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Anti-Tumour Treatment

Balancing treatment efficacy, toxicity and complication risk in elderly patients with metastatic renal cell carcinoma

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ABSTRACT

The number of elderly patients with renal cell carcinoma is rising. Elderly patients differ from their younger counterparts in, among others, higher incidence of comorbidity and reduced organ function. Age influences outcome of surgery, and therefore has to be taken into account in elderly patients eligible for cytoreductive nephrectomy. Over the last decade several novel effective drugs have become available for the metastatic setting targeting angiogenesis and mammalian target of rapamycin. Immune checkpoint blockade with a programmed death 1 antibody has recently been shown to increase survival and further studies with immune checkpoint inhibitors are ongoing. In this review we summarize the available data on efficacy and toxicity of existing and emerging therapies for metastatic renal cell carcinoma in the elderly. Where possible, we provide evidence-based recommendations for treatment choices in elderly.
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Introduction

Approximately one half of the patients who are diagnosed with renal cell carcinoma (RCC) are aged 65 years or more and almost a quarter is over 75 years of age. Given the global increase of life expectancy, the number of elderly patients with RCC will increase significantly in the near future [1]. In 2012 it was estimated that 338,000 patients were newly diagnosed with kidney cancer worldwide, which equals 2.4% of all cancers and an age-specific rate of 4.4 per 100,000 population [2]. In general, elderly is defined as individuals over 65 years of age. But it may be more meaningful to further divide elderly into three age groups namely younger-old (65–74 years), mid-old (75–84), and old–old (⩾85 years) [3]. Moreover, chronological age alone is not very informative for clinical decision-making. Since the '90 s, an increase in use of terms like 'frailty' or 'biological age' indicates that clinicians prefer to classify patients rather according to functional characteristics than to age alone [4]. Frailty is a state of vulnerability to poor resolution of homeostasis following a stressor event, such as nephrectomy or systemic anti-cancer treatment [5]. Frailty in older patients with any stage of solid or hematological malignancy ranges from 6% to 86% [6]. Frail patients and patients with pre-frailty have an increased risk of all-cause mortality, postoperative complications and mortality and chemotherapy intolerance. Across trials, a remarkable range of cut-off points and several different approaches to identify frailty have been used [6]. However, geriatric assessments have seldom been incorporated in phase III cancer trials. This may be due to lack of validation of these instruments. Currently there is neither solid evidence designating the best type of geriatric assessment tool nor whether outcome is improved by applying these instruments in older cancer patients. Nonetheless, the National Comprehensive Cancer Network (NCCN) guideline for elderly recommends using a comprehensive geriatric assessment (CGA) [7]. Additional studies are warranted for validation of such tools [8]. There are important differences between elderly and younger individuals that can potentially affect tolerance of treatment. Firstly, a decline in normal organ function can result in different drug metabolism and clearance. Kidney function for example starts declining at the age of 40. This limited reserve capacity is a factor to take into account when considering a tumor nephrectomy. A reduced pulmonary or cardiac function in turn, may complicate surgical

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treatment. Secondly, aging comes with physiologic changes such as a relative increase of body fat, reduced water content and reduced muscle mass, which influences drug distribution. Furthermore, elderly patients are likely to be prescribed multiple drugs for co-morbid conditions, resulting in potential interactions with renal cancer treatment. Finally, elderly patients who look back on a fulfilled life might have a different perception and acceptation of cancer diagnosis and appreciation of cancer treatment side effects compared to younger individuals, which might result in different decision-making [9].

Traditionally, systemic treatment for metastatic renal cell carcinoma (mRCC) consisted of cytokine therapy. The value of cytoreductive nephrectomy is well established in this setting. Over the last decade, therapies targeting the vascular endothelial growth factor A (VEGF-A) pathway and mammalian target of rapamycin (mTOR) have been the mainstay of treatment. Recently the programmed death 1 (PD-1) antibody nivolumab was shown to increase overall survival after VEGF-A targeting therapy compared to the mTOR inhibitor everolimus. Several studies testing immune checkpoint inhibitors alone or in combination in mRCC are ongoing. It is unknown whether age-related changes of the immune system like immune exhaustion affect the efficacy of immunotherapy in elderly patients.

Specific information on how to treat elderly patients with mRCC is scarce. This is the consequence of a disproportionate small share of elderly patients in clinical trials [10]. The percentage of elderly enrolled in cancer drug registration trials between 1992 and 2002 was 36, 20, and 9 for patients aged over 65, 70, and 75 years, whereas the corresponding estimated percentages of cancer patients in the US were 60, 46, and 31 respectively [11]. Despite acknowledging this underrepresentation and recommendations to increase enrollment of elderly patients in clinical trials, similar percentages were accrued in more recent registration trials between 2007 and 2010 [12]. An important reason for underrepresentation of elderly patients in clinical trials is that exclusion criteria often comprise co-morbidity, reduced performance status, use of certain medications and impaired functional organ capacity, resulting in ineligibility of many elderly patients. Furthermore, physicians' perception that older patients are at higher risk for toxicity and are less likely to benefit from treatment has contributed to the low accrual rate for older patients [13]. Physician surveys revealed that co-morbid conditions and fear for toxic effects of treatment are the most frequently cited barriers to recruitment of older patients [14,15]. Consequently, the elderly patients who do participate in clinical trials do not represent the general elderly patient population and trial results cannot be generalized to daily practice without caution. The aim of this review is to summarize the available data for efficacy, complication risk and toxicity of surgical and approved systemic treatment for elderly mRCC patients. In this era with multiple treatment options available, tools to guide treatment decisions are extremely useful. Simultaneously, different rating scales for systemic treatments have been developed by NCCN, European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) [16–18]. In this article, we present modified NCCN evidence blocks as an example to visualize the available data in elderly and to support treatment choices for this subgroup. In addition, we describe the influence of aging on the immune system and discuss the potential implications for treatment of elderly patients with novel immune-modulating agents.

Search strategy

Data for this review consists of reports of phase III clinical trials and expanded access programs of approved drugs for mRCC.

