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Elderly patients with metastatic renal cell carcinoma: position paper from the International Society of Geriatric Oncology

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Therapy for metastatic renal cell carcinoma should be tailored to the circumstances and preferences of the individual patient. Age should not be a barrier to effective treatment. Systematic geriatric screening and assessment contributes to the goal of personalised management, in addition to the involvement of a multidisciplinary team. A task force from the International Society of Geriatric Oncology (SIOG) updated its 2009 consensus statement on the management of elderly patients with metastatic renal cell carcinoma by reviewing data from studies involving recently approved targeted drugs and immunotherapies for this disease. Overall, it seems that age alone does not appreciably affect efficacy. Among the pivotal studies that were included, there is a striking scarcity of analyses that relate toxic effects to patient age. Even if the adverse effects of therapy are no more frequent or severe in elderly patients than in their younger counterparts, the practical, psychological, and functional impact of treatment may be greater, especially if toxic effects are chronic and cumulative.

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Introduction

Renal cell carcinoma is frequently a disease of elderly people and its incidence is strongly related to age. According to data from the Surveillance, Epidemiology, and End Results Program from the USA, 49% of people diagnosed with kidney cancer are aged 65 years or older.[1] In the UK, 50% of newly diagnosed cases of renal cell carcinoma were in people aged 70 years or older between 2011 and 2013.[2] Given the growing ageing population across the globe, elderly patients with renal cell carcinoma will increase both in absolute numbers and as a proportion of those affected by the disease. It is therefore important to consider issues that are specific to their management.

Progression-free survival and overall survival in patients with metastatic renal cell carcinoma have been significantly extended by drugs that target tumour angiogenesis or intracellular pathways mediating proliferation. When immunotherapy with interferon-alfa was the only option, the median overall survival was around 13 months. Now, overall survival is 24–30 months.[3] A systematic review[4] published in 2009 by a task force from the International Society of Geriatric Oncology suggested that the survival benefits in patients aged 65 years and older were similar to those in younger patients, and that the frequency and severity of major toxic effects did not differ according to age.

However, the authors of that systematic review[4] acknowledged the absence of trials that had been specifically done in elderly patients, and that the conclusions drawn from retrospective subgroup analyses by age must be treated with caution, because of smaller sample sizes and other biases affecting the analyses. The authors had also mentioned that elderly patients that had been included in pivotal studies for metastatic renal cell carcinoma typically have more robust general health than unselected elderly patients, and had fewer comorbidities that complicate management. Although expanded access studies somewhat address this problem, their data are neither as rigorously collected, nor are as complete, as those collected in controlled trials.

The 2009 systematic review[4] from the SIOG task force considered the following drugs for renal cell carcinoma: the tyrosine kinase inhibitors (TKIs) sorafenib and sunitinib, the mTOR inhibitors temsirolimus and everolimus, and the anti-angiogenic antibody bevacizumab given together with interferon-alfa. Since then, the number of targeted drugs used to treat metastatic renal cell carcinoma has doubled with the advent of new TKIs, such as axitinib, pazopanib, cabozantinib, and lenvatinib, and of the programmed cell death-1 (PD-1) checkpoint inhibitor nivolumab and other similar drugs.

In this Series paper, we consider the full range of drugs that are available for elderly patients with metastatic renal cell carcinoma. We define elderly patients as being at least 65 years old. We only considered systemic therapy and did not address the role of surgery in the management of these patients. Since clear cell carcinoma is by far the most frequent form of sporadic renal cell carcinoma in adults, we focused mainly on this histology. Given the scarcity of data that are specific to elderly people, recommendations are provided at the level of expert opinion. However, where possible, we drew our conclusions on data from clinical trials, including pivotal studies, which are clinical trials that had practice changing outcomes leading to the approval of a particular therapy.

Several authoritative guidelines cover the management of metastatic renal cell carcinoma in general.[5,6] Overall, recommendations for elderly patients are likely to be similar to those for younger patients; however, specific considerations for elderly patients also need to be taken into account. It is helpful that recent guidelines[5] emphasise the need to individualise therapy. In the absence of controlled clinical trial data that are specific to

