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Efficacy of Targeted Therapy for Metastatic Renal Cell Carcinoma in the Elderly Patient Population

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Abstract

Targeted therapy has become the mainstay of treatment for metastatic renal cell carcinoma (mRCC), and the efficacy of this therapy in the older population is poorly understood. Data from 1381 patients with mRCC treated with first-line anti-vascular endothelial growth factor (VEGF) therapy were collected through the International mRCC Database Consortium from 12 centers. When adjusted for poor prognostic factors, age 75 years and older was not found to be associated with poorer overall survival or shorter treatment duration. This suggests that advanced age alone should not preclude a patient from targeted therapy.

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Disclosure

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Introduction/Background—Targeted therapy has become the mainstay of treatment for mRCC. The efficacy of this therapy in the older population is poorly understood.

Patients and Methods—Data from patients with mRCC treated with first-line anti-VEGF therapy were collected through the International mRCC Database Consortium from 12 centers. Patient characteristics, data on second-line therapy, and outcomes including treatment duration and overall survival, were evaluated using summary statistics and multivariate analysis.

Results—All patients (n = 1381) were treated with front-line targeted therapy; 144 (10%) were 75 years old or older. Six patients (4%) were favorable risk, 99 patients (69%) intermediate risk, and 39 patients (27%) poor risk according to Heng Journal of Clinical Oncology 2009 prognostic factors. The initial treatment for those 75 years of age was sunitinib (n = 98), sorafenib (n = 35), bevacizumab (n = 7), and AZD217 (n = 4). Twenty-three percent of older patients and 39% of the younger patients went on to receive second-line therapy ($P < .0001$). The overall response rate, median treatment duration, and overall survival for the older versus younger group were 18% versus 25% ($P = .0975$), 5.5 months versus 7.5 months ($P = .1388$), and 16.8 months versus 19.7 months ($P = .3321$), respectively. When adjusted for poor prognostic factors, age 75 years and older was not found to be associated with poorer overall survival (hazard ratio [HR], 1.002; 95% confidence interval [CI], 0.781–1.285) or shorter treatment duration (HR, 1.018; 95% CI, 0.827–1.252). The retrospective study design was the primary limitation.

Conclusion—The use of advanced age as a selection criterion for targeted therapy requires further study, with data suggesting no clinically meaningful differences in overall response rate, treatment duration, and overall survival between older and younger age groups.

Keywords

Age; Geriatric; mRCC; Prognostic factors; Vascular endothelial growth factor

Introduction

Renal cell carcinoma (RCC) caused an estimated 13,680 deaths in the United States in 2013, and an additional 65,150 individuals were newly diagnosed with the disease.¹ Since the discovery of the role of Von Hippel-Lindau (VHL) mutations and its effects on vascular endothelial growth factor (VEGF) and angiogenesis, targeted therapy against the VEGF pathway, with drugs such as sunitinib, sorafenib, and bevacizumab, has become the mainstay of treatment for metastatic RCC (mRCC). However, there is relatively little known about their efficacy in the older patient population.

Older individuals constitute a large proportion of patients with RCC, with a median age at diagnosis of 60 years.² The pathophysiology of RCC might vary with age, because older patients might present with increased prevalence of VHL mutations and a greater frequency of clear cell histology.^{3–5} Furthermore, older individuals have decreased liver and renal function, potentially affecting the drug metabolism of most of the small-molecule targeted agents reliant on the cytochrome P450 system and drugs dependent on renal excretion.^{6–9} Decreased blood flow to the gut and poor gastric motility could also affect absorption of oral therapies.

Polypharmacy is also a concern when treating older patients. Drug–drug interactions and increased potential for side effects are just a few of the problems that might further influence drug levels and therapeutic efficacy. In addition, higher rates of comorbid illnesses concomitant with these factors make treatment of RCC in the elderly population a very complex issue.¹⁰

In patients with mRCC treated with targeted therapy, this study retrospectively compared disease outcomes (response rate, treatment duration, and overall survival) between individuals aged 75 years and older with patients younger than 75 years to determine if there was a difference in efficacy of treatment.

