Published in final edited form as:

Clin Genitourin Cancer. 2013 June ; 11(2): 149–154. doi:10.1016/j.clgc.2012.09.006.

Quality of life in patients with metastatic renal cell carcinoma: Assessment of long-term survivors

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Abstract

Background—An emerging literature describes the potential for long-term survival with targeted agents, but the health-related quality of life (HR-QOL) in patients who receive chronic therapy with these agents is poorly defined.

Methods—From an institutional database including 562 patients with RCC, patients were identified who: (1) were alive 3 years beyond initiation of systemic therapy for mRCC and (2) received a targeted therapy as a component of their treatment. EORTC QLQ-C30 and FKSI-15 questionnaires were administered via telephonic survey. Data from questionnaires were compared to historical estimates derived from pivotal studies evaluating targeted agents.

Results—A total of 38 patients met eligibility criteria for the study, and 28 patients participated in the telephonic survey. Most were male and had clear cell histology (75% for both). All patients had either good- or intermediate-risk disease by Heng criteria. The mean QLQ-C30 Global QOL score in the present cohort was higher than the mean score amongst patients evaluated at baseline in the phase III evaluations of pazopanib (73.5 v 65.8, P=0.07) and everolimus (73.5 v 61.0, P=0.007). The FKSI-15 score in the present cohort was similar to the mean score amongst patients evaluated at baseline in the phase III evaluation of sunitinib (45.1 and 46.5, respectively; P=0.41).

Conclusions—In this small pilot study, long-term survivors with mRCC who received targeted therapies appear to have a HR-QOL comparable to patients who participated in relevant phase III studies. Given the many emerging treatment options for mRCC, the HR-QOL of long-term survivors warrants greater attention.

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Keywords

Quality of life; metastatic; renal cell carcinoma; targeted therapy

Introduction

In 2002, Motzer *et al* reported a pooled analysis of clinical outcomes across six prospective studies evaluating interferon- α (IFN- α) therapy for metastatic renal cell carcinoma (mRCC).¹ Median progression-free survival (PFS) and overall survival (OS) were 4.7 and 13 months, respectively, and the authors suggested that this could serve as a benchmark for future phase II and phase III studies in this disease. Since that time, a total of seven agents have been approved – these include drugs that inhibit signaling through the vascular endothelial growth factor receptor (VEGFR), such as axitinib, bevacizumab, pazopanib, sorafenib, and sunitinib, and drugs that inhibit signaling through the mammalian target of rapamycin (mTOR), such as everolimus or temsirolimus.^{2–8} These agents have led to revised expectations of survival for patients with mRCC; for instance, the median OS associated with sunitinib in a pivotal phase III study was 26.4 months.⁶ As a second example, a phase II study assessing second-line axitinib therapy reported a 5-year survival rate of 20.6%.⁹

In an emerging group of long-term survivors, several considerations arise. Firstly, certain toxicities associated with targeted agents are thought to be cumulative and it is unclear whether chronic therapy may exacerbate these. Secondly, although certain targeted agents have been shown to prevent symptomatic deterioration over a limited time-frame, there are no studies that evaluate health-related quality of life (HR-QOL) in long-term survivors. Amongst the pivotal phase III studies leading to the approval of the aforementioned targeted therapies, several do employ baseline and serial HR-QOL assessments.^{10–15} The tools utilized across these studies are heterogeneous and there have been limited data to suggest the HR-QOL in patients who experience extended survival with these treatments.

In the current study, we seek to characterize the HR-QOL of long-term survivors with mRCC. Given current benchmarks, we defined long-term survival as survival in excess of 3 years from the time of diagnosis with metastatic disease.

Patients & Methods

Patients

Patients with a primary diagnosis of renal cell carcinoma diagnosed from January 2000 onwards were identified from an institutional database. To be considered for the current study, patients had to meet the following eligibility criteria: (1) patients must have been alive at least 3 years beyond a diagnosis of stage IV RCC and (2) patients must have received a targeted therapy (either VEGF- or mTOR-directed therapy) as a component of their systemic management. Of 562 patients, a total of 270 patients were noted to have stage IV disease. Amongst patients with stage IV disease, 38 patients had vital status data collected beyond 3 years and were noted to be alive at most recent follow-up, and all had received at least one targeted therapy. Through an IRB approved protocol (COH IRB 11211), we received permission to contact patients with a telephonic questionnaire. Verbal consent to the telephonic questionnaire was documented.