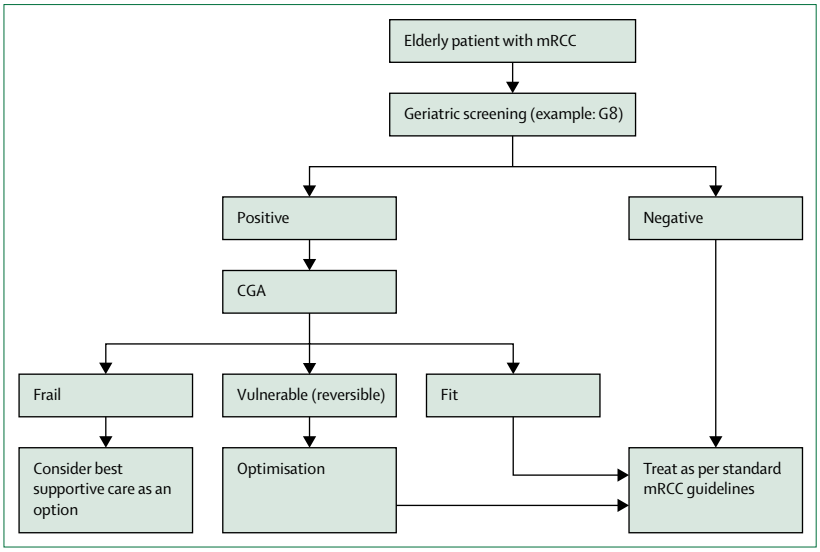

Figure: **Algorithm for the management of elderly patients with mRCC**
CGA=comprehensive geriatric assessment. mRCC=metastatic renal cell carcinoma.

elderly populations, it is also appropriate to emphasise the value of clinical judgment and experience when tailoring treatments to each patient.

Treatment from a geriatrics perspective

Although chronological ageing is uniform for all individuals, biological ageing is not since it is determined by many genetic and environmental factors. Age should not prevent access to the most effective treatments, as long as the patient is sufficiently fit for the likely benefits of treatment to outweigh the possible adverse effects.

Reduced physiological reserve enhances the risk of toxic effects, and elderly patients might differ from younger patients in their willingness to accept toxic effects and in the value they place on the survival gains that might be obtained from treatment. The balance of benefits and adverse effects is affected by a range of biological and psychological considerations, including the risks of mortality and the presence of comorbidities.

In elderly patients, the comprehensive geriatric assessment adds to the information provided by the Eastern Cooperative Oncology Group performance status[7], for example, and provides the best estimate of individual functioning, life expectancy, and cognitive and psychiatric status.[8] It identifies comorbidities, assesses risk factors such as poor nutrition that might interact with cancer management, and suggests preventive geriatric interventions. For example, patients with metastatic renal cell carcinoma who have malnutrition are at a significantly increased risk of mortality from targeted drugs.[9] The impact of nutritional status on mortality might be explained by the close relationship between malnutrition and systemic inflammation, but also by the increased risk of drug toxicity due to pharmacokinetics issues.

At the other end of the spectrum, there is benefit to be had from prehabilitation strategies to maximise functional capacity ahead of treatment initiation.[10,11] The comprehensive geriatric assessment also provides valuable information about a patient's sources of social support. However, since the comprehensive geriatric assessment is time consuming and hence not practical for use in all elderly patients with metastatic renal cell carcinoma, the G8 screening tool is helpful in identifying patients requiring a full geriatric assessment and takes little time to administer.[12] The figure shows an algorithm that can be used to stratify an elderly patient with metastatic renal cell carcinoma by their comprehensive geriatric assessment findings to provide them with the most appropriate treatment.

Age-related physiological, pharmacological and psychological factors potentially affecting efficacy and tolerability of anticancer therapy are listed in table 1. The factors listed in this table draw attention to the possible need for dose adjustment due to reduced renal function[13,14,20] but also as a potential consequence of polypharmacy (eg, due to the co-administration of warfarin and sunitinib).[21] Polypharmacy is frequent in elderly people; in a review[16] of elderly, ambulatory patients with cancer, the median number of medications being taken at any one time was nine. Therapeutic drug monitoring of TKIs could be particularly relevant for elderly patients who have large inter-individual differences in terms of pharmacokinetics and variable adherence to medication recommendations.[22,23]

Frailty increases the likelihood of toxic effects of chemotherapy. With targeted drugs, the impact of frailty may be less clear. However, chronic toxic effects can be debilitating in elderly people, especially in relation to autonomy.[17–19] This debilitating effect emphasises the case for using patient-reported outcomes in clinical trials.[18] Diarrhoea is particularly troublesome in elderly patients, as are any adverse cardiac and renal effects in people who already have reduced physiological reserves. In certain elderly patients, even low-grade adverse events can have considerable impact. Stomatitis can lead to malnutrition and impair the ability to drink. Dehydration, whether due to stomatitis or to diarrhoea, can eventually lead to functional renal insufficiency.

