Sunitinib followed by sorafenib or vice versa for metastatic renal cell carcinoma—data from the Czech registry

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Received 23 December 2010; revised 9 February 2011; accepted 10 February 2011

Background: Sequential therapy with tyrosine kinase inhibitors (TKIs), sunitinib and sorafenib, is a common treatment choice for patients with advanced/metastatic renal cell carcinoma (mRCC) despite lack of randomised trials. The aim of this retrospective registry-based study was to analyse the outcomes of RCC patients treated with sunitinib–sorafenib or sorafenib–sunitinib sequence.

Patients and methods: The Czech database containing information on patients treated for mRCC using targeted agents was used as a source of data for retrospective analysis. There were 138 patients treated with sunitinib–sorafenib sequence and 122 patients treated with sorafenib–sunitinib sequence.

Results: Progression-free survival (PFS) was 17.7 months for patients treated with sunitinib–sorafenib sequence and 18.8 months for those receiving sorafenib followed by sunitinib (P = 0.47). Overall survival (OS) at 1 year was 83% [95% confidence interval (CI) 77% to 90%] for patients treated with sunitinib–sorafenib and 84% (95% CI 77% to 91%) for sorafenib–sunitinib patients (P = 0.99). Treatment toxic effects were predictable but a significant proportion of patients (up to 14%–25% for different lines of therapy and used TKI) switched between TKIs or discontinued TKI therapy because of toxicity.

Conclusions: In contrast to most of the previously published reports, we have not observed improved PFS or OS for mRCC patients treated with the sorafenib–sunitinib sequence as compared to the sunitinib-sorafenib sequence.

Key words: renal cell carcinoma, sorafenib, sunitinib

introduction

Tyrosine kinase inhibitors (TKIs) are currently a standard treatment option for advanced/metastatic renal cell carcinoma (mRCC) due to the efficacy and generally manageable side-effects. Sunitinib as a first-line therapy has been shown to prolong progression-free survival (PFS) and overall survival (OS) in comparison with interferon-α (IFN-α) in a randomised phase III study [1]. There is also evidence that sorafenib extends PFS and OS in patients with mRCC progressing after cytokine treatment [2, 3]. However, virtually all patients treated with either drug eventually relapse or progress. Only recently, everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has become available as a treatment option for patients progressing on TKIs [4].

Sequential use of the two TKIs is a common therapeutic strategy despite the lack of data from randomised trials. Recent data from retrospective studies have suggested that the order of TKI sequence may have a significant impact on PFS and OS of mRCC patients [5].

In the Czech Republic, targeted agents are reimbursed only when administered in 1 of 13 comprehensive cancer centres. All patients requiring this therapy are referred to one of these centres, and a registry of all patients receiving targeted drugs for mRCC has been set up to facilitate reimbursement.

We present here an analysis of the outcome of mRCC patients treated sequentially with sunitinib followed by sorafenib or vice versa based on data from a Czech registry of patients with mRCC treated with targeted agents.

patients and methods

study design and patients

Data on mRCC patients treated with either sunitinib–sorafenib (designated as group A) or sorafenib–sunitinib sequence (group B) were obtained from the Czech Clinical Registry of Renal Cell Cancer Patients (RENIIS), a database of patients treated with TKIs, and analysed retrospectively. We have included all patients treated between May 2006 and October 2010 whose data had been entered into the database.

Until October 2009, neither sunitinib nor sorafenib had been reimbursed when used as first-line therapy by local health insurance companies, and thus all mRCC patients were required to undergo a trial of other systemic treatment (mostly conventional dose IFN-α) and could
have only received TKIs after progression or toxicity on this first-line systemic treatment.

The RENIS database contains anonymised data on all mRCC patients treated with targeted agents in 13 designated hospitals or hospital networks where biological antineoplastic treatments are funded by public health insurance according to Czech healthcare regulations. These centres have agreed to enter and update the patient records regularly via an electronic link four times yearly. Response evaluation is usually carried out every 3–4 months according to institutional policies.

**treatment**

The standard dose of sorafenib was 800 mg daily orally in two divided doses continuously, and the standard regimen of sunitinib was 50 mg daily orally in a single dose for 28 days of a 42-day cycle. There was no predefined number of cycles and the treatments were continued until progression or severe toxicity. Dose modifications were at the discretion of attending medical oncologist. Disease response was assessed using the RECIST criteria.

