Safety and activity of sunitinib in elderly patients
(≥70 years) with metastatic renal cell carcinoma:
a multicenter study

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Received 20 April 2012; revised 9 June 2012; accepted 24 July 2012

Background: Actual tolerability of sunitinib is still poorly documented in elderly patients with metastatic renal cell carcinoma (mRCC).

Patients and methods: Charts of elderly patients treated with sunitinib for mRCC were reviewed in six Italian centers to assess safety (primary objective), efficacy and correlation of toxicity with comprehensive geriatric assessment (CGA) (secondary objectives).

Results: Sixty-eight patients were eligible, and the median age was 74 years. CGA was carried out in 34 patients (41% fit, 41% vulnerable and 18.5% frail). The dose reduction to 37.5 mg was made upfront or soon after the first cycle in 69.1%. More frequent toxic effects were fatigue (80.9%), mucositis (61.8%) and hypertension (58.8%). Cardiac
events occurred in nine patients. In 10 patients, therapy was interrupted early due to rapidly progressive disease (10.3%) or severe toxicity (4.4%; 1 cardiac failure, 1 fatigue, 1 febrile neutropenia). At a median follow-up of 27.1 months, the median OS was 18.3 months and the median PFS was 13.6 months. Correlation was not found between frailty at CGA with severe toxicity nor with response.

**Conclusions:** Treatment with sunitinib is effective in elderly patients; yet early interruptions were frequent. Starting treatment at reduced dose and escalating in the absence of severe toxicity could be suggested.

**Key words:** comprehensive geriatric assessment, elderly, renal cell carcinoma, sunitinib, toxicity

### introduction

Sunitinib is a small molecule acting as tyrosine-kinase inhibitor (TKI) of vascular endothelial and platelet-derived growth factor receptors [1]. Sunitinib has been shown to significantly prolong progression-free survival (PFS) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC) [2].

The main described side-effects are hypertension, fatigue, diarrhea, hand and foot syndrome and hypothyroidism. Most of them are well managed, yet chronic treatment could be worrisome in patients having high burden of comorbidity, such as the elderly population.

The elderly represent a consistent portion of all cancer patients, but they are under-represented in clinical trials [3]. Benefits and tolerance of oncologic treatments are expected to be different in this age class, but very limited data are available [4]. The manageable safety profile and the oral route of TKIs represent major advantages in treating elderly patients but actual tolerability is still poorly documented in this age class. Recently some retrospective reviews have been carried out to evaluate tolerability and efficacy of sunitinib in elderly patients enrolled in clinical trials [5], yet data on routine clinical practice are still lacking.

### patients and methods

Charts of elderly patients treated with sunitinib for mRCC were reviewed in six Italian centers to assess adverse events (primary objective), efficacy and correlation of toxicity with comprehensive geriatric assessment (CGA) (secondary objectives).

Patient and tumor data were collected from clinical records of the participating hospitals: Istituto Oncologico Veneto-IOV (Padua), Medical Oncology Division, Hospital of Verona, Medical Oncology Division, Hospital of Rovigo, Medical Oncology Department at the University of Udine, Medical Oncology Division, Hospital of Vicenza, Medical Oncology at Hospital of Versilia.

All patients with histological diagnosis of RCC consecutively diagnosed with advanced disease and starting treatment with sunitinib between May 2006 and April 2010 were included. The observation period for each patient extended from the initiation of treatment to the earliest of disease progression, death, loss to follow-up or end of the observation period for this publication.

Retrieved information included age at diagnosis, presence and site of metastases at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, presence of associated diseases, date of surgery, previous treatments for metastatic disease, start and stop date for sunitinib treatment, baseline and follow-up cardiological examinations when present, toxicity, response, date of progression, date of death, cause of death when available.

Comorbidities were recorded and rated according to CIRS-G scale [6]. Patients for which CGA was present were classified as ‘fit’ (no functional dependence on activities of daily living (ADL) [7] and instrumental activities of daily living (IADL) [8], no relevant comorbidities, no geriatric syndromes), ‘vulnerable’ (dependence on one or more IADL but not ADL, manageable comorbidities, mild memory disorder and depression, no geriatric syndromes) or ‘frail’ (age ≥85 years, dependence on one or more items of ADL, geriatric syndromes, >3 grade 3 comorbidities (CIRS-G) or one severe/life-threatening comorbidity) [9].