Age as a factor in treatment efficacy and toxicity

Even though pivotal metastatic renal cell carcinoma trials did not have an age limit, patients aged 65 years and older only represented around a third of the population included (table 2). However, in non-selected populations, around half of metastatic renal cell carcinoma cases are in people aged 65 years and older.[1] Elderly patients are therefore substantially under-represented in major clinical studies. Moreover, elderly patients who do meet the eligibility criteria for randomised trials are likely to be in better overall health than elderly patients in the general population. Most age-related data are derived from subgroup analyses. To our knowledge, there have

	Specific considerations relevant to treatment of metastatic RCC	Screening, monitoring, and supportive measures
Drug metabolism affecting PK and PD		
Decreased liver mass and cytochrome p450 activity[12]	Most small molecule TKIs are metabolised via cytochrome p450 3A4	..
Renal ageing leading to abnormal glomerular filtration rate or renal insufficiency[13,14]	Only 19% of sorafenib and 16% of sunitinib is excreted in urine[13] but renal insufficiency may also reduce hepatic metabolism through accumulation of uraemic toxins, leading to reduced parent drug elimination and overdosage	..
Decreased splanchnic blood flow, gastric motility, cardiac function	Age-related modifications of gastric motility and/or acidity might affect absorption of oral drugs	..
Immune function		
Immunosenescence[15]	Possible implications for checkpoint inhibitors and other forms of immunotherapy	..
Comorbidities		
Increased risk of coronary artery disease	Need to consider sunitinib-associated heart failure	Screening; prevention; education of patients, their family, and their carers; monitoring; early intervention; and consideration of dose adjustment
Increased risk of cardiac dysfunction and hypertension[14]	Possible worsening with TKIs and bevacizumab	Screening; prevention; education of patients, their family, and their carers; monitoring; early intervention; and consideration of dose adjustment
Increased risk of diabetes	Possible need for blood glucose monitoring to prevent hypoglycaemia (and hence falls) while on multi-kinase inhibitors	Screening; prevention; education of patients, their family, and their carers; monitoring; early intervention; and consideration of dose adjustment
Polypharmacy		
Increased risk of drug interactions[16]	Most TKIs are metabolised via cytochrome p450 3A4, involved in metabolism of about 80% of drugs; the risk of drug interactions is therefore very high	Assess need for comedication, use online tools to identify potential interactions
Psychological factors		
Increased emphasis on maintaining quality of life and independent functioning, reduced willingness to accept toxic effects[17]	Need to avoid domino effect—ie, the cumulative impact of multiple chronic adverse events such as fatigue, diarrhoea, stomatitis, and skin toxic effects, even if each is low-grade[18,19]	Consider exercise to combat fatigue, take steps to identify and alleviate skin toxicities and other toxicities
Cognitive impairment	Might be worsened by targeted drugs causing fatigue or by dehydration caused by diarrhoea	Hydration, exercise
Impaired memory, eyesight, and motor function and difficulty coping with polypharmacy	Might be difficult to comply with specific advice and oral therapy in general—eg, sorafenib is taken on an empty stomach	Evaluate patient's abilities and social support

RCC=renal cell carcinoma. PK=pharmacokinetics. PD=pharmacodynamics. TKI=tyrosine kinase inhibitor.

Table 1: **Physiological, pharmacological, and psychological factors that change with age and potentially affect efficacy and tolerability of anticancer therapy**

been no prospective randomised clinical trials that are specific to frail elderly patients. Approved therapies for the treatment of metastatic renal cell carcinoma are discussed according to their line of treatment.

First-line treatments

Until recently, high-dose interleukin-2 was the only first-line treatment shown to confer a durable survival benefit, albeit for a small group of patients with metastatic renal cell carcinoma (about 2·5%) and has generally been limited to younger patients (up to 60 years old) due to its high toxicity.[43] However, a study[44] with 22 patients 65 years and older, and 82 patients younger than 65 years, has shown that its use in the elderly population resulted in survival outcomes that were not so different from those of the younger population and with a tolerable toxicity profile. Many physicians think that the advent of checkpoint inhibitors will reduce the use of high dose interleukin-2 used in the treatment of metastatic renal cell carcinoma. However, an expert task force on immunotherapy for metastatic renal cell carcinoma has recommended that patients should still discuss the use of high-dose interleukin-2 and be referred to centres of excellence for consideration when appropriate.[45]

Sunitinib and pazopanib, along with bevacizumab plus interferon, are first-line options for patients with favourable-risk to intermediate-risk disease, according to Memorial Sloane Kettering Cancer Center criteria.[6] In pivotal renal cell carcinoma studies, subgroup analyses showed that there were no substantial differences in terms of progression-free survival benefit between younger and older patients (table 2).[24–27,31–33] However, these studies did not report age-stratified toxicity profiles.

