Optimizing Dose Intensity for Patients with Metastatic Renal Cell Carcinoma

Treatment regimens for oral therapies; dosing instructions; common side effects; and dose modifications and schedule changes for sunitinib therapy in metastatic renal cell carcinoma

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Abstract

Kidney Cancer is a relatively rare cancer, and often community oncologists do not treat many cases over the course of a year. Dr. Roberto Pili, a Professor of Oncology and the then Chief of the Genitourinary Section at *Roswell Park Cancer Institute* (RPCI), identified a clinical performance gap and an underlying educational need in the area of optimizing treatment strategies for patients with metastatic renal cell carcinoma (mRCC). Teaming with *Medscape, LLC*, Dr. Pili and RPCI developed an internet-accessible CME activity, worth 0.5 credits, to meet this need.

A live, roundtable discussion between Dr. Pili and a community oncologist, Dr. Michael Krabak, was videotaped, during which they explored the management of mRCC, using case studies to illustrate their reasoning in patient-management choices. At the conclusion of viewing this activity via *Medscape*, eight-hundred thirteen (813) physicians and four-hundred sixty-nine (469) other practitioners took the credit award test at the end, resulting in 401 CME hours and 234.5 non CME credits being awarded. Ninety-one percent (91%) of those participating in this activity reported that they would recommend it to others, with 96% believing participation in this activity promoted better health care.

Purpose

This program was designed to encourage oncologists and urologists to appropriately utilize dose modifications and schedule changes for their patients with metastatic renal cell carcinoma (mRCC), with the aim of maximizing positive treatment outcomes while minimizing adverse events. Upon completion of this activity, participants will be able to:

1. Identify standard treatment for mRCC with regard to dosing schedule; adverse effect profiles; dosing flexibility, and dose intensity;

2. Identify common adverse effects associated with agents used to treat mRCC, and strategies for managing toxicities;

3. Describe the effect of dose reductions and interruptions on clinical outcomes;

4. Identify customized dosing strategies to maximize drug exposure for patients being treated with targeted therapies for mRCC;

5. Develop a comprehensive care plan to monitor and manage patients with mRCC.

Scope/Methods

Oncologists, urologists, nephrologists and other physicians who care for patients with mRCC need to be aware of the impact of medication dose modifications on clinical benefit, and be knowledgeable about strategies to maintain dose intensity. Dr. Pili's personal experience in providing care for patients with mRCC within the community and at Roswell Park Cancer Institute led him to identify that oncologists, at least sometimes, delayed or decreased the dose of a medication due to side effects. Local consultations with community oncologists, plus RPCI information (data, pts referred to RPCI) confirmed the need to inform and educate oncologists on ways to manage dose control and side effects of biologic therapies.

To address knowledge and clinical practice gaps at the community level, a foundational and case-based roundtable discussion was created and videotaped with the intention of distributing it nation-wide via Medscape to educate oncologists and other interested health care professionals about pitfalls occurring when treating this rare cancer. Participating in this videotape were Dr. Michael Krabak, an oncologist with a large Western NY community medical practice, and Dr. Roberto Pili, then a Professor of Oncology and Chief of the Genitourinary Section, in the Department of Medicine at RPCI. After review of the content by Dr. Pili and the Medscape Education Oncology Scientific Director, S. Freida Pierce, PhD, for content accuracy, a compliance review was conducted by an external reviewer with no conflicts of interest to ensure compliance.

Case-based discussions were used to focus on:

1) the impact of side effects on need for dose modifications and schedule changes in mRCC;
2) the importance of maintaining dose intensity in treatment of mRCC;
3) clinical data on the relationship between dose exposure and clinical benefit;
4) strategies for maximizing dose intensity, schedule changes, side effect management, and utilization of biomarkers to optimize patient benefit.

Through real-world case presentations, it was hoped that clinician participants viewing the videotape discussion would learn about best practices in managing treatment dose modifications, and therefore, be better able to analyze their clinical patient situations. Four test questions were created to assess knowledge attained, and the application of that knowledge relating to the learning objectives (Attachment A). Three additional questions to assess application of that knowledge (Attachment B), and twelve evaluation questions were also used to evaluate the activity.

To measure the effects of this educational intervention, for approximately one month, Feb 6, 2014 – March 15, 2014 (37 days), oncologists participating in this activity were given pre and post test questions, comparing same participant responses pre and post activity exposure to the same questions. A paired 2-tailed t-test was used to assess whether the mean pre-assessment score was different from the mean post-assessment score. A Pearson's $\chi 2$ statistic was used to measure changes in responses to individual questions. Probability values (*P* values)

were also calculated for both t-test and χ2 statistics to determine significance level (α). This report considers a *P* value of less than .05 as meeting statistical significance, demonstrating that a change occurred from the pre-assessment to the post-assessment. The calculated effect size of the educational intervention also is reported. This **Linked-Learning Impact** analysis can be used to validate the effectiveness of this educational activity.

Results

During the course of a calendar year (February 6, 2014 – February 5, 2015), 1,273 people viewed the Drs. Pili and-Krabak's *Medscape* Roundtable Discussion: *Optimizing Dose Intensity for Patients With Metastatic Renal Cell Carcinoma*, (which can be viewed at: (http://www.medscape.org/viewarticle/819837). Of these participants, 813 were physicians, and 469 "other" health care professionals, such as pharmacists, nurses/NPs, physician Assistants, and one "consumer." Of the 813 physicians, 804 correctly completed the certification test, resulting in their receiving .5 AMA CME credit and a CME Completion Certificate. All 469 non-CME participants successfully completed the post-activity test, with each receiving a post-activity completion certificate worth .5 hour of CE credit. A combined total of 635.50 continuing education credits were awarded.

