.0001$) had a longer PFS. And, patients with a better ECOG performance status and a low risk profile according to MSKCC risk groups progressed later (both < 0.0001).

Discussion

In this study, we describe the longitudinal self-reported QoL of patients undergoing second-line treatment with the TKIs sorafenib and sunitinib for metastatic kidney cancer. The observed deterioration of the mean global quality of health at week 4, improved 2 weeks later, and persisted on acceptable levels considering the clinical benefit for the patients with improvement of PFS, which was demonstrated in several studies before (Escudier et al. 2007; Motzer et al. 2006a, b). During the first four weeks of therapy 7 (13.7%), patients had to reduce doses because of severe drug-related adverse events. Only 3 (5.9%) more patients had to reduce doses between weeks 4 and 16 mainly because of rash, hand-food-skin reaction, and/or gastrointestinal symptoms. Fatigue, diarrhoea and hypertension were most often found during the first 4 weeks of treatment with few grade 3 and 4 events. However, the summation of these events might have led to reduced functional aspects such as physical and emotional stress, and subsequently to a deterioration of QoL. Moreover, we assume that these new side effects that had arisen were unfamiliar to the patients, who previously underwent cytokine therapy and suffered from different symptoms. Not only did the new side effects impair the patient himself, but also his family and social life as well as his activities of daily living. Since all our patients were treated in an outpatient setting, new side effects alienated both the patient and his loved ones, who were inevitably involved in organisation of patients everyday life. Heinzer et al. had similar results, when they investigated inhalational IL-2 therapy for metastatic kidney cancer in 1999. Using the same questionnaire, the mean global quality of health deteriorated significantly after 4 weeks of treatment due to changes in the patient's everyday life, resulting from the multiple daily dosing schedules and the side effects that were predominantly coughing and minor general impairment. After 4 weeks of treatment, patients adapted to the immunotherapy and had considerable improvement in QoL thereafter (Heinzer et al. 1999). Although these data seem to correlate with our results, inhalative immunotherapy and the application of TKIs is not comparable because we deal with two completely different types of drugs. Inhalative immunotherapy is effective via the respiratory tract, while TKIs can be administered orally. Immunotherapy provokes an immune response, while TKIs are generally accepted as angiogenesis inhibitors. Furthermore, the side effect profiles are essentially different. Nevertheless, the QoL in both groups seemed to behave similar, in fact, to rise after 4 weeks of treatment and persist constantly at acceptable levels. This might lead to enhanced patient motivation to continue therapy despite adverse events, when this information will be imparted to the patient during the first 4 weeks of therapy.

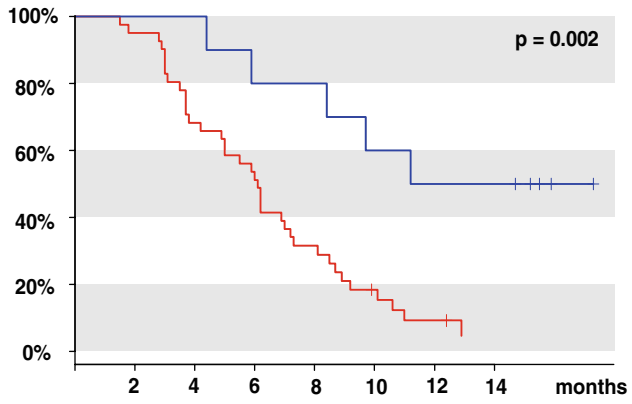

Fig. 3 Progression free survival assigned to global quality of life (QoL) at baseline (*upper line* QoL > median, *lower line* QoL ≤ median)

In our study, patients in the sunitinib group tended to have a better mean global quality of health compared to the sorafenib group at baseline, although not statistically significant. This might explain the higher number of partial responders and fewer patients with PD (again not significant). However, it did not have an impact on changes of global quality of health during treatment between the groups. Moreover, functional scales, symptom scales and physical symptoms were generally similar compared to sorafenib over a period of 16 weeks, and persisted on

acceptable levels at the end of the study. At that time all physical functions were comparable to baseline. Fatigue, pain, appetite loss and diarrhoea still significantly influenced patients health and made side effect management due to drug-related symptoms important for both the patient and doctor, even after 16 weeks of therapy.

Regarding the clinical benefit of the treatment in terms of median PFS, which was 6.2 months in our study, while Escudier et al. saw a PFS of 5.5 months for sorafenib (Escudier et al. 2007) and Motzer saw a PFS of 8.2 months for sunitinib (Motzer et al. 2006b), we presume both TKIs show an acceptable decrease of global QoL during second-line therapy of progressive kidney cancer during the first 4 weeks with comprehensible improvement thereafter.

To date, only one study reported on QoL during second-line therapy of metastatic kidney cancer patients (Bukowski et al. 2007). Using the questionnaires FACT-G and FKSI no difference in mean scores could be found between sorafenib and placebo patients at baseline and over time. Individual items of the FKSI showed a beneficial impact of sorafenib on QoL and kidney-cancer symptom improvement such as less coughing, less problems with loss of breath, fewer fevers, a greater ability to enjoy life, and less worry about their disease. More patients in the sorafenib group were bothered by side effects. Nevertheless, the self-reported physical, social, and emotional function were not influenced, but even improved in a statistically significant manner. Similar to our study baseline FKSI score and several individual items were predictive of survival. These data indicate that questionnaires like the FKSI and the QLQ-C30 are not only helpful to describe the patient's clinical performance status during therapy, but are able to serve as prognostic tools for risk-adapted therapy recommendations. Recently, Cella et al. reported on QoL for metastatic kidney cancer patients treated with sunitinib during a first-line trial versus placebo (Cella et al. 2007). They used the questionnaires FACT-G, FKSI-DRS and EQ-VAS and demonstrated that all three baseline QoL variables were predictive of PFS. Similar to our study, better baseline scores were associated with a longer PFS. In a subgroup analysis of our study, a good ECOG performance status and a low risk profile according to MSKCC criteria, as well as a better physical function at baseline predicted PFS. However, neither the ECOG status, nor the MSKCC criteria had an impact on baseline QoL, which is in contrast to patients with lung cancer, where a strong correlation between the QLQ-C30 and the Karnofsky performance status could be demonstrated (Guzelant et al. 2004). Mystakidou et al. compared patients with a poor performance status to those with a better one, and displayed statistically higher levels of all functioning scales, higher global quality of life and lower levels on the fatigue and financial impact scales in terminal cancer patients receiving palliative care (Mystakidou et al. 2001). These studies implicate that the baseline clinical performance status strongly correlates to QoL and to the prediction of a better tolerability during palliative systemic cancer treatment. In contrast, for metastatic kidney cancer the baseline ECOG status and MSKCC criteria are not suitable to be used for prediction of intra-individual changes of QoL during treatment with sorafenib and sunitinib.

To summarise, second-line treatment with sorafenib and sunitinib severly affects patients global QoL during the first 4 weeks of treatment and has a negative, but temporary impact on most aspects of self-reported QoL that typically recover through week 16. These findings may be useful as a tool to inform patients regarding what to expect during their course of disease. Moreover, the evaluation of baseline QoL status might help to predict PFS, which may lead to other treatment recommendations to patients with a lower baseline QoL.

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