Outcomes based on age in patients with metastatic renal cell carcinoma treated with first line targeted therapy or checkpoint immunotherapy: Older patients more prone to toxicity

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ABSTRACT

Objectives: Older patients with metastatic renal cell carcinoma (mRCC) were underrepresented in pivotal trials.

Materials and methods: Consecutive patients with mRCC treated at Aarhus University Hospital with first line tyrosine kinase inhibitors (TKI), mTOR inhibitors, or checkpoint immunotherapy (CPI) were retrospectively analyzed in age-subgroups; ≥ 75, 65–74, and < 65 years, with overall survival (OS), time-to-treatment discontinuation (TTD), and progression-free survival (PFS) as endpoints. Hazards ratios were adjusted (aHR) for International Metastatic RCC Database Consortium (IMDC) risk factors, histology, and age.

Results: Of 838 patients, 159 (19%) were ≥ 75 years, 324 (39%) 65–74 years, and 355 (42%) < 65 years. Treatments were TKI in 729 (87%) patients, mTOR in 43 (5%) and CPI in 67 (8%). Older patients ≥ 75 years compared with 65–74 years and < 65 years had lower toxicity-adjusted median doses of pazopanib, 300 mg vs. 400 mg vs. 600 mg, respectively, (p < 0.001), and sunitinib, 25 mg vs. 37.5 mg vs. 50 mg, respectively (p < 0.001); numerically fewer doses of CPI, median 2 vs. 5 vs. 5, respectively, (p = 0.2); a higher proportion had dose reduction/interruption, 76% vs. 55% vs. 41%, respectively, (p < 0.001); and shorter mean time to dose reduction/interruption, 0.5 months vs. 1.9 months vs. 3.4 months, respectively, (p < 0.001). After adjusting IMDC prognostic factors and histology in multivariate analyses, age did not impact OS (aHR 1.0; 95% CI 0.99–1.01, p = 0.92); a higher proportion had dose reduction/interruption, 76% vs. 55% vs. 41%, respectively, (p < 0.001); and shorter mean time to dose reduction/interruption, 0.5 months vs. 1.9 months vs. 3.4 months, respectively, (p < 0.001). Treatment of older patients with mRCC were more prone to toxicity; but age did not impact outcomes. Proactive dose modification/interruption and awareness may help to reduce toxicity while maintaining efficacy.

Conclusion: Older patients with mRCC were more prone to toxicity; but age did not impact outcomes. Proactive dose modification/interruption and awareness may help to reduce toxicity while maintaining efficacy.

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1. Introduction

Cancer appears with increasing incidence in regard to age, and approximately half of all cancer cases develop in senior citizens; this also applies for kidney cancer peaking in the late sixties [1]. Though diagnosis of renal cell carcinoma (RCC) most frequently occurs in individuals older than 65 years, this age group represented only around a third of the study population in the pivotal phase III trials in metastatic RCC (mRCC) that led to the approval of eight targeted therapies [2,3] and two checkpoint inhibitors (CPI) [4,5]; median age of trial participants was 60 years.

The beginning of a new era for patients with mRCC appeared with major improvements in treatment regimens in the years after 2006 as targeted therapies became available [6,7]. This also applied to older patients with mRCC. Before this era, treatment options were few and the prognosis was accordingly poor, with a median survival of three months being noted for untreated patients with biopsy verified mRCC [7].

Nevertheless, the under-representation of older patients in clinical studies as well as the fact that trial-eligible older adults are more likely to be in a better health condition compared to peers in the general population have resulted in lack of data in older patients [3,8]. Therefore, a critical question confronting clinical practice is whether efficacy and toxicity results generated in a younger trial population can be extrapolated to older real-world patients.

