The medical treatment of metastatic renal cell cancer in the elderly: Position paper of a SIOG Taskforce

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Abstract

Treatments currently recommended for metastatic renal cell cancer (mRCC) have not been evaluated specifically in elderly patients. Here we consider what may be learned by analysing according to age the efficacy and toxicity data from key phase III trials of the targeted agents sorafenib (Nexavar), sunitinib (Sutent), temsirolimus (Torisel), and bevacizumab (Avastin), and from a study of expanded access to sunitinib and sorafenib. This paper represents the first systematic review of the role of targeted agents specifically in the elderly population.

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Retrospective subgroup analyses of clinical trial data cannot be considered definitive. However, they suggest in general that the progression-free and overall survival benefits seen in mRCC patients aged 65 years and over are similar to those in the younger age group. The frequency of major toxicities in elderly patients treated with targeted agents is no greater than in younger patients, although such toxicities may have greater impact on the quality of life. That said, no meaningful data are available for patients over 85 years.

To confirm and extend these conclusions, prospective studies should be undertaken in the elderly to determine whether recommendations made for the wider mRCC population apply equally to this group of patients in whom comorbidities, comedication and the greater impact of low-grade toxicity may influence the efficacy and tolerability of treatment. Such studies are increasingly needed, given the growing number of elderly people and their rising life expectancy. Meanwhile, when considering the most appropriate drug to use in a particular patient, the toxicity profiles of the individual targeted agents – and any implications for specific comorbid conditions – should be taken into account.

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Keywords: Metastatic renal cell cancer; Elderly; Sunitinib; Temsirolimus; Sorafenib; Bevacizumab; Interferon

1. Conclusions and recommendations

On the limited information available, which comes mostly from retrospective analysis of subgroups in controlled and uncontrolled clinical trials, it would appear that patients aged over 65 years benefit as much from targeted therapies as younger patients and do not experience more frequent or severe toxicity. However, no data are available for patients aged over 85 years.

a. It is accepted that analysing clinical trial data by age alone provides only limited guidance since eligibility criteria relating to performance status, biological parameters and comorbidity mean that patients entered into studies may be unrepresentative of the wider population of that age.

b. To assess the effect of comorbidities, clinical trials should record not only the frequency but also the severity of potentially complicating medical conditions such as diabetes and hypertension that are highly prevalent in the elderly.

c. Definitive publication of clinical trials should wherever possible report whether age and comorbidity had any influence on treatment efficacy and toxicity.

d. The impact of low-grade toxicities may be greater in elderly patients than in their younger counterparts. This should be taken into account when initiating treatment and assessing the possible need for dose reduction in the individual patient.

e. In addition to general recommendations about the tolerability of targeted agents in the elderly, it would be helpful to have clear guidance specific to individual drugs or classes of drug. To date, we have no data from controlled, head to head comparisons of these agents. Hence, it is not possible to say whether they differ significantly in spectrum and severity of toxicity. However, there is a clear feeling that these agents do have toxicity profiles that differ in ways relevant to the elderly population. It would be helpful to conduct randomised studies to confirm or refute this and to broaden our understanding of the impact of treatment on elderly patients’ quality of life.

f. In the meantime, it would be appropriate to monitor patients with a relevant clinical history for evidence of thyroid and cardiac dysfunction, hypertension, loss of glycaemic control and potential drug interactions. Such potential problems are relevant to all ages of mRCC patient being treated with targeted agents but may have more severe consequences in the elderly.

2. Introduction

The incidence of renal cell cancer increases with age. According to the most recent analysis of data from the Surveillance Epidemiology and End Results (SEER) registries, the average age at presentation is 62 years in both men and women [1]. Given that the number of elderly people is rapidly rising, both in absolute terms and in proportion of the population, we must expect an escalating burden of renal cell cancer.

Many of those affected will be “old”, which, for regulatory purposes, is frequently taken to mean 65 years and over. This definition is arbitrary and considerations relevant to the management of an individual patient should more properly depend on biological rather than chronological age.