Toxic effects were registered according to NCI-CTC version 3.0 [10]. Number of cycles, dose reductions and interruptions were recorded along with the reasons for dose reduction and/or interruption. The response was assessed by the treating physician according to RECIST criteria; in the case of non-measurable disease eventual clinical benefit from therapy was recorded.

Survival was measured from day 1 of treatment with sunitinib to death for any cause. PFS was measured from day 1 of therapy to progression of disease in any site or death in the absence of progressive disease. The method of Kaplan and Meier was used for survival analysis [11].

For data input and numerical and graphical evaluations, we used the statistical software Statistica, version 6.0 (StatSoft Inc, Tulsa, OK). Comparisons were tested for statistical significance using the log-rank test. The results of significance tests were expressed in *P* values, with *P* < 0.05 indicating statistical significance.

### results

Between May 2006 and April 2010, sixty-eight patients were registered. The median age was 74 years (range 70–88). Sixty-two patients (91.2%) had undergone prior nephrectomy. Patients’ characteristics are outlined in Table 1.

Twenty-four patients were metastatic at time of renal cell RCC diagnosis; sixty patients (88.2%) had measurable disease and forty-three (63.2%) were symptomatic. Twenty-one patients (30.8%) had been previously treated with immunotherapy (IL-2, INF), and thirteen patients (19.1%) had previously undergone chemotherapy.

Before starting treatment with sunitinib, patients were evaluated for cardiovascular associated diseases. Fifty-five patients (80.9%) had one or more risk factors as displayed in Table 2. Cardiovascular risk factors were mostly hypertension, alone or associated with other risk factors. Forty-one patients (60.3%) were evaluated by means of an echocardiogram, and the median left ventricular ejection fraction (LVEF) was 60% [standard deviation (SD) 6%].

### distribution of patients according to CGA

Thirty-four patients (50%) underwent a CGA. Stratification of patients according to the CGA allowed us to classify 13 patients as fit, 14 patients as vulnerable and 7 patients as frail.

Associated diseases were present in 60 patients (88.2%), with a mean number of 1.9 comorbidities (range 1–5). Grade 3 or 4
comorbidities according to the CIRS-G scale were present in nine patients, mainly cardiovascular (arrhythmias, ischemic cardiomyopathy and previous cardiac transplantation).

**treatment and toxicity**

All the patients were treated with sunitinib, either as first-line therapy for metastatic disease (46 patients, 67.6%) or after progression on IFN-α or IL-2 and/or other chemotherapy (22 patients, 32.4%). For twenty-one patients (30.9%) treatment was still ongoing at the moment of data analysis. The mean number of cycles was 7.6 (range 1–26), and the mean total dose of sunitinib received was 7.497 mg (range 250–27.150 mg).

Adverse effects are shown in supplementary Tables S1 and S2, available at *Annals of Oncology* online. Haematological toxic effects were mostly grade 1–2, and so were non-hematological toxic effects, with the only reported grade 4 toxic events being neutropenia, with no febrile complication, and acute myocardial infarction. The most common non-hematologic adverse events were fatigue (80.9%, 55 patients), mucositis (61.8%, 42 patients) and hypertension (58.8%, 40 patients).

Globally, there were nine cardiac events (13.3%), of which one was grade 4 (acute myocardial infarction), one was grade 3 (congestive heart failure) and all the others were grade 1–2, mainly asymptomatic decrease of LVEF or arrhythmias. No correlation was found between frailty at CGA with G3–4 toxicity.