In general, phase 3 studies of sunitinib and pazopanib showed little, if any, evidence that age affects efficacy. However, in the phase 3 COMPARZ study,[29] which was

	Reference	Disease risk group*	Number of patients per group	Age of patients†		Median survival (months)		Main toxic effects‡	Age-related efficacy and toxicity
				Median age (range)	Proportion of patients aged 65 years or older	PFS	OS		
First-line treatments									
Sunitinib *vs* interferon alfa	Motzer et al 2007,[24] 2009[25]	Favourable or intermediate	375 *vs* 375	62 (27–87)	36%	11 *vs* 5 (p<0·001)	26 *vs* 22 (p=0·049)	Sunitinib: diarrhoea, vomiting, hypertension, PPE, neutropenia, anaemia, thrombocytopenia	PFS benefit almost identical between patients aged <65 years and those aged ≥65 years
Pazopanib *vs* placebo	Sternberg et al 2010,[26] 2013[27]	Favourable	290 *vs* 145	59 (25–85)	35%	9·2 *vs* 4·2 (p<0·0001)	22·9 *vs* 20·5 (p=0·224)	Pazopanib: diarrhoea, vomiting, hypertension, hair change, nausea, anorexia, ALT and AST rise	Analysis by age (<65 *vs* ≥65 years) showed younger patients had a lower HR with pazopanib
Temsirolimus *vs* interferon alfa	Hudes et al 2007[28]	74% poor	209 *vs* 207	59 (23–81)	30%	5·5 *vs* 3·1 (p<0·001)	10·9 *vs* 7·3 (p=0·008)	Temsirolimus: rash, oedema, stomatitis, nausea, hyperglycaemia, hyperlipidaemia	Overall survival benefit of temsirolimus *vs* interferon alfa was only seen in patients aged <65 years
Sunitinib *vs* pazopanib	Motzer et al 2013[29] (COMPARZ)	86% favourable or intermediate	553 *vs* 557	62 (18–88)	39%	9·5 *vs* 8·4 (95% CI 0·90–1·22)§	29 *vs* 28 (p=0·28)	Sunitinib: fatigue, diarrhoea, nausea, hypertension, leucopenia, thrombocytopenia; pazopanib: diarrhoea, fatigue, hypertension, nausea; common adverse events (any grade) significantly more common in the sunitinib group than in the pazopanib group included hand-foot syndrome, mucosal inflammation, stomatitis, hypothyroidism, dysgeusia, dyspepsia, epistaxis, and fatigue; adverse events that were significantly more frequent in the pazopanib group were change in hair colour, weight loss, and alopecia; patients in the sunitinib group had more grade 3–4 fatigue and hand-foot syndrome; quality of life was better with pazopanib	Among patients aged ≥65 years, there was a trend towards longer PFS with sunitinib
Bevacizumab and interferon alfa *vs* Interferon alfa alone	Escudier et al 2007,[30] 2010[31]	91% favourable or intermediate	327 *vs* 322	62 (18–88)	37%	10·2 *vs* 5·4 (p=0·0001)	23·3 *vs* 21·3 (p=0·336)	Fatigue, asthenia	Little influence of age
Bevacizumab and IFN *vs* IFN alone	Rini et al 2008,[32] 2010[33] (CALGB 90206)	90% favourable or intermediate	369 *vs* 363	61 (56–70)¶	NA	8·5 *vs* 5·2 (p<0·0001)	18·3 *vs* 17·4 (p=0·069)	Addition of bevacizumab produced more bleeding, hypertension, and proteinuria; extent of hypertension correlated with efficacy	No age-related data on efficacy or toxicity published in this paper

(Table 2 continues on next page)

designed to show the non-inferiority of pazopanib to sunitinib in the first-line setting, a non-significant trend favoured sunitinib in both the overall population and in patients aged 65 years and older. However, age-stratified toxicity data were not reported (table 2).

An exploratory analysis[46] of six prospective sunitinib trials and an expanded access programme showed broadly similar adverse event profiles across the two age groups that were compared (<70 years or 70 years and older). From this exploratory analysis, fatigue (69% *vs* 60%), anaemia (25% vs 18%), decreased appetite (29% *vs* 13%), and thrombocytopenia (26% vs 16%) were significantly more common among elderly patients. In a prospective, non-randomised study,[47] older age predicted more severe toxicity.

