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Exploring the Effect of Medication Features in Renal Cell Carcinoma: A Patient Preference Study

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INTRODUCTION

- The introduction of targeted therapies has greatly improved outcomes in patients with metastatic renal cell carcinoma (mRCC). However, these treatments often vary in efficacy, in terms of progression-free survival (PFS) and response rate, and have different toxicity profiles.
- Three previous studies that examined patient preferences for RCC treatment options with respect to clinical benefit (PFS) and risks (treatment-related toxicities and serious adverse events [AEs]) found that both potential efficacy and toxicities influenced patients' treatment preferences.[1–3]
  - Prolonging PFS was identified as the most important treatment characteristic in two studies; however, patients were also willing to accept shorter PFS to avoid some severe types of toxicity.
- These three studies, however, presented treatment profiles with no uncertainty surrounding expected PFS and did not consider that some AEs may be correlated with efficacy.[4–9]
- In addition, none of these studies examined patients' preferences for dosing options, that is, continuous daily dosing or dosing schedules that include a treatment break.
- Here we report the results of an online survey of RCC patients in the USA and Canada that explored patient preferences with regard to mRCC treatment attributes.

OBJECTIVE

- The objective of this study was to explore patient preferences for hypothetical mRCC medicines with different features, presented as tradeoffs between potential efficacy and possible side effects.
  - Specifically, patients were asked to choose between medicines that (1) were associated with uncertainty in efficacy (i.e. different chances of achieving a longer PFS) and (2) had different dosing schedules (i.e. with or without a 2-week break), each choice associated with a different side-effect profile.
  - In addition, the study investigated the effect on preferences when patients were provided with information about potential correlations between treatment-related toxicity and efficacy.

METHODS

Study Population

- Patients were recruited through the Kidney Cancer Association and Kidney Cancer Canada in October and November 2014.
- All respondents were 18 years of age or older and had self-reported mRCC or non-metastatic RCC.
- Prior to participating in the online survey, eligible respondents were required to provide informed consent by clicking "I agree to participate in this study" to signal that they had read and understood the informed consent text, explaining pertinent aspects of the study.
- This study was run in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and was approved by an institutional review board at RTI Health Solutions (Research Triangle Park, NC, USA).

Survey

- An online survey to measure patient preferences for hypothetical mRCC medicines with different characteristics was developed with input from clinicians who work with RCC patients, the Kidney Cancer Association, and Kidney Cancer Canada.
- The survey was pretested using face-to-face cognitive interviews with 20 RCC and mRCC patients.
  - The pretesting focused on patient comprehension, the accuracy of question wording, and the completeness of the response categories.
- Patients were presented with choices between medicines with different characteristics and asked to select their preferred option.
- Half of the respondents were provided with information about a potential correlation between toxicity and efficacy: based on existing literature, they were told that three AEs might be linked to longer PFS (fatigue, hand–foot syndrome, and hypertension)[4,5,7,8] and that a fourth AE (diarrhea) was not.
  - These AEs are also common to many targeted therapies, important to patients, and represent toxicities that improve when treatment is interrupted.
  - After the description of each side effect, respondents were asked what level of the side effect they thought they could tolerate.
- General patient characteristics (age, gender, time since diagnosis, presence of metastatic disease, current and past treatment[s], and experience with selected AEs) were collected to characterize the population sample and serve as explanatory variables in the choice analysis.
- A series of exploratory questions assessed patient tradeoffs between (1) the chance of longer PFS (2+ years) but with more severe toxicity during targeted treatment (Figure 1) and (2) continuous daily dosing versus dosing schedules with a 2-week break with regard to the occurrence of side effects (Figures 2–4).

Figure 1. Survey question on uncertainty in efficacy (i.e. the chance of longer PFS [2+ years]) and potentially more severe toxicity.

Suppose that your doctor tells you that there are two hypothetical medicines you can take – Medicine A and Medicine B. Both medicines will work for about 9 months on average. After 9 months, when the medicine stops working, people would have to take a different medicine. But for some patients, the medicine worked for 24 months (2 years) or more.

Please indicate below which medicine you would choose if these were the only options available.

