Systemic Therapies for Metastatic Renal Cell Carcinoma in Older Adults

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Abstract

The introduction of targeted therapies has radically changed the treatment paradigm for metastatic renal cell carcinoma (mRCC). However, multiple clinical dilemmas have emerged. For instance, limited data are available to juxtapose the safety and efficacy profile of targeted therapies between older and younger adults. Herein, pivotal trials of vascular endothelial growth factor (VEGF)- and mammalian target of rapamycin (mTOR)-directed

therapies are assessed in the context of their implications in treating older adults with mRCC. In general, subset analyses from these pivotal studies suggest similar efficacy of targeted therapies amongst older adults. Aging is accompanied by a multitude of physiological changes, as well as an increased prevalence of co-morbidities. The age-related toxicity profiles of targeted agents for mRCC are detailed to provide a framework for the risks and benefits of these therapies in older adults. Ultimately, tools such as the Comprehensive Geriatric Assessment (CGA) that account for physiological (as opposed to chronological) age may prove useful in the evaluation and treatment of older adults with mRCC.

1. Introduction

Within the last 5 years, an enhanced understanding of the biology of metastatic renal cell carcinoma (mRCC) has led to the development of multiple targeted therapies. These agents have largely supplanted immunotherapy in the current therapeutic paradigm.^[1] The approved targeted therapies for mRCC can be divided into two principal categories: (i) agents directed at the vascular endothelial growth factor (VEGF) ligand or receptor; and (ii) agents directed at the mammalian target of rapamycin (mTOR). The first category includes the monoclonal antibody bevacizumab and the tyrosine kinase inhibitors (TKIs) pazopanib, sunitinib and sorafenib. Phase III studies for bevacizumab, pazopanib and sunitinib have led to category 1 recommendations from the National Comprehensive Cancer Network for use in treatment-naïve patients.^[2-5] In contrast, phase III data for sorafenib support its use in patients who have progressed on prior immunotherapy.^[6] In the second category, two mTOR inhibitors are currently approved for use in mRCC. Everolimus was approved by the US FDA based on a phase III trial that showed a progression-free survival (PFS) benefit compared with placebo in patients who had previously received sunitinib and/or sorafenib. Temsirolimus was approved based on a phase III study that demonstrated an overall survival (OS) benefit compared with immunotherapy with interferon- α (IFN α) in patients who had poor-risk disease (as classified by the Memorial Sloan Kettering Cancer Center [MSKCC] risk criteria).^[7,8]

In attempts to optimize use of available therapies, investigators have generated numerous algorithms. From table I, it is readily apparent that in certain clinical scenarios there are multiple options. For instance, in treatment-naïve patients with mRCC there are no data to discern any

Table I. A proposed treatment algorithm for patients with metastatic renal cell carcinoma

Intervention	Level of evidence	
	category 1 ^a	category 2 ^b
First-line therapy		
Good- or intermediate-risk disease ^c	Sunitinib	HD IL-2
	Bevacizumab/IFN α	Sorafenib
	Pazopanib	Temsirolimus
Poor-risk disease ^c	Temsirolimus	Same as above
Second-line therapy		
Prior cytokine	Sorafenib	Sunitinib
	Sunitinib	Sorafenib
	Pazopanib	Temsirolimus
		Bevacizumab
Prior VEGFR inhibitor	Everolimus	IFN α
		IL-2
		Same as above
Prior mTOR inhibitor	No data available	No data available

- a Data derived from well designed, randomized, controlled, phase III studies.
- b Data derived from well designed, non-randomized, controlled studies.
- c As classified by the Memorial Sloan Kettering Cancer Center risk criteria.

HD IL-2 = high-dose interleukin-2; **IFN α** = interferon- α ; **mTOR** = mammalian target of rapamycin; **VEGFR** = vascular endothelial growth factor receptor.

differences in the relative efficacies of bevacizumab, sunitinib and pazopanib. Likewise, for patients with cytokine-refractory disease, treatment with either sorafenib or pazopanib is supported by level 1 evidence (i.e. data derived from well designed, randomized, controlled, phase III studies). With few comparative trials currently comparing these therapeutic options against one another, a variety of options are available and the adverse effect profile can play an integral role in the decision to utilize one therapy over another.^[9] Ultimately, it is hoped that molecular profiling techniques will individualize therapy. However, to date, no such biomarkers have been sufficiently validated to use for this purpose.^[10]