However, there is no doubt that an elderly population – however defined – is more likely than a younger group to include patients with comorbidities that have an impact on performance status and complicate treatment decisions (Table 1). These include problems which may contra-indicate nephrectomy, enhance surgical morbidity and mortality and reduce tolerance of medical therapy. Up to two thirds of 75

Table 1
Factors to consider in the elderly patient with mRCC

<table>
<thead>
<tr>
<th>Factors</th>
<th>Possible consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>Ageing body systems</td>
</tr>
<tr>
<td>Pathological</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>Drug interactions</td>
</tr>
<tr>
<td>Psychological</td>
<td>Less (or possibly greater) acceptance of toxicity, with implications for compliance</td>
</tr>
<tr>
<td>Professional</td>
<td>Could clinician bias or lack of available clinical trial data and guidelines be limiting the treatment options?</td>
</tr>
</tbody>
</table>
year olds with renal cancer have been found to suffer from conditions such as hypertension, cardiovascular disease or diabetes [2]. Gastrointestinal disorders are also frequent in elderly patients. Several of the novel, targeted agents are associated with toxicities such as hypertension or diarrhoea which have special relevance to an elderly population.

A further consequence of comorbidities is that drugs taken to manage them (such as anti-hypertensives and oral anticoagulants) may interact with agents given to treat malignancy, altering pharmacokinetics and so potentially increasing toxicity, reducing efficacy, or both.

Certain elderly patients, who perceive their life expectancy as already limited, may differ from their younger counterparts by being less willing to tolerate side effects and so comply with treatment. Others, in contrast, may be more stoic in their acceptance of toxicity, especially if adverse events (such as fatigue) are interpreted as unavoidable results of age rather than of treatment.

In general, though, it should be emphasised that – even if the toxicity is no more frequent – its impact, may be greater in elderly patients than in their younger counterparts. This is true of diarrhoea and stomatitis, for example, which – even when scored as low-grade – can quickly lead to dehydration. Similarly, even a small degree of additional neurotoxicity in an elderly patient may significantly worsen disability and dependence. Such factors should be taken into account when initiating treatment and assessing the possible need for dose reduction in the individual patient.

Recently, the potential risks and benefits of cytoreductive nephrectomy in elderly renal cancer patients have been compared with those in a younger group [3]. In both age groups, 79% of patients had distant metastases. Although 80% of patients went on to have systemic therapy, this was not with targeted agents.

The study confirmed the additional surgical risk in patients aged over 75 years: perioperative mortality (i.e. within a month of surgery) was 21% (5 deaths in 24 patients), compared with 1% in a large cohort of younger patients with similar disease characteristics and performance status. Early mortality in the elderly was associated with longer surgery time and greater blood loss, which the investigators suggest puts unsustainable strain on diminished physiological reserves. However, even when these early deaths were included, the median overall survival (OS) among patients aged over 75 was 16.6 months. This was not significantly different from the 13.7 month median OS in younger patients, although it should be noted that the number of patients involved in the study was small.

In what appears to be the first attempt to clarify the possible role of age in the era of targeted therapies, Rini et al. conducted a small retrospective study of 43 evaluable mRCC patients, all with an ECOG performance status of 0 or 1, who were treated with drugs targeting vascular endothelial growth factor (VEGF) [4]. Although few patients were involved in this analysis, age (65 years and older versus less than 65) had no significant effect on time to progression (TTP). Neither did baseline LDH, corrected serum calcium or performance status. However, longer TTP was predicted by higher baseline haemoglobin and lack of hepatic metastases.

Given the limited information reviewed above, it would be appropriate to comment that patients aged over 65 are more likely to encounter post-operative complications. Although selected patients undoubtedly do well, the decision to undertake nephrectomy should be approached with caution. This is perhaps especially so now that targeted therapies are available, since the necessity for nephrectomy in these changed circumstances has still to be demonstrated.