Patients and Methods

Patient Characteristics

Data from patients diagnosed with mRCC (of any pathologic subtype) treated with anti-VEGF targeted therapy were collected through the International mRCC Database Consortium from 12 centers: Tom Baker Cancer Centre (University of Calgary, Calgary, Alberta, Canada), Dana-Farber Cancer Institute and Harvard Medical School (Boston, MA), Vancouver Cancer Center, British Columbia Cancer Agency (Vancouver, British Columbia, Canada), Cross Cancer Institute (Edmonton, Alberta, Canada), Sunnybrook Odette Cancer Centre (Toronto, Ontario, Canada), Karmanos Cancer Institute, Wayne State University (Detroit, MI), Queen Elizabeth II Health Sciences Centre (Halifax, Nova Scotia, Canada), London Regional Cancer Program (London, Ontario, Canada), Cleveland Clinic Taussig Cancer Center (Cleveland, OH), Aarhus University (Aarhus, Denmark), Princess Margaret Hospital (Toronto, Ontario, Canada), and the National Cancer Centre (Singapore). Demographic, clinical, laboratory, and outcome data were collected using uniform data collection software and standardized definitions from 2005 to 2009 (as described by Heng et al¹¹). Patient characteristics, data on second-line therapy, and outcomes were analyzed. This study received institutional review board approval from each participating center.

Statistical Analyses

Summary statistics were performed to estimate means and medians of appropriate demographic characteristics. Data from patients who were 75 years old or older were compared with those who were younger than 75 years. Kaplan-Meier plots were constructed to compare treatment duration and overall survival of these 2 groups. Hazard ratios (HRs) for death were calculated using proportional hazards regression multivariate analysis, which adjusted for known poor prognostic factors: hemoglobin less than the lower limit of normal, Karnofsky performance status < 80%, increased corrected serum calcium (greater than the upper limit of normal [ULN]), increased serum neutrophil and platelet counts (> ULN), and time from diagnosis to treatment interval < 1 year.¹¹

Results

Patient Characteristics

A total of 1381 patients with mRCC receiving targeted therapy were included. Of these, 144 (10.4%) individuals were aged 75 years or older (median, 78 years; range, 75–89 years); 103 were men and 41 were women. The initial treatment for patients ≥75 years of age was sunitinib (n = 98), sorafenib (n = 35), bevacizumab (n = 7), and AZD2171 (n = 4). There was no statistical difference between the therapy types used for older and younger populations.

Among the elderly population, six patients (4%), 99 patients (69%), and 39 patients (27%) had favorable-, intermediate-, and poor-risk disease, respectively. There was no statistical difference in the distribution of prognostic groups between the older (≥75 years) and younger populations (<75 years) ($P = .1779$). Previous nephrectomy, more than 1 site of metastases, sarcomatoid differentiation, and nonclear cell histology are listed in Table 1. Differences of note included fewer nephrectomies (71% vs. 80%; $P = .0133$) and fewer brain metastases (3% vs. 9%; $P = .0128$) in the older population.

Only 33 out of 144 (23%) older patients went on to receive second-line therapy compared with 487 (39%) in the younger population ($P < .0001$). The types of second-line therapies in the older and younger populations were sunitinib (27% [n = 9] vs. 31% [n = 149]), sorafenib (36% [n = 12] vs. 36% [n = 173]), axitinib (3% [n = 1] vs. 2% [n = 8]), bevacizumab-based regimens (3% [n = 1] vs. 4% [n = 17]), temsirolimus (15% [n = 5] vs. 15% [n = 71]), everolimus (9% [n = 3] vs. 9% [n = 42]), and immunotherapy (3% [n = 1] vs. 6% [n = 27]); specific second-line therapy information was unavailable for 1 individual in the older population.

Outcomes

The median treatment durations for the older versus younger group were 5.5 months and 7.5 months ($P = .1388$), respectively (Fig. 1, Table 2). The overall response and median survival rates were also similar between the 2 populations: 18% versus 25% ($P = .0975$) and 16.8 months versus 19.7 months ($P = .3321$), respectively (Fig. 2, Table 2).