Medicine features	Medicine A	Medicine B
Percentage of patients for whom the medicine worked for **2 years or more**	10% of patients (medicine worked for less than 2 years for 90% of patients)	15% of patients (medicine worked for less than 2 years for 85% of patients)
Side effects • Feeling weak and tired • Sores on hands and feet • Diarrhea	Mild	Moderate
Which medicine would you choose if these were the only options available?	**Medicine A** ○	**Medicine B** ○

Figure 2. Survey question on dosing schedule with no information provided about the side effects during targeted treatment.

Some RCC medicines are taken every day, while some include a break when you do not take the medicine.

Which medicine schedule would you prefer? Assume that both medicines are equally effective at treating your RCC.

- ○ **I would prefer a medicine schedule without a break that has a constant level of side effects**
- ○ **I would prefer a medicine schedule that includes a 2-week break during which the side effects get better**
- ○ **Don't know/not sure**

Figure 3. Survey question on dosing schedule, including a description of the side effects during targeted treatment (moderate vs. mild to severe).

Compared to medicines you take every day, medicines that include a break in the schedule can sometimes have more intense side effects while you are taking the medicine. During the break, the side effects diminish or go away.

Please look at the two medicines below and think about which schedule you would prefer. Assume that both medicines are equally effective at treating your RCC.

Medicine features	Medicine A	Medicine B
Schedule and side effects	Take one pill every day • Moderate side effects all the time This continues until you stop taking the medicine	Take one pill every day for 4 weeks • Side effects increase from none or mild to severe by the end of the 4 weeks 2-week break (no pills) • Side effects decrease to mild or none during the 2-week break This continues until you stop taking the medicine
Which medicine would you choose if these were the only options available?	**Medicine A** ○	**Medicine B** ○

Figure 4. Survey question on dosing schedule, including a description of the side effects during targeted treatment (mild vs. none to moderate).

Compared to medicines you take every day, medicines that include a break in the schedule can sometimes have more intense side effects while you are taking the medicine. During the break, the side effects diminish or go away.

Please look at the two medicines below and think about which schedule you would prefer. Assume that both medicines are equally effective at treating your RCC.

Medicine features	Medicine A	Medicine B
Schedule and side effects	Take one pill every day • Mild side effects all the time This continues until you stop taking the medicine	Take one pill every day for 4 weeks • Side effects increase from none to moderate by the end of the 4 weeks No pills for 2 weeks • Side effects decrease to none during the 2-week break This continues until you stop taking the medicine
Which medicine would you choose if these were the only options available?	**Medicine A** ○	**Medicine B** ○

Models and Analysis

- Analyses examined the impact on survey choices of patient characteristics, disease status, current targeted treatment status, and whether the respondent received information about potential correlations between AEs and efficacy.
- The final models included demographic variables (gender, age), disease status (diagnosed within the last 3 years, metastatic disease at diagnosis, whether the patient reported that they did not have a tumor in their kidney anymore, whether the patient reported that they would be willing to tolerate severe side effects), and whether the respondent was provided information about potential correlations between AEs and efficacy.
- Other variables were investigated based on previous findings and pretest interviews, but were consistently insignificant in the model, including whether the respondent had been on other targeted treatments in the past, whether or not they had children under the age of 18, educational attainment, and whether the respondent thought hypothetical cancer medicines would work better than average for them.
- Survey questions regarding respondent choice in medicine were analyzed using mean values and logistic regression models.
  - Using separate models, odds ratios (with standard errors) were calculated to indicate which medicine was chosen by respondents for the following categories of survey questions:
    - uncertainty in efficacy (PFS) (Figure 1): the dependent variable = 1 if the respondent selected the option with the higher probability of 2+ years of PFS and worse side effects, and = 0 if the respondent selected the option with the lower probability
    - dosing schedule (Figures 3 and 4): the dependent variable = 1 if the respondent selected the option with the 2-week break, and = 0 if the respondent selected continuous daily dosing.
  - The independent variables in the models were the patient characteristics of the survey respondents (Table 1), including whether the respondent received information about potential correlation of AEs with efficacy.

Table 1. Patient characteristics of survey respondents.