Patient Assessment

Demographic and clinicopathologic information was obtained from patient charts, including age, gender, and histologic subtype. Additional data were obtained to determine the appropriate Heng risk classification (a validated prognostic tool in patients with mRCC receiving targeted therapy).¹⁶ As per this classification scheme, patients were characterized as either good-, intermediate- or poor-risk. First-, second-, and third-line systemic therapy regimens were also collected for each patient.

A questionnaire was devised that included 3 sections: (1) the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30, (2) the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-15, and a series of questions related to co-morbidity.^{17–19} The QLQ-C30 has been used to assess HR-QOL across a variety of malignancies and incorporates several distinct domains assessing symptomatology (nausea, vomiting, pain, and fatigue) and functional status (physical, social, emotional, and cognitive) through a 30-item questionnaire (available at <http://www.eortc.be/home/qol>). In contrast, the FKSI-15 is a 15-item questionnaire that assesses symptoms perhaps more specific to RCC, including fevers and hematuria. A full version of this survey is available at <http://www.facit.org/FACITOrg/Questionnaires>.

The additional questions related to co-morbidity were designed to encompass potentially relevant long-term treatment effects not ascertained in the EORTC QLQ-C30 or FKSI-15 questionnaires. These items were presented as follows:

1. Do you have high blood pressure?
2. Did you develop high blood pressure after beginning treatment for kidney cancer?
3. Do you have high cholesterol?
4. Did you develop high cholesterol after beginning treatment for kidney cancer?
5. Do you have discomfort in your hands or feet?
6. Did you develop discomfort in your hands or feet after beginning treatment for kidney cancer?

Patients were asked to provide a “yes” or “no” response to these items.

Statistical Analysis

Summary scores for the EORTC QLQ-C30 and FKSI-15 were generated as per the questionnaire guidelines. Using a two-tailed unpaired t-test, these summary scores were compared to historical estimates derived from pivotal phase III studies evaluating targeted agents. EORTC QLQ-C30 scores from the current study were compared to scores from pivotal studies of pazopanib and everolimus, whereas FKSI-15 scores were compared to those reported for sunitinib.^{10,12–13,20} Descriptive statistics were applied to questionnaire data derived from the additional comorbidity queries.

Results

Patient Characteristics

From our database of 562 patients with RCC, 38 patients were identified who were: (1) alive at last follow-up, (2) at least 3 years beyond initiation of systemic therapy for stage IV disease, and (3) had received a targeted agent as a component of their systemic therapy to date. Of these 38 patients, contact could not be established with 8 patients and 2 patients refused to participate.

Of the 28 patients who participated in the survey, the median time elapsed from initiation of systemic therapy to administration of the survey was 61 months (range, 36–133 months). The majority was male and possessed clear cell histology (75% for both; see Table 1). Notably, no respondents were characterized as having poor-risk disease by Heng criteria. Rather, similar proportions were characterized as having good-risk (53.6%) or intermediate-risk (46.4%) according to this schema. Approximately 10% of patients received immunotherapy as their first-line treatment, while the remainder received VEGF- or mTOR-directed therapies (see Table 2).

EORTC QLQ-C30/FKSI-15 Results and Comparison

Composite scores from the EORTC QLQ-C30, stratified by domain, are presented in Table 3. The mean Global QOL score for the cohort was 73.5 (standard deviation [SD], 21.0). Mean scores and associated SDs using the QLQ-C30 Global QOL instrument have been previously published in the context of phase III registration studies assessing pazopanib and everolimus therapy. In the phase III study evaluating pazopanib, patients were randomized to either pazopanib or placebo in the setting of treatment-naïve or cytokine refractory disease.⁴ Patients were surveyed at multiple time points during the course of therapy with results shown in Table 4. Although the mean Global QOL score was numerically higher as compared to assessments performed at any time point during pazopanib therapy, there was no significant difference in score at baseline ($P=0.07$), 12 weeks ($P=0.18$), 24 weeks ($P=0.21$), or 48 weeks ($P=0.47$).¹⁰

In contrast to the phase III registration study of pazopanib, the phase III study evaluating everolimus included patients who had been previously treated with sunitinib and/or sorafenib and the majority of patients in this study had also received prior cytokines.⁸ Amongst 224 patients from whom survey data is available, the mean Global QOL score was 61.0 (SD, 23.1).¹⁰ The mean Global QOL score was significantly higher in the current study ($P=0.007$).

