Editorial Commentary

Systemic therapy for metastatic renal cell carcinoma—is timing everything?

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Provenance: This is an invited article commissioned by the Section Editor Xiao Li, MD (Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Iacovelli R, Galli L, De Giorgi U, *et al.* The effect of a treatment delay on outcome in metastatic renal cell carcinoma. Urol Oncol 2019;37:529.e1-7.

Submitted Jun 27, 2019. Accepted for publication Jul 16, 2019.

doi: 10.21037/atm.2019.07.46

View this article at: http://dx.doi.org/10.21037/atm.2019.07.46

Timeliness of medical care for patients with newly diagnosed cancer has long been recognized as a cornerstone metric for healthcare quality. For patients with renal cell carcinoma (RCC), such considerations have largely focused on patients with localized disease awaiting curative surgery (1,2). Delays, though, often occur for patients with metastatic disease, particularly in those with symptomatic disease, and may also affect treatment outcomes. As therapeutic strategies for patients with metastatic disease continues to evolve, individualized treatment strategies, an ever-increasing number of approved regimens and multidisciplinary approaches have added significant complexity to clinical decision making. Unsurprisingly, treatment delays (TDs), defined as the time from diagnosis to treatment, continue to lengthen over time for both surgery and systemic therapy (2,3). Recognizing the therapeutic implications of TDs remains a major priority to the field. In an important step towards understanding the risks of TDs, Iacovelli and colleagues provide insight on the association between TDs and metastatic RCC patient outcomes, laying the groundwork for future efforts that optimize clinical care delivery (4).

In a large, multi-center, retrospective cohort study of metastatic clear cell RCC patients treated in Europe, Iacovelli *et al.* studied clinical outcomes of patients receiving first-line sunitinib or pazopanib (4). In their cohort of 635 patients, of whom none pursued active surveillance as an initial management strategy, the median TD was 6.3 weeks (interquartile range, 3.4–11.1 weeks). When comparing patients with TDs above and below this median, those with longer TDs were found to have a higher prevalence of metastatic disease at diagnosis (54.9% versus 34.7%, P<0.001), and were more frequently found to have osseous metastatic disease (35.9% versus 25.3%, P=0.004). However, cancer specific outcomes were comparable for patients with TDs above or below this median, including progression-free survival (PFS) (HR =1.03; 95% CI: 0.86–1.22; P=0.78) and overall survival (OS) (HR =1.04; 95% CI: 0.86–1.27; P=0.68). Importantly, no significant difference was also found when more stringent time cut-offs were used (4-week intervals between 4–16 weeks), or when adjusting for baseline prognostic factors like International Metastastic RCC Database Consortium (IMDC)-risk. In sum, these findings suggest that those patients who sustain a TD do not have inferior outcomes.

In the dynamic landscape of RCC disease management, this study is a welcome addition to the growing body of research addressing timing of treatment for patients with advanced RCC. With the development of serial anti-angiogenic agents, immune checkpoint inhibitors, and combinations of these approaches (5-7), there is a growing need for a better understanding of timeliness of therapy and optimization of treatment sequencing. For instance, large-scale efforts have investigated the timing and benefit of up-front or delayed cytoreductive nephrectomy and systemic therapy start (8,9). New endpoints including

treatment-free survival and progression-free survival of second-line therapy (PFS2) have now been introduced as outcome measures for immune checkpoint agents (10,11). Lastly, more attuned recognition and understanding of disease heterogeneity and variability in clinical courses has allowed deliberate TDs, prolonged surveillance periods and even planned treatment interruptions as a therapeutic option for select patients (12,13).

This study's results remain congruent with a similar analysis by Woldu and colleagues (14). In a cohort of 2,716 advanced RCC patients treated with anti-angiogenic targeted agents, investigators found a median TD of 2.1 months (interquartile range, 1.3–3.23 months). Further, utilizing cut-offs of <2, 2–4, 4–6, and >6 months, sustaining a TD was not independently associated with OS (14). Since both studies utilize different time scales, understanding the clinical significance of a TD in the context of other factors incorporated in up-front therapy management is important. Firstly, there often is an expected delay in medical care due to logistics of coordinating care delivery after the diagnosis of cancer. Even at a high volume cancer center with programs in place to improve time-to-treatment, delays of at least 3–4 weeks are usual (15). In addition, anticipating time-to-response (TTR) for first-line treatments provides perspective on the importance and potentials risks of TDs when considering systemic therapy for patients with metastatic disease. In an unplanned cross-trial analysis of objective response rates to sunitinib across six clinical trials for advanced RCC, the median TTR was 2.7 months (range, 0.7–23.6 months) (16). Median TTRs for patients treated with newer agents have also remained similar: combination ipilimumab plus nivolumab, axitinib plus pembrolizumab or axitinib plus avelumab were 2.8 months (range, 0.9–11.3months), 2.8 months (range, 0.7–15.2 months) and 1.6 months (PD-L1+ cohort, range, 1.2–10.1 months), respectively (5,6,17). Although TTR does not seem to have shifted significantly, the continued wide ranges listed here stress that some patients face long delays in response even after therapy has commenced. Appreciating these benchmarks provides additional context for the clinical significance of delays, particularly as new treatments emerge.