The condition of an older patient is characterized by a reduced physiological reserve and age-related changes, making older patients more vulnerable to cancer treatment toxic effects. The balance of adverse effects (AEs) and clinical benefits are affected by a range of biological aspects, including comorbidities, polypharmacy, and lifestyle. There, consideration of a patient’s profile, both functional, psychological, as well as physiological impairment, must be taken into account [9–11]. With a continuous growing population of older patients across the globe, older patients with mRCC will increase in both absolute and relative numbers as a proportion to total number of affected individuals. However, age-stratified data on available therapeutic agents to help guide treatment decisions are limited, emphasizing the need for investigation on the relation of toxic effects to treatment efficacy [3]. For
that reason, uncovering the management of this age group and particularly issues specific to treatment course will have implications in clinical practice.

This paper retrospectively compared disease outcomes, treatment exposure, and dose reductions in patients with mRCC according to age, in order to determine whether differences in age influenced treatment efficacy and toxicity.

2. Materials and Methods

2.1. Patients and Data Collection

Patients with biopsy proven mRCC, of any histological subtype, undergoing first line treatment at the Department of Oncology, Aarhus University Hospital, were identified in the Aarhus University Hospital mRCC database comprising data on consecutive patients with mRCC treated at the department from 1994 to 31 December 2019. Patients > 70 years were not treated at the department with systemic therapy until 2006 and consequently patients treated before 2006 were not included in the analysis. Approvals were obtained from The Danish Patient Safety Authority (31–1521–314) and the Danish Data Protection Agency (1–16–02–236-20).

The database contained detailed information on demographics, clinicopathological facts, laboratory results, and outcome data related to individual patients. Clinical data was extracted from medical files, pathology data was extracted from the Danish Pathology Register and mortality data from the Danish Civil Registration System. The database had regular data quality checks. Data related to diagnosis and first line treatment with targeted therapy or CPI was collected. First line of therapy was a specific therapeutic agent used to treat mRCC, comprising one of the following drug classes: tyrosine kinase inhibitors (TKI), mammalian target of rapamycin (mTOR) inhibitors, or CPI. Dosing of targeted therapy was adjusted according to tolerability (toxicity-adjusted dosing) or interrupted in case of severe AEs. We proactively aimed for Common Terminology Criteria for Adverse Events (CTCAE) grade 1 toxicity in patients treated with targeted therapy, as lack of toxicity (grade 0 toxicity) was interpreted as under-dosing, and grade ≥ 2 toxicity was interpreted as unacceptable in real life patients receiving life-long therapy, with hypertension CTCAE grade 3 (≥ 2 antihypertensive drugs) as the only exception. The final dose after adjustment for toxicity was recorded.

CPI therapy was interrupted in case of toxicity; per standard practice no dose reduction was performed. Data encompassed date of primary diagnosis and date of diagnosis of mRCC, date of treatment initiation, administered drug type, drug dose, date of dose reduction, date of discontinuation of therapy, and reason for discontinuation. Moreover, data was available to characterize prognostic risk scores for each individual based on International Metastatic RCC Database Consortium (IMDC) guidelines [12]. The model stratified patients into prognostic groups of three: favorable-, intermediate-, and poor-risk. This was based on six prognostic parameters: Karnofsky Performance Status < 80%, time between primary diagnosis and start of systemic therapy < 1 year, hemoglobin < lower limit of normal (LLN) (female 7.3 mmol/L, men 8.3 mmol/L), corrected serum calcium > upper limit of normal (ULN) (UNL, neutrophils > ULN (7 × 10^9/L), and thrombophils > ULN (female 400 × 10^9/L, men 350 × 10^9/L) [12].

Patients with 0 risk factors were categorized favorable IMDC risk group, 1–2 risk factors IMDC intermediate risk group, and those with 3–6 risk factors were categorized IMDC poor risk group.

2.2. Statistical Analysis

Patient demographics and baseline characteristics were described using proportions (%) for categorial variables and medians (interquartile range) for continuous variables. Differences in distribution were assessed with Chi-square test. Outcome measurements included: overall survival (OS) defined as time from initiation of therapy to death for any reason; progression free survival (PFS) defined as time from initiation of therapy to progression or death for any reason, whichever came first; and time to treatment discontinuation (TTD) defined as time from treatment initiation to discontinuation for any reason (toxicity, progression, death, or other).