In addition, we performed a search in PubMed and used references from relevant articles using the search terms "kidney cancer/renal (cell) carcinoma", "elderly", "age/aging", "PD-1", "PD-L1", "CTLA-4" and "immune checkpoint". Only articles published in English between 1990 and November 2015 were considered. Applicable abstracts presented in 2014 and 2015 at ASCO annual, ASCO GU and ESMO meetings concerning CTLA-4, PD-1 and PD-L1 inhibitors in RCC patients were added. The NCCN guidelines "kidney cancer" (version 2.2016) and "Older Adult Oncology" (version 1.2016) and the European Association of Urology (EAU) and ESMO guidelines on renal cell carcinoma of respectively 2015 and 2014 were used.

Prognosis of elderly mRCC patients

Large studies from the US, Japan and Europe together comprising almost 13,000 patients show that age is an independent prognostic factor of survival in patients with RCC [19–21]. However, for mRCC this is only the case for low-grade tumors. The effect of age becomes secondary to disease characteristics in patients with stage II–IV or high-grade tumors [22].

The immune system plays a critical role in disease control and activity and has traditionally been the target for systemic RCC treatment [23]. With aging, immune senescence and immune exhaustion may occur [24]. However, there is little evidence of a causal relation between age-associated changes of the immune system and development and progression of cancer [25,26].

Cytoreductive nephrectomy

mRCC patients with a potentially resectable primary tumor, no brain metastases and an excellent performance status, could be candidates for cytoreductive nephrectomy before commencing systemic therapy according to the NCCN guidelines [27]. This is based on two randomized trials in the pre-targeted therapy era, where patients with mRCC treated with cytoreductive nephrectomy followed by interferon-α2b had a median overall survival (OS) benefit of 7 months compared to patients treated with interferon-α2b alone [28,29]. It is still unclear whether cytoreductive nephrectomy results in a survival benefit when followed by targeted therapy compared to targeted therapy alone. According to the EAU, cytoreductive nephrectomy is recommended in appropriately selected patients with mRCC [30], based on a meta-analysis of two randomized studies [31]. In the ESMO guidelines, similar recommendations are made [32]. In routine practice, cytoreductive nephrectomy is recommended in patients with good performance status and large primary tumors with limited volumes of metastatic disease and for patients with a symptomatic primary tumor.

A population based retrospective analysis of 328 Dutch mRCC patients demonstrated that elderly patients were less likely to undergo a cytoreductive nephrectomy (OR 0.95 per year increase) [33]. An alarmingly high peri-operative mortality rate (PMR), defined as death occurring within the first 30 days after cytoreductive nephrectomy or during the initial hospital stay, of 21% for patients 75 years of age or older ($n = 24$) has been reported for cytoreductive nephrectomy compared to 1.1% for younger patients ($n = 380$) [34]. However, a population-based analysis of patients treated with a cytoreductive nephrectomy between 1988 and 2004 ($n = 24.535$) demonstrated a 30-day PMR of 4.7% in patients aged 70–79 years [35]. The highest PMR was recorded for patients aged over 80 (8.2%). A retrospective analysis compared 504 mRCC patients 75 years or older with 2796 younger counterparts and showed a PMR of 4.8 versus 1.9% [36]. There was a higher rate of postoperative complications, blood transfusions and prolonged hospitalization in the elderly patient group. Another study in 180 patients over 80 years of age (range 80–92), undergoing partial

($n = 22$) or complete ($n = 158$) nephrectomy for suspected (m)RCC [37], showed that 38.8% of the patients experienced one or more complications, and six patients (3.3%) died as a consequence of post-operative complications. Median hospitalization was 13 days (range 4–60). An ECOG performance status of 2–4 and a glomerular filtration rate less than 30 mL/min were independent risk factors for post-operative morbidity. *Recommendations*: Taking into account the lack of evidence of benefit of cytoreductive nephrectomy when followed by targeted therapy, and the higher mortality and morbidity in elderly patients, cytoreductive nephrectomy is not advised for this group. Only in fit elderly mRCC patients with a symptomatic primary tumor, limited metastatic burden and a reasonable life expectancy, nephrectomy could be considered.

Angiogenesis inhibitors

Angiogenesis is a prominent feature of RCC caused by mutation or silencing of the Von Hippel-Lindau gene which is an early event in the majority of RCC tumors. Lack of functional Von Hippel–Lindau protein results in hypoxia inducible factor 1α (HIF-1α) accumulation. HIF-1α regulates angiogenesis, tumor growth, cell proliferation and metastatic spread, and glucose metabolism by acting as a transcription factor for critical downstream effectors including VEGF-A, platelet-derived growth factor (PDGF), epidermal growth factor receptor and insulin-like growth factor [38]. Inhibition of angiogenesis has become the mainstay of treatment in patients with mRCC with clear cell histology. Bevacizumab is a monoclonal antibody targeting VEGF-A and several tyrosine kinase inhibitors (TKIs) inhibit the VEGF pathway at the VEGF receptor (VEGFR) level.

Bevacizumab

By binding VEGF-A, bevacizumab prevents VEGF-A from activating VEGFR on endothelial cells. In a phase III study mRCC patients were randomized to receive bevacizumab (10 mg/kg intravenously every 2 weeks plus 9 million international units (MIU) interferon-α2a subcutaneously three times weekly, $n = 327$) or interferon-α2a plus placebo ($n = 322$) [39]. The bevacizumab combination overall significantly increased the PFS, with a hazard ratio (HR) of 0.77 (95% confidence interval (CI) 0.58–1.03) in the subgroup of patients ⩾65 years ($n = 239$). For patients <40 ($n = 26$) and 40–64 ($n = 384$) years of age, HR were 0.65 (0.28–1.52) and 0.54 (0.43–0.68) respectively (see Tables 1 and 2). No information on toxicity related to age was reported.