**statistical analysis**

Standard robust summary statistics were used to describe sample data set, i.e. median, range, percentiles. Significance of differences in initial categorical parameters between two groups was estimated using the Fisher’s F-test; the maximum likelihood c2 test was applied for more than two groups. Comparisons of treatment groups in continuous variables were based on the nonparametric Mann–Whitney U test. Profiles of OS and PFS were calculated since the start of first TKI treatment and estimated using the standard Kaplan–Meier method. PFS was defined as time from the onset of TKI therapy to the progression on the second TKI or death due to any cause. Time on TKIs was calculated for patients who had discontinued both TKIs by the cut-off date.

Statistical significance of the differences in survival time between the two groups was determined using the log-rank test. Comparison of treatment groups in continuous variables was based on the nonparametric Mann–Whitney U test. Profiles of OS and PFS were calculated since the start of first TKI treatment and estimated using the standard Kaplan–Meier method. PFS was defined as time from the onset of TKI therapy to the progression on the second TKI or death due to any cause. Time on TKIs was calculated for patients who had discontinued both TKIs by the cut-off date.

Statistical significance of the differences in survival time between the two groups was determined using the log-rank test. Both univariate and multivariate strategy was applied to quantify predictive power of examined variables to the defined time-to-event end points, OS and PFS. All potential predictors were coded as binary factors according to their risk values and then processed in univariate and multivariate Cox proportional hazard regression models. Hazard ratio was estimated with appropriate 95% confidence limits and supported by significance level. The final set of independent prognostic factors was identified by backward stepwise selection algorithm. The enter method of Cox proportional hazard regression model was used for analysis of selected factors.

**results**

**patient characteristics**

As of 20 October 2010, the RENIS register contained data on 1127 mRCC patients treated with sunitinib, sorafenib or both. We identified 260 patients with mRCC treated with both sunitinib and sorafenib, including 138 patients treated with sunitinib–sorafenib sequence (group A) and 122 patients treated with sorafenib–sunitinib sequence (group B). A higher proportion of patients who had completed sorafenib therapy tended to continue with sunitinib compared with the other sequence [122 of 294 (41.5%) versus 138 of 399 (34.6%)] but the difference did not reach statistical significance (Pearson’s chi-square test, \( P = 0.063 \)). The remaining 434 patients in the registry still continue on their first TKI (\( n = 373 \)) or have received other targeted agent (\( n = 61 \)).

Baseline characteristics of the patients receiving both sunitinib and sorafenib are shown in Table 1. All patients had clear cell RCC. A great majority of patients in both groups (85% in group A and 96% in group B) had received immunotherapy and/or chemotherapy before TKIs due to the regulatory requirements at the time as explained above. Median duration of cytokine therapy was similar in the sunitinib–sorafenib group and in the sorafenib–sunitinib group (4.2 versus 4.0 months, \( P = 0.223 \)). Similar proportion in either group (almost 90%) of patients had had nephrectomy before starting TKI therapy (Table 1). The baseline characteristics were well balanced between the two groups.

**reasons for switch between TKIs**

The reason for the switch from sunitinib to sorafenib was disease progression in 107 patients (78%), sunitinib toxicity in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sunitinib–sorafenib ((n = 138))</th>
<th>Sorafenib–sunitinib ((n = 122))</th>
<th>Statistical significance ((P))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>61 (34–79)</td>
<td>60 (34–79)</td>
<td>0.647</td>
</tr>
<tr>
<td>Age ≤60 years, (n) (%)</td>
<td>66 (48)</td>
<td>62 (51)</td>
<td>0.623</td>
</tr>
<tr>
<td>Sex (male/female), (n) (%)</td>
<td>100/38 (72/28)</td>
<td>82/40 (67/33)</td>
<td>0.357</td>
</tr>
<tr>
<td>Previous nephrectomy, (n) (%)</td>
<td>124 (90)</td>
<td>109 (89)</td>
<td>0.893</td>
</tr>
<tr>
<td>Previous cytokine therapy, (n) (%)</td>
<td>117 (85)</td>
<td>115 (94)</td>
<td>0.197</td>
</tr>
<tr>
<td>ECOG performance status at the beginning of treatment (0/1/2/3/4), (n) (%)</td>
<td>33/86/17/0/1 (24/62/12/0/2)</td>
<td>28/74/17/1/1 (23/61/14/1/1)</td>
<td>0.821</td>
</tr>
<tr>
<td>MSKCC score (0/1–2/more), (n) (%)</td>
<td>76/60/2 (55/43/2)</td>
<td>63/53/2* (53/45/2)</td>
<td>0.197</td>
</tr>
<tr>
<td>Median follow-up since TKI treatment, (range), months</td>
<td>15.1 (2.7–52.8)</td>
<td>16.7 (3.5–42.0)</td>
<td>0.695</td>
</tr>
<tr>
<td>Median follow-up since time of diagnosis (range), months</td>
<td>39.7 (4.6–406.0)</td>
<td>45.9 (4.6–225.5)</td>
<td>0.224</td>
</tr>
<tr>
<td>Reasons for switch between TKIs (progression/adverse events/others), (n) (%)</td>
<td>107/20/8* (79/15/6)</td>
<td>84/31/3* (71/26/3)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*Available values only (weighted to 100%).

ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan–Kettering Cancer Center; TKI, tyrosine kinase inhibitor.
Table 2. Duration of therapy with tyrosine kinase inhibitors for patients treated with sunitinib–sorafenib sequence

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sunitinib–sorafenib (n = 138)</th>
<th>Sorafenib–sunitinib (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time on individual TKIs (range), months</td>
<td>6.3 (0.5–26.8)</td>
<td>3.2 (0.3–30.6)</td>
</tr>
<tr>
<td>Median time on TKI treatment (range), months</td>
<td>11.9 (2.2–36.2)</td>
<td>5.7 (0.4–28.6)</td>
</tr>
</tbody>
</table>

*aThe difference was not statistically significant (P = 0.473).

TKI, tyrosine kinase inhibitor.

20 patients (14%), and patients’ request in 4 patients (3%). In group B, the reasons for the sorafenib to sunitinib switch were as follows: disease progression, 84 patients (69%) and sorafenib toxicity, 31 patients (25%). The information was missing for seven patients in each group.

treatment duration

Ninety-nine patients in group A and 81 patients in group B had discontinued TKIs by the time of data cut-off. The reason for TKI treatment discontinuation was progression or death in 74 (75%) and 58 (72%) patients, adverse event (AE) or toxicity in 9 (9%) and 12 (15%), and other reasons including patient’s withdrawal of consent and loss of follow-up in 16 (16%) and 11 (14%) patients for groups A and B, respectively. The median treatment duration for the patients who have discontinued TKI therapy is shown in Table 2.

treatment toxicity

The toxicity profiles were consistent with adverse effects of both agents described in registration trials (Table 3) [1, 2]. The most common AEs in patients treated with sunitinib were gastrointestinal and haematological. For sorafenib, the most frequently encountered AEs were skin and gastrointestinal. Overall AE rates for sunitinib and sorafenib were significantly lower if the agent was used as the second TKI (P = 0.031 for sunitinib and P < 0.001 for sorafenib). The rate of serious AEs was significantly lower for sorafenib used after sunitinib than vice versa (P < 0.001) (Table 3).

PFS and OS

Median follow-up was 15.1 months (range 2.7–52.8) and 16.7 months (range 3.5–42.0) for sunitinib–sorafenib and sorafenib–sunitinib patients, respectively. PFS was 17.7 months in group A and 18.8 months in group B; the difference was not statistically significant (P = 0.47). Median OS was 35.4 months in group A and 30.0 months in group B; the difference was not statistically significant (P = 0.99) (Figure 1). For patients treated with sunitinib–sorafenib sequence, OS at 1 year was 83% [95% confidence interval (CI) 76% to 89%], while it was 84% (95% CI 77% to 91%) for sorafenib–sunitinib patients. Gender, age and initial Memorial Sloan–Kettering Cancer Center (MSKCC) score [6] had no impact on PFS or OS. MSKCC scoring system version for cytokine pretreated patients [7] or its individual components did not predict OS or PFS with the exception of serum calcium where normal values were associated better OS (hazard ratio 2.3, 95% CI 1.0–4.9, P = 0.041).

Time from diagnosis to the start of TKI therapy influenced OS and PFS. Patients with time 21 year from diagnosis had 1-year OS of 90.5% (95% CI 85.8% to 95.3%) versus 69.6% (95% CI 59.7% to 79.4%) for patients with <1 year from diagnosis; 2-year OS was 73.8% (95% CI 65.7% to 81.9%) and 48.1% (95% CI 35.4% to 60.8%), respectively. PFS at 1 year was 81.9% (95% CI 75.9% to 88.0%) for patients ≥1 year from diagnosis versus 55.5% (95% CI 45.0% to 66.0%) for patients <1 year from diagnosis; 2-year PFS was 46.7% (95% CI 37.7% to 55.7%) and 22.7% (95% CI 12.0% to 33.4%), respectively (Figure 1).