The specific age cut-offs for analysis were selected according to the median age at the time of diagnosis of mRCC, the distribution of age in a clinical setting, and recommendations in prior reviews [13–15]. Age was used as a categorial variable with stratification into binary age groups < 75 vs. ≥ 75 years and in decennium subgroups (age < 50, 50–59, 60–69, 70–79, ≥ 80 years). Some decennium subgroups were critically small due to low number of patients. Endpoints PFS, TTD, and OS were for that reason estimated in three age-stratified subgroups with more robust sizes: age ≥ 75 years, age 65–74 years, and age < 65 years. Each of the three groups were furthermore subdivided according to the specific type of treatment during first line course: TKI, mTOR, or CPI.

For each of the subgroups the Kaplan-Meier method was used to characterize median OS, TTD, and PFS, comparing differences with the log-rank testing.

Using a Cox regression model, age was also evaluated as a continuous variable with one year of increase in association to OS, PFS, and TTD. P-values and 95% confidence intervals (CI) were considered descriptive. Furthermore, adjusted hazard ratios (aHR) were calculated using a multivariate Cox regression analysis adjusting for individual IMDC risk factors [12], histology (clear cell vs. non-clear cell), and age (assessed as a continuous factor with one year of increase or dichotomized by age ≥ 75, 65–74, and < 65 years).

In order to assess treatment course related to specific age groups, median daily end doses of pazopanib and sunitinib after adjustment due to toxicity and the number of administered CPI treatments were estimated for individual patients, stratified within the three age groups. Kruskal-Wallis or Chi-square test were used as appropriate methods for calculating differences between subgroups. The mean time from treatment initiation to first dose reduction or interruption was determined using the Kaplan-Meier method.

All data analysis was performed using SPSS version 26.

3. Results

3.1. Patients Characteristics

From January 2006 to December 2019, 838 consecutive patients with advanced mRCC that were treated with first line targeted therapy or checkpoint immunotherapy in a routine clinical setting at the Department of Oncology, Aarhus University Hospital, were identified and included. Of these, 159 (19%) were 75 years or older, 324 (39%) between 65 and 74 years, and 355 (42%) patients were below the age of 65 years. 701 patients (84%) had clear cell histology and 137 patients (16%) had non-clear cell histology. First line treatments were: TKI (sunitinib, pazopanib, sorafenib, axitinib, cabozantinib) in 728 patients (87%), mTOR inhibitors (temsirolimus, everolimus) in 43 patients (5%), and CPI (atezolizumab/bevacizumab, ipilimumab/nivolumab, pembrolizumab, or nivolumab) in 67 patients (8%). Choice of treatment was at the discretion of the treating physician, according to national guidelines; the majority of non-clear cell histology patients received mTOR inhibitors. The median duration of follow-up for surviving patients was 53.7 months (range 0.1–124 months).

Baseline characteristics of older and younger adults are summarized and stratified by first line treatments: TKI, mTOR, and CPI (Table 1). Prognostic factors and clinical characteristics were generally balanced in each treatment subgroup, despite the non-randomized nature of the study. However, the time from diagnosis to initiation of systemic treatment was longer in adults ≥ 75 years receiving TKI with a median of 9.7 months in contrast to 1.3 months and 3.4 months for the younger subgroups. For patients 75 years or older treated with mTOR or CPI, a higher proportion was IMDC poor risk category. Approximately half of the patients had lymph node and lung metastases, a fifth had liver
metastases, and a third had bone metastases. For patients ≥ 75 years receiving mTOR and CPI a higher tumor burden was noted with approximately 60% having bone metastases. The main reasons for stopping treatment were progression and toxicity for every subgroup.