In a three-arm trial[28] of temsirolimus versus interferon-alfa versus both in patients with poor-risk metastatic renal cell carcinoma, there was a significant interaction

	Reference	Disease risk group*	Number of patients per group	Age of patients†		Median survival (months)		Main toxic effects‡	Age-related efficacy and toxicity
				Median age (range)	Proportion of patients aged 65 years or older	PFS	OS		
(Continued from previous page)									
Second-line treatments									
Sorafenib *vs* placebo	Escudier et al 2007;[34] Eisen et al 2008[35] (TARGET)	100% favourable or intermediate	451 *vs* 452	58 (19–86)	30% (13% aged ≥70 years)	5·5 *vs* 2·8 (p<0·01)	17·8 *vs* 15·2 (p=0·146)	Fatigue, diarrhoea, nausea, rash	Median PFS in sorafenib-treated patients aged ≥70 years was similar to that in younger patients (26 *vs* 24 weeks), as were clinical benefit rates (84% in both groups). Frequency of AEs was not related to age.
Axitinib *vs* sorafenib	Rini et al 2011[36] (AXIS)	66% favourable or intermediate	361 *vs* 362	61 (20–82)	34%	6·7 *vs* 4·7 (p<0·0001)	20·1 *vs* 19·2 (p=0·374)	Axitinib: diarrhoea, hypertension, fatigue; sorafenib: diarrhoea, PPE, alopecia	Significant PFS benefit seen in both <65 years and ≥65 years age groups
Cabozantinib *vs* everolimus	Choueiri et al 2015,[37] 2016[38] (METEOR)	87.6% favourable or intermediate	330 *vs* 328	62 (31–84)	40%	7·4 *vs* 3·9 (p<0·0001)	21·4 *vs* 16·5 (p=0·00026)	Cabozantinib: hypertension, diarrhoea, fatigue; everolimus: anaemia, fatigue, hyperglycaemia	On subgroup analysis, patients >65 years also show overall survival benefit with cabozantinib
Everolimus *vs* placebo	Motzer et al 2010[39]	85% favourable or intermediate	272 *vs* 138	61 (27–85)	37%	4·9 *vs* 1·9 (p<0·0001)	14·8 *vs* 14·4 (p=0·162)	Infections, dyspnoea, fatigue	Age (<65 years *vs* ≥65 years) was not shown to be prognostic for overall survival or PFS
Lenvatinib and everolimus *vs* lenvatinib *vs* everolimus	Motzer et al 2015,[40] 2016[41]	61% favourable or intermediate risk	51 *vs* 52 *vs* 50	61 (44–79)	NA	14·6 *vs* 7·4 *vs* 55·5 (p=0·0005)	25·5 *vs* 19·1 *vs* 15·4 (p=0·024)	Lenvatinib: diarrhoea, proteinuria, anaemia	No age stratified data published
Nivolumab *vs* everolimus	Motzer et al 2015[42]	85% favourable or intermediate risk	406 *vs* 397	62 (18–88)	39%	4·6 *vs* 4·4 (p=0·11)	25·0 *vs* 19·6	Fatigue, nausea, pruritus, stomatitis, anaemia; toxicity profile with nivolumab differs from that with anti-VEGF drugs and mTOR inhibitors	Overall survival benefit seen in patients aged <65 years and those aged 65–75 years but not in those who were aged ≥75 years; benefit was independent of PD-L1 expression

PFS=progression-free survival. OS=overall survival. PPE=palmar-plantar erythrodysaesthesia. ALT=alanine aminotransferase. AST=aspartate aminotransferase. HR=hazard ratio. NR=not reported. *These categories are they based on Memorial Sloane Kettering Cancer Center criteria: 0=favourable, 1–2=intermediate, >3=poor. †All studies included patients aged older than 80 years. The age of the oldest patient enrolled ranged from 81 years in the temsirolimus trial[28] to 88 years in the trial of nivolumab and sunitinib/pazopanib.[29,42] ‡The toxicities identified and described are those commonly mentioned in the articles cited and are of interest in the context of the elderly patient and not based on any threshold in terms of percentage of patients affected. §This was a non-inferiority trial, and no p value was reported. ¶Median (IQR).

Table 2: **Major metastatic renal cell carcioma trials by patient characteristics, setting, efficacy, toxicity, and age-related data**

between efficacy and age. Temsirolimus improved overall survival compared to interferon-alfa only in patients younger than 65 years, but did not improve overall survival in patients older than 65 years. Meanwhile, CABOSUN, a phase 2 study[48] looking specifically at patients with intermediate-risk and poor-risk renal cell carcinoma, showed that cabozantinib had superior progression-free survival when compared with sunitinib. Although there were no age-stratified data available for this study, cabozantinib may present another treatment option for elderly patients with poor-risk metastatic renal cell carcinoma.