3. Expanding range of agents effective in mRCC

For several decades, the systemic management of metastatic renal cell cancer (mRCC) was confined to the use of interferon (IFN) and interleukin-2 (IL-2). Both agents can achieve responses; and, in the case of IL-2, these are durable in a small proportion of patients [5]. However, benefit appears confined to patients with limited disease and good performance status. For the majority, especially those elderly patients who are less fit, the toxicities of cytokine therapy have proved a major obstacle to treatment.

Recently, options for the medical management of mRCC have been improved through the introduction of agents targeting tumour angiogenesis or intracellular pathways mediating growth and proliferation [6]. Among these agents are the small molecule inhibitors sorafenib (Nexavar), sunitinib (Sutent), temsirolimus (Torisel) and everolimus, and the monoclonal antibody bevacizumab (Avastin). Sorafenib and sunitinib are orally bioavailable, small molecule tyrosine kinase inhibitors (TKIs). They have a broad range of targets, and both inhibit VEGF and platelet-derived growth factor (PDGF) receptor tyrosine kinases. In addition, sorafenib is an inhibitor of RAF kinase, thus interrupting the RAS/RAF/MEK intracellular signalling pathway as well as inhibiting angiogenesis. Temsirolimus and everolimus differ from these agents in targeting mTOR (mammalian target of rapamycin), part of a cell growth and proliferation pathway which is frequently activated in metastatic advanced renal cell cancers. The monoclonal antibody bevacizumab targets different isofoms of VEGF itself, and has anti-angiogenic activity.

All these targeted agents have been shown significantly to extend progression-free or overall survival or both when compared with placebo or IFN therapy in the treatment of mRCC (Table 2) [7–13]. Data have been published or presented on six major randomised phase III trials of targeted agents in mRCC. These are:

(i) of sunitinib 50 mg once daily on a four weeks on/two weeks off regimen versus IFN alpha (given subcutaneously three times per week at doses rising from 3 to 9 MU) in first-line, good and intermediate risk patients [8,9];
Table 2
Summary of phase III clinical trials with targeted agents

<table>
<thead>
<tr>
<th>Trial design (ref.)</th>
<th>Line of treatment/patient characteristics</th>
<th>Benefit from novel agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib versus placebo [7]</td>
<td>2nd line/ECOG 0–1</td>
<td>Median PFS 5.5 versus 2.8 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better OS (censoring data for crossover)</td>
</tr>
<tr>
<td>Sunitinib versus IFN [8,9]</td>
<td>1st line/ECOG PS 0–1</td>
<td>Median PFS 11 versus 5 months</td>
</tr>
<tr>
<td>Bevacizumab plus IFN versus placebo plus IFN [11]</td>
<td>1st line</td>
<td>Median PFS 10.2 versus 5.4 months</td>
</tr>
<tr>
<td>Bevacizumab plus IFN versus IFN [12]</td>
<td>1st line</td>
<td>Median PFS 8.5 versus 5.2 months</td>
</tr>
<tr>
<td>Temsirolimus versus IFN [10]</td>
<td>1st line (poor risk)</td>
<td>Median OS 11 versus 7 months^b</td>
</tr>
<tr>
<td>Everolimus versus placebo [13]</td>
<td>2nd line post TKI</td>
<td>Median PFS 4.0 versus 1.9 months</td>
</tr>
</tbody>
</table>

^a Significant when patients crossing over from IFN to sunitinib are excluded.

^b Comparison is temsirolimus versus IFN; median OS in the temsirolimus plus IFN arm was 8 months.