When adjusted for known poor prognostic factors,¹¹ the HR for age ≥75 years and older was not found to be associated with a difference in overall survival (HR, 1.002; 95% confidence interval [CI], 0.781–1.285) or shorter treatment duration (HR, 1.018; 95% CI, 0.827–1.252) (Fig. 2, Table 2). Additional analyses were performed adjusting for sarcomatoid histology, nephrectomy status, and the presence of brain metastases because there was an imbalance in these characteristics between the 2 age groups. HRs for treatment duration and overall survival did not differ substantially.

Discussion

The advent of targeted therapy for mRCC has raised new questions regarding efficacy of drug use in the elderly patient population. This international multicentered study provides insight into this question and, to the authors' knowledge, is the largest study of its kind.

Patients were treated with a variety of targeted agents in academic research centers and community oncology centers.

In the later decades, patients with RCC also present with other medical conditions such as hypertension, diabetes, cardiovascular and cerebrovascular diseases, and other respiratory illnesses.¹² Because of these age-related comorbidities, it is thought that treatment might not be well-tolerated.^{12,13} For instance, older patients with other types of genitourinary cancers are less likely to receive treatment in general.^{14,15}

Berdjis et al published a study in 2006 on surgical outcomes of RCC patients in Germany.¹⁶ They found that even though older patients had a higher prevalence of comorbid disease, age was not associated with a greater incidence of intraoperative or early postoperative complications, and that even patients with significant comorbidities benefit with treatment. A more recent European study on drug therapy in 2009 supported this claim, showing that improvement in prognosis is observed with treatment in all patients regardless of age.¹⁷ Furthermore, there was also no difference in side effects when individuals across age groups were compared. It was physiologic age (or functional age), not chronologic age, that seemed to determine treatment efficacy and disease prognosis.

A retrospective subgroup analysis of TARGET (Treatment Approach in Renal Cancer Global Evaluation Trial) data in 2008 by Eisen et al, comparing older (≥ 70 years) and younger (< 70 years) patients, concluded that sorafenib improves outcomes in patients regardless of age.¹⁸ A multicentered study on the safety of sorafenib across subpopulations of patients (age: < 55, 55 to < 65, 65 to < 75, and ≥ 75) by Procopio et al in 2010 revealed that older patients had a safety profile similar to that of younger patients in terms of tolerating side effects.¹⁹ Although all of these studies did not collect and adjust for known prognostic factors that might otherwise bias the results, they suggested that the previous belief by some oncologists regarding the decreased efficacy and tolerance of targeted therapy in the elderly population might be incorrect.

Results of the current study focus on patients older than 75 years, which is an even older subgroup than studied in the previously-mentioned studies, adds to the analyses in the previously-mentioned studies by addressing patients given other types of targeted therapies. The data suggest that age is not associated with poorer outcome in patients who receive VEGF-targeted therapy for metastatic renal cancer. Overall survival and treatment duration were statistically similar between the younger (< 75 years) and older (≥ 75 years) patient groups. Admittedly, although larger sample sizes might have yielded statistical differences, clinically meaningful differences were not observed between the point estimates of the 2 age groups. Furthermore, when adjusted for known poor prognostic factors,¹¹ the HR for age ≥ 75 years and older was not found to be associated with poorer overall survival or shorter treatment duration.

An important issue is that the denominator of all elderly patients considered for treatment with targeted therapy is not possible to capture. There are certainly patients that have too many comorbidities or very poor performance status that would preclude them from treatment even if they were in the younger population. These patients are not included in this

analysis, which might impose a selection bias. The older patient population did have fewer nephrectomies and brain metastases, suggestive of a selection bias in the original treatment population. Sarcomatoid features, an indicator of poorer prognosis,^{20,21} was present in fewer individuals 75 years and older. When treatment durations and overall survival were adjusted for these potential confounders, the HR did not change substantially. A lower percentage of older individuals who received second-line therapy (23% vs. 39%) might also be the result of a treatment bias. These factors highlight a limitation in this retrospective study, particularly in the inability to control for patient selection, leading to slight differences in population characteristics; however, the analyses were adjusted to the known prognostic factors thereby strengthening the ability to compare the 2 age groups. There are also inherent limitations in controlling for other covariates (comorbidities, drug availability, side effects). Furthermore, the retrospective nature of the study might have predisposed it to issues of missing data and selection bias. However, the amount of missing data was low (< 1%) and patients were derived from consecutive series to prevent selection bias.