Second-line treatments

Sorafenib was the first VEGF TKI to be approved in the second-line setting for patients with metastatic renal cell carcinoma who had progressed on, or were intolerant to, previous cytokine therapy. One pivotal study[34] showed a significant progression-free survival benefit for the sorafenib group when compared to placebo (table 2).

A subset analysis[35] of this study found that progression-free survival and the proportion of patients achieving a response were similar for elderly patients (aged over 70 years) when compared with younger patients. In that study, elderly patients on sorafenib were more likely to report gastrointestinal toxicity and fatigue than their younger counterparts.

Everolimus, an mTOR inhibitor, was compared with placebo in patients with mRCC who had progressed after first-line treatment, and showed a significant progression-free survival benefit.[39] The original report included no age-stratified data for progression-free survival or toxicity. A subsequent exploratory analysis showed similar progression-free survival outcomes in elderly patients (two elderly subgroups were analysed, patients aged ≥65 years and patients aged ≥70 years) and the overall study population.[49] However, this retrospective analysis found that older patients reported more cough, rash, peripheral oedema, and diarrhoea.

In a subgroup analysis of the METEOR trial,[38] cabozantinib, a multi-kinase inhibitor of AXL, MET, and VEGF, was superior to everolimus in terms of overall survival for patients aged 65 years or older (table 2). In quantitative terms, the benefit of this treatment was greater in patients younger than 65 years, but elderly patients benefited from the drug nonetheless. The toxic effects were not stratified by age, so the toxic profiles could not be compared.

In the AXIS phase 3 trial,[36] which compared axitinib with sorafenib, progression-free survival did not differ between groups after age stratification, although axitinib showing a consistent benefit in both older (65 years and older) and younger patients (less than 65 years). There were no age-stratified toxicity data in that study.

Nivolumab, a human IgG4 anti-PD-1 monoclonal antibody, is an immune checkpoint inhibitor that enhances T-cell activation by binding to the PD-1 receptor and blocking its interaction with PD-L1 and PD-L2, which releases the inhibition of an immune response to cancer cells. Nivolumab, administered intravenously, was studied as a second-line treatment for patients with metastatic renal cell carcinoma and achieved its primary endpoint of improved overall survival when compared with oral everolimus (table 2).[42] In a retrospective analysis[50] of key baseline factors used in this study, elderly patients (65 years and older) were found to have a similar survival benefit when compared with their younger counterparts and found that all-grade toxic effect did not differ between older and younger patients.

A second-line combination treatment for patients with metastatic renal cell carcinoma recently approved by the US Food and Drug Administration is lenvatinib plus everolimus. Lenvatinib is a multikinase inhibitor of VEGFR, FGFR, PDGFR, c-kit, and Ret. The lenvatinib and everolimus combination was studied in a randomised phase 2 study[40] of patients who had progressed after first-line treatment. The combination conferred a significant survival benefit when compared with either drug alone.[40,41] However, there was no age stratification in terms of efficacy or toxicity to provide any insight about the impact of the drug on elderly patients.

Overall, axitinib, everolimus, sorafenib, cabozantinib, and nivolumab showed similar efficacy when given to older and younger patients, although the lenvatinib study did not provide any age-stratified outcome data. An analysis[51] of six randomised trials and two expanded access programme studies involving sorafenib showed similar toxicity profiles for patients in all age groups, although patients 75 years and older had a higher incidence of grade 3 and 4 toxic effects and experienced more gastrointestinal adverse events and fatigue when compared with younger patients

Third-line treatments

A recent observational study[52] from the International Metastatic Renal Cell Cancer Database Consortium showed that everolimus was the drug most frequently used for third-line treatment for metastatic renal cell carcinoma. However, age was not included in the list of patient characteristics. Data were obtained from 25 centres across North America, Europe, and Singapore, where the median overall survival was reported to be 12·4 months and the median progression-free survival was 3·9 months. These data make everolimus a viable option in a select group of patients fit for third-line treatment

Evidence to date

Our overall conclusion is that age does not seem to appreciably affect the efficacy of systemic therapy when comparing outcomes between younger and older patients. Among the pivotal studies that were included in our assessment, there is a striking absence of analyses that relate toxic effects to patient age. Another study[53] from the International Metastatic Renal Cell Cancer Database Consortium database found that being 60 years or older was a significant independent predictor of toxicity-related discontinuation of treatment among 936 patients with metastatic renal cell carcinoma who were treated with VEGF-targeted drugs. 77% of these patients were treated with sunitinib and 18% with sorafenib. Other factors that were predictive of toxicity-related discontinuation were renal function, number of metastatic sites, and baseline sodium levels.