(ii) of temsirolimus versus IFN alpha versus both in poor risk patients, first-line [10]. Patients in the monotherapy arms received either 25 mg temsirolimus i.v. once weekly or subcutaneous IFN three times a week up to a maximum dose of 18 MU. Patients on the combination arm received weekly 15 mg temsirolimus and IFN at a dose of up to 6 MU;

(iii) of sorafenib 400 mg twice daily versus placebo in second-line patients [7];

(iv) two studies of the effect of adding bevacizumab to IFN alpha. The European study compared IFN given subcutaneously three times per week at a dose of 9 MU plus either bevacizumab (i.v. 10 mg/kg every 2 weeks) or placebo, in the first-line setting [11]. The United States study, also in first-line patients, compared IFN monotherapy against IFN plus bevacizumab given at the same doses used in the European trial. [12] The latter trial has been presented but not yet fully published.

(v) A trial of everolimus 10 mg per day versus placebo second-line following progression on a VEGF receptor tyrosine kinase inhibitor (sunitinib or sorafenib or both) [13].

In addition to the studies noted above and in Table 2, there has been a randomised phase II (in 189 patients with ECOG performance status 0–1) of sorafenib versus IFN, first-line [14]. The median PFS was 5.7 months with sorafenib, which was not significantly different from the 5.6 months PFS seen with IFN. However, quality of life, clinical benefit and tumour shrinkage were better in patients treated with sorafenib than in those receiving the cytokine.

4. Age of patients included in recent pivotal trials

None of the fully published phase III trials listed in Table 2 had an upper age limit to recruitment. This itself is of interest, since a maximum age would generally have been stipulated in similar studies carried out a decade ago. Across these studies and their treatment arms, the average age of patients entered was remarkably similar (the lowest median being 58 years in the sorafenib arm of the placebo-controlled phase III, and the highest a median of 62 years, in the sunitinib arm of the study versus IFN). These trials were also very consistent in the range of ages included (typically, the youngest patients entered were 25–35 years old, and the most elderly 80–86 years).

Interestingly, the mean age of patients entered into the PERCY Duo study (which had an upper age limit of 70) was 55 years, the oldest patient entered being 74 [15]. In this trial, patients received IFN, intravenous IL-2 or both. The comparatively low average age of those involved may reflect the fact that intravenous IL-2 was perceived as more difficult for elderly patients to tolerate than recently introduced agents. Similar considerations may underlie the relatively young population (median age 50 years) included in the phase II trial which looked at the effect of escalating sorafenib to two or even three times the standard dose [16]. This compares with the median age of 59 years for patients taking part in the trial of continuous daily sunitinib, which allows downward titration of dose according to tolerability [17].

All the recent randomised phase III trials that have been fully published report the proportion of patients aged 65 years or over. This was 36% in the sunitinib study, 30% in the sorafenib study, 30% in that involving temsirolimus, and 37% in the bevacizumab trial. This proportion – roughly one third – certainly under-represents the proportion of patients aged over 65 in the general population of patients with mRCC. However, since these trials were large, there were sufficient elderly patients involved to allow at least some assessment of the relationship between age and the efficacy and tolerability of treatment.

While these trials were similar in age characteristics, they differ somewhat in the apparent effect of age on the benefits of treatment. The sunitinib and European bevacizumab studies suggest the effect of these targeted agents is little-if at all-influenced by age. In the sorafenib study, however, it seems that the benefit of this TKI relative to placebo is greater in more elderly patients than in the younger group. Hazard ratios from the subset analysis of the temsirolimus study suggest a trend towards the reverse effect, but confidence intervals around these estimates are wide and no definite conclusion can be drawn on this point without a prospective study.
5. Analysis of trial data by age

5.1. Sunitinib

5.1.1. Phase III data

In the pivotal ph III comparison against IFN in the first-line setting, all patients had an ECOG performance status of 0 or 1, and the great majority had good or intermediate-risk disease according to the MSKCC prognostic index [8]. Overall, treatment with sunitinib was associated with a highly significant benefit in PFS (median 11 months, compared with 5 months in patients randomised to IFN; corresponding to an HR of 0.42). Importantly in the present context, the HR in the 275 patients aged 65 or over was almost identical to that in the 475 patients aged under 65 years. Data on OS have so far been published only in an abstract which makes no reference to the effect – if any – of age [9].