3.2. Treatment Exposure and Dose Reductions

Older patients received a lower dose of TKI. The daily median end dose of pazopanib, after adjusting for toxicity, was 300 mg (range: 40–1000 mg) for patients ≥ 75 years, 400 mg (range: 40–1000 mg) for patients 65–74 years, and 600 mg (range: 40–1200 mg) for patients < 65 years, \( p < 0.001 \) (Table 2). End median dose of sunitinib after toxicity-adjustments was 25 mg (range: 12.5–50 mg) vs. 37.5 mg (range: 12.5–62.5 mg) vs. 50 mg (range: 12.5–62.5 mg), for patients aged ≥75 years, 65–75 years, and < 65 years, respectively, \( p < 0.001 \). Older patients ≥75 years received numerically fewer CPI treatments; the median number of CPI treatments was two treatments (range: 1–35 treatments) for age ≥ 75 years, five (range: 1–38 treatments) for age group 65–74 years, and five (range: 1–40 treatments) for age group < 65 years, \( p = 0.22 \).

Table 2
Treatment exposure and dose reductions.

<table>
<thead>
<tr>
<th></th>
<th>Age &lt; 65</th>
<th>Age 65–74</th>
<th>Age ≥ 75</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity-adjusted Pazopanib dose ( ^{a} ), mg</td>
<td>600</td>
<td>400</td>
<td>300</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Toxicity-adjusted Sunitinib dose ( ^{a} ), mg</td>
<td>50</td>
<td>37.5</td>
<td>25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number CPI treatments, n, median</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>0.22</td>
</tr>
<tr>
<td>Reduction/interruption of dose, n (%)</td>
<td>144 (41)</td>
<td>177 (55)</td>
<td>121 (76)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to first dose reduction/interruption, mos, mean (95% CI)</td>
<td>3.4 (2.4–4.4)</td>
<td>1.9 (1.2–2.7)</td>
<td>0.5 (0.3–0.7)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CPI = checkpoint inhibitor; CI = confidence interval.

\(^{a}\) Final end dose after adjustments due to toxicity.
A significantly higher proportion of older patients ≥ 75 years underwent dose reductions or interruptions (76%) compared with individuals aged 65–74 years (55%) and < 65 years (41%), (p < 0.001). The mean time from initiation of therapy to first dose reduction/interruption was significantly shorter for older patients: 0.5 months for age ≥ 75 years (95% CI 0.3–0.7), 1.9 months for age 65–74 (95% CI 1.2–2.7), and 3.4 months for age < 65 (95% CI 2.4–4.4), (p < 0.001).

3.3. Efficacy and Outcomes

Outcomes according to age had no significant differences. Overall, median OS from first line therapy initiation was 14.3 months (95% CI 12.3–16.3). OS was generally higher for patients treated with CPI and lowest in patients treated with mTOR inhibitors; similar OS was observed for each treatment subgroup, irrespective of age. No difference in survival was found between age groups analyzed per decennium.

Fig. 1. Similar outcomes from first line targeted therapy or check point immunotherapy in patients with mRCC, irrespective of age. The figure depicts similar 1A, overall survival (OS), 1B, time to treatment discontinuation (TTD), and 1C, progression-free survival (PFS), irrespective of age (≥ 75 years, 65–74 years, and < 65 years).
Stratified that older patients with mRCC were more prone to toxicity compared to their younger counterparts. Moreover, older patients shorter time from therapy initiation to dose reduction/interruption. Further investigation of outcomes based on age in a real-world population of patients treated with CPI, indicating older age as a continuous or dichotomized variable was not independently associated with OS (aHR 1.0; 95% CI 0.99–1.01, p = 0.7). After multivariable adjustments for IMDC individual prognostic factors and histology, older age as a continuous variable was not independently associated with PFS (1.0, 95% CI 0.99–1.02, p = 0.2) (Table 4).

Overall median TTD from first line therapy was 6.6 months (95% CI 5.7–7.5). TTD was not statistically associated with age when analyzing age as a continuous variable (HR 1.0; 95% CI 0.99–1.0, p = 1). No significant difference was observed for median TTD with 6.6 months (95% CI 4.6–8.6) for age ≥ 75 years vs. 6.2 months (95% CI 4.9–7.4) for age 65–74 years vs. 7.1 months (95% CI 5.8–8.5) for age < 65 years, (p = 0.9) (Fig. 1B). Neither was older age associated to worse TTD when subdividing the cohort into subgroups according to treatments (Table 3). After multivariable adjustments for IMDC individual prognostic factors and histology, older age as a continuous or dichotomized variable was not independently associated with TTD (aHR 1.0; 95% CI 0.99–1.01, p = 0.4) (Table 4).