Characteristic	Overall (N=378)
Male, %[a]	65
Mean age, years[a]	57.3
Country of residence, %[a]	
USA	76
Canada	20
Other or missing	4
Diagnosed within the last 3 years, %	32
mRCC at diagnosis, %	50
Currently on targeted treatment	59[b]
Not currently on targeted treatment	41[b]
Currently on targeted treatment, %	31
Patient reported that they did not have a tumor in their kidney anymore, %	81
Received information regarding correlation of AEs with efficacy, %	47
Patient reported that they would be willing to tolerate severe fatigue, hand–foot syndrome, or diarrhea, %	15

[a]The number of respondents who answered questions regarding gender, age, and country of residence were 364, 360, and 356, respectively, rather than 378.
[b]Percentage based on number of patients with mRCC.

RESULTS

Patient Characteristics of Respondents

- In total, 378 respondents completed the survey, of whom 32% were diagnosed within the last 3 years; 50% were diagnosed with mRCC and 31% were currently on targeted treatment; 76% were from the USA and 45% were male (Table 1).
  - The numbers of respondents included in the logistic regression models ranged from 343 to 345, after excluding respondents who skipped questions or answered "I don't know."
- Overall, 19% of respondents with mRCC reported a willingness to tolerate at least one severe side effect compared with 11% of respondents who did not have metastatic disease (P-value 0.03 using a Pearson chi-square test).

Respondents' Preferences Regarding Uncertainty in Efficacy

- Overall, 40% of respondents (50% of respondents with mRCC) selected the medicine with a 15% chance of longer PFS [2+ years] (5% higher chance than with the other medicine) and worse side effects.
- In the logistic regression model (Table 2), the following respondents were significantly more likely to prefer the option of a medicine with a higher probability of longer PFS and worse side effects: men, all patients with mRCC, those who received information about potential correlations between AEs and efficacy, and those who reported that they would be willing to tolerate severe side effects.
  - Compared with patients without metastatic disease, respondents with mRCC who were currently on targeted treatment were more than 3 times as likely to make this choice and mRCC patients not on targeted treatment were 2.4 times as likely.
  - Respondents who received information about correlations of AEs with efficacy or who reported that they would be willing to tolerate severe side effects were more than twice as likely to make this choice, compared with those who did not receive this information or did not report a willingness to tolerate severe side effects, respectively.

Table 2. Logistic regression analysis of factors predictive for respondents' choice in medicine.

	Odds ratio [SE]		
	Uncertainty in efficacy	Dosing schedules	
Independent variable	Choice of medicine with 15% chance of longer PFS (moderate side effects) vs. 10% chance of longer PFS (mild side effects) (n=345)[a]	Choice of medicine with 2-week dosing break (mild to severe side effects) vs. continuous daily dosing (moderate side effects) (n=343)[a]	Choice of medicine with 2-week dosing break (none to moderate side effects) vs. continuous daily dosing (mild side effects) (n=345)[a]
Male	1.775* [0.438]	0.790 [0.182]	1.382 [0.317]
Age	0.989 [0.013]	0.979 [0.013]	1.001 [0.013]
Diagnosed within the last 3 years	1.504 [0.415]	0.633 [0.174]	0.889 [0.230]
mRCC at diagnosis and currently on targeted treatment	3.254** [0.945]	2.044** [0.556]	1.686 [0.461]
mRCC at diagnosis and currently not on targeted treatment	2.442** [0.776]	1.287 [0.390]	1.645 [0.481]
Patient reported that they did not have a tumor in their kidney anymore	1.487 [0.495]	0.875 [0.266]	0.818 [0.255]
Received information regarding correlation of AEs with efficacy	2.302** [0.549]	1.012 [0.229]	1.272 [0.283]
Patient reported that they would be willing to tolerate severe fatigue, hand–foot syndrome, or diarrhea	2.002* [0.679]	0.912 [0.300]	0.964 [0.300]
Constant[b]	0.187* [0.151]	2.581 [2.159]	0.486 [0.390]

SE, [robust] standard error.
*P<0.05 and **P<0.01 (*z*-test).
[a]The analysis sample does not include respondents who skipped questions or answered "I don't know."
[b]The constant is the mean value for the reference group (i.e. the group for which all other variables = 0).