The mean FKSI-15 overall score for the cohort in the present study was 45.1 (SD, 8.8). These results were compared to the mean FKSI-15 overall score obtained in a baseline assessment of patients enrolled in the phase III registration trial of sunitinib therapy. In this study, patients were randomized to receive either sunitinib or IFN- α .⁶ Amongst 375 patients treated with sunitinib who completed the FKSI-15 assessment, the mean overall score was 46.5 (SD, 8.5), not significantly different from the cohort assessed in the current study ($P=0.41$).¹¹

Co-Morbidity Results

The majority of respondents reported a diagnosis of hypertension (59.2%), with most of these patients (62.7%) indicating that their diagnosis of hypertension occurred after initiation of systemic therapy for mRCC. Similarly, a substantial proportion of patients noted persistent hand and foot symptoms (46.4%), mostly beginning after initiation of systemic therapy (76.9%). A smaller proportion of patients reported hypercholesterolemia (29.6%), and the majority of this subset had a pre-existing diagnosis (75.0%).

Discussion

Until recently, long-term survival for patients with mRCC was a phenomenon only thought possible in association with high-dose (HD) IL-2 therapy.²¹ Emerging evidence suggests that treatment with targeted therapies (i.e., VEGF- and mTOR-directed treatments) can also yield such outcomes.⁹ A key distinction however, is that while HD IL-2 can induce durable remissions with no need for subsequent therapy, targeted agents are administered

chronically. Long-term survivors of targeted therapy are therefore exposed to drug toxicities for an extended duration and these may have an impact on HR-QOL. To our knowledge, this represents the first effort to characterize HR-QOL in this population.

The study reported herein takes a cross-sectional approach, assessing the current HR-QOL of 28 long-term survivors at a single time point. Ideally, the baseline HR-QOL of this cohort (i.e., prior to the start of any systemic regimen for mRCC) could be compared to the current HR-QOL. In the absence of this information, we have elected to compare the current HR-QOL of this cohort to QOL reported in pivotal phase III studies evaluating targeted therapies for mRCC. A challenge in making such a comparison is the lack of uniformity of QOL metrics employed in these studies. The EORTC QLQ-C30 tool has been used across a wide spectrum of malignancies, and includes separate domains evaluating function, symptoms, and global health.^{22–24} In the setting of mRCC, the EORTC QLQ-C30 tool has been used in the phase III studies evaluating everolimus and pazopanib.^{10,13} In the phase III comparison of pazopanib and placebo in patients who were either treatment-naïve or cytokine refractory, the tool was administered at multiple time points during the course of therapy.¹⁰ Across four sequential time points (baseline, 12 weeks, 24 weeks, and 48 weeks), global QOL assessed by the QLQ-C30 appeared to rise during the course of pazopanib therapy. Numerically however, the global QOL assessed in our cohort was higher. The pazopanib study highlights the issue of compliance, a fundamental challenge of QOL research in long-term survivors. Specifically, although 141 patients (out of 290 randomized to pazopanib) completed the QLQ-C30 at baseline, only 24 patients were captured at 48 weeks of treatment. The lack of survey completion cannot be completely attributed to attrition from the therapeutic study due to disease progression or toxicity. In fact, 189 patients (32%) remained on pazopanib beyond one year. Baseline QLQ-C30 data from the RECORD-1 study evaluating everolimus was also used as a comparator for the current cohort.¹³ In RECORD-1, patients were pretreated with sunitinib and/or sorafenib and a substantial proportion of patients (53%) had received prior cytokine therapy as well.⁸ Global QOL in our cohort was significantly higher based on the QLQ-C30 assessment.

While the QLQ-C30 does interrogate multiple domains relevant to all cancer patients, the FKSI-15 includes several items specific to RCC pathophysiology (i.e., hematuria).¹² We found no significant difference in FKSI-15 scores obtained from our study to those obtained at baseline in the pivotal phase III study of sunitinib (sunitinib versus IFN- α in patients with treatment-naïve mRCC).¹¹ A recent report established a predictive model associating baseline FKSI-15 scores with both PFS and OS in the pivotal sunitinib study.^{20,25} Interestingly, interpolating this model suggests that our cohort (with a median of 5.1 years elapsed from initiation of systemic therapy) would have had near perfect FKSI-15 scores at the time of treatment initiation (~60). Although highly speculative, this implies that HR-QOL in our cohort (at least through parameters estimated by the FKSI-15 scale) may have declined over time.