Overall median PFS from first line therapy was 8.3 months (95% CI 7.4–9.3). Age analyzed as a continuous variable was not found to be associated with shorter PFS (HR 0.99; 95% CI 0.99–1.0, p = 0.9). No statistically significant difference was observed for median PFS for age groups ≥ 75 years (11.5 months, 95% CI 7.5–15.4) vs. 65–74 years (8.2 months, 95% CI 6.5–10.0) vs. < 65 years (8.2 months, 95% CI 7.0–9.4), (p = 0.4) (Fig. 1C). When assessing PFS in subgroups of treatment categories, no difference was observed (Table 3). After multivariable adjustments for IMDC individual prognostic factors and histology, older age as a continuous or dichotomized variable was not independently associated with PFS (aHR 1.0, 95% CI 0.99–1.01; p = 0.9) (Table 4).

### 4. Discussion

To our knowledge, this study represents the largest single-center investigation of outcomes based on age in a real-world population of patients with mRCC treated with targeted agents and CPI. A total of 58% in the study were > 65 years, whereas this age group was represented by around only a third in the pivotal phase III trials [2,3]. We demonstrated that older patients with mRCC were more prone to toxicity while maintaining efficacy. The toxicity-adjusted dose of TKI was significantly lower with increasing age. Older patients ≥ 75 years experienced a higher rate of toxicity-related dose reduction/interruption and a shorter time from therapy initiation to dose reduction/interruption compared to their younger counterparts. Moreover, older patients ≥ 75 years received numerically fewer doses of CPI, albeit not statistically significant. The number of patients in this subgroup was low, warranting further assessment in larger group of patients in the future. Intriguingly, no differences were observed in OS, PFS, or TTD between older and younger individuals according to treatment received, despite a tendency towards a more extensive metastatic burden and poorer IMDC prognosis category among older patients. This was evident in univariate analyses, and also after adjusting for individual IMDC prognostic factors and histology in multivariate analyses, with age analyzed as both a continuous and dichotomized variable. In contrast to other studies reporting lower PFS and OS in non-clear cell RCC [16], we demonstrated worse outcomes in patients with clear cell histology. This may reflect the heterogeneity among non-clear cell subsets.

In accordance with our findings, several other studies have shown that older age does not independently associate with poorer survival in patients with mRCC. These conclusions apply in the case of both targeted agents and CPI, although there is a scarcity of data on the clinical outcomes among older patients treated with CPI [2,3,14,17–23]. The impact of age on therapies for mRCC have been reported in other retrospective real-world experiences, however, those reports presented a smaller numerosity than our study and they lack a direct comparison with a homogeneous group of younger patients [24,25]. Moreover, targeted therapies showing efficacy in both younger and older individuals reported from pivotal trials rely on retrospective age analyses with age cut-offs at 65 years. On the other hand, frequency and severity of major toxic events leading to dose reductions and discontinuations differ according to patient age [3,13]. A study [26] from the International Metastatic Renal Cell Cancer database identified older age to be a predictive factor of toxicity-related discontinuations of treatment among patients treated with targeted therapeutic agents. Likewise, Miyake et al. [27] found that the proportion of older patients undergoing a modified sunitinib regimen, whereby the initial dose was reduced due to toxicity, was larger when compared with younger adults. A similar trend was observed for cabozantinib and everolimus with more frequent dose reductions and discontinuations together with a shorter median time to AE among older patients ≥ 75 years [21]. Notably, a retrospective analysis [20] of the CheckMate 025 trial reported a similar incidence of all-grade toxicity between older and younger individuals treated with nivolumab. Most of these studies were age-subset analyses of clinical trials, thereby able to provide detailed information about toxicity in a standardized manner, demonstrating tolerability of targeted therapies in all age group. As our study was conducted in real world patients, we were not able to provide detailed toxicity information. However, we proactively aimed for CTCAE grade 1 toxicity as this was interpreted related with an acceptable quality of life (QoL).