Overall, forty-six patients (67.7%) on Sunitinib at the dose of 50 mg; sixteen patients (23.5%) were started at 37.5 mg daily and six patients (8.8%) were started at 25 mg daily. Globally, dose reductions had to be done in 47 patients (69.2%). Dose reduction was made upfront because of frailty (22 patients, 32.4%) or after the first cycle (12 patients, 17.6%) or subsequent cycles (13 patients, 19.1%) for toxicity. Twenty-five of the patients starting at full dose required reduction. Nine patients needed dose reduction after first cycle, despite a lower starting dose of 37.5 mg. Out of the six patients who started treatment with a dose of 25 mg, and were maintained on that dose until progression, one patient required reduction to 12.5 mg due to hematological toxic effects, but still showing ongoing response at the time of data analysis. Forty-one patients (60.3%) had treatment interrupted due to progressive disease or toxicity after a median number of four courses. In 10 patients, treatment was interrupted early (after first cycle) due to rapidly progressive disease (7 patients, 10.3%) or severe toxicity (3 patients 4.4%: 1 cardiac event, 1 severe fatigue, 1 febrile neutropenia). Treatment had to be stopped in another patient due to cardiac failure after five courses of treatment.

One patient (1.5%) experienced dose escalation after starting treatment at reduced dose.

**radiological response and clinical benefit**

Out of 60 patients with measurable disease, a partial response was observed in 26 (RR 43.3%), stabilization of disease in 24 (40%); progressive disease (PD) in 4 patients (6.7%). For nine
patients, an evaluation of the response was not possible according to RECIST criteria.

Clinical benefit was observed for 47 patients overall (69.1%). No correlation was found between frailty at CGA with response.

progression and survival

At a median follow-up time of 27.1 months, 40 patients (58.8%) are dead, with a median OS of 18.3 months (Figure 1).

No difference in survival was observed for pretreated or naïve patients, with median OS for patients receiving sunitinib as-first-line treatment and patients treated after progression on other therapies of 17.8 and 18.3 months, respectively.

Progression occurred in 42 patients so far (61.7%), with a median time to progression of 13.6 months. For pretreated patients, OS was 18.3 months and PFS was 10 months (Figure 2).

A difference was observed for OS between fit and unfit (vulnerable plus frail) patients, though not statistically significant ($P = 0.07$) (supplementary Figure S1, available at Annals of Oncology online).

A trend for better survival was observed for patients who developed all grades of hypertension versus those who did not ($P = 0.07$), statistically significant if only events ≥grade 2 are considered ($P = 0.01$) (Figure 3).

discussion

age

Our data show that sunitinib is active and tolerated in a robust cohort of unselected elderly patients from different Italian centers.

In the published data from the registrative trial [2] and from the expanded-access program (EAP) of sunitinib in patients with mRCC [12], a third of the enrolled patients were aged ≥65 years. In both the trials, though, the median age was 59 years and patients had an overall good health status.

A recent review undertaken in a tertiary Oncology center in Italy [13] shows that the median age of the 85 patients treated with sunitinib in the common practice was 62.5 years. Age 65 and over is frequently adopted as an arbitrary limit for defining people as elderly, yet the boundary between the middle age and old age cannot be defined exactly. It has been suggested that subjects over 65 should be divided into younger–old (65–74 years), mid–old (75–84 years), and old–old (>85 years) [14].

Because the incidence of age-related physiologic changes occur predominantly between 70 and 75 years, we believe that a better cut-off point for defining older cancer patients should be 70 years.

Recently, data showing a similar efficacy and tolerability were reported for patients aged ≥70 years [5] compared with younger patients. Yet, these data likely reflect the top of the iceberg of ‘fit’ elderly patients, who satisfy strict inclusion criteria for randomized trials; therefore, results cannot be...
representative of the more general and heterogeneous elderly population.

toxicity
Toxicity was mostly low grade, yet this could be influenced by the high rate of dose reductions and drug discontinuation. The rates for some adverse events observed in the present study were higher than may be expected compared with findings from the EAP. For example, the observed rates (any grade) for fatigue/asthenia of 80.9% and for mucositis of 61.8% appear to be considerably higher than what may be expected based on the sunitinib EAP (37% and 28%, respectively), or based on the review of elderly enrolled in randomized trials by Hutson et al. Such differences may be justified by selection biases due to inclusion criteria for trials, since rates of these events are instead similar to those reported by Porta et al. [13].

Therefore, greater attention must be paid to prevention and treatment of toxicity in elderly patients receiving sunitinib, since adverse events, even if low grade, may have serious complications such as severe dehydration if G2 diarrhea and G2 mucositis develop concomitantly.