While the MSKCC risk criteria have been adapted for patients receiving selected targeted therapies, age is omitted from this model.^[11] Since the median age at diagnosis of RCC is 65 years, older adults constitute a large proportion of patients with RCC, yet are less likely to receive optimal dose intensity with many cancer treatments, which can potentially compromise therapeutic efficacy.^[12-18] Moreover, the biology of the disease may vary in older adults. For instance, von Hippel Lindau (*VHL*) gene mutations (a key driver in RCC pathogenesis) may be more frequent in this demographic.^[19] In contrast to earlier series, recent reports suggest that older adults may have a higher frequency of clear-cell histology.^[20-26] With respect to the less common histologies, one study noted a higher frequency of papillary RCC and a lower frequency of chromophobe RCC with age.^[27]

These key variations in RCC biology with age beg the question of whether the efficacy of targeted therapies may vary in older adults. In a retrospective analysis across multiple malignancies, 401 patients who had received various targeted agents were assessed, and no significant differences in toxicity were seen between the older and younger age groups.^[28] mRCC represents a somewhat unique scenario (akin to chronic myelogenous leukaemia, gastrointestinal stromal tumour, etc.) where monotherapy with targeted agents has yielded meaningful clinical benefit.^[29,30] Herein, pharmacological considerations that should be taken into account with older adults are reviewed,

and the available data on the efficacy and safety of targeted agents for mRCC specific to this group of patients are discussed. Particular emphasis is placed on recently emerging subset analyses from pivotal, phase III trials in mRCC that have led to the approval of targeted therapies. These data are available both in the peer-reviewed, published literature (accessible via MEDLINE) and in recent conference proceedings.

2. Age-Related Considerations with Targeted Therapies

The physiological changes that accompany age may have an impact on the pharmacokinetics of targeted therapies. Table II provides a general summary of the pharmacokinetics of mRCC targeted agents. With age, a decrease in liver mass and cytochrome P450 (CYP) enzyme content has been reported.^[31,32] Because the majority of small molecule targeted agents for mRCC are processed by CYP3A4, this could have a substantial impact on drug metabolism.^[32,33] Renal blood flow also declines with age, as does glomerular filtration rate.^[34-36] Among targeted therapies for mRCC, sorafenib and sunitinib rely most heavily on renal excretion (16% and 19%, respectively).^[2,6] In contrast, less than 5% of systemic pazopanib, everolimus and temsirolimus are eliminated by this route. With oral therapies such as sunitinib, sorafenib, everolimus and pazopanib, decreased splanchnic blood flow and gastric motility that accompany age could affect absorption.^[37,38] Pharmacokinetic variability with age has been assessed prospectively in multiple studies of cytotoxic agents.^[39-44] However, such data are lacking for VEGF- and mTOR-directed therapies.

It is well documented that older age is accompanied by an increase in the number of co-morbid illnesses.^[45] Several studies have suggested decreasing utilization of cytotoxic agents for patients with co-morbidities.^[46-48] The presence of specific co-morbidities may also raise unique concerns about targeted agents. For instance, hypertension has been observed as a class effect with VEGF-directed therapies.^[49] While treatment-related hypertension has been associated with greater efficacy in the context of sunitinib and

Table II. Pharmacokinetic properties of targeted agents

Agent	Half-life	Hepatic metabolism	Excretion (%)
Everolimus	30 h	CYP3A4, P-glycoprotein	Faecal: 80 Renal: 5
Sunitinib	40–60 h	CYP3A4	Faecal: 61 Renal: 16
Sorafenib	24–48 h	CYP3A4, UGT1A9	Faecal: 51 (unchanged), 26 (metabolites) Renal: 19
Temsirolimus	17 h	CYP3A4	Faecal: 78 Renal: 4
Pazopanib	31 h	CYP3A4 (major), CYP1A2 and CYP2C8 (minor)	Faecal: extensive Renal: <4
Bevacizumab	20 d	None	Faecal: 0 Renal: 0 Reticuloendothelial: 100

CYP = cytochrome P450 enzyme; **UGT** = uridine diphosphate glucuronosyltransferase.

bevacizumab therapy, the presence of uncontrolled baseline hypertension may limit application of these agents.^[5,50] Similarly, the mTOR inhibitors are known to disrupt the metabolic profile.^[7,8] Consideration of this class effect is important in patients with diabetes mellitus and/or coronary disease.^[51]