Importantly, the increased incidence of treatment interruptions and dose reductions among older patients in our analysis did not impact on overall efficacy, despite the significantly lower TKI doses observed. To ensure clinical benefit of targeted drugs, the sustained drug exposure in each individual patient, rather than the numerical dose in mg per se, is important [28]. As the threshold of exposure varies from individual

### Table 3

<table>
<thead>
<tr>
<th>Treatment outcomes based on age stratified by treatment.</th>
</tr>
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<tbody>
<tr>
<td><strong>TKI</strong></td>
</tr>
<tr>
<td>Age &lt; 65 (N = 308)</td>
</tr>
<tr>
<td>OS, mos, (95% CI)</td>
</tr>
<tr>
<td>p-value</td>
</tr>
<tr>
<td>TTD, mos, (95% CI)</td>
</tr>
<tr>
<td>p-value</td>
</tr>
<tr>
<td>PFS, mos, (95% CI)</td>
</tr>
<tr>
<td>p-value</td>
</tr>
</tbody>
</table>

TKI = tyrosine kinase inhibitor; mTOR = mammalian target of rapamycin; CPI = checkpoint inhibitor; CI = confidence interval; NE = non evaluable; TTD = time to treatment discontinuation.

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to individual, adequate drug level is not only depending on optimal starting dose but more importantly titration of tolerated dose according to clinical parameters, including toxicity and QoL. In the aggregate, a dosing that is just right is characterized by a combination of antitumor effects, together with manageable toxicity and hence not the absence of AEs [29,30]. The same phenomenon might apply to the clinical use of CPI. On investigating the effect of nivolumab and ipilimumab in patients with mRCC, neither discontinuation due to immune-related AEs nor the overall incidences of AEs negatively affected OS [31]. In fact, because a positive trend between AEs and OS was seen, these early AEs might reflect an immune activation, suggesting a potentially positive prognostic value of AEs to long-term survival with CPI [31,32].

To this point, recommendations concerning therapeutic intervention and management for older patients with mRCC resemble the one for younger. However, one size does not fit all and because of the heterogeneity of senescence and the possible variable value older patients place on survival gains obtained from cancer therapy, they might differ from younger adults in both tolerance to cancer therapy and their willingness to accept AEs. All of this increasing the relevance of management of QoL at several time points in the overall course of cancer treatment [3]. Furthermore, the definition of “old” is arbitrary and chronological age alone is an insufficient surrogate for aging [15,33]. To detect unaddressed geriatric problems, a geriatric risk profile assessment has been suggested [34]. In older patients with cancer, the geriatric assessment (GA) adds valuable information to that given by the performance status in the interest of developing an integrated and coordinated plan for care, treatment and follow-up. Not only life expectancy, individual functioning, cognitive and psychiatric status are elaborated on, sources of social support and the like are clarified too [15,34,35]. Still, evaluating the older patient with mRCC in a real-life clinical setting can be regarded an infeasible time-consuming procedure. On the other hand, it has been suggested that the extra time required for GA provides the essential information about impairments, risks, etc., in order to avoid costs of future additional medical investigation and/or treatment [36]. Although this study gains insight into a mRCC setting with similar treatment outcomes between older and younger patients, regardless of an absence of a conventional GA, the retrospective nature of the study makes it vulnerable to selection bias, hence GA should be encouraged, as recommended by SIOG [34]. Tools to reduce the time requested for geriatric evaluations exist, and one way to select the appropriate older patients for GA would be to do a screening test like the G8. The G8 screening tool was developed to identify older patients who would benefit from a comprehensive GA and might be of practical use in the daily clinical practice [37,38].