In another phase III trial, in which previously untreated mRCC patients were randomly assigned to receive either bevacizumab (10 mg/kg intravenously every 2 weeks) plus interferon-α2b (9 MIU subcutaneously three times weekly) or single agent interferon-α2b, no subgroup analyses for PFS and toxicity stratified for age were provided [40,41]. Separately, efficacy and safety data for patients ⩾65 years of the AVOREN trial [40] were reported. Efficacy was equal for patients <65 ($n = 410$) and ⩾65 ($n = 239$) years of age. The incidence of adverse events was similar, however, the incidence of grade ⩾3 adverse events was higher in de elderly. They also experienced more fatigue and asthenia [42].

Sunitinib

Sunitinib is an orally administered multiple TKI of VEGFR, PDGF receptors (PDGFR) and other receptor tyrosine kinases. A landmark study in treatment-naive mRCC patients demonstrated a PFS benefit of 6 months over interferon-α2a (11 versus 5 months) with a HR of 0.42 that was similar for patients <65 years ($n = 475$) and patients ⩾65 years ($n = 275$) [43]. In an expanded access trial, 4371 patients received open-label sunitinib [44]. Thirty-two percent of the patients were 65 years or older. Response rate, median PFS and median OS in this elderly subgroup were comparable to the outcome of the entire study population. Also frequencies of the most common grade 3–4 treatment-related adverse events were similar (see Table 3).

Data from six trials were pooled to compare efficacy and toxicity of sunitinib in mRCC patients over 70 years of age with that of younger patients [45]. PFS and OS were comparable between the groups. Older patients experienced more fatigue, cough, peripheral edema, anemia, decreased appetite, weight decrease, dizziness, hypothyroidism, dehydration, urinary tract infection and thrombocytopenia. Older patients also had more grade 3 toxicity (68% versus 53%). On the other hand, patients younger than 70 years experienced more often hand-foot syndrome, chest pain and hair color changes. No difference in grade 4 toxicity or treatment related deaths was observed. Retrospectively, 68 patients ⩾70 years of age who were treated with sunitinib were analyzed for frailty and sunitinib efficacy and toxicity [46]. Although sunitinib was effective, early interruptions occurred frequently. The rates of adverse events in this study were higher than the rates found in the above mentioned expanded access trial [44] and pooled data analysis [45]. No correlation was found between frailty at CGA and toxicity or treatment response.

Sorafenib

Sorafenib is another TKI of VEGFR but also inhibits Raf kinases. A PFS advantage for sorafenib over placebo was demonstrated in mRCC patients who had progressive disease after one line of systemic treatment (in 81% consisting of prior cytokine treatment) [47]. A retrospective subgroup analysis on safety and efficacy in patients ⩾70 years ($n = 115$) compared to patients <70 years of age ($n = 787$) has been published [48]. Median PFS was not affected by age. The proportions of patients with a response or stable disease after 6 weeks of sorafenib were also similar for the two age groups (83.5% and 84.3%, respectively) and superior to those who received placebo (53.8% and 62.2%, respectively). More grade 3–4 adverse events occurred in elderly patients (45.7% versus 36.7%). VEGFR-TKIs are known to be associated with cardiac toxicity in up to 33.8% of the patients [49]. Fatal cardiac ischemia occurred in 2 out of 115 older sorafenib treated patients in addition to one patient with grade 3 left ventricular systolic dysfunction and one patient with grade 4 cardiac ischemia. In 10 out of 787 younger patients cardiac ischemia or infarction was observed, and three patients developed left ventricular dysfunction. None of the placebo-treated patients had cardiac adverse events. Treatment was permanently discontinued in 8.1% of younger and 21.4% older sorafenib-treated patients for toxicity. Most common reasons for the older patients to discontinue sorafenib were gastrointestinal (5.7%) and dermatological (4.3%) side effects. Additionally, dose reductions were required in 11.3% of the younger and 21.4% of the older sorafenib-treated patients. The time to self-reported health status deterioration was delayed by sorafenib among both older patients (121 days versus 85 days with placebo) and younger patients (90 days versus 52 days with placebo).

In an expanded access study in Europe, 1159 patients received sorafenib for mRCC in what the authors reported to be a 'real-world setting' [50] and subgroup analyses for 883 patients <70 years and 265 patients ⩾70 years were performed. Although there was a trend for longer PFS in older compared to younger patients (8.0 versus 6.4 months), disease control rates at 8 and 12 weeks were similar. Sorafenib treatment was generally well tolerated without major differences between both age groups, apart from fatigue, which was more common in the elderly patients (44% versus 31%).

Table 1
Progression free survival of approved systemic treatments for mRCC in elderly and non-elderly patients.

