KIDNEY CANCER UPDATE

Highlights in Kidney Cancer

From the American Society of Clinical Oncology Genitourinary Cancers Symposium
February 16-18, 2017 • Orlando, Florida

Computer Assistance Reduces Errors in Evaluation of Tumor Response

The use of computer assistance reduces errors in the evaluation of tumor response via computed tomography (CT) scans, according to a retrospective study. Accurate evaluation is important because "response to systemic therapy as measured on CT images determines critical endpoints in patient care," said study author Brian C. Allen, MD, of Duke University Medical Center in Durham, North Carolina, during his presentation.

The study was based on the paired baseline and initial follow-up CT scans of 20 randomly selected patients with metastatic renal cell carcinoma (mRCC) who had received sunitinib (Sutent, Pfizer) as part of a completed phase 3 multi-institutional study.

A total of 11 readers from 10 institutions evaluated tumor response using both the manual method and the computer-assisted method. Images were evaluated according to 3 different response criteria: Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, Choi criteria, and Morphology, Attenuation, Size, and Structure (MASS) criteria. Computer-assisted response evaluation involved the use of a software platform that provided stepwise guidance; interactive methods of error identification and correction; and automatic tumor metric extraction, calculations, response categorization, and data/image archival.

All patients were evaluated by the manual method and the computer-assisted method. A crossover design, patient randomization, and a 2-week washout period were used to reduce recall bias between reading sessions.

Overall, 30.5% of patients assessed by all 3 criteria had at least 1 error. The percentage of patients with at least 1 error was 11.0% with RECIST 1.1 criteria, 24.5% with Choi criteria, and 23.0% with MASS criteria. In contrast, there were no errors in patients evaluated using the computer-assisted method ($P<.001$). The researchers noted that errors were more common when applying Choi criteria and MASS criteria than when applying RECIST 1.1 criteria, which only look at change in tumor length. "When we start adding attenuation and subjective assessment of necrosis, it adds complexity," Dr Allen said. As a result, "more errors were made." Mistakes in data transfer and arithmetic were the most common errors; with computer assistance, these steps are automated and errors can be eliminated.

In addition, using computer assistance halved the time needed for evaluation from 13.1 minutes to 6.4 minutes ($P<.001$).

Dr Allen cautioned that this was a retrospective study that was not designed to assess objective response re-classifications, but concluded that "computer-assisted response evaluation reduced errors and time of evaluation, and indicated better overall effectiveness than a manual tumor response evaluation method that is the current standard of care."

Allen B, Florez E, Sirous R, et al. Comparative effectiveness of tumor response assessment methods: standard-of-care versus computer-assisted response evaluation [ASCO GU abstract 432]. *J Clin Oncol.* 2017;35(suppl 6).

Study Supports Use of Active Surveillance in Metastatic Renal Cell Carcinoma

Active surveillance of mRCC is an effective strategy for delaying the start of systemic treatment that rarely leads to worsening of prognostic class, according to a single-center retrospective analysis. However, this approach was associated with an increase in tumor burden.

Lead study author Davide Bimbatti, MD, of the University of Verona in Verona, Italy, explained in his presentation that targeted therapies have been shown to improve survival in mRCC. These agents are not curative, however, and cause toxicities that may decrease

quality of life, which makes active surveillance an attractive approach.

For the study, the researchers analyzed data on 52 patients in their oncology department who underwent active surveillance for mRCC between January 2007 and April 2016. The patients had a median age of 70 years, and most were male with clear cell RCC. The International mRCC Database Consortium (IMDC) class was favorable in 69% of patients, intermediate in 25% of patients, and poor in 6% of patients. Most patients (85%) had 0 or 1 IMDC risk factors. The most represented sites of metastases at baseline were the lung (56%), lymph nodes (23%), and pancreas (19%); only 6% of patients had bone metastases and no patients had liver metastases. The tumor burden was 1 site in 65% of patients, 2 sites in 31% of patients, and more than 2 sites in 4% of patients.

After a median follow-up of 38.5 months, 67% of patients were still alive. The median time on surveillance—defined as the time from the start of active surveillance to the beginning of therapy or last follow-up—was 19.9 months, after which 67% of patients started a targeted therapy. Just 1 patient experienced progression as the best response.

Significant differences were found in time on active surveillance between patients in the IMDC favorable (20.2 months) or intermediate (18.3 months) classes vs those in the poor (5.0 months) class ($P<.05$). When targeted therapy began, the main sites of metastases were the lung (69%), lymph nodes (42%), bone (12%), adrenal gland (8%), pancreas (21%), and central nervous system (8%). The tumor burden was 1 site in 35% of patients, 2 sites in 48% of patients, and more than 2 sites in 17% of patients. A total of 22 patients had new sites of disease. Although the IMDC class shifted from favorable to intermediate in 4 patients, there was no shift in patients to the poor-class group. The median overall survival (OS) was 39.1 months from the start of targeted therapy, and 77.6 months from the start of active surveillance.

Dr Bimbatti said that the time on surveillance and median OS in his study were similar to those in the 6 other studies (5 retrospective and 1 prospective) that have been conducted in these patients. Two major limits to this study were the retrospective design, and the fact that cessation of surveillance was left to the discretion of the physician.

He concluded that active surveillance in selected patients allows for a delay in the start of systemic treatment, which postpones toxicity related to treatment. Active surveillance rarely worsens prognostic class and does not appear to affect the efficacy of subsequent therapies. On the other hand, active surveillance is associated with an increase in tumor burden that, if substantial, "may worsen subsequent survival."

Bimbatti D, Sava T, Massari F, et al. Changes in tumor burden and IMDC class after active surveillance (AS) for metastatic renal cell carcinoma (mRCC) [ASCO GU abstract 435]. *J Clin Oncol*. 2017;35(suppl 6).

Dose Escalation of Sunitinib Associated With Improved Survival

Dose escalation of sunitinib in mRCC is associated with a prolonged progression-free survival (PFS) and an acceptable toxicity profile, according to a single-institution retrospective review that was presented as a poster.

For the review, Jacques Raphael, MD, of Sunnybrook Odette Cancer Centre in Toronto, Ontario, Canada, and colleagues reviewed data on 25 patients with mRCC who had received sunitinib between October 2009 and January 2016. All patients had begun sunitinib treatment with a 50-mg dose, and had received dose escalation to 62.5 mg or 75 mg after disease progression if toxicity permitted. The mean age of the patients was 54 years (standard deviation, 12.4 years), and the majority were men (88%) and had undergone cytoreductive surgery