Another factor was heterogeneity in the treatment, because individuals were treated with several agents including sunitinib, sorafenib, bevacizumab, and AZD2171 in the first- and second-line settings. However, this provides the real-world experience of targeted therapy on a population level, whereas clinical trials examining these drugs are more homogeneous and prone to selection bias because they tend to select for healthier individuals.^{22–25} Although toxicity data were not collected at the time of this study, the treatment duration of the elderly and younger groups was similar, providing an indirect measure of drug tolerance and efficacy.

Conclusion

Overall response rates, treatment duration, and overall survival rates were similar between the older and younger populations. The elderly population in this study might have been more selected but when adjusted for known poor prognostic factors, the HR for age 75 years and older was not found to be associated with poorer overall survival or shorter treatment duration. Therefore, targeted therapies require more study in the elderly population.

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Clinical Practice Points

- Since the discovery of the role of VHL mutations and its effects on VEGF and angiogenesis, targeted therapy against the VEGF pathway, with drugs such as sunitinib, sorafenib, and bevacizumab, has become the mainstay of treatment for mRCC. There is relatively little known about their efficacy in the older patient population, even though the elderly population constitutes a large proportion of patients with RCC.
- This study retrospectively compared disease outcomes (response rate, treatment duration, and overall survival) between individuals aged 75 years or older to patients younger than 75 years to determine if there was a difference in efficacy of treatment.
- The topic is an area of significant controversy because many of the existing trials have a selection bias toward healthier individuals. In this study, data from 1381 patients treated with front-line targeted therapy were collected from 12 centers. Of those, 144 (10%) were 75 years old or older.
- When adjusted for poor prognostic factors, age of 75 years and older was not found to be associated with poorer overall survival (HR, 1.002; 95% CI, 0.781–1.285) or shorter treatment duration (HR, 1.018; 95% CI, 0.827–1.252).
- This suggests that the use of targeted therapy in elderly patients warrants further study and that advanced age alone should not preclude patients from targeted therapy.

Figure 1.
Kaplan-Meier Curve of Treatment Duration, Comparing Older Individuals (≥ 75 Years of age) With Those Younger Than 75 Years of age

Figure 2.
Kaplan-Meier Curve of Overall Survival, Comparing Older Individuals (≥ 75 Years of age) With Those Younger Than 75 Years of age

Table 1

Patient Characteristics

Variable	Age, Years		P
	<75	75	
Sex			.6275
Male	73.42 (n = 906)	71.53 (n = 103)	
Female	26.58 (n = 331)	28.47 (n = 41)	
Heng Prognostic Category			.1779
Favorable	9	4	
Intermediate	65	69	
Poor	26	27	
Increased LDH (>ULN)	30.99	30.36	.891
Poor KPS (<80)	28.07	32.35	.2954
Increased Ca (>ULN)	11.29	12.4	.7061
Diagnosis to Treatment Interval (>1 Year)	50.2	58.57	.0604
Increased Neutrophils (>ULN)	15.68	12.12	.2829
Increased Platelet Count (>ULN)	21.31	17.16	.264
Low Hb (<LLN)	54.75	61.76	.1191
Metastatic (>1 Site)	76.13	70.92	.1723
Non-Clear Cell	10.26	10.69	.8792
Brain Metastases	8.73	2.84	.0128
Nephrectomy	79.68	70.92	.0133
Sarcomatoid	9.22	3.51	.0394

Data are presented as percentages. Numbers might not add up to total number of patients in each group because of missing data. Percentages might not add up to 100% because of rounding.

Abbreviations: Hb = hemoglobin; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; LLN = lower limit of normal; ULN = upper limit of normal.

Table 2

Older and Younger Population Groups Compared Based on Final Outcomes

Outcome	Age, Years		<i>P</i>
	<75	75	
Median Treatment Duration, Months	7.5	5.5	.1388
Median Survival, Months	19.7	16.8	.3321
Overall Response Rate, %	25	18	.0975