With many treatment options and data supporting the use of up to three lines of treatment for patients with renal cell carcinoma, one of the many challenges faced by oncologists is the optimal sequencing of treatment. Although there is evidence from the RECORD-3 trial[54] to support the use of a VEGF TKI (sunitinib) over an mTOR inhibitor (everolimus) in the first-line treatment of metastatic renal cell carcinoma, there is little evidence to support this approach in elderly patients. This is

specifically because of a lack of age-stratified data to support its use. In the near future, novel regimens and drugs, such as the combination of nivolumab and ipilimumab or the use of oral cabozantinib in patients with poor-risk metastatic renal cell carcinoma, might be added as new first-line options, although their role for elderly patients with mRCC still remains uncertain if age-stratified data are not available.

After progression on a VEGF TKI, choosing the best treatment option is challenging since there are positive phase 3 data to support the use of either cabozantinib or nivolumab. For elderly patients, the choice should take into account comorbidities and potential interactions with other drugs that the patient might be taking.[18]

Looking to the future

Several ongoing or completed, but not fully reported, trials of promising combination therapies might prove practice changing in the treatment of metastatic renal cell carcinoma. The CheckMate-214 phase 3 trial of one such combination therapy, recently reported in abstract form at the 2017 European Society for Medical Oncology meeting,[55] found that the combination of the two checkpoint inhibitors nivolumab and ipilumumab achieved a better progression-free survival than sunitinib, the current standard of care, in intermediate-risk and poor-risk patients with metastatic renal cell carcinoma. Although there were no age-stratified data to elucidate the role of this combination in elderly people specifically, we can infer from the relatively tolerable adverse event profile reported for the study population that the combination would be reasonably well tolerated in the elderly. Immune checkpoint inhibitors are unlike the targeted therapies discussed in the paragraphs above, because they have fever side-effects and are better tolerated, with fewer drug–drug interactions.

Quality of life and adherence to treatment in the elderly

Compared with younger patients, quantity and quality of life (QOL) might have different value to the elderly, and they should be balanced when determining optimal management. Older patients are more often treated with non-curative intent and are more vulnerable to toxic effects of treatment than younger patients. Those two factors increase the relevance of QOL in treatment decisions, which should be assessed at every stage of a patient's management. Decisions about cancer care and treatment should take into account not only the age of patients, but crucially their condition and expectations relating to their disease, leading to the creation of an individualised care plan. The needs of an elderly patient may lead to the implementation of dose-reduced and alternative regimens at the outset, to avoid detrimental treatment effects and the possibility of treatment interruption.

A four-stage strategy has been proposed by the SIOG task force to improve the care of elderly patients with cancer, and it applies both to patients with metastatic renal cell carcinoma and to elderly patients with other tumour types. The first step is a multidisciplinary assessment involving oncologists, geriatricians, nurses, dietitians, and social workers.[56] Screening scales, such as the G8, are a useful means of identifying patients needing a comprehensive geriatric assessment.[12,57] The second step involves prehabilitation, during which issues such as malnutrition, pain, and social isolation can be addressed, along with previously unmet medical needs. This step optimises the physical and mental condition of the patient before anticancer therapy is started because cognitive disorders at baseline are correlated with anxiety, depression, and fatigue, and have an adverse impact on QOL.[58,59] The third step involves minimising toxic effects to provide the patient with the best chance of completing treatment. There should be a particular focus on toxic effects relative to QOL in the elderly. These include peripheral neuropathy, nausea, vomiting, and neutropenia, but also pain, disruption of sleep, reduced appetite, and risk of malnutrition. It is important to remember that adverse events are often under-reported by physicians.[60,61] The final step is to offer rehabilitation, or management of end-of-life care for patients with advanced disease. A randomised trial[62] in patients with metastatic lung cancer showed that introducing palliative care early on in the care pathway significantly prolonged overall survival when compared with standard palliative care, and led to better QOL outcomes and fewer symptoms of depression.[62,63]

In the phase 3 CheckMate 025 trial, Cella and colleagues[64] showed that nivolumab improved health-related QOL significantly more than everolimus did in previously treated, advanced renal cell carcinoma. Patient preference studies should also be considered, such as the PISCES study,[65] which showed a clear preference for pazopanib over sunitinib despite showing similar efficacy in the non-inferiority COMPARZ study.