From the tested variables, only time from diagnosis to the start of TKI therapy was assessed as a significant predictor of OS and PFS in a multivariate Cox model (Table 4). Previous nephrectomy had no impact on OS or PFS albeit the numbers of patients without nephrectomy were low in our cohort.

Next, we have analysed whether selected clinical variables are associated with improved PFS or OS for any of the two sequences. This analysis was carried out for those categories that included significant number of patients from both cohort A and cohort B. However, none of the tested parameters predicted success of either sequence of TKIs (Table 5).

discussion

To our knowledge, this is the largest study published so far assessing sequential therapy with TKIs for mRCC. In comparison
to other reports, our cohort of patients was more homogeneous and had a significantly longer follow-up. No differences in OS or PFS between sunitinib–sorafenib and sorafenib–sunitinib sequences have been identified in univariate and multivariate analysis. Another important observation in our study is the failure of conventional clinical parameters to predict the outcome. Of the analysed variables, only interval from diagnosis to therapy was an independent prognostic factor for OS and PFS. Time from diagnosis to treatment start represents a well-characterized prognostic factor for first-line therapy.

Retrospective studies on sequential therapy with TKIs in mRCC published to date have included data on ∼500 patients [8–17]. These data have been recently reviewed by Merseburger et al. [5]. All of the above studies were retrospective and relatively small, and therefore freighted with selection bias. The most important factor that could potentially skew the results of these analyses is the retrospective allocation of patients into one of the two subgroups. Thus, only patients who had been in reasonably good general condition after the first TKI proceeded to therapy with the second TKI and were eventually included in the analysed cohort. However, in the RENIS registry that was used as a source for our study, the percentages of patients who continued to sunitinib after sorafenib out of all sorafenib-treated patients and of those receiving sorafenib after failing on sunitinib out of all sunitinib-treated patients were not significantly different, limiting the impact of this type of bias to some extent.

The very high OS rates in our cohort can be explained in part by the survivor treatment selection bias that is inherent to similar retrospective studies.

Another major problem is that sunitinib and sorafenib are often given as a second or later line of therapy (e.g. after cytokines or bevacizumab), introducing more heterogeneity into patient cohorts [18]. Thus, only an intention-to-treat analysis of data from a prospective randomised study could answer the question of optimal TKI sequence.

There were potentially important differences in some patient characteristics between our study and previously published reports that included details on baseline patient profile. In our study, cytokine pretreatment (85% and 95% in groups A and B, respectively) was more common than in studies by Choueiri et al. [9] where the patients received TKIs or bevacizumab in as first-line therapy, Dudek et al. (80% and 55% cytokine pretreated patients in the two groups, respectively) [16] and Sablin et al. (41% and 50%, respectively) [13]. Cohorts of Sablin et al. [13] and Dudek et al. [16] and Porta et al. [15] also included 14%–20% of patients with nonclear cell histologies. It is possible that these variations may in part explain the different conclusions of our study, although the impact of the

Figure 1. Kaplan–Meier graphs for progression-free survival (A) and overall survival (B) of patients treated with sunitinib–sorafenib (full line) or sorafenib–sunitinib sequence (dashed line) and for PFS (C) and OS (D) of patients with time from diagnosis to TKI <1 year (full line) or ≥1 year (dashed line). Progression-free survival was calculated as a time from the start of the first tyrosin kinase inhibitor to progression on the second tyrosin kinase inhibitor or death due to any cause.
above parameters in terms of sequential therapy outcome is uncertain.

Albeit most of the above arguments are also applicable to our study, evidence from prospective, randomised trials that could guide us in selection of sequential strategies for mRCC is still some way off. A study (National Center for Biotechnology Information identifier NCT00732914) randomising to sunitinib–sorafenib versus sorafenib–sunitinib sequences is currently enrolling patients but is only open to patients unable to receive cytokines. This requirement may limit the applicability of its results to general mRCC patient population which is considerably more heterogeneous [19].