Trial	Treatment	Age of study population	Progression Free Survival			
			Overall study		Non-elderly	Elderly
Bevacizumab + IFN vs placebo + IFN [39] phase III, 1st line	Bevacizumab plus IFN (n = 327) Placebo plus IFN (n = 322)	Median 61 years (range 30–82) Median 60 years (range 18–81)	10.2 mo 5.4 mo	HR 0.63 (95% CI 0.52–0.75)	<40 years HR 0.65 (95% CI 0.28–1.52) 40–64 years HR 0.54 (95% CI 0.43–0.68)	⩾65 years HR 0.77 (95% CI 0.58–1.03)
Bevacizumab + IFN vs IFN [40] phase III, 1st line	Bevacizumab plus IFN (n = 369) IFN (n = 363)	NR	8.5 mo (95% CI 7.5–9.7) 5.2 mo (95% CI 3.1–5.6)	HR 0.72 (95% CI 0.61–0.83)	NR	NR
Sunitinib vs IFN [43] phase III, 1st line	Sunitinib (n = 375) IFN (n = 360)	Median 62 years (range 27–87) Median 59 years (range 34–85)	HR 0.42 (95% CI 0.33–0.52)		"Equal to elderly"	"Equal to non-elderly"
Sunitinib [44] expanded access, ⩾1st line	Sunitinib (n = 4371)	⩾65 years: 32%	10.9 mo (95% CI 10.3–11.2)		NR	⩾65 years 11.3 mo (95% CI 10.7–12.3)
Sunitinib [45] pooled data, ⩾1st line	First line (n = 783)	Overall ⩾ 70 years: 19%	NR		<70 years 9.9 mo (95% CI 8.3–10.7)	⩾70 years 11.0 mo (95% CI 9.0–14.8)
	Cytokine-refractory n = 276)				<70 years 8.1 mo (95% CI 7.8–8.7)	⩾70 years 8.4 mo (95% CI 6.3–14.3)
Sunitinib [46] review, ⩾1st line	Sunitinib (n = 68)	Median 74 years range 70–88)	NR		NR	13.6 months
Sorafenib vs placebo [46] and subset analysis [48] 2nd line	Sorafenib (n = 451) Placebo (n = 452)	Median 59 years, ⩾ 70 years: 12.7%, of which 60.8% was assigned to sorafenib	HR 0.44 (95% CI 0.35–0.55)		<70 years HR 0.55 (95% CI 0.47–0.66)	⩾70 years HR 0.43 (95% CI 0.26–0.69)
Sorafenib [50] expanded access, ⩾2nd line	Sorafenib (n = 1150)	Median 62 (range 18–84), ⩾70: 23%	6.6 mo		<70 years 6.4 mo	⩾70 years 8.0 mo
Sorafenib [51] expanded access, ⩾1st line	Sorafenib (n = 2504)	Median 63 (range 13–93) ⩾ 0 years: 29.4%	NR		<70 years 35 weeks (95% CI: 33–46 weeks)	⩾70 years 42 weeks (95% CI: 36–48 weeks)
Pazopanib [53] hase III, 1st line or post-cytokines	Pazopanib (n = 290) Placebo (n = 145)	Median 59 years (range 28–85) Median 60 years (range 25–81)	HR 0.46 (95% CI 0.34–0.62)		NR	NR
Pazopanib vs sunitinib [54] phase III, 1st line	Pazopanib (n = 557) Sunitinib (n = 553)	Median 61 years (range 18–88) Median 62 years (range 23–86)	8.4 mo (95% CI 8.3–10.9) 9.5 mo (95% CI 8.3–11.1)		HR ∼ 1.0	HR favors sunitinib, but CI crosses 1.0
Axitinib vs sorafenib [55] phase III, 1st line	Axitinib (n = 192)	Median 58 years (range 23–83)	10.1 mo (95% CI 7.2–12.1)	HR 0.77 (95% CI 0.56–1.05)	<65 years HR 0.80 (95% CI 0.60–1.24	⩾ 65 years HR 0.68 (95% CI 0.33– .39)
	Sorafenib (n = 96)	Median 58 years (range 20–77)	6.5 mo (95% CI 4.7–8.3)			
Axitinib vs sorafenib [56] phase III, post sunitinib, bevIFN, temsirolimus or cytokines	Axitinib (n = 361) Sorafenib (n = 362)	Median 61 years (range 20–82) Median 61 years (range 22–80)	HR 0.67 (95% CI 0.54–0.81)		<65 years HR 0.68 (95% CI 0.53–0.86)	⩾ 65 years HR 0.68 (95% CI 0.33– .39)
Everolimus vs placebo [58] phase III, post TKI	Everolimus (n = 272) Placebo (n = 138)	Median 61 years (range 27–85) Median 60 years (range 29–79)	HR 0.30 (95% CI 0.22–0.40)		<65 years HR 0.32	⩾65 years HR 0.29
Everolimus vs placebo [59] subgroup analysis of [59]	Everolimus (n = 277)	⩾65 years: 36.8% / ⩾70 years: 17.5%	4.9 mo	HR 0.33 (95% CI 0.25–0.43)	NR	⩾65 years 5.5 mo/ ⩾70 years 5.1 mo — ⩾65 years HR 0.33 (95% CI 0.21–0.51) / ⩾ 70 years HR 0.19 (95% CI 0.09–0.37)
	Placebo (n = 139)		1.9 mo			⩾65 years 2.2 mo/ ⩾70 years 1.9 mo
Temsirolimus + bevacizumab vs IFN + bevacizumab [63] phase III, 1st line	Temsirolimus plus bevacizumab (n = 400)	Median 59 years (range 22–87)	9.1 mo (95% CI 8.1–10.2)		<65 years 9.2 mo (95% CI 8.1–10.5)	⩾65 years 8.5 mo (95% CI 7.2–12.8)
	IFN plus bevacizumab (n = 391)	Median 58 years (range 23–81)	9.3 mo (95% CI 9.0–11.2)		<65 years 9.1 mo (95% CI 7.4–10.9)	⩾65 years 11.6 mo (95% CI 7.5–16.4)

Abbreviations: NR = not reported, HR = hazard ratio, CI = confidence interval, vs = versus mo = months, IFN = interferon, TKI = tyrosine kinase inhibitor.

Table 2
Overall survival of approved systemic treatments for mRCC in elderly and non-elderly patients.