Along with increased co-morbidity, polypharmacy is another common issue amongst older adults with cancer. A retrospective analysis including 100 chemotherapy recipients aged ≥70 years suggested that these patients received an average of nine medications.^[52] Few adjustments were made to standard prescriptions despite the presence of multiple potential interactions. As noted in table II, CYP3A4 plays a major role in the metabolism of the oral small molecule inhibitors used in RCC. Concomitant use of strong CYP3A4 inhibitors (e.g. macrolide antibacterials, chloramphenicol, azole antifungals) may lead to sustained blood concentrations of these targeted agents and consequently exacerbate toxicity. On the other hand, strong CYP3A4 inducers (e.g. phenytoin, rifampicin [rifampin], phenobarbital) may reduce drug concentrations and efficacy. Furthermore, data from other tumour types suggest that the presence of polypharmacy may impact outcome.^[53–55] When counselling the older adult with mRCC, a thorough review of concomitant medications prior to embarking on systemic therapy is critical.

3. Efficacy and Safety of Specific Targeted Therapies

3.1 Vascular Endothelial Growth Factor-Directed Therapies

3.1.1 Sorafenib

Sorafenib was the first targeted agent approved for the treatment of mRCC.^[56] In the phase III TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) study, 903 patients with mRCC were randomized to receive either sorafenib (400 mg orally twice daily) or placebo.^[6] All patients were required to have progressed on what was considered standard therapy at the time (approximately 82% of patients had received cytokine-based therapy). Furthermore, patients were required to demonstrate an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and were required to have low- or intermediate-risk disease by MSKCC criteria. The study included patients ranging in age from 19 to 86 years, with a median age of 59 years. Therapy with sorafenib compared with placebo led to an improvement in median PFS from 2.8 to 5.5 months (hazard ratio [HR] 0.44; 95% CI 0.35, 0.55; *p* < 0.01). However, the study failed to improve OS based on the O’Brien-Fleming threshold.

Since the original publication of the TARGET trial, a subgroup analysis has been reported with specific attention to older adults.^[57] Clinical endpoints and toxicities incurred by 115 patients

aged ≥ 70 years were compared with those of 788 patients aged < 70 years. Treatment with sorafenib yielded a substantial benefit in PFS in both younger (HR 0.55; 95% CI 0.47, 0.66) and older patients (HR 0.43; 95% CI 0.26, 0.69). Clinical benefit was similar between the two groups with 83.5% of younger patients and 84.3% of older patients having either a complete response (CR), partial response (PR) or stable disease (SD) as a best response to sorafenib therapy, which exceeded the placebo-treated groups (53.8% and 62.2% for younger and older patients, respectively). More grade 3/4 toxicities were reported in older patients than in younger patients (45.7% vs 36.7%). In general, older patients experienced more gastrointestinal adverse effects and fatigue compared with younger patients, whereas younger patients more frequently experienced hypertension, pruritus and neuropathy. The rate of treatment discontinuation was higher amongst older patients (21.4% vs 8.1%). However, the reasons for discontinuation varied between the groups. Older patients were more apt to discontinue therapy because of gastrointestinal or dermatological adverse effects, whereas younger patients discontinued therapy more often because of pulmonary or constitutional symptoms.

A North American expanded access programme for sorafenib offered a larger opportunity to evaluate differences in efficacy and safety based on age.^[58] The programme ultimately enrolled a total of 2504 patients, with 736 patients (29%) aged ≥ 70 years. No significant difference in OS was observed amongst subgroups divided by age (46 weeks and 50 weeks in patients aged ≥ 70 and < 70 years, respectively), and the PR rate was equivalent (4% in both groups). Unlike the TARGET trial, the frequency of specific grade 3/4 toxicities was quite similar between groups, with the most common events including rash, hand-foot syndrome and hypertension.

3.1.2 Sunitinib

In contrast to sorafenib, the pivotal trial of sunitinib assessed treatment-naïve patients with mRCC.^[2] In this phase III study, a total of 750 patients were randomized to receive either sunitinib or IFN α . Sunitinib was administered at

50 mg/day orally for continuous 6-week cycles (4 weeks on therapy followed by 2 weeks off), whereas IFN α was administered at 9 million units (MU) subcutaneously three times per week. The median age of patients receiving sunitinib was 62 years (range 27–87 years). Therapy with sunitinib compared with IFN α led to prolongation of median PFS from 5 to 11 months (HR 0.42; 95% CI 0.32, 0.54; $p < 0.01$). A recent report suggested preservation of OS benefit initially observed with sunitinib therapy (median 26.4 vs 21.8 months with IFN α ; HR 0.82; 95% CI 0.67, 1.00; $p = 0.013$) despite substantial crossover.^[59] The most frequent toxicities incurred with sunitinib therapy were diarrhoea, fatigue and nausea.