Data most inevitable indicates that older patients ought not to be restricted in their access to both therapeutic options and several treatments in succession. Present data reveals the message that AEs and the consequences hereof were not necessarily unfavorable; treatment efficacy depends on the proactive toxicity-adjusted dosage of drugs. This is why a possible strategy concerning older adults could imply a greater deal of counselling and cautiousness resulting in more profound care and surveillance of AEs managed by physicians and other care-takers. Each patient’s point of view must be taken into account, not only managing short-term goals but also long-term goals, concerns, expectations, and needs. On the same note, decisions about cancer treatment should not only take age into account but crucially their disease related condition, resulting in individualized patient centered interventions.

There are some limitations to be noted in this study, primarily the retrospective nature of the study. Most certainly there may be a number of patients precluded from treatment due to a number of comorbidities and/or a very poor performance status, evidently common in the older population, presumably imposing a selection bias. We did not have information about comorbidity or frailty. The study is also limited by the differing age sample sizes with comparatively small numbers in some age groups, especially older patients ≥ 75 years receiving CPI. The heterogeneous patient population in proportion to several different treatment types might be confining but on the other hand provides a reflection of a real-world population experience, thus improving the study’s generalizability.

5. Conclusion

Older patients with mRCC were more prone to toxicity; but age did not impact outcomes. For that reason, older age should not preclude patients with mRCC from therapy. Proactive dose modification/interruption, and patient and physician awareness may help to reduce toxicity while maintaining efficacy.

Author Contributions

C.K.H. and F.D contributed to study concept and design, data acquisition and take responsibility for the integrity and interpretation of the data. F.D. were in charge of analysis of data. C.K.H. drafted first manuscript. C.K.H. and F.D. contributed to manuscript preparation, editing and review.

Declaration of Competing Interest

C.K.H. certifies that all conflict of interest, including specific financial interests, relationships, and affiliations relevant to the subject of matter or materials discussed in the manuscript are the following: F.D. received research grant support from Pfizer, Ipsen and MSD.

Acknowledgements

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### Table 4

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p</th>
<th>HR (95% CI)</th>
<th>p</th>
<th>HR (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, continuous</td>
<td>1.01 (0.99–1.02)</td>
<td>0.2</td>
<td>1.0 (0.99–1.01)</td>
<td>0.4</td>
<td>1.0 (0.99–1.01)</td>
<td>1.0</td>
</tr>
<tr>
<td>Karnofsky Performance Status &lt;80%</td>
<td>1.94 (1.63–2.32)</td>
<td>&lt;0.001</td>
<td>1.53 (1.25–1.81)</td>
<td>&lt;0.001</td>
<td>1.51 (1.27–1.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial diagnosis to systemic therapy &lt;1 yr</td>
<td>1.74 (1.44–2.1)</td>
<td>&lt;0.001</td>
<td>1.58 (1.13–1.86)</td>
<td>&lt;0.001</td>
<td>1.7 (1.43–2.04)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hemoglobin &lt; LLN</td>
<td>1.67 (1.42-1.97)</td>
<td>&lt;0.001</td>
<td>1.36 (1.11–1.5)</td>
<td>&lt;0.001</td>
<td>1.44 (1.23–1.69)</td>
<td>&lt;0.001</td>
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<tr>
<td>Corrected calcium &gt; ULN</td>
<td>1.28 (1.06–1.55)</td>
<td>0.01</td>
<td>1.33 (1.11-1.6)</td>
<td>0.002</td>
<td>1.26 (1.05–1.52)</td>
<td>0.01</td>
</tr>
<tr>
<td>Neutrophils &gt; ULN</td>
<td>1.71 (1.45–2.02)</td>
<td>&lt;0.001</td>
<td>1.61 (1.37–1.89)</td>
<td>&lt;0.001</td>
<td>1.63 (1.39–1.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Histology (clear cell)</td>
<td>1.27 (1.03–1.57)</td>
<td>0.03</td>
<td>1.36 (1.11–1.66)</td>
<td>0.002</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CI = confidence interval; LLN = lower limit of normal; ULN = upper limit of normal.
References