The 10 principal non-haematological toxicities with sunitinib (all grades) were, in descending order of frequency: asthenia, rash, fatigue, nausea, stomatitis, vomiting, hypertension, hand-foot syndrome, mucosal inflammation, rash and asthenia. The five most frequent haematological and laboratory abnormalities were leukopenia, neutropenia, anemia, increased creatinine and thrombocytopenia. (Table 3.)

5.1.2. Expanded access

A formal subpopulation analysis is part of the expanded access study of sunitinib which is intended to enrol 5000 patients. Data have recently been presented [2]. These data suggest, for example, a trend for the improved survival of sunitinib patients (compared with IFN) to be greater in tumours of non-clear cell histology (HR versus IFN 0.55) than in clear cell tumours (compared with IFN) to be greater in tumours of non-clear cell histology (HR versus IFN 0.55) than in clear cell tumours (HR 0.85). However, the confidence intervals of the hazard ratios overlap each other.

Similarly, there is a trend for patients aged less than 65 to show a greater benefit than their older counterparts from being treated with sunitinib rather than IFN. The haz-
ard ratio versus IFN is 0.67 (CI 0.52–0.87) in those patients younger than 65 years, and 1.15 (CI 0.78–1.68) in more elderly patients. The confidence intervals of the hazard ratios are again wide, but they only barely overlap. Among patients aged less than 65 years, median OS was longer with temsirolimus than with IFN: 12 versus 6.9 months. Among patients aged 65 or older, there was no appreciable difference: median OS 8.6 versus 8.3 months. However, temsirolimus had a better side effect profile than IFN among elderly patients (see below), which would be clear grounds for using it in preference to IFN, even if the efficacy of the two agents were similar. The potential interaction between the benefit of temsirolimus and age should be investigated further in a prospective study.

5.2.2. Toxicity

In patients aged 65 years and over, the rates of grade 3–4 asthenia were 14% in patients treated with temsirolimus and 33% in those receiving IFN. For nausea, the corresponding figures were 2% and 10%; for fever 0% and 5%; and for neutropenia 2% versus 10% (all relate to grade 3/4 toxicity). The grade 3/4 adverse events that were more frequent with temsirolimus than with IFN were dyspnoea (10% versus 6%) and hyperglycaemia (13% versus 0%).

Age seemed to have little influence on the incidence of grade 3/4 toxicities caused by temsirolimus. For asthenia, the figures for patients aged over 65 and under 65 years were 14% and 10% respectively; for dyspnoea 10% and 8%; for anaemia 19% and 20%; for neutropenia 2% and 3%; and for hyperglycaemia 13% and 10%.

5.2.3. Everolimus

The placebo-controlled study of this mTOR inhibitor used second-line following progression on sorafenib or sunitinib showed a clear benefit in PFS (median 4.0 versus 1.9 months) [13]. The most frequently reported drug-related adverse events were stomatitis, rash and fatigue.

5.3. Sorafenib

5.3.1. Phase III data

In the TARGET trial of sorafenib versus placebo, patients had failed a prior systemic therapy but were of ECOG performance status 0 or 1 [7]. The doubling of PFS from 12 weeks with placebo to 24 weeks with sorafenib was highly significant. Benefit was also seen in the estimated 39% improvement in overall survival: HR 0.72. The treatment effect on PFS was somewhat higher among patients aged over 65 years (HR sorafenib versus placebo of 0.37, CI 0.27–0.51) than in the younger group (HR sorafenib versus placebo of 0.61, CI 0.50–0.74). However, in terms of statistical significance, the improvement in PFS seen with sorafenib was independent of age.

The principal non-haematological toxicities (all grades) experienced in patients taking sorafenib (listed as the ten most common, in descending order of frequency) were diarrhoea, rash, fatigue, hand-foot syndrome, alopecia, nausea, pruritis, hypertension, anorexia and vomiting. No haematological toxicity occurred with a frequency greater than 10%.

