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'Conditional Survival' Important in Kidney Cancer

Yael Waknine | September 11, 2012

September 11, 2012 — Over the past few years, a number of new drugs have been approved for use in kidney cancer, but they have made only small improvements in the overall survival times of these patients.

A study published in the September issue of the *Lancet Oncology* offers a new approach to quantifying the benefits of therapy.

The researchers adjusted prognoses on the basis of time since initial treatment or duration of therapy to get more accurate survival estimates for patients with metastatic renal cell carcinoma receiving first-line vascular endothelial growth factor (VEGF)-targeted therapy.

They assessed conditional survival (CS), which implies that, on average, long-term cancer survivors have a better prognosis than newly diagnosed patients. Using this approach, for patients who were alive 18 months after beginning therapy, 2-year CS increased from 44% to 51%.

"CS can be used by clinicians to suggest better outcomes with time for patients who pass certain landmarks, especially those with poor-risk disease at baseline who have a worse outcome at the beginning of therapy and less hope," lead author Toni K. Choueiri, MD, told *Medscape Medical News* in an interview. Dr. Choueiri is director of the Kidney Cancer Center at the Dana-Farber Cancer Institute/Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts

Survival Probability Is Dynamic

According to the researchers, the development of targeted therapies in the past 7 years has "outstripped our understanding of how the drugs work." The usual correlation between treatment response and improved outcome does not apply to metastatic renal cell carcinoma, they write. Rather, survival probability is dynamic and directly dependant on time elapsed from treatment initiation and duration of therapy.

"With time...the prognosis and the estimation of survival is different and possibly better, and the actual 'numbers' from clinical trials that cite a median survival of *x* months do not apply much," Dr. Choueiri explained.

Now might be time to pause for breath in renal cancer.

"Now might be time to pause for breath in renal cancer," suggest Tom Powles, MD, from Barts Cancer Institute, Queen Mary University of London, United Kingdom, and Thomas E. Hutson, MD, from the Sammons Cancer Center at Baylor University Medical Center in Dallas, Texas, in an accompanying comment.

They note that newer agents have not pushed back survival as had been hoped, and truly predictive biomarkers seem out of reach. In addition, progression-free survival might not be useful in the prediction of outcome, which raises questions about current trial design, they write.

"The addition of newer agents to the range of drugs available for treatment on the basis of progression-free survival advantage might only confuse the situation further. A wiser approach might be to find better ways of using what is already available to us, with novel trial design and analysis," they write. The results of this study provide "a practical step in this direction," they add.

However, Nicholas J. Vogelzang, MD, from the Comprehensive Cancer Centers of Nevada in Las Vegas, noted that the approach described is "novel" and "positive," but that it requires more work before it becomes clinically applicable.

"This is excellent population-based work, but I'm not sure how well it will apply to individual patients," Dr. Vogelzang told *Medscape Medical News*.

"For example, if the patient is alive at 18 months and has a 'favorable status,' the patient has a 90% chance of living another 2 years," Dr. Vogelzang explained. "However, for a patient with 'favorable status' who is alive after 3 years, these curves provide

no information."

In addition, he pointed out, patients often improve while they are on therapy, but "these curves lock the patient into their baseline status."

"Further work is needed to refine the prognostication index for patients alive at 2, 3, and more years," Dr. Vogelzang concluded.

Data From More Than 1500 Patients

To evaluate the use of CS for prognosis, the researchers analyzed data from the International mRCC Database Consortium for 1673 patients with metastatic renal cell carcinoma who were treated with first-line sunitinib, sorafenib, bevacizumab, pazopanib, or axitinib from April 7, 2003 to October 12, 2010 at institutions in Canada, Denmark, Singapore, South Korea, and the United States.

Median follow-up for living patients was 20.1 months. On the basis of time survived, 2 year CS increased from 44% (95% confidence interval [CI], 41% to 47%) at the initiation of targeted therapy to 51% (95% CI, 46% to 55%) 18 months later (whether or not the patient was still receiving first-line targeted therapy).

This increase was driven by prognostic changes in the poor-risk group, in which survival estimates rose from 11% (95% CI, 8% to 15%) at the initiation of therapy to 33% (95% CI, 8% to 48%) 18 months later. No significant changes were observed in the favorable-risk or intermediate-risk groups.

"That the greatest improvement occurred in the patients with poor risk further draws attention to the fact that these patients can have disease that is responsive to VEGF-inhibitor treatment. Clinically, this finding is important because patients with such unfavorable prognoses have been understudied in most targeted therapy registration trials with the exception of temsirolimus," the researchers write.

When CS was based on the duration of targeted therapy, the 2-year survival estimate improved from 44% (95% CI, 41% to 47%) at the initiation of therapy to 68% (95% CI, 60% to 75%) 18 months later in the overall population. In the poor-risk group, CS increased from 11% (95% CI, 8% to 15%) to 73% (95% CI, 43% to 89%); in the favorable-risk group, it increased from 74% (95% CI, 68% to 79%) to 90% (95% CI, 77% to 96%); and in the intermediate-risk group, it increased from 49% (95% CI, 45% to 53%) to 57% (95% CI, 45% to 67%).

"Notably, the risk-group convergence from poor to favorable occurred only in patients who remained on targeted therapy at later timepoints and was not as pronounced in patients who were simply survivors.... [The improvement in survival] might be most attributable to treatment-responsive disease, differences in the disease biology, and unmeasured or unknown predictive factors," the researchers write.

In their editorial, Drs. Powles and Hutson concur. "We can extrapolate from the data that targeted therapy might be altering the natural biology of the diseases, particularly in the group with poor prognosis," they write. They point out the difference between CS in the population in general and CS in those who continued on targeted therapy, and suggest that "the differences in the [survival graphs] are probably indicative of distinct biological features of subgroups."

Limitations of the study include the absence of adjustment for subsequent treatments that could have affected overall survival and the exclusion of patients who received non-VEGF-targeted treatments such as the mTOR inhibitors temsirolimus and everolimus.

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