Beyond the questions included in the EORTC QLQ-C30 and FKSI-15 scales, our questionnaire included items interrogating three toxicities highly relevant to patients receiving VEGF- or mTOR-directed therapies: hypertension, hypercholesterolemia, and hand-foot syndrome. A caveat of this data is that no particular toxicity grade was ascertained and thus patients simply reported the presence or absence of these symptoms. Nonetheless, a substantial number of patients reported ongoing issues with hypertension and hand-foot syndrome, and the vast majority of these patients incurred issues subsequent to beginning systemic therapies. Of note, both hypertension and hand-foot syndrome have been implicated as potential predictors of favorable clinical outcome in patients with mRCC and this could potentially explain the prevalence of these issues in our cohort of long-term survivors.^{26–27} The impact of hand-foot syndromes on HR-QOL is quite tangible, whereas

hypertension may not be perceived to have a direct effect. However, several recent studies have suggested that HR-QOL is poorer in patients with hypertension as compared to non-hypertension controls.

Outside of our exploration of HR-QOL indices, the current study offers an opportunity to explore demographic and clinicopathologic features of long-term survivors with mRCC. The distribution of age and gender in our cohort was not particularly unique, nor was the distribution of clear cell and non-clear cell histology. However, it is worth noting that none of the patients in our cohort were classified as having “poor-risk” disease per Heng criteria.¹⁶ This lends some support to this novel prognostic schema, specifically designed for use amongst patients who have received targeted therapy for mRCC. In terms of therapeutic strategy, the vast majority of patients (67.6%) received VEGF-directed agents as their first systemic regimen, while mTOR-directed therapies were the most prevalent second-line regimen (48.0%).

There are several limitations to the current study. As already noted, the cross-sectional approach offers an assessment of our cohort at only a single time-point. A wide range of time had elapsed from initiation of systemic therapy to administration of the survey (varying from 3 years to just over 11 years), and it is possible that HR-QOL could vary substantially within this timeframe. Furthermore, the definition of “long-term survivor” (i.e., survival at least 3 years beyond the initiation of systemic therapy) is worthy of debate – although the reference standard of 13 months was established during the cytokine era, the median OS in the pivotal trial of sunitinib was in excess of 26 months. As we have previously noted, the comparisons to existing datasets are not ideal – optimally, patients could serve as their own control and the HR-QOL characteristics of long-term survivors could be compared to their own characteristics prior to initiation of systemic therapy. Such a study would truly allow us to ascertain the impact of chronic therapy with targeted agents. However, the study would be immense – with the generous assumption that 25% of patients may be “long-term survivors” of targeted therapy as we have defined it, we would require over 100 patients. To account for the poor compliance that has been observed in previous longitudinal HR-QOL studies (i.e., the aforementioned pazopanib study), this number may have to increase several fold. Finally, several HR-QOL metrics used in previous pivotal studies in mRCC (i.e., FACT-General [FACT-G], FKSI-Disease Related Symptoms [FKSI-DRS], etc.) were not incorporated in our assessment. The possibility arises that these metrics could have yielded different accounts of HR-QOL in our study population. However, in designing our questionnaire, we were sensitive to the issue of survey fatigue and selected those instruments used most consistently across phase III studies in mRCC. With the additional comorbidity questions we incorporated, our questionnaire included a total of 51 items, nearing the threshold of what we thought was reasonable for a telephonic survey.

Despite these limitations, our study provides some initial insights into the HR-QOL of long-term survivors of mRCC therapy. Akin to the cohort we have identified, several studies highlight an emerging group of patients with extended survival with targeted therapies. There are rare instances in which discontinuation of targeted therapy can be considered in this favorable group – recent data suggests that patients who mount a complete response (CR) to therapy can contemplate this, but CRs are very infrequent.²⁸ For the vast majority of these individuals, targeted therapies will be administered chronically. As a counterbalance to our progress in extending the longevity of our patients, it will be critical to ensure that we are concomitantly preserving their HR-QOL. As we have acknowledged, our small sample size precludes far reaching determinations, but the data cited herein will serve as the basis for longitudinal, prospective efforts to characterize QOL in long-term survivors with mRCC receiving targeted therapies.

