How Much Do Patients with Renal Cell Carcinoma (RCC) Value Progression-free Survival in Medical Decision Making—Results from a Benefit-Risk Conjoint Study

ABSTRACT 27007

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ABSTRACT

Background: Overall survival (OS) has been traditionally used as the primary endpoint in oncology trials; however, crossover to 2nd line agents may result in biases for OS. Recent trials have used progression-free survival (PFS) as the primary endpoint. An understanding of patient preferences regarding expected PFS versus avoidance of risk for toxicities in medical decision-making is needed.

Objective: To estimate RCC patients' willingness to accept toxicities and medication-related risks to increase PFS.

Methods: US residents aged 18 years and over with RCC completed a web-enabled, choice-format conjoint survey that presented a series of 12 trade-off questions, each including a pair of hypothetical RCC medication profiles. Each profile was defined by efficacy (PFS), tolerability effects (fatigue, diarrhea, hand-foot syndrome, mouth sores), and medication-related risks (liver failure, blood clot). OS was held constant at 32 months. Trade-off questions were based on predetermined experimental design with known statistical properties. Random-parameters logit model was used to estimate a preference weight for each attribute level. Preference weights were used to calculate maximum levels of risks that patients were willing to accept for increases in PFS.

Results: 138 US patients completed the survey. PFS was the most important attribute to patients over the range of levels included in the survey, while remaining attributes were ranked in order of importance as: fatigue, diarrhea, liver failure, hand-foot syndrome, blood clot, mouth sores. Increasing PFS by 10 months was as important as avoiding severe fatigue and 2-times as important as avoiding severe mouth sores. Patients were willing to accept blood-clot risks up to 5.5% (95% CI: 3.6% - 8.6%) and liver-failure risks up to 3.6% (95% CI: 2.6% - 4.8%) to increase PFS by 10 months.

Conclusion: PFS is a clinical outcome that is important to RCC patients. Patients were willing to accept higher treatment-related risks to increase PFS.

BACKGROUND

- Overall survival (OS) has been traditionally used as the primary endpoint in oncology trials; however, crossover to second-line agents may bias the OS analysis
- Recent trials have used progression-free survival (PFS) as the primary endpoint
- Understanding patient preferences regarding expected PFS compared to avoidance of risk for toxicities is needed in medical decision-making

OBJECTIVE

- To estimate the willingness of patients with renal cell carcinoma (RCC) to accept toxicities and medication-related risks to increase PFS

METHODS

Patients

- Inclusion criteria
  - Aged ≥ 18 years
  - United States (US) resident
  - Self-reported physician-made diagnosis of RCC
- Recruitment
  - Kidney Cancer Association
    - Member panel
  - Study was approved by RTI's institutional review board
  - All patients provided online informed consent
  - Final sample population was 138

Survey Instrument

- Web-enabled survey instrument
- Discrete-choice experiment (choice-format conjoint survey method)
  - Elicits patient trade-offs among alternatives with varying levels of different attributes
  - The most valid and reliable technique available for quantifying preferences[2,3,4]
- 12 trade-off questions from among constructed medication profiles, each described by efficacy (PFS), tolerability effects (fatigue, diarrhea, hand-foot syndrome, mouth sores), and medication-related risks (liver failure, blood clot) (**Table 1**)
  - OS was held constant at 32 months
  - Patients were asked to choose the option they would prefer if these were the only options available to them (**Figure 1**)

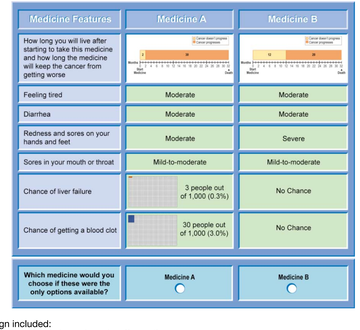
METHODS (continued)

Table 1. Treatment Attributes and Levels Used in the Survey Instrument

Attribute	Abbreviated Label	Levels
How long you will live after starting to take the medicine and how long the medicine will keep the cancer from getting worse	Progression-free survival	PFS = 24 months; OS = 32 months PFS = 12 months; OS = 32 months PFS = 2 months; OS = 32 months
Feeling tired	Tiredness	No tiredness Mild tiredness Moderate tiredness Severe tiredness
Diarrhea	Diarrhea	Mild Moderate Severe
Redness or sores on your hands or feet	Hand-foot syndrome	Mild Moderate Severe
Sores in your mouth or throat	Mouth sores	Mild Mild to moderate Severe
Chance of liver failure	Liver failure	No chance 3 out of 1,000 (0.3%) 15 out of 1,000 (1.5%) 30 out of 1,000 (3.0%)
Chance of getting a blood clot	Blood clot	No chance 3 out of 1,000 (0.3%) 15 out of 1,000 (1.5%) 30 out of 1,000 (3.0%)

OS, overall survival (ie, how long you will live after starting to take the medicine); PFS, progression-free survival (ie, how long the medicine will keep the cancer from getting worse).