Subset analyses suggested that this PFS benefit was preserved across the majority of subsets – including groups divided by age < 65 years ($n = 475$) or ≥ 65 years ($n = 275$). When Cox modelling was used to determine the impact of certain prognostic factors on OS, age was not found to be a predictor. Unfortunately, there are no data available on the relative frequency of toxicities by age group from this phase III study. However, such analyses were performed in the expanded access trial of sunitinib therapy.^[60] A total of 2158 patients were evaluated in this study, with a median age of 59 years (range 19–85 years). The incidence of common toxicities (again, diarrhoea, fatigue and nausea) did not vary by age. Additionally, median PFS was 10.1 months in patients aged ≥ 65 years, compared with 8.9 months in the entire cohort.

3.1.3 Bevacizumab

Bevacizumab has been assessed in two pivotal phase III trials.^[4,5] In Cancer and Leukemia Group B (CALGB) 90206, a total of 732 patients with treatment-naïve mRCC were randomized to receive either bevacizumab with IFN α or IFN α alone.^[4] Bevacizumab was administered at 10 mg/kg intravenously every 2 weeks, while IFN α was administered at 9 MU subcutaneously three times per week. The median age at study entry was 61 years. The addition of bevacizumab to IFN α failed to generate an improvement in OS (the primary endpoint of the study), although it did result in an improvement in median PFS from 5.2 to 8.5 months (HR 0.71; 95% CI 0.61, 0.83;

$p < 0.0001$).^[61] Treatment with bevacizumab also led to an increase in grade 3 toxicities, including hypertension, anorexia and fatigue.

Subset analyses did not reveal any marked differences in OS benefit across subgroups divided by age.^[61] The HR for OS amongst patients aged <65 years was 0.80 (95% CI 0.64, 1.01) compared with 0.95 for patients aged ≥65 years (95% CI 0.75, 1.21). No data are available to distinguish differences between toxicity profiles of older and younger patients.

The second phase III trial to assess the regimen of bevacizumab with IFN α was the AVOREN (Avastin and Roferon in Renal Cell Carcinoma) study.^[5] In AVOREN, 649 patients with treatment-naïve mRCC were randomized to receive IFN α with either bevacizumab or placebo – the doses employed were identical to those in the CALGB 90206 study.^[4] The median age of the study population was 61 years (range 18–82 years).^[5] As in CALGB 90206, the study failed to meet its primary OS endpoint ($p = 0.13$). However, there was a significant benefit in PFS with the addition of bevacizumab (median 10.2 vs 5.4 months; HR 0.63; 95% CI 0.52, 0.75; $p = 0.0001$).^[62] Adverse events incurred in this study were similar to those noted in the CALGB 90206 study.^[4]

Subset analyses of OS included only two groups: patients aged <65 years (HR 0.83; 95% CI 0.65, 1.05) and patients aged ≥65 years (HR 1.07; 95% CI 0.80, 1.45).^[4] In subset analyses of PFS, the relative benefit of bevacizumab therapy was defined in three age-based cohorts: (i) patients aged <40 years (HR 0.65; 95% CI 0.28, 1.52); (ii) patients aged 40–64 years (HR 0.54; 95% CI 0.43, 0.68); and (iii) patients aged ≥65 years (HR 0.77; 95% CI 0.58, 1.03). No significant interaction was observed between age and PFS benefit ($p = 0.08$). No age-based stratification of toxicity has been reported.

3.1.4 Pazopanib

The most recent VEGF-directed therapy to gain FDA approval is the small molecule pazopanib. In a pivotal phase III study, patients were randomized in a 2 : 1 fashion to either pazopanib or placebo.^[3] The study was designed and initiated just as data for sorafenib and sunitinib were

emerging. Consequently, while the study was originally designed to only include cytokine-refractory patients, treatment-naïve patients were also included. The study enrolled a total of 435 patients with a median age of 59 years (range 25–85 years). The study met its primary endpoint of PFS, with pazopanib therapy improving median PFS from 4.2 to 9.2 months (HR 0.46; 95% CI 0.34, 0.62; $p < 0.0001$). Predefined subgroup analyses show a consistent benefit in PFS in both older and younger adults. In patients aged <65 years, the HR for PFS was 0.41 (95% CI 0.28, 0.61), while in patients aged ≥65 years, the HR for PFS was 0.52 (95% CI 0.33, 0.82) [Sternberg CN, personal communication].