Though an increased risk of severe hypertension could be justified on the basis of a high prevalence of such condition in elderly subjects, and also taking into account that mononephric subjects are at increased risk of hypertension, our data seem to confirm literature findings suggesting that patients experiencing high-grade hypertension have a better prognosis [15].

In addition, recent data suggest that oral multi-TKI may have a hypoglycemic effect [16]. In our cohort, diabetes was present in almost one-fifth of patients; therefore, patients should be monitored for hyperglycemia/hypoglycemia, especially those on antidiabetic medications, as well as for thyroid and cardiac dysfunction, hypertension, and potential drug interactions, as also the International Society of Geriatric Oncology has recommended [17].

activity and efficacy
Available data indicate that there might be age-associated differences in efficacy and treatment benefit among targeted agents. Though comparison of the different agents is not possible given the lack of direct comparative studies, from the published trials [2, 18–20] one could speculate that there is little influence of age on the benefit to PFS for sunitinib and bevacizumab plus IFN, and that there seems to be a greater benefit in the elderly compared with younger patients for sorafenib, while the reverse is suggested for temsirolimus [21].

Our data on response rates and median survival were compared with published series for sunitinib, and activity and efficacy data from randomized trials, EAP and retrospective cohort studies are outlined in Table 3.

Though only speculative comments are possible, given the different nature of these studies and considering that outside clinical trials more infrequent assessments of disease status could lead to overestimating PFS, tumor response rates and PFS are quite similar across the different studies, whereas there are greater differences in OS.

The median OS in our cohort of elderly patients seems lower than what was found in the registrative trial, yet it is comparable with that of patients in the EAP [12] and with that of unselected cohorts of patients treated in the common practice [22].

Noteworthily, in the post-hoc pooled analysis of elderly patients enrolled in six randomized, controlled trials [5], data showed a similar efficacy of sunitinib for older compared with younger patients regardless of treatment setting (first versus subsequent lines). This holds true also in our cohort, where OS for patients receiving sunitinib as first-line treatment was superimposable to that of patients being treated after progression on other therapies.

cardiac toxicity
Cardiovascular events have been increasingly reported in patients treated with sunitinib [23, 24]. Noteworthily, cardiac dysfunction is not always completely reversible, even after termination of sunitinib treatment. In the registrative trial [2], incidence of decrease of LVEF of all grades was 3.5%, and grade 3 was 0.08%. In the EAP, only symptomatic congestive heart failure rate is reported (<1%). Sunitinib-associated cardiac toxicity in the overall population has been

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Table 3. Comparison of activity data of sunitinib from different studies: randomized trial [2] EAP [12], a phase II trial [33], retrospective cohorts [33, 22, 5].

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<tbody>
<tr>
<td>N</td>
<td>375 (total 750)</td>
<td>4564</td>
<td>51</td>
<td>57</td>
<td>56</td>
<td>202</td>
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<tr>
<td>Median age (years)</td>
<td>62</td>
<td>59</td>
<td>56.6</td>
<td>58</td>
<td>61</td>
<td>73</td>
</tr>
<tr>
<td>N elderly (%)</td>
<td>275 (36.7%)-65 years</td>
<td>1418 (32%)-65 years</td>
<td>NR</td>
<td>7 (35%)-60 years</td>
<td>NR</td>
<td>202 (100%)-70 years</td>
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<tr>
<td>Clinical benefit (CR + PR + SD)</td>
<td>77%</td>
<td>77%</td>
<td>52.9% (ORR)</td>
<td>82%</td>
<td>78% (PR + SD)</td>
<td>NR</td>
</tr>
<tr>
<td>Progression-free survival (months)</td>
<td>11</td>
<td>11.3</td>
<td>12.2</td>
<td>15.3</td>
<td>12.2</td>
<td>10.9</td>
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<tr>
<td>Overall survival (months)</td>
<td>26.4</td>
<td>18.2</td>
<td>33.1</td>
<td>35.8</td>
<td>18.2</td>
<td>23.7</td>
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NR, not reported.