Trial	Treatment	Age of study population	Overall Survival					
			Overall study		Non-elderly		Elderly	
Bevacizumab + IFN vs IFN [40] phase III, 1st line	Bevacizumab plus IFN (n = 369)	NR	18.3 mo (95% CI 16.5–22.5)	HR 0.86 (95% CI 0.73–1.01)	<44.8 years 18.1 mo (95% CI 14.1–21.7)	HR 0.803 (95% CI 0.639–1.009)	>44.8 years 20.8 mo (95% CI 16.4–27.1)	HR 0.951 (95% CI 0.750–1.207)
	IFN (n = 363)		17.4 mo (95% CI 14.4–20.0)		<44.8 years 16.2 mo (95% CI 13.4–20.0)		>44.8 years 18.8 mo (95% CI 13.8–27.0)	
Sunitinib [44] expanded access, ⩾1st line	Sunitinib (n = 4371)	⩾65 years: 32%	18.4 mo (95% CI 17.4–19.2)		NR		⩾65 years 18.2 mo (95% CI 16.6–19.8)	
Sunitinib [45] pooled data, ⩾1st line	First line (n = 783) Cytokine-refractory (n = 276)	Overall ⩾70 years: 19%	NR		<70 years 23.6 mo (95% CI 21.2–27.6) <70 years 20.2 mo (95% CI 16.2–25.1)		⩾70 years 25.6 mo (95% CI 21.7–38.4) ⩾70 years 15.8 mo (95% CI 13.7 – 24.0)	
Sunitinib [46] review, ⩾1st line	First line ⩾second line	Median 74 years (range 70–88)	NA		NA		17.8 months 18.3 months	
Sorafenib vs placebo [47] ⩾2nd line	Sorafenib (n = 451) Placebo (n = 452)	Median 59 years, ⩾65 years: 29.9%	HR 0.77 (95% CI 0.63–0.95)		NR		NR	
Sorafenib [51] expanded access, ⩾1st line	Sorafenib (n = 2504)	Median 63 (range 13–93) ⩾70 years: 29.4%	NR		50 weeks (95% CI: 47–53 weeks)		46 weeks (95% CI: 42–53 weeks)	
Temsirolimus vs temsirolimus + IFN vs IFN [61] phase III, 1st line	Temsirolimus (n = 209)	Median 58 years (range 32–81)	10.9 mo (95% CI 8.6–12.7)		NR		HR > 1.0 for temsirolimus compared to IFN in elderly ⩾65 years	
	Temsirolimus + IFN (n = 210)	Median 59 years (range 32–82)	8.4 o (95% CI 6.6–10.3)					
	IFN (n = 207)	Median 60 years (range 23–86)	7.3 mo (95% CI 6.1–8.8)					
Nivolumab vs everolimus [69] phase III, post 1 or 2 regimens anti-angiogenesis	Nivolumab (n = 410)	Median 62 years (range 23–88)	25 mo (95% CI 21.8–not estimable)	HR 0.73 (98.5% CI 0.57–0.93)	<65 years HR 0.78 (0.60–1.01)		⩾65 to <75 years HR 0.64 (0.45–0.91)	
	Everolimus (n = 411)	Median 62 years (range 18–86)	19.6 mo (95% CI 17.6–23.1)				⩾75 years HR 1.23 (0.66–2.31)	

Abbreviations: NR = not reported, NA = not available, HR = hazard ratio, CI = confidence interval, vs = versus mo = months, IFN = interferon, TKI = tyrosine kinase inhibitor.

Of the 2504 patients enrolled in the North American expanded access trial, 736 (29%) were aged over 70 years [51]. Treatment efficacy in terms of PFS and OS was similar between the age groups. Dose reduction, treatment interruption and treatment discontinuation rate was comparable in patients ⩾70 and <70 years and the rates of the most common adverse events of ⩾grade 3 were similar, including cardiovascular events, fatigue and fatal toxicity.

Efficacy of first-line systemic treatment with sunitinib, sorafenib and bevacizumab in elderly patients with mRCC was evaluated within a database consortium. No difference was found between younger and older age groups [52].

Pazopanib

Pazopanib is a second generation TKI inhibiting VEGFR and PDGFR. In a phase III trial comparing pazopanib with placebo in treatment-naive and cytokine pre-treated mRCC patients, both elderly (n = 154 patients ⩾65 years) and younger patients (n = 281 patients <65 years) had prolonged PFS on pazopanib compared to placebo, with a HR of 0.46 for the whole population (95% CI 0.34–0.62). No difference in toxicity profile between the age groups was reported [53].

Pazopanib has been compared with sunitinib as first-line therapy in a randomized trial of 1110 mRCC patients and proven non-inferior regarding PFS [54]. Subgroup analysis revealed no difference for patients of 65 years and older (n = 434, 39%) compared to younger patients. The toxicity profile, and health related quality of life was in favor of pazopanib, however with a continuous dosing schedule for pazopanib and a 4 week on, 2 week off schedule for sunitinib, these data are difficult to interpret. No separate information on toxicity and quality of life for elderly was reported.

Axitinib

Axitinib is a second generation TKI that selectively blocks VEGFR-1, -2 and -3 with a high potency. A phase III trial randomized treatment-naive mRCC patients between axitinib (n = 192) and sorafenib (n = 92) [55]. The median age in this trial was 58 (range 20–83), and for both the 219 patients <65 years of age and the 69 patients ⩾65, PFS did not differ between the treatment arms.

Another phase III trial compared axitinib with sorafenib as second-line therapy in mRCC [56]. The median PFS was 6.7 months for axitinib versus 4.7 months for sorafenib. The HR for PFS was similar for patients ⩾65 years of age and younger patients. No information was provided about toxicity stratified for age.

Recommendations: All angiogenesis inhibitors appear to have similar efficacy in elderly and younger patients. Available data are summarized in Fig 1. Bevacizumab combined with interferon, sunitinib and sorafenib have slightly worse toxicity profiles in elderly. For pazopanib and axitinib toxicity data in elderly are not available. Therefore, angiogenesis inhibitors can be used in elderly, but patients should be followed closely for evaluation of side effects. Most evidence in elderly is available for sunitinib as first-line regimen and sorafenib as second-line regimen.

Table 3
Adverse events of approved systemic treatments for mRCC in elderly patients.