3.2 Mammalian Target of Rapamycin Inhibitors

3.2.1 Everolimus

The pivotal trials of mTOR inhibitors have each assessed unique subpopulations of mRCC patients. The phase III RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily) study randomized 416 patients who had progressed on sunitinib and/or sorafenib to either everolimus or placebo in a 2 : 1 fashion.^[7] The median age of the study population was 61 years (range 27–85 years). The primary endpoint of the study was met, with an improvement in median PFS from 1.9 to 4.9 months with everolimus therapy (HR 0.33; 95% CI 0.25, 0.43; $p < 0.001$).^[63]

This report also included a breakdown of efficacy and toxicity by age.^[63] A total of 153 enrolled patients were aged ≥65 years. In this subset, median PFS with everolimus was 5.4 months compared with 2.2 months with placebo. In patients aged ≥75 years, everolimus led to an improvement in median PFS from 1.9 to 5.1 months (HR 0.19; 95% CI 0.09, 0.37; $p < 0.001$). Adverse events were more commonly seen in patients aged ≥65 years, with the most frequent grade 3/4 toxicities being anaemia (14.4%) and infection (10.8%). Haematological adverse effects were also more pronounced in this group.

3.2.2 Temsirolimus

In contrast to RECORD-1, the phase III ARCC (Advanced Renal Cell Carcinoma) study evaluating

temsirolimus included only treatment-naïve patients.^[8,64] A total of 626 patients were randomized to either temsirolimus with IFN α , temsirolimus alone or IFN α alone. Uniquely amongst the other pivotal trials of targeted therapy in mRCC, the ARCC study allowed enrolment of patients with non-clear-cell histology – ultimately constituting 20% of the study population. Furthermore, patients were required to have three of six predictors of shorter survival: (i) lactate dehydrogenase >1.5 times the upper limit of normal; (ii) haemoglobin less than the lower limit of normal; (iii) corrected calcium >10 mg/dL; (iv) time from initial diagnosis of RCC to randomization of <1 year; (v) Karnofsky performance status 60 or 70; or (vi) metastases in multiple organs. The median age of the study population was 59 years (range 23–86 years). An OS advantage with temsirolimus alone (compared with IFN α alone) was observed (10.9 vs 7.3 months; HR 0.73; 95% CI 0.58, 0.92; $p=0.008$). The most frequent non-haematological toxicities observed were asthenia, rash, nausea and anorexia.

Subset analyses based on age indicated a potentially greater benefit in younger patients.^[65] With respect to OS for temsirolimus alone versus IFN α alone, the HR for patients aged <65 years was 0.67 (95% CI 0.52, 0.87) compared with 1.15 (95% CI 0.78, 1.68) for patients ≥ 65 years.

3.3 Immunotherapy

To date, the only treatment that has been reported to achieve durable remissions in patients with mRCC has been high-dose intravenous interleukin-2 (IL-2). Although response rates of up to 29% were noted in the recent SELECT study,^[66] the probability of a durable remission was estimated to be between 3–5% in previous series.^[67] However, this therapy is very toxic, is often administered in an intensive care unit setting, and has traditionally been limited to young, fit patients who are likely to tolerate treatment. To address this, one group of investigators conducted a study in which they reduced the dose of IL-2 by 20% in a variety of regimens in patients aged >60 years.^[68] Older patients had similar outcomes to younger patients despite the dose

reductions. Limitations of this study, however, included the fact that toxicity differences were not reported and that the combination regimens used are not currently in use in clinical practice.

4. Combating the ‘Treatment Gap’ in Older Adults

Despite the large number of older adults with cancer, older adults with genitourinary malignancies are less likely to be offered treatment for cancer than younger adults.^[69–71] Reasons for this ‘treatment gap’ are multi-factorial but could include poorer perceived or actual treatment tolerance, poorer access to care, fewer data on older adults in clinical trials to guide clinicians in relation to risks and benefits, increased co-morbidities influencing the choice of treatment, and/or patient or physician preference.^[70,72–77] The issues surrounding whether or how to treat older adults with RCC are complicated. It is unclear how much of the treatment gap is due to ‘ageism’ and how much is due to true effects of age that predispose older adults to worse outcomes.