*Mean.
rated to develop in ~3% of the patients [23], and a recent meta-analysis confirmed an overall incidence of congestive heart failure of 4.1%, with grade 3–4 events occurring in 1.5% of cases [25].

Cardiac toxicity in our study was much more relevant (>13%), mostly asymptomatic decrease in LVEF, but in two cases events were severe (acute myocardial infarction and congestive heart failure requiring hospital admission).

The higher rate of cardiac events has a possible explanation in the higher prevalence of cardiovascular comorbidities, and particularly of pre-existing coronary artery disease, which constitutes a risk factor for sunitinib-associated cardiac toxicity.

dose reductions and early interruption

Dose reductions were carried out in more than two-thirds of patients, including those who started treatment at a lower dose, and those who needed dose reduction after at least one cycle. This is twice as much as the dose reductions observed in the EAP, in which about one-third of the patients was downescalated from 50 to 37.5 mg, with further reductions to 25 mg in 13% of the patients and from other patient data reviews such as that of Porta et al., in which dose reduction is reported to occur in about one-third of patients.

It has been reported that treatment interruptions or dose modifications occur more often within an average of the first 2 weeks [26], and in our cohort treatment interruption or dose modifications at first cycle or soon after the first cycle for adverse events were as high as 73.6%.

Elderly patients usually have associated diseases for which they assume several drugs—in our cohort 88.2%—and assume several drugs which could be inhibitors or substrates of cytochrome p450 CYP3A4 and may therefore increase plasma concentration of sunitinib despite reduction of total daily dose. In addition, it has been shown that interindividual variations of the area under the curve can cause different concentrations of sunitinib and its primary active metabolite [27], therefore dosage reductions may not be directly translated into reduction of exposure to the drug.

Recently, Motzer et al. reported the results of a randomized phase II [28] trial comparing a lower but continuous dosing schedule of sunitinib (37.5 mg qd) with the classical schedule of sunitinib (50 mg 4 weeks on/2 weeks off), showing a possible inferiority of the continuous schedule. Again, patients in this study had median age of 61 (classical schedule) and 64 years (continuous schedule), and extending such findings to the older patients could be misleading.

Because the high rate of dose reductions after first course was mainly due to G3/G4 toxicity, it could be suggested that in elderly patients first course should be started at reduced dose (37.5 mg), to be escalated if no severe toxicity is observed.

Supportive measures are of primary relevance in the elderly patients, yet very few data are available on the interaction between hematopoietic growth factors both for white and red blood cells, which are commonly used in the clinical practice, and TKIs.

stratification for prognosis

Studies on risk stratification models of patients with advanced RCC treated with targeted therapies are warranted, particularly for elderly patients, for whom CGA has a prognostic value beyond pathological risk classification. Some studies have highlighted the prognostic role of a CGA in elderly cancer patients [29] as well as its role in the set of variables taken into account in some toxicity risk scores recently developed for chemotherapy regimens, such as the CRASH score [30] or the score by Hurria et al. [31].

Our data do not provide definite results on the prognostic role of CGA, yet it must be acknowledged that only half of the patients in our cohort were evaluated by means of a CGA.

Our results also suggest that prognostic models other than the MSKCC should be developed and validated for decisions in elderly patients with mRCC.

conclusions

With the caution and limitations of retrospective data, we found that treatment with sunitinib is feasible and effective in elderly patients.

In more than two-thirds of the patients, dose was reduced upfront or soon after the first cycle for toxicity. It is likely that sunitinib dosing schedule is not optimal for elderly patients and that most of them could be over treated, resulting in unnecessary adverse events. On the other hand, patients who do not experience any toxicity may be undertreated. Given these considerations, in elderly patients starting treatment at a reduced dose to escalate if no toxicity is observed may be an option.

Since cardiac events occurred in ~13% of patients, cardiac monitoring when administering sunitinib is mandatory for elderly patients.

disclosures

Following authors have indicated conflicts of interest: UB (speaker’s fee from Pfizer, research and travel grants from Pfizer), VZ (speaker’s fees for Pfizer, Roche, GSK) and RDV (speaker’s bureau for Pfizer, Novartis, GSK). All other authors have declared no conflicts of interest.

references