Figure 1. Example of a Trade-off Question



- The experimental design included:
  - Combinations of attribute levels in each trade-off question
  - A statistically efficient experimental design with known statistical properties[5,6,7]
  - 2 survey versions with different combinations of 12 trade-off questions, randomly assigned to patients
- Survey instrument also collected standard demographic information (eg, age, gender, race, marital status, and education) and items about the patients' experiences with RCC and RCC treatments

Analysis

- Estimated relative preference weights using multivariate, random-parameters, or mixed-logit estimation[8,9]
  - Importance weights for each medication feature
- Maximum acceptable risk (MAR) was considered as follows:
  - MAR is a measure of risk tolerance—the mean maximum level of treatment-related risk that patients are willing to accept for a given improvement in RCC symptoms or outcomes
  - Statistically, MAR is the ratio of the relative importance of a change in a given benefit level divided by the relative importance of a change in treatment-related risk, controlling for the fact that a given patient will not experience a specified benefit if the adverse event is fatal
  - MARs were estimated for liver failure and blood clot for various improvements in RCC symptoms and outcomes

RESULTS

Demographic Characteristics (N = 138)

- Mean age: 57 years (SD = 9.3)
- White: 96%
- Female: 51%
- Married: 76%
- Some college education or higher: 96%

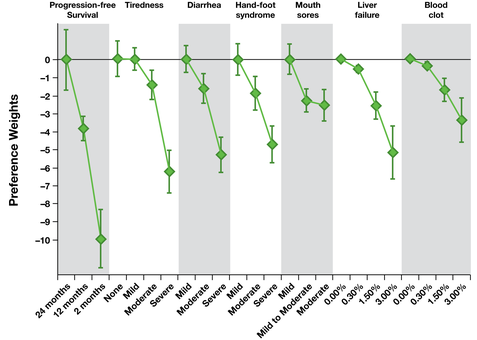
RCC Treatment Experience (N = 138)

- Diagnosed at least 2 years prior: 67%
- Treated by nephrectomy (surgical removal of kidney): 98%
- Spread to another part of the body: 37%
- Currently treated with prescription medication: 24%

Preference Weights (Figure 2)

- Relative preference weights for each medication attribute and level were scaled between 0 and –10
  - A preference weight of 0 was assigned to the best level for each attribute (eg, 24 months for PFS)
  - All other attribute levels were scaled relative to the best level for each attribute
  - More-preferred outcomes had higher preference weights than less-preferred outcomes
- Estimated preference weights for all 7 attributes were consistent with the natural ordering of the categories
  - Better clinical outcomes were preferred to worse clinical outcomes
- The vertical distance between adjacent preference weights represents the relative importance of moving from 1 level of an attribute to an adjacent level of that attribute
  - The relative importance of an improvement in PFS of 10 months (2 months to 12 months) was ~ 6.1
  - The relative importance of avoiding severe fatigue (severe tiredness to no tiredness) was ~ 6.2
  - The relative importance of an improvement in mouth sores from moderate to mild was ~ 2.5
  - Therefore, increasing PFS by 10 months was as important as avoiding severe fatigue and 2-times as important as an improvement in mouth sores from moderate to mild
- PFS was the most important attribute
- The remaining attributes were ranked in decreasing order of importance as follows:
  - Fatigue (tiredness)
  - Diarrhea
  - Liver failure
  - Hand-foot syndrome
  - Blood clot
  - Mouth sores

Figure 2. Preference Weights for Attributes and Levels



Note: The vertical bars surrounding each mean preference weight denote the 95% confidence interval about the point estimate.

RESULTS (continued)

Maximum Acceptable Risk (Table 2)

- In general, the MARs for blood clot were higher than those for liver failure for the same benefit
- To improve PFS by 10 months (from 2 months to 12 months), patients' MARs were:
  - 5.5% (95% CI: 3.6% - 8.6%) for blood clot
  - 3.6% (95% CI: 2.6% - 4.8%) for liver failure

Table 2. Maximum Acceptable Risk Estimates

	Liver Failure	Blood Clot
Improvement	MAR (95% CI)	MAR (95% CI)
Progression-free survival		
2 months to 24 months	5.77% (4.09% - 7.92%)	8.86% (5.97% - 13.52%)
2 months to 12 months	3.55% (2.58% - 4.82%)	5.45% (3.59% - 8.55%)
12 months to 24 months	2.22% (1.14% - 3.51%)	3.41% (1.76% - 5.59%)
Tiredness		
Mild to none	2.35% (0% - 0.78%)	0.04% (0% - 1.17%)
Moderate to none	0.83% (0% - 1.99%)	1.27% (0% - 3.03%)
Severe to none	3.59% (2.42% - 5.28%)	5.51% (3.59% - 8.92%)
Moderate to mild	0.80% (0.21% - 1.65%)	1.23% (0.33% - 2.59%)
Severe to mild	3.57% (2.53% - 5.05%)	5.48% (3.67% - 8.74%)
Severe to moderate	2.77% (1.85% - 3.89%)	4.25% (2.66% - 6.83%)
Diarrhea		
Moderate to mild	0.94% (0.22% - 1.89%)	1.44% (0.33% - 3.19%)
Severe to mild	3.06% (2.18% - 4.29%)	4.69% (2.98% - 7.86%)
Severe to moderate	2.12% (1.30% - 3.07%)	3.25% (1.79% - 5.49%)
Hand-foot syndrome		
Moderate to mild	1.09% (0.20% - 2.19%)	1.67% (0.29% - 3.81%)
Severe to mild	2.73% (1.93% - 3.71%)	4.19% (2.63% - 6.71%)
Severe to moderate	1.65% (0.78% - 2.47%)	2.53% (1.18% - 4.02%)
Mouth sores		
Mild-to-moderate to mild	1.33% (0.67% - 2.20%)	2.04% (0.93% - 3.87%)
Moderate to mild	1.47% (0.54% - 2.77%)	2.25% (0.80% - 4.65%)
Moderate to mild-to-moderate	0.14% (0% - 0.98%)	0.21% (0% - 1.52%)

CI, confidence interval; MAR, maximum acceptable risk.

CONCLUSIONS

- PFS is a clinical outcome that is important to patients with RCC
- Patients were willing to accept higher treatment-related risks to increase PFS

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ACKNOWLEDGMENTS

Presented at: International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 15th Annual Meeting; May 15-19, 2010; Atlanta, Georgia.

This research was supported by GlaxoSmithKline, Collegeville, Pennsylvania, USA.