While certain declines in organ function are universal as the human body ages, the rate and consequences of this decline on everyday function proceed at a unique pace in each individual. Therefore, chronological age tells us relatively little about the specific individual. A more detailed evaluation of an older adult patient is needed in order to capture factors other than chronological age that predict for morbidity and mortality. Evaluation of functional status, co-morbid medical conditions, cognitive function, nutritional status, social support, psychological state and a review of medications may help better predict ‘physiological age’. These measures together have been combined into a tool known as the Comprehensive Geriatric Assessment (CGA).

The CGA has been used in the general geriatric population to aid in an evaluation of life expectancy, to identify vulnerable older adults, and to guide interventions to optimize care.^[78–80] It has been postulated that the CGA might be used to guide treatment strategies in older adults with cancer. Various cancer-specific geriatric assessments have been proposed, with one currently

being tested in cooperative groups.^[80-83] In patients with diffuse large B-cell lymphoma, the CGA was able to identify patients who were able to tolerate treatment, and recent data suggest that elements of the CGA might also be helpful in determining treatment tolerance in adults with a variety of solid tumours.^[84-86] Consensus guidelines recommend the routine use of the CGA for older adults with cancer.^[87,88] In medical practice, a CGA can be used both to facilitate decisions regarding management of the older adult with cancer and to make decisions about other aspects of their care (e.g. treating depression). The CGA consists of a number of domains for measurement, including evaluations of functional status, co-morbid conditions, cognitive status, psychological state, social support, nutritional status and a review of medications.^[89] Evaluation of functional status and co-morbidity, in particular, may predict both life expectancy and ability to tolerate treatment among older adults.^[80,90-92]

5. Supportive Care Considerations in Older Adults

A number of recommendations exist for the management of adverse events from cytotoxic chemotherapy in older adults.^[93] Few recommendations, however, exist for supportive care in the elderly specifically for targeted agents used in mRCC. Likely, many of the principles of supportive care for cytotoxic therapy may be applied. In addition, agent-specific toxicities have been identified that could either disproportionately affect older adults or potentially result in increased morbidity in older adults as a result of decreased functional reserve and increased likelihood of co-morbidities.

5.1 Hypertension

In a meta-analysis of studies of bevacizumab, Ranpura et al.^[94] reported a relative risk of 5.28 in the development of grade 3–4 hypertension among patients receiving bevacizumab. Patients receiving VEGF-TKIs for mRCC also have increased development of severe hypertension. In meta-analyses, grade ≥ 3 hypertension has been reported in up to 6.8% of patients taking sunitinib^[95]

and up to 5.4% of patients taking sorafenib, while in the pivotal study of pazopanib, high-grade hypertension was seen in 4% of patients.^[96] No increase in hypertension in older adults was seen with the use of these agents.^[97] Treating hypertension in the older adult is important. Goal systolic/diastolic blood pressure should be lower than 135/85 mmHg,^[98] and preferred agents include ACE inhibitors, although any antihypertensive is likely to be effective (with the possible exception of non-dihydropyridine calcium channel antagonists).^[98]

5.2 Arterial Thromboembolism

A rare but serious adverse effect of the VEGF-directed agents is arterial thromboembolic events (ATEs), usually myocardial infarction or stroke. Although in initial reports of mRCC arterial thromboembolism occurred in only 1% of patients taking bevacizumab, a pooled analysis of bevacizumab use in various malignancies (although not including any studies of mRCC) showed that age ≥ 65 years was associated with increased risk of ATEs.^[99] Older patients taking bevacizumab had a 7.1% risk of thromboembolic events compared with a 3.8% prevalence in the study populations as a whole.^[99] Both sunitinib and sorafenib have also been associated with an increased risk of ATEs, with one meta-analysis showing an overall risk of 1.4% (95% CI 1.2, 1.6) and a relative risk of 3.03 (95% CI 1.25, 7.37; $p=0.015$).^[100] An observational study of 74 patients taking sunitinib or sorafenib revealed a 33.8% risk of cardiac events, defined as increased cardiac enzymes, symptomatic arrhythmia requiring treatment, new left ventricular dysfunction, or acute coronary syndrome.^[101] In the pivotal trial of pazopanib, 3% of patients had an ATE.^[3] Although prophylactic anticoagulation has been found useful for other prothrombotic anti-cancer agents (such as thalidomide), the VEGF-targeting agents have a potentially increased risk of bleeding as well as thrombosis (13% of patients in the pazopanib pivotal study had haemorrhagic complications^[102]), making the utility and safety of anticoagulants somewhat uncertain.^[103] As such, clinical trials are needed to further define the role of anticoagulants