Trial	Results
Bevacizumab + IFN vs placebo + IFN [39] phase III, 1st line	NR
Bevacizumab + IFN vs IFN [40] phase III, 1st line	NR
Bevacizumab + IFN vs IFN [41] phase III, 1st line	NR
Bevacizumab + IFN [42] subgroup analysis of [40]	AE incidence equal to younger adults, but incidence of grade ⩾3 AEs was higher. Also more fatigue and asthenia
Sunitinib vs IFN [43] phase III, 1st line	NR
Sunitinib [44] expanded access	Incidences of most commonly reported grade 3–4 related AEs did not differ in elderly patients compared to the total population
Sunitinib [45] pooled data, ⩾1st line	Overall, the incidence profile of common AEs was broadly similar. However, older patients are more likely to have a highest severity AE of grade 3, while for younger patients a greater proportion had highest severity of grade 1 or 2. There was no difference in the occurrence of highest grade 4 or 5. Significantly more frequent related AEs: fatigue, cough, peripheral edema, anemia, decreased weight, decreased appetite, thrombocytopenia, dizziness, hypothyroidism, dehydration, UTI. Less hand-foot syndrome (24% vs 32%)
Sunitinib [46] Compared to [44,45]	Fatigue/asthenia and mucositis occur more often in elderly compared to the whole group, resp. 80.9% vs 37% and mucositis 61.8% vs 28%. Twice as much dose reductions occurred (>2/3). Cardiac events ~13%, compared to estimated ~3%
Sorafenib vs placebo [47,48] ⩾ 2nd line	Grade 3 toxicity in 40.0% vs 29.4% in younger adults. More fatigue and gastrointestinal symptoms, but less hypertension, sensory neuropathy and pruritis in patients that received sorafenib. 21.4% permanently discontinued treatment vs 8.1%, dose reductions occurred in 21.4% vs 11.3%
Sorafenib [50] expanded access, ⩾2nd line	Incidence and severity comparable with overall population. 16% drug-related SAEs vs 14% in younger patients. Compared to younger patients, more fatigue
Sorafenib [51] expanded access, ⩾1st line	Compared to younger patients, elderly patients more often discontinued treatment due to AE with also slightly more dose reductions. Most common grade ⩾3 AEs were similar, however, drug-related cardiovascular events grade ⩾3 occurred more often in elderly. More grade ⩾3 fatigue. SAEs and proportion of deaths were equal
Pazopanib [53] phase III, 1st line or post-cytokines	NR
Pazopanib vs sunitinib [54] phase III, 1st line	NR
Axitinib vs sorafenib [55] phase III, 1st line	NR
Axitinib vs sorafenib [56] phase III, post sunitinib, bevIFN, temsirolimus or cytokines	NR
Everolimus vs placebo [58,59] phase III, post TKI + subgroup analysis	Similar, with generally consistent grade 3/4 rates between the whole population and elderly. Most common grade 3/4 in elderly: anemia, infection, lymphopenia, hyperglycemia. Higher rates peripheral edema, cough, rash, diarrhea. Age did not affect SAE incidence. Patients ⩾70 more often dose reductions and/or interruptions, resulting in lower mean dose intensity
Temsirolimus [61] phase III, 1st line	NR
Temsirolimus [63] phase III, 1st line	NR
Nivolumab vs everolimus [69] phase III, post 1 or 2 regimens anti-angiogenesis	NR

Abbreviations: AEs = adverse events, SAEs = serious adverse events, UTI = urinary tract infection.

mTOR inhibitors

Another important oncogenic pathway that is frequently upregulated in RCC is the mTOR pathway [57]. mTOR is involved in cell proliferation, cell growth and survival and angiogenesis.

Everolimus

Everolimus is an orally administered inhibitor of mTOR. A phase III trial comparing everolimus with placebo, showed a prolongation of PFS from 1.9 to 4.9 months in mRCC patients [58]. There was however no difference in the time to definitive deterioration of patient reported outcomes or OS. The efficacy and safety of everolimus in elderly patients who participated in the trial was analyzed separately [59]. Analyses were performed both for patients aged ⩾65 years and for patients ⩾70 years of age. Patients ⩾65 years of age had a median PFS of 5.4 months in the everolimus arm ($n = 111$) and 2.2 months in the placebo arm, for patients ⩾70 years of age this was 5.1 ($n = 52$) versus 1.9 months. In all everolimus-treated patients ($n = 274$), only 1.8% had a partial tumor response and no responses were observed in the placebo group. Overall response rates were 2.7% for patients ⩾65 and 3.8% for those ⩾70 years of age.

Consistent with the complete study population, no difference in median OS was observed in everolimus-treated patients compared with those receiving placebo in patients aged ⩾65 and ⩾70 years.

Everolimus was well tolerated by elderly, with low rates of grade 3–4 adverse events. However, more dose-interruptions were needed in the elderly patients; in 55.8% of patients ⩾70 years and in 49.5% of patients ⩾65 years of age one or more dose-interruptions were needed whereas 46.4% of all patients had treatment interruptions. Some adverse events were more frequent in elderly patients, irrespective of treatment, including peripheral edema, cough, rash, and diarrhea. Importantly, no increase in everolimus-related pneumonitis was observed compared with younger patients.

Between July 2008 and June 2010 1367 mRCC patients with intolerance to or progressive disease on VEGFR-TKI therapy were enrolled in an expanded access program with everolimus. The study reported that patients ⩾65 years of age were less likely to be on treatment for more than 6 months compared to younger patients [60].

Temsirolimus

Temsirolimus is an intravenously administered mTOR inhibitor. In a 3-arm study in patients with poor-prognosis mRCC, temsirolimus (25 mg weekly intravenously), was compared with interferon-α2a (3 MIU increasing to a target dose of 18 MIU 3 times weekly subcutaneously) and the combination (temsirolimus 15 mg weekly plus interferon-α2a 6 MIU 3 times weekly) [61]. Single