The reasons for the putative clinical difference between the sunitinib–sorafenib and sorafenib–sunitinib sequences remain speculative. Compared with sorafenib, sunitinib inhibits a wider spectrum of tyrosine kinases [20]. It has been proposed that the lower affinity of sorafenib to its respective target tyrosine kinases permits later salvage with sunitinib that overcomes the resistance because of greater affinity and wider spectrum of cancer-related pathways inhibited by sunitinib [5, 16].

Table 4. Univariate analysis of overall and progression-free survival (a) and the multivariate Cox model for overall survival (b) of patients treated with a sequence of tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subgroups</th>
<th>N</th>
<th>HR for OS (95% CI)</th>
<th>P</th>
<th>HR for PFS (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>TKI sequence</td>
<td>Sorafenib-sunitinib versus sunitinib-sorafenib</td>
<td>122 versus 138</td>
<td>0.9 (0.6–1.4)</td>
<td>0.680</td>
<td>1.1 (0.8–1.5)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female versus male</td>
<td>78 versus 162</td>
<td>1.0 (0.6–1.7)</td>
<td>0.891</td>
<td>1.2 (0.8–1.7)</td>
<td>0.443</td>
</tr>
<tr>
<td>Age</td>
<td>≤60 versus &gt;60 years</td>
<td>128 versus 132</td>
<td>1.2 (0.8–1.8)</td>
<td>0.453</td>
<td>0.8 (0.6–1.2)</td>
<td>0.317</td>
</tr>
<tr>
<td>Previous nephrectomy</td>
<td>With versus without</td>
<td>233 versus 27</td>
<td>1.4 (0.7–2.6)</td>
<td>0.310</td>
<td>1.3 (0.8–2.2)</td>
<td>0.280</td>
</tr>
<tr>
<td>Time from diagnosis to TKI*</td>
<td>≥1 versus &lt;1 year</td>
<td>93 versus 166</td>
<td>0.4 (0.2–0.6)</td>
<td>&lt;0.001</td>
<td>0.5 (0.4–0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>MSKCC score*</td>
<td>No risk factors versus one or more risk factors</td>
<td>139 versus 117</td>
<td>0.8 (0.5–1.3)</td>
<td>0.466</td>
<td>0.9 (0.7–1.3)</td>
<td>0.677</td>
</tr>
<tr>
<td>(b)</td>
<td>OS</td>
<td>≥1 versus &lt;1 year</td>
<td>93 versus 166</td>
<td>0.4 (0.3–0.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFS</td>
<td>≥1 versus &lt;1 year</td>
<td>93 versus 166</td>
<td>0.5 (0.4–0.7)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Available values only.

HR, hazard ratio; OS, overall survival; CI, confidence interval; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; MSKCC, Memorial Sloan–Kettering Cancer Center. Statistically significant differences are highlighted in bold.

Table 5. Impact of selected clinical variables on the outcome of patients treated by the two TKI sequences. Log-rank test was used for the analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sorafenib-sunitinib</th>
<th>Sunitinib-sorafenib</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>N</td>
<td>OS median (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≤60</td>
<td>62</td>
<td>30.4 (N/A)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>60</td>
<td>26.6 (18.9–34.4)</td>
</tr>
<tr>
<td>MSKCC score</td>
<td>No risk factors</td>
<td>28</td>
<td>27.3 (N/A)</td>
</tr>
<tr>
<td></td>
<td>1 or more risk factors</td>
<td>93</td>
<td>30.0 (24.3–35.6)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0</td>
<td>63</td>
<td>Not reached</td>
</tr>
<tr>
<td></td>
<td>&gt;0</td>
<td>55</td>
<td>26.6 (23.1–30.2)</td>
</tr>
<tr>
<td>PFS</td>
<td>N</td>
<td>PFS median (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≤60</td>
<td>62</td>
<td>18.5 (14.6–22.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>60</td>
<td>18.8 (16.0–21.5)</td>
</tr>
<tr>
<td>MSKCC score</td>
<td>No risk factors</td>
<td>28</td>
<td>20.1 (17.0–23.2)</td>
</tr>
<tr>
<td></td>
<td>1 or more risk factors</td>
<td>93</td>
<td>18.0 (15.8–20.3)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0</td>
<td>63</td>
<td>19.5 (16.5–22.6)</td>
</tr>
<tr>
<td></td>
<td>&gt;0</td>
<td>55</td>
<td>18.0 (14.7–21.2)</td>
</tr>
</tbody>
</table>

OS, overall survival; CI, confidence interval; N/A, not available MSKCC, Memorial Sloan–Kettering Cancer Center; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival.
hypothesis, acquired resistance to sunitinib would prevent later efficacious treatment with sorafenib, a drug with relatively lower affinity to its molecular targets.