Table III. Summary of available efficacy data (divided by age) for approved targeted agents for metastatic renal cell carcinoma (mRCC)

Study	Treatment	Patient population	Age [y; median (range)] ^a		Efficacy	
			overall	by treatment group	outcome: age group (y)	HR (95% CI)
AVOREN						
Escudier et al. ^[5,62]	Bevacizumab + IFN vs placebo + IFN	Treatment-naïve mRCC [n = 649]	60–61 (18–82)	Bevacizumab + IFN: 61 (30–82) [n = 327] Placebo + IFN: 60 (18–81) [n = 322]	OS: <65 [n = 410] ≥65 [n = 239] PFS ^b : <40 [n = 26] 40–64 [n = 384] ≥65 [n = 239]	0.83 (0.65, 1.05) 1.07 (0.80, 1.45) 0.65 (0.28, 1.52) 0.54 (0.43, 0.68) 0.77 (0.58, 1.03)
TARGET						
Escudier et al. ^[6,106] Eisen et al. ^[57]	Sorafenib vs placebo	Clear-cell mRCC with one previously failed systemic therapy [n = 903]	59 (19–86)	Sorafenib: 58 (19–86) [n = 451] <70: 57 (19–69) [n = 381] ≥70: 72 (70–86) [n = 70] Placebo: 59 (29–84) [n = 452] <70: 58 (29–69) [n = 407] ≥70: 73 (70–84) [n = 45]	PFS: <70 [n = 788] ≥70 [n = 115]	0.55 (0.47, 0.66) 0.43 (0.26, 0.69)
ARCC						
Hudes et al. ^[8] Dutcher et al. ^[64]	Temsirolimus vs IFN vs temsirolimus + IFN	Treatment-naïve, advanced RCC with poor prognosis [n = 626]	59 (23–86) <65 [n = 440] ≥65 [n = 186]	Temsirolimus: 58 (32–81) [n = 209] <65: [n = 145] ≥65: [n = 64] IFN: 60 (23–86) [n = 207] <65: [n = 142] ≥65: [n = 65] IFN + temsirolimus: 59 (32–82) [n = 210] <65: [n = 153] ≥65: [n = 57]	OS (temsirolimus vs IFN): <65 [n = 287] ≥65 [n = 129] PFS (temsirolimus vs IFN): <65 [n = 287] ≥65 [n = 129]	0.62 (0.47, 0.82) ND 0.61 (0.47, 0.79) ND
Sunitinib vs IFN						
Motzer et al. ^[2,59]	Sunitinib vs IFN	Treatment naïve, clear-cell mRCC [n = 750]	59–62 (27–87)	Sunitinib: 62 (27–87) [n = 375] IFN: 59 (34–85) [n = 375]	PFS: <65 [n = 475] ≥65 [n = 275]	ND ND
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Table III. Contd

Study	Treatment	Patient population	Age [y; median (range)] ^a		Efficacy	
			overall	by treatment group	outcome: age group (y)	HR (95% CI)
CALGB 90206						
Rini et al., ^[61] Halabi et al. ^[107]	Bevacizumab + IFN vs IFN	Treatment naive, clear-cell mRCC [n = 732]	61 (55–70)	Bevacizumab + IFN: 61 (56–70) ^c [n = 369] IFN: 62 (55–70) ^c [n = 363]	OS: <65 [n = 363] ≥65 [n = 369]	0.80 (0.64, 1.01) ^d 0.95 (0.75, 1.21) ^d
VEG105192						
Sternberg et al. ^[3]	Pazopanib vs placebo	Treatment-naive and cytokine-pretreated locally advanced and/or clear-cell mRCC [n = 435]	59 (25–85)	Pazopanib: 59 (28–85) [n = 290] Placebo: 60 (25–81) [n = 145]	PFS: <65 [n = 281] ≥65 [n = 154]	0.41 (0.28, 0.61) ^e 0.52 (0.33, 0.82) ^f
RECORD-1						
Motzer et al., ^[7,108] Osanto et al. ^[105]	Everolimus vs placebo	VEGFR-TKI-refractory, clear-cell mRCC [n = 416, final analyses; n = 410, interim analyses]	61 (27–85)	<i>Final analyses:</i> Everolimus: 61 (27–85) [n = 277] ≥65: 69 (65–85) [n = 112] ≥70: 74 (70–85) [n = 53] Placebo: 60 (29–79) [n = 139] ≥65: 69 (65–79) [n = 41] ≥70: 73 (70–79) [n = 20] <i>Interim analyses:</i> Everolimus: 61 (27–85) [n = 272] Placebo: 60 (29–79) [n = 138]	<i>Final analyses:</i> PFS [n = 416]: <65 [n = 263] ≥65 [n = 153] <i>Interim analyses:</i> PFS [n = 410]: <65 [n = 259] ≥65 [n = 151]	0.33 (0.21, 0.51) ^g 0.19 (0.09, 0.37) ^g 0.32 ^{e,h} 0.29 ^{e,h}