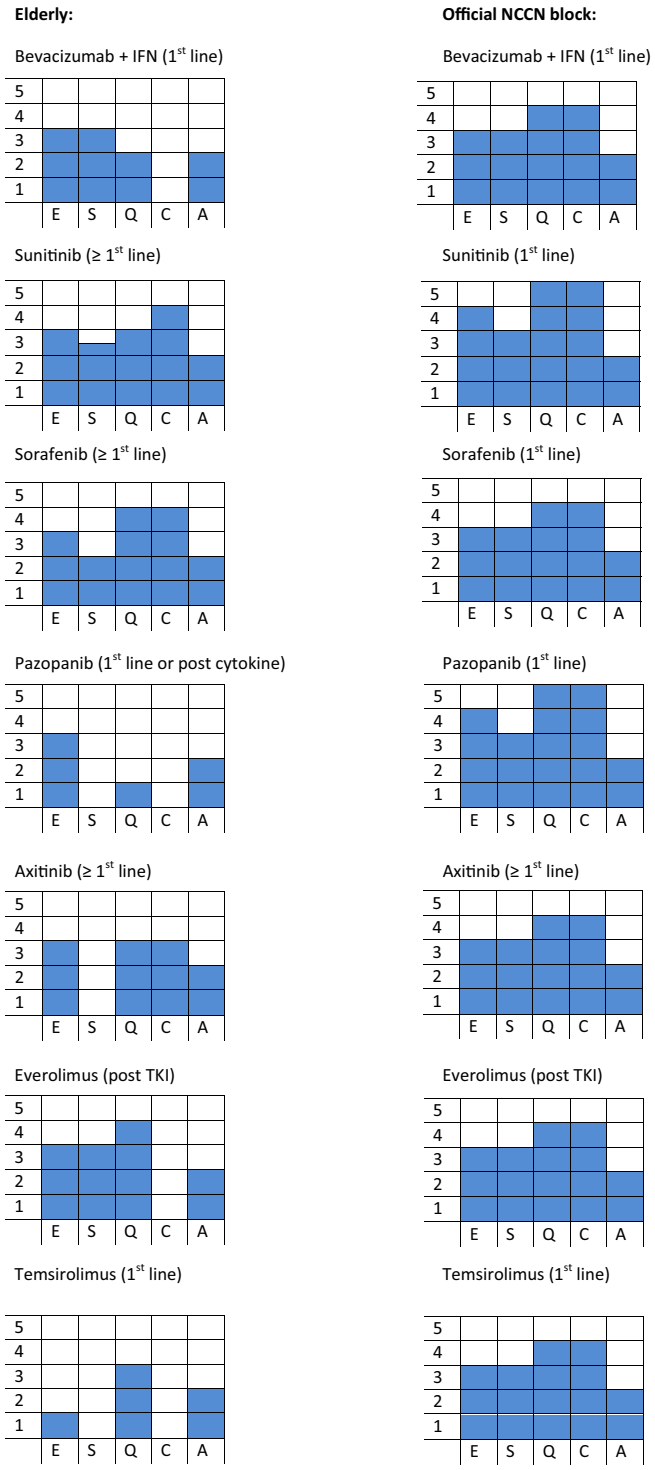

Fig. 1. Modified NCCN evidence blocks for elderly (left) compared to the official NCCN evidence block (right). Column Q was modified for the elderly. The other columns kept the original definition. E = Efficacy of Regimen/Agent. S = Safety of Regimen/Agent. Q = Quality of Evidence. C = Consistency of Evidence. A = Affordability of Regimen/Agent. Quality and quantity of evidence in elderly: 5 Meta-analysis in elderly, 4 Separate publication(s) comparing efficacy and toxicity in older adult patients to the overall or younger patient population of ⩾1 randomized phase III trial(s) or expanded access trial(s). 3 Separate publication on efficacy and toxicity in older adult patients without comparison to the overall or younger patient population. 2 Subgroup analysis in >1 randomized phase III trials or expanded access trials 1. Subgroup analysis in 1 randomized phase III trial or expanded access trial.

agent temsirolimus resulted in a 3.6 months median OS prolongation compared to interferon-α2a alone. The combination of temsirolimus plus interferon-α2a did not improve OS. For the subgroup of elderly patients treated with temsirolimus alone ($n = 64$) compared to interferon-α2a alone ($n = 65$) however, the HR for death was >1.0. Information about toxicity related to age was not mentioned in this study.

A retrospective analysis showed that serum LDH above the upper limit of normal was a negative prognostic but a positive predictive biomarker for survival benefit of temsirolimus over interferon-α2a [62]. Patients with a high LDH were more likely to be younger of age than patients with a normal LDH, which might have contributed to the lack survival benefit of temsirolimus over interferon-α2a in elderly in this study.

No difference in efficacy was found between temsirolimus plus bevacizumab versus interferon plus bevacizumab in mRCC patients [63].

Recommendations: Everolimus can be prescribed to elderly mRCC patients who progressed on VEGF targeting therapy but these patients should be closely followed for toxicity. Elderly patients with poor prognosis mRCC do not seem to benefit from temsirolimus, see Fig. 1.

Aging and immunity

With ageing, immune senescence and immune exhaustion of T cells occur. Exhaustion is characterized by loss of essential functional activity necessary for immune protection and senescence is a loss of replicative capacity of antigen-specific T cell populations [24]. These processes are considered a consequence of repeated antigenic stimulation during life. The resulting declined immune function in elderly might contribute to development and progression of cancer. RCC is considered an immunogenic malignancy [64] and boosting immune function is clearly of interest to improve the outcome for patients with advanced disease.

Cytokine therapy induces non-specific activation of the immune system resulting in low rates but sometimes long lasting tumor responses. To increase the likelihood of anti-tumor activity, novel targeted immune checkpoint blockade aims to improve tumor specific T cell activity. Recently, the PD-1 antibody nivolumab has been approved by the Food and Drug Administration for patients with advanced RCC patients who have received prior anti-angiogenic therapy. First-line immune checkpoint inhibitor studies are ongoing as well as combination studies including antibodies against PD-1 or its ligand PD-L1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). It would be of interest to evaluate whether efficacy of immune checkpoint inhibitors differs between age groups.

Cytokine therapy

Interferon-α and interleukin-2 (IL-2) were the standard of treatment for mRCC before the era of targeted therapy. Elderly patients appeared to do no worse than younger patients [65–67], but with the introduction of angiogenesis inhibitors, there is no role anymore for single agent cytokine therapy.

PD-1 and PD-L1 inhibitors

To escape auto-immunity, tumor cells can express a PD-1 ligand. Those ligands bind to the immune checkpoint protein PD-1 on T cells, resulting in T cell anergy. Reversing immune

exhaustion of tumor-specific T cells by PD-1 blockade has demonstrated antitumor activity in mRCC and several other cancer types.