We have not observed any differences in PFS or OS between the two subgroups. We have also studied whether any clinical parameter is associated with better outcome with either of the sequences. Identification of such clinical variable would be of considerable interest because it might provide a basis for selection of initial TKI. However, we have not been able to find any parameter predicting success of therapy with one sequence over the other (Table 5).

MSKCC scoring system has been validated for newly diagnosed patients with mRCC and for patients progressing after cytotoxic agents [6, 7]. Failure of MSKCC index to achieve significance in our cohorts is probably another consequence of retrospective cohort identification where only patients who are reasonably fit after cytotoxics and one TKI continue to the second TKI. Thus, the ability to undergo such sequential therapy is associated with relatively nonaggressive disease course, as also suggested by the long OS of our patients.

AE rates for the two sequences suggest some degree of interaction between sunitinib and sorafenib administered in sequence. Thus, previous treatment with sunitinib attenuated toxicity of sorafenib and vice versa (Table 3). This is in line with the common clinical experience that TKI-induced skin toxicity gradually regresses over time even if the therapy continues [21]. A similar attenuation of toxicity was observed for gastrointestinal AEs of sorafenib (Table 3).

The quest for the optimal sequence of biological therapies in advanced or metastatic RCC has been further complicated by the recent registrations of everolimus for the therapy for RCC progressing on sorafenib, sunitinib or both and of pazopanib for the first or second line of therapy. Neither of these drugs was available outside of a clinical trial in the Czech Republic during the period of data acquisition in our study. Monoclonal antibody therapy with bevacizumab in combination with IFN is another option for first-line treatment and is one that is apparently not cross-resistant with TKIs such as sorafenib, sunitinib or pazopanib [18, 22]. Thus, the landscape of targeted agents for the treatment of advanced/mRCC is complex, and we are unlikely to ever have the definitive answers on the optimal sequence for all available drugs.

Recently, a theory has been proposed that treatment with an mTOR inhibitor between TKIs may re-sensitise tumour cells to TKI therapy [23]. While no prospective trials have been carried out for this strategy, it is certain that everolimus will maintain its efficacy if given as a third-line treatment after sunitinib and sorafenib [4]. Therapy with everolimus outside of clinical trial has been reimbursed by the health insurance companies only since September 2010 and bevacizumab is only available for first-line therapy for mRCC. Therefore, any subsequent treatment with everolimus or other agents approved for mRCC was unlikely to significantly influence OS of the cohort.

The principal weaknesses of our study are its retrospective design as discussed above and the use of tumour registry. It is known that similar databases are prone prone due to incomplete or late entries of clinical data. We have not analysed tumour response rates as these are less meaningful end points in mRCC treated with targeted agents compared with PFS or OS. Moreover, although response evaluation was based on modified RECIST criteria, no independent response evaluation has been carried out. Modest numbers in the various subgroups may have precluded the identification of small but potentially significant differences.

In conclusion, sequential therapy with sunitinib and sorafenib is well tolerated and effective in advanced/mRCC. In a large, retrospective registry-based study, we have not been able to show the superiority of sorafenib–sunitinib sequence in terms of PFS or OS that has been reported by several other groups.

acknowledgements

We would like to thank the following heads of the comprehensive cancer centres for their permission to use data of patients from their respective regional networks: Vaclav Janovsky, Ceske Budejovice; Jindrich Finek, Plzen; Jiiri Vorlicek, Brno; Lubomir Slavicek, Jihlava; Renata Soumarova, Novy Jicin; Jiiri Bartos, Liberec; David Feltl, Ostrava; Jana Prausova, Prague; Milan Lysy, Usti nad Labem; Milan Kohoutek, Zlin; Jiiri Petera, Hradec Kralove.

We are also indebted to all physicians who provided data for the RENIS registry.

funding

The RENIS database is maintained with partial support by Pfizer and Bayer Schering Pharma, the manufacturers of sunitinib and sorafenib, respectively.

disclosure

TB has received honoraria for lectures from Bayer-Schering Pharma and Roche. BM has received honoraria for lectures from Bayer-Schering Pharma, Roche, Novartis and Glaxo-Smith Kline. Other authors have declared no conflict of interest.

references