a Except where otherwise stated.

b No significant interaction between age and PFS benefit.

c Interquartile range.

d p=not statistically significant.

e p<0.0001.

f p=0.0005.

g p<0.001.

h Confidence interval not available.

HR=hazard ratio; IFN=interferon; ND=no data; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor.

in this setting. As older adults appear specifically susceptible to these events, much care should be taken to screen for coexisting risk factors, treat them when possible, and to consider use of an mTOR inhibitor if the patient is at high risk for development of such an event, since inhibitors of mTOR have not been associated with increased risk of ATEs.^[104]

5.3 Gastrointestinal Toxicity

Diarrhoea, mucositis, nausea, vomiting and weight loss are adverse effects seen in various frequencies in all agents currently used for mRCC. Diarrhoea was the most common adverse effect seen for both sunitinib (61%) and sorafenib (43%), while sunitinib (30%) and everolimus (40%) both had high rates of stomatitis.^[6,7,59,105] Stomatitis was reported more often in older adults than in younger adults with everolimus. Nausea and vomiting were seen with the use of all agents.^[97] It is also known that older adults are less likely to tolerate vomiting, diarrhoea, or decreased fluid intake than younger adults as a result of decreased fluid reserve and increased sensitivity to electrolyte imbalances.^[93] Because of this, it would not be unreasonable to extend similar prophylactic and treatment considerations for gastrointestinal toxicity to older adults receiving treatment for mRCC as are currently extended to older adults receiving cytotoxic chemotherapy. All treating personnel and caregivers should be aware of the risks of developing these complications and learn to recognize when urgent treatment is indicated. Diarrhoea, dehydration and mucositis should be treated proactively and liberally in older adults.^[93]

5.4 Myelosuppression

Both VEGF-directed therapies and mTOR inhibitors have been associated with suppression of haematopoiesis.^[97] Both sunitinib and pazopanib have been associated with high rates of neutropenia, leukopenia and thrombocytopenia, although these adverse-effects are usually of low grade. However, up to 11% of patients treated with sunitinib in the pivotal trial developed grade 3 neutropenia.^[2] As myelosuppression is often unanticipated with the use of targeted agents, a

high index of suspicion is necessary. Support with granulocyte colony-stimulating factor has not been studied extensively. However, it should be noted that the incidence of febrile neutropenia was low across the pivotal trials of targeted agents for mRCC.

6. Conclusions

To date, subset analyses of pivotal trials in mRCC suggest no marked differences in the efficacy of targeted therapies in older adults compared with younger adults (table III). However, it is challenging to derive generalizable interpretations from these largely unplanned subset analyses. Age-specific studies would better contribute to understanding specific considerations that should be taken into account when administering targeted therapies in older adults. Studies that have assessed therapy for older adults with lung cancer have largely shown that appropriately selected older adults can benefit from similar treatments as younger adults with acceptable levels of toxicity.^[109] An important caveat, however, is that a provider must be mindful of the need to appropriately assess the older adult with mRCC to identify predictors of poor outcomes and tolerance. The CGA can aid the provider in identifying vulnerable older adults and pinpointing factors that might require intervention prior to initiating therapy.^[89] Finally, aggressive supportive care measures specific to older adults should be undertaken when giving therapy, focusing on the specific adverse effects that commonly occur with the discussed targeted agents.

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