Respondents' Preferences Regarding Dosing Schedules

- The majority of the patients (59%) preferred a targeted treatment with a 2-week break in the dosing schedule, compared with continuous daily dosing, when provided with no information about potential differences in side effects during treatment (Figure 2); 25% selected continuous daily dosing and 16% were unsure.
- Forty percent (46% of respondents with mRCC) preferred a targeted treatment with a 2-week break in the dosing schedule with side effects that varied from mild to severe, compared with continuous daily dosing with moderate side effects (Figure 3).
- Similarly, 42% (50% of respondents with mRCC) preferred a targeted treatment with a 2-week break in the dosing schedule when side effects varied from none to moderate, compared with continuous daily dosing with mild side effects (Figure 4).
- In the logistic regression model (Table 2), respondents with mRCC who were currently on targeted treatment were twice as likely to prefer the medicine with the 2-week break and mild to severe side effects, compared with continuous daily dosing and moderate side effects.
  - Although approximately equal proportions of respondents selected the medicine with the 2-week break in the two questions (Figures 3 and 4: 40% vs. 42%, respectively), 30% of respondents switched from Medicine A to B or from Medicine B to A when answering the second question.

DISCUSSION

- Our findings suggest that patients with mRCC are more willing to accept medicines with more severe side effects for the chance of a better outcome. However, patterns of response indicated highly individualized preferences with regard to the tradeoffs that patients are willing to make.
- This is consistent with earlier studies in which patients were found to be willing to make such tradeoffs.[1–3] However, the earlier studies did not provide information regarding potential associations between side effects and efficacy and failed to assess dosing schedule preferences.
- The responses to the dosing schedule questions suggested that patients with mRCC who were currently on targeted treatment were more likely to perceive a benefit from the schedule with the 2-week break (with mild to severe side effects) than patients who do not have metastatic disease. This may be due to their reported willingness to accept more severe side effects, but with a treatment break included.
- Based on the logistic regression analysis, patients with multiple characteristics associated with a choice in medicine (e.g. received information about potential correlations between side effects and efficacy and reported a willingness to tolerate severe side effects), would be likely to experience an additive effect in which the odds of selecting that medicine were even higher than if they had only one such characteristic.
- Limitations to this study included potential selection bias that may have been introduced by the study recruitment process and survey administration method: the respondents for this study were recruited by patient support organizations and respondents took the survey online with their own computers, tablets or smart phones.
- Another potential limitation was that diagnosis of RCC or mRCC was self reported.
- Finally, the data are based on responses to hypothetical choice profiles. These choices are intended to simulate possible clinical decisions, but obviously do not have the same clinical, financial, or emotional consequences of actual decisions. Thus, differences can arise between stated and real-world choices.
- Additional discrete choice experiment (DCE) analysis is underway and will provide more results on patient preferences for medication profiles, including the importance of information received.

CLINICAL IMPLICATIONS

- These findings suggest that patients have diverse preferences regarding medicine features and outcomes, but that many may be willing to continue targeted treatment, even in the presence of severe AEs, if there is a chance of improved clinical benefit.
- Physicians need to provide patients with comprehensive information about medication features, including side effects and efficacy (and their potential correlation), to provide a personalized and optimal approach to treatment.
- Finally, many patients may be willing to accept potentially higher levels of AEs but, in turn, subsequently prefer a dosing schedule with a break (which is also preferred by the majority, when provided no information about side effects).

REFERENCES

1. Wong MK, Mohamed AF, Hauber AB, et al. *J Med Econ* 2012;15:1139–1148.
2. Park MH, Jo C, Bae EY, Lee EK. *Value Health* 2012;15:933–939.
3. Mohamed AF, Hauber AB, Neary MP. *Pharmacoeconomics* 2011;29:977–988.
4. Poprach A, Pavlik T, Melichar B, et al. *Ann Oncol* 2012;23:3137–3143.
5. Rini BI, Cohen DP, Lu DR, et al. *J Natl Cancer Inst* 2011;103:1–11.
6. Rautiola J, Donskov F, Peltola K, et al. *BJU Int* 2014; Sep 23 [Epub ahead of print].
7. Michaelson MD, Cohen DP, Li S, et al. *J Clin Oncol* 2011;29(Suppl. 7) (Abstract 320).
8. Davis MP, Figlin RA, Hutson TE, et al. *Eur J Cancer* 2011;47(Suppl. 1):S135 (Abstract 1139).
9. Donskov F, Cams A, Barrios CH, et al. *Eur J Cancer* 2011;47(Suppl. 1):S136 (Abstract 1141).

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