Participant comments repeatedly described the activity as "good" or "excellent," There were no "negative" comments, just one constructive criticism comment who wished we would have had an option on post-test questions for participants to choose if they did not treat patients with mRCC. When participants were asked about other topics that they would like to see on future educational programs, oncology topics were mentioned most often, followed by more renal-related topics. The case studies were also appreciated, and it was mentioned as something participants would like to see more often in "all fields."

In the **Linked-Learning Impact** Analysis part of this activity **(**February 6, 2014 to March 15, 2014) a total of 54 oncologists answered all the assessment questions in the activity. *(Note: Percentages are rounded to the nearest whole number.)* For oncologists who participated in this part of the CME activity, comparison of responses to individually linked pre-assessment questions to their respective post-assessment questions demonstrates statistically significant improvements (n = 54; *P* <.05). Correct responses on post-assessment questions were higher after CME completion (compared with pre-assessment responses).

For the oncologists who participated in the CME Linked-Learning Impact activity assessment, analysis shows a statistically-significant impact of education. On average, participants selected the best response for 2 out of 4 questions prior to education and for 3 out of 4 questions after education. The effect size is large at 0.907 for this educational intervention. A table of metrics is below:

Metric	Pre-assessment	Post-assessment
Sample Size	**54**	**54**
Mean (Correct Answers)	**2.407**	**3.315**
Standard Error	**0.097**	**0.118**
Median (Correct Answers)	**2**	**4**
Standard Deviation	**0.714**	**0.865**
Sample Variance	**0.51**	**0.748**
Effect Size	**—**	**0.907**
***P* Value**	**—**	**<.05**

Summary

For the *Linked-Learning Impact* oncologists who participated in this CME activity, improved knowledge and competence demonstrates impact of the intervention. Improvement was demonstrated in recognizing strategies for managing treatment-related toxicities and retaining efficacy without changing therapies (e.g., maintaining dose but changing schedule of treatment). While the *Linked Learning Impact* analysis only tracked 37 days of participation, based upon participation comments and the successful completion rate of *all participants* viewing this program (99 %), this continuing medical education event on *Optimizing Dose Intensity for Patients with Metastatic Renal Cell Carcinoma* clearly increased participants' medical knowledge about treating mRCC, meeting a need for physicians and other practicing health care providers.

Future mRCC education could be provided in identifying the standard FDA-approved doses for tyrosine kinase inhibitors (TKI) in mRCC, and in providing education on how to adjust treatment schedules and dosing to maintain efficacy of TKI therapy. Additionally, based upon participant comments, more programing in oncology and renal disease would also be appreciated.

Attachment A

Assessment Questions

What is the standard dosing schedule for patients just beginning sunitinib? *(Learning Objectives 1, 2)*

- ☐ A) 2 weeks on/1 week off
- ◉ B) 4 weeks on/2 weeks off
- ☐ C) Continuous dosing
- ☐ D) Depends on the patient

Answer = B

What is the next therapeutic step when a patient is unable to tolerate the initial standard treatment with sunitinib? *(Learning Objective 3)*

- ☐ A) Maintain same dose but switch to a 2 weeks on/1 week off schedule
- ☐ B) Reduce dose but maintain a 4 weeks on/2 weeks off schedule
- ☐ C) Reduce dose and change to continuous dosing schedule
- ☐ D) Switch to a different drug

Answer = A

If a patient develops a significant toxicity (eg, hypertension) to a TKI treatment at the recommended dosing level, what should be your next course of action? *(Learning Objectives 2, 4)*

- ◉ A) Treat the hypertension and continue at the recommended treatment levels
- ☐ B) Reduce the dosing level
- ☐ C) Change the dosing schedule
- ☐ D) Discontinue use and try a different class of drug

Answer = A

What effect on clinical outcomes can result from dose reductions in and schedule change of TKI treatment? *(Learning Objectives 1, 4)*

- ◉ A) The same clinical benefit as without dose reduction/schedule change and with reduced toxicities
- ☐ B) A decreased clinical benefit compared with going without dose reduction/interruption
- ☐ C) A reduced clinical benefit, with dose reduction/schedule change and with reduced toxicities

Answer = A

Attachment B

Application Questions

Which of the following is an early adverse effect of treatment with tyrosine kinase inhibitors (TKIs)?

- ☐ A) Mucositis
- ◉ B) Hypertension
- ☐ C) Hand-Foot Syndrome
- ☐ D) Fatigue

Answer = B

A 65-year-old man who was diagnosed with clear-cell kidney cancer underwent a nephrectomy for a mass on his right kidney. After 6 months, new lesions appeared on his lung. He was given the standard regimen of sunitinib at 50 mg daily, 4 weeks on and 2 weeks off. What factor or measurement would indicate that this patient would respond to this dose or higher/lower dose of treatment?

- ☐ A) Maintain same dose but switch to a 2 weeks on/1 week off schedule
- ◉ B) Reduce dose but maintain a 4 weeks on/2 weeks off schedule
- ☐ C) Reduce dose and change to continuous dosing schedule
- ☐ D) Switch to a different drug

Answer = B

Under which conditions should the use of TKIs be discontinued, as opposed to interrupted?

- ◉ A) Grade 3 or 4 drug-related hepatic adverse events that cannot be resolved
- ☐ B) The presence of clinical manifestations of congestive heart failure
- ☐ C) Cases of severe hypertension
- ☐ D) Patients undergoing major surgical procedure

Answer = A