The authors notably point out that one of the inherent challenges of this retrospective review was the inability to completely characterize underlying reasons for TD for each patient. As 55% of patients who sustained a prolonged delay had metastatic disease at diagnosis, and this *de novo* presentation was significantly higher compared to the non-delayed cohort, understanding the reasoning for these delays may impact our interpretation of survival outcomes. In practice, many patients undergo metastatic site directed therapy with either surgery or radiation and hence purposeful delays often occur in starting systemic therapy as patients recover from these interventions. An area of interest for future efforts should be to investigate similar endpoints but distinguish those patients who sustained a delay due to medical need from those who may have sustained a delay because of care logistics or patient preference.

Beyond this, work which identifies the specific reasoning for TDs also has broader value as it could add perspective to healthcare disparities and barriers to care. For instance, racial disparities have been shown to have a significant influence on survival outcomes for patients receiving anti-angiogenic targeted agents (18,19). A highlighted retrospective observational study of the growing nationalized healthcare program in the United States highlights the potential for a reduction in racial disparities in healthcare (20), and the field awaits further work on whether closing these gaps has the capability of equalizing survival outcomes amongst different ethnicities. Therefore, a broader analysis of additional factors like healthcare access or socioeconomic status may provide a wider context and help inform thoughtful interventions to improve upon other aspects of healthcare quality (21).

Future investigations should also encompass a patient's individual perspective to a TD, as this aspect factors into joint decision making. Depressive symptoms have been identified as a significant factor for metastatic RCC survival, and translational work has recognized inflammatory biological changes related to mood in advanced RCC patients (22). It has also been shown that measures of anxiety, depression and quality of life metrics do not significantly change over time when selected patients undergo active surveillance (13). This, however, may not be the case before a management plan is formulated and presented by the treating physician. So, how can the timing of treatment initiation, not the actual regimen, be individualized to a patient's need and communicated to the patient? In other words, what degree of TD may be acceptable for one patient but not the next? Many clinicians utilize the Memorial Sloan Kettering Cancer Center (MSKCC) or IMDC risk criteria to help prognosticate a patient's disease course and formulate a treatment plan. The authors importantly recognize how these risk metrics impact survival and incorporate IMDC risk stratification

in their analysis. As clinicians become better armed with enhanced predictive models which incorporate genomic data (23), application of molecular profiling to this type of dataset may provide tumor biological characteristics that identify patients who can safely undergo a TD or a prolonged surveillance period without a detrimental impact on survival.

Iacovelli and colleagues provide much needed evidence on how metastatic RCC patients who sustain prolonged TDs have similar outcomes when compared to those who start systemic anti-angiogenic targeted agents earlier. As TDs remain a common occurrence in cancer care, the authors should be commended for their meticulous work as their results respond to a question many patients deliberate on after diagnosis. While these results provide clinicians with the confidence to reassure patients when uncontrollable delays occur, future studies focusing on why TDs happen provides additional context that can be applied in clinical practice. Most importantly, studies such as this should also not detract from larger efforts aimed at optimizing timeliness of medical care. Initiatives that uncover barriers or disparities continue to remain vital so that all patients may be promptly seen and treated.

Acknowledgments

None.

Footnote

Conflicts of Interest: MH Voss has received research support from Bristol-Myers Squibb, Genentech, Novartis and Roche, travel and accommodation support from Eisai, Novartis and Takeda and has been a paid consultant for Alexion, Bayer, Calithera, Corvus, Eisai, Exelixis, GlaxoSmithKline, Natera, Novartis and Pfizer. RR Kotecha has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kotecha RR, Voss MH. Systemic therapy for metastatic renal cell carcinoma—is timing everything? Ann Transl Med 2019;7(Suppl 6):S185. doi: 10.21037/atm.2019.07.46