Many therapies for metastatic renal cell carcinoma are given orally so fewer hospital visits are required and the risk of adverse events related to intravenous administration is reduced.[66] However, older patients might take oral drugs less reliably than younger patients because of cognitive and physical impairments. This issue, along with the increased chance of polypharmacy in elderly patients, raises the possibility of reduced efficacy either due to under-treatment or because of increased toxic effects if patients persist in taking a drug despite emerging adverse events or if they take a drug when scheduled not to. Before starting oral anticancer drugs at home, physicians should assess the patient's support system of family and friends, arrange for community follow-up to monitor adherence and adverse events, and ensure the patient is aware of the importance of compliance and adverse event reporting.[67]

Search strategy and selection criteria

Published data for this Series paper were identified by searches of MEDLINE and the Cochrane database. Authors also identified articles by searching through their own files. Original articles, review papers, and conference abstracts were included if they were published in English between 2008 and 2017. Past pivotal trials were added. Trials were determined to be pivotal if they intended to provide evidence for a drug marketing approval, eg, by the US Food and Drug Administration. All phase 3 trials were assumed to be pivotal. The search was performed using the MeSH terms "kidney neoplasms/secondary", "aged", "frail elderly", "aged, 80 and over" and text words "metastatic renal cell carcinoma", "kidney cancer", "geriatric" and "elderly". We used the terms "clinical Trial" and "humans" as limits. Clinical trials were excluded if elderly patients were not included.

Conclusion

Survival outcomes for patients with metastatic renal cell carcinoma have improved considerably over the past 15 years. When immunotherapy with interferon-alfa was the only therapeutic option for this disease, which was available only to a select group of patients, median overall survival was around 13 months. Now, with the advent of targeted treatments, median overall survival is roughly 24–30 months.[3] These treatment advances mean that metastatic renal cell carcinoma has the potential to become a chronic, treatable disease through combined or sequential use of agents with different mechanisms of action and non-overlapping toxic effects. However, we are still at an early stage in our understanding in how this goal can be achieved, especially for elderly patients.

Although elderly people might experience adverse events similarly to younger patients, their management needs to take into account the additional susceptibility involved. Patients should also be educated to detect and report adverse events early, to regularly monitor the emergence of adverse events and impact on their QOL and functioning, and to manage mild toxic effects. The availability of drugs with different adverse event profiles is particularly relevant for elderly patients who have comorbidities. For example, mTOR inhibitors are associated with hyperglycaemia and should perhaps be avoided in patients with diabetes, while nivolumab might be contraindicated in patients with active autoimmune disorders.

In addition to the fact that the population of patients recruited in clinical trials differs from one trial to another, as does the means of assessing toxic effects, the absence of head-to-head studies means that it is difficult to compare different drugs in terms of frequency and severity of adverse events. However, the adverse event profile of different drugs could be considered when selecting treatment for elderly patients. One key aspect to the selection process would involve the use of a screening tool such as the G8 to identify patients who are in need of a comprehensive geriatric assessment.

Many patients with metastatic renal cell carcinoma are elderly, and although there have been major advances over the past 10 years in extending the survival of people with this disease, there is still a scarcity of data on the benefit and toxic effects of these drugs in the elderly population. Hence, there is a pressing need for the inclusion of more elderly patients in trials and for the reporting of results that are stratified by age.

Contributors

RK and OLS contributed to the study design, data interpretation, manuscript writing including coming up with the first draft, editing of the subsequent drafts, and approval of the final manuscript. RM, TKC, VL-V, FS, and JB contributed to the study design, data interpretation, manuscript writing, and approval of the final manuscript.

Declaration of interests

JB reports honoraria or consulting fees from Merck and Pfizer, and institutional research funding or support from Pfizer. VL-V reports honoraria from talks or consulting fees from Amgen, Bayer, Pierre Fabre Oncology, Merck, Onxeo, Roche, Sandoz, Takeda, Tesaro, and Teva. FS reports honoraria from Roche, Vifor, MSD, TEVA, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, Sanofi, AMGEN, Pierre Fabre Oncology, and TESARO. RK reports honoraria or consulting fees from MSD, Pfizer, Novartis, Johnson & Johnson, Astellas, Mundipharma, BMS, Roche, Bayer, Amgen, Sanofi, and Boehringer. RM reports being a consultant for Pfizer, Eisai Inc, and Novartis and receiving research support to employer from Bristol Myers Squibb, Novartis, Pfizer, Genentech Roche, and Eisai Inc. TKC reports consulting for AstraZeneca, Bayer, BMS, Cerulean, Eisai, Foundation Medicine Inc, Exelixis, Genentech Roche, and GlaxoSmithKline and receiving research funding from AstraZeneca, BMS, Exelixis, Genentech, GlaxoSmithKline, Merck, Pfizer, Roche, Tracon, and Eisai. OLS declares no competing interest

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