



## Anti-Tumour Treatment

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



R.R.H. van den Brom<sup>a,1</sup>, S.C. van Es<sup>a,1</sup>, A.M. Leliveld<sup>b</sup>, J.A. Gietema<sup>a</sup>, G.A.P. Hospers<sup>a</sup>, I.J. de Jong<sup>b</sup>, E.G.E. de Vries<sup>a</sup>, S.F. Oosting<sup>a,\*</sup>

<sup>a</sup> University of Groningen, Department of Medical Oncology, University Medical Center Groningen, The Netherlands

<sup>b</sup> University of Groningen, Department of Urology, University Medical Center Groningen, The Netherlands

## ARTICLE INFO

## Article history:

Received 10 December 2015

Received in revised form 6 April 2016

Accepted 8 April 2016

## Keywords:

Renal cell carcinoma

Elderly

Nephrectomy

Angiogenesis inhibitors

Mammalian target of rapamycin inhibitors

Programmed death 1

Immunotherapy

## 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 ( $\geq 85$  years) [3]. Moreover, chronological age alone is not very informative for clinical decision-making. Since the '90s, 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

\* Corresponding author at: Department of Medical Oncology, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel.: +31 50 361 61 61; fax: +31 50 361 48 62.

E-mail address: [s.oosting@umcg.nl](mailto:s.oosting@umcg.nl) (S.F. Oosting).

<sup>1</sup> Both authors contributed equally.

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 acceptance 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- $\alpha$ 2b had a median overall survival (OS) benefit of 7 months compared to patients treated with interferon- $\alpha$ 2b 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

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