A more extensive subgroup analysis by age was undertaken, focusing on clinical benefit and quality of life [21]. Relevant clinical variables such as performance status and prior exposure to cytokines were well balanced across age and treatment groups. There was a non-significant trend for the benefit of sorafenib on PFS to be higher in the older age group. This cannot be taken as demonstration of greater efficacy in the elderly: but it does at least demonstrate that elderly patients in this trial were not experiencing any reduced efficacy, such as might follow, for example, from a lower exposure to drug necessitated by undue toxicity (see below). Clinical benefit (i.e. objective response plus stable disease) was noted in 83% of patients younger than 65 years and in 86% of the elderly group.

The incidence of treatment related adverse events was similar across the two age subgroups. Thus, 23% of patients aged over 65 who received sorafenib reported some form of grade 3 or 4 event. The figure among younger patients was 22%. For grade 3–4 hypertension, the corresponding figures were 1% and 3%. There was a similar lack of influence of age on the frequency of fatigue, diarrhoea, hand-foot syndrome and anaemia. Interestingly, in the placebo arm, elderly patients seem somewhat less inclined to report fatigue than patients under 65.

The effect of sorafenib treatment on health-related quality of life, symptomatology and time to deterioration of health status was again similar in the over and under 65-year-old groups. In the TARGET trial, the proportion of patients aged 65 years and over who had to discontinue treatment due to adverse events was 7.5% in the sorafenib arm and 2.3% in the placebo arm. Among elderly patients randomised to sorafenib, 32% had some form of dose interruption or reduction. Among the whole population of patients randomised to sunitinib in the pivotal phase III trial first-line versus interferon, there was a 38% rate of dose interruption because of adverse events and a 32% rate of dose reduction [8].

5.3.2. Expanded access

The safety and efficacy of sorafenib has been evaluated in a subset of 1135 patients aged 65 or over who received 400 mg bid of the drug as part of a North American expanded access programme [22]. Patients with active coronary artery disease, ischaemia, hypertension and requirement for dialysis were excluded. Response rates seen in this elderly group were said to be comparable with those seen in younger patients in the expanded access programme, and with results from the phase III study. However, the focus of this analysis (which has not been peer reviewed and is published only in abstract) was toxicity. The incidence of grade 3 or 4 AEs among the elderly patients in this cohort was similar to that in younger patients. The frequency of hand-foot skin reaction in patients aged 65 and over was 9%, while that in younger patients was...
10%. The frequency of hypertension was 5% in both groups, and of diarrhoea 3%. The incidence of anorexia and nausea was similar across age groups (2–3% for each AE). Two toxicities showed greater frequency with age: the incidence of rash/desquamation was 6% in the elderly compared with 4% in the younger group; and the corresponding figures for fatigue were 8% and 4%. However, the absolute frequency with which these AEs occurred was low in both groups.

5.4. Bevacizumab plus interferon

Protocol-specified analysis of data from the European study by age (under 65 years versus 65 and over) demonstrated that adding bevacizumab to interferon benefited older patients to much the same extent as their younger counterparts [23]. For PFS (which became the regulatory endpoint of the trial), the HR among patients receiving combination therapy was 0.77 (95% CI 0.58–1.03) in older patients, and 0.54 (CI 0.43–0.68) in those under 65 years. In both arms of the study (IFN plus bevacizumab versus IFN plus placebo), 37% of patients were in the older age group.

In both age groups, the combination of bevacizumab and IFN was well tolerated. However, there was a slight increase overall in the proportion of elderly patients who experienced an adverse event of grade 3 or greater severity. Among patients receiving the combination of antibody and cytokine, the proportion with a grade 3 or greater AE was 66% in the elderly group and 58% in the younger group. Among patients in the IFN plus placebo arm, the corresponding figures were 48% and 45%. The age-related excess in AEs was accounted for predominantly by fatigue and asthenia. In both instances, the incidence of AEs among older patients receiving the combination was double that in the younger group (18% versus 9% for fatigue and 14% versus 7% for asthenia).