Interestingly, mRCC patients with overexpression of PD-L1 in the primary tumor have a shorter median PFS when treated with sunitinib compared to patients without PD-L1 overexpression (10 versus 19 months, $P = 0.01$) [68].

In the CheckMate 025 study, a phase III randomized trial comparing nivolumab with everolimus in mRCC patients previously treated with a VEGFR-TKIs, 821 patients were randomized [69]. They received nivolumab 3 mg/kg IV every 2 weeks or everolimus 10 mg/day orally. OS was 25.0 months for nivolumab versus 19.6 months for everolimus, with a HR for death of 0.73 (95% CI 0.57–0.93). The unstratified HR for death was 0.78 (0.60–1.01) for patients <65 years ($n = 497$), 0.64 (0.45–0.91) for patients ⩾65 to 75 years ($n = 250$) and 1.23 (0.66–2.31) for patients ⩾75 years of age ($n = 73$). In 79% of patients receiving nivolumab an adverse event occurred; the most common adverse events were fatigue, nausea and pruritis. No distinction was made between age groups.

A dose escalation phase I trial assessed safety and activity of BMS-936559, a monoclonal antibody directed against PD-L1 [70], included 17 patients with mRCC. All mRCC patients received 10 mg/kg, and 2 objective responses were observed. Seven patients had stable disease at 24 weeks, and the PFS rate was 53% at 24 weeks.

A phase I trial with MDPL3280A, another PD-L1 antibody, included 53 mRCC patients evaluable for toxicity with a median age of 62 (range 33–79) [71]. Grade 3–4 toxicity caused by MDPL3280A was found in 13% of the patients. Thirty-nine patients were evaluable for efficacy, showing a 24-week PFS of 50%.

From these studies it can be concluded that immunotherapy is a breakthrough for mRCC. Even in heavily pre-treated patients efficacy is documented. More studies are ongoing and results are eagerly awaited, especially about the role of immunotherapy as first-line treatment. Of special interest are also combination regimens with anti-angiogenic agents and immunotherapy (clinicaltrials.gov NCT02420821, NCT02348008, NCT002210117, NCT02133742, NCT01984242, NCT02014636, NCT01472081). So far, only limited subgroup analyses for age were performed in immunotherapy trials, which is clinically highly relevant. Below we present some data in other tumor types.

CTLA-4 inhibitors

Ipilimumab is a monoclonal antibody against CTLA-4. Blocking the immune checkpoint protein CTLA-4 sustains T cell activation, thereby enhancing autoimmune activity. In a phase II study 61 mRCC patients received either 3 mg/kg ipilimumab intravenously followed by 1 mg/kg or all doses at 3 mg/kg every 3 weeks [72]. Thirty-three percent of the patients experienced grade 3–4 autoimmune mediated toxicity such as enteritis and endocrine deficiencies. Six patients experienced a partial response, and responses were seen in patients who had not responded to high-dose IL-2 treatment. Patient age ranged from 31 to 70 years, with median age under 60. No age related data was described.

Efficacy and toxicity of immune checkpoint inhibitors in elderly melanoma and non small cell lung cancer patients

In the CheckMate 067 study, comparing nivolumab, ipilimumab and nivolumab + ipilimumab in patients with advanced melanoma, a subgroup analysis was done for patients <65 ($n = 565$), ⩾65 to <75 ($n = 262$) and ⩾75 ($n = 118$). No meaningful differences were found in the incidence of side effects between the groups. The PFS of patients <65 years of age was 11.7 months (combination), 5.5 months (nivolumab) and 2.8 months (ipilimumab). For patients ⩾65 to <75 this was 11.1 months, 12.7 months and 2.9 months. Average PFS could not be determined for patients ⩾75 on the combination treatment because these patients had not progressed yet. PFS in this subgroup was 5.3 months (nivolumab) and 4.0 months (ipilimumab) [73]. A subset analysis was performed to assess safety and efficacy of nivolumab in elderly with melanoma, in which patients <65 and ⩾65 years of age were compared. There was neither a difference in immune related adverse events, nor in OS. Moreover, a significant OS benefit was seen in patients of all ages experiencing any grade of immune related adverse event [74]. In non-squamous non-small-cell lung cancer, a phase III trial comparing nivolumab to docetaxel showed improved OS for nivolumab, with unstratified HR of 0.81 (0.62–1.04) for patients <65 year ($n = 339$), 0.63 (0.45–0.89) for patients ⩾65 to <75 year ($n = 200$) and 0.90 (0.43–1.87) for patients ⩾75 year ($n = 43$). No toxicity results stratified for age were published [75].

Recommendations: Very limited data suggest that nivolumab might be less effective in patients ⩾75 year. Clinicians should take life expectancy and expected ability to cope with side effects into account, when deciding whether or not to recommend nivolumab treatment to elderly.

Discussion

Approximately 50% of the patients with mRCC are elderly. With multiple systemic treatment options available, instruments rating clinical benefit are highly relevant. For this purpose, the NCCN developed evidence blocks, ESMO developed a magnitude of clinical benefit scale and ASCO introduced a value framework. However, these tools are created for the entire patient population and are not necessarily applicable to elderly. We presented modified evidence blocks with for elderly mRCC patients. This grading for the elderly is neither created by a panel of experts nor has it been validated, but it is meant as an illustration and should be interpreted with caution.

Regretfully for several treatment options, solid proof for the use in elderly is lacking. Next to underrepresentation of elderly in clinical trials, often results of subgroup analyses for elderly that participated in the trials are not published. Over time a transition is warranted where collecting and publishing data representing the treatment effects in elderly becomes self-evident. The power of building warehouses to retrieve information is increasingly appreciated [76]. It might be of interest to stock a warehouse with data of mRCC patients who participated in prospective studies. This would allow dedicated research groups to retrieve efficacy and safety data of different mRCC regimens in large numbers of the elderly patients and accommodate the unmet need of solid proof in elderly.

Conflict of interest

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