Acknowledgments

Dr. Pal's efforts are supported by the NIH Loan Repayment Plan (LRP) and NIH K122K12CA001727-16A1.

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CLINICAL PRACTICE POINTS

1. In the era of targeted therapies, an emerging population of long-term survivors has recently been recognized
2. Preservation of quality of life (QOL) amongst these individuals have not been definitively addressed
3. Our study suggests that despite the chronic nature of targeted therapies, patients can preserve their overall quality of life
4. This study is hypothesis-generating and will inform planned longitudinal studies at our institution to assess QOL in patients with mRCC receiving targeted agents

Table 1

Clinicopathologic characteristics of patients who completed the telephonic survey (n=28)

Characteristic	Value
Gender, n (%)	
Female	7 (25%)
Male	21 (75%)
Age (range)	58 (40–72)
Histology	
Clear cell	21 (75.0%)
Papillary	3 (10.7%)
Chromophobe	1 (3.5%)
Other	3 (10.7%)
Heng Risk Category, n (%)	
Good	15 (53.6%)
Intermediate	13 (46.4%)
Poor	0 (0%)

Table 2

Systemic therapy regimens of patients who completed the survey (n=28). Of note, 8 patients (28.5%) received more than 3 lines of systemic therapy

Systemic Therapy	n (%)
1 st Line Therapy (n=28)	
Immunotherapy	
Interferon	2 (7.1%)
Interleukin-2	1 (3.5%)
VEGF-Directed	
Bevacizumab	2 (7.1%)
Cediranib	1 (3.5%)
Pazopanib	2 (7.1%)
Sorafenib	1 (3.5%)
Sunitinib	13 (46.4%)
mTOR-Directed	
Everolimus	1 (3.5%)
Temsirolimus	1 (3.5%)
2 nd Line Therapy (n=25)	
Immunotherapy	
Interferon	1 (4.0%)
Interleukin-2	1 (4.0%)
VEGF-Directed	
Cabozantinib	1 (4.0%)
Sorafenib	2 (8.0%)
Sunitinib	6 (24.0%)
mTOR-Directed	
Everolimus	8 (32.0%)
Temsirolimus	4 (16.0%)
Other	
CRLX101	1 (4.0%)
3 rd Line Therapy (n=18)	
VEGF-Directed	
Pazopanib	8 (44.0%)
Sorafenib	5 (27.8%)
Sunitinib	1 (5.6%)
mTOR-Directed	
Everolimus	2 (11.1%)
Temsirolimus	1 (5.6%)

Table 3

Results of functional, symptom and global health assessments ascertained through the EORTC QLQ-C30 survey.

Domain	Mean	SD
<i>Functional scales</i>		
Physical functioning	76.2	9.3
Role functioning	79.2	24.3
Emotional functioning	82.4	14.6
Cognitive functioning	85.7	16.8
Social functioning	75.0	27.8
<i>Symptom scales/items</i>		
Fatigue	32.9	25.2
Nausea and vomiting	16.7	23.1
Pain	14.3	17.4
Dyspnea	22.6	32.8
Insomnia	26.2	27.8
Appetite loss	15.5	23.1
Constipation	13.1	26.2
Diarrhea	25.0	34.7
Financial difficulties	22.6	27.3
<i>Global health status</i>		
Global QOL	73.5	21.0

Table 4

Comparison of EORTC QLQ-C30 Global QOL scores amongst patients in the current study, patients treated with pazopanib in the phase III evaluation of the agent, and patients treated with everolimus in the phase III evaluation of the agent.

Population	N	Score (SD)	P-value
Long-term survivors (current study)	28	73.5 (21.0)	-
Pazopanib			
Pazopanib (Baseline)	141	65.8 (20.2)	0.07
Pazopanib (Week 12)	82	67.5 (19.8)	0.18
Pazopanib (Week 24)	49	67.3 (20.7)	0.21
Pazopanib (Week 48)	24	69.4 (19.9)	0.47
Everolimus			
Everolimus (Baseline)	224	61.0 (23.1)	0.007