Data relating efficacy and toxicity to age have not yet been published for the confirmatory CALGB trial.

6. Discussion

In the field of oncology as a whole, elderly patients are at risk of receiving sub-optimal therapy. In part, this may reflect patients’ preference to avoid aggressive interventions. However, it may also reflect the bias of clinicians, or the lack of relevant clinical data and management guidelines. As far as we know, this paper represents the first systematic review of the role of targeted agents specifically in the elderly population.

Recent pivotal trials in mRCC (at least, those that are fully published) are notable for the fact that they have not restricted eligibility by age. All included some patients over the age of 80 years, and around a third of those accrued were aged over 65. This offers the opportunity for subgroup analyses to assess the relationship of age to treatment benefit. Since such analyses have been undertaken retrospectively, they should be regarded as hypothesis-generating, and certainly not as definitive. Nevertheless, they provide grounds for further investigation.

In the absence of controlled comparisons between them, it is not possible to say that any of the agents reviewed is more or less suited to use in elderly patients in general. Even indirect comparison of the relative frequency or severity of a specific toxicity is inappropriate since the phase III studies, which provide the most robust toxicity data, were conducted in different populations and the side effects of treatment were assessed by different groups of investigators.

However, considering the ranking of toxicities as they appeared for each agent in the pivotal phase III studies (Table 3) might be reasonable when assessing treatment options in an individual patient with comorbidities. A definitive answer to the question of whether drugs should be selected according to specific comorbidities will require prospectively designed trials.

A more general caveat should be repeated. In the trials discussed here, as more widely, patients were selected according to defined clinical and performance criteria. Willingness to participate in a trial is in itself an indication of relative fitness, and indeed of motivation. In both respects, patients entering these studies will not have been entirely representative of the wider population with mRCC. This may be particularly true of the more elderly participants for whom readiness to risk adverse events, and capacity to tolerate treatment, will have been an important consideration additional to formally prescribed eligibility criteria. Any attempt to generalise our conclusion that age does not decrease the likelihood of benefit from targeted agents, nor increase risk of toxicity, should therefore be treated with caution.

Differences in the median age of patients included in several recent studies suggest that investigators’ perceptions of the tolerability of novel agents may play a role – perhaps subtle, perhaps not fully acknowledged – when deciding which treatment to give. In addition to the trials already mentioned, two retrospective studies of sequential use of the two VEGF-targeted TKIs provide an interesting example [24,25]. In both studies, patients who were given sunitinib initially and then sorafenib were appreciably younger than those who were treated first with sorafenib and then sunitinib. (In the two studies respectively, the median ages were 56 and 58 years for first-line sunitinib compared with 60 and 65 years for first-line sorafenib).

To conclude, as discussed in this paper, data from clinical studies gives some guidance for the treatment choice in elderly patients, with the caveat that patients entered into studies may not be representative of the general population [26].

Conflict of interest statements

JB has been a consultant or advisor to Pfizer, Bayer and Roche and has received research funding from Pfizer.
SN was a consultant for Pfizer, Wyeth and Roche and has received honoraria from Pfizer, Wyeth and Bayer.

BE has to disclose honorarium from the following drug companies: Bayer, Roche, Wyeth, Novartis, Pfizer, Inate Pharma, Antigenics.

AA has been an advisor to Bayer and Wyeth.

MA is consultant to Merck, Pfizer, Roche and Bayer/Schering.

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References

Chairman of the group’s Advanced Bladder Committee and Coordinator of the Intergroup study in advanced transitional Cancer (EORTC 30987) and EORTC study 30986 in unfit patients. His research interests include new drugs, translational and early clinical research in the area of growth factor receptors and downstream molecules as targets for cancer therapy. Dr. Bellmunt has published over 70 peer-reviewed articles and over 100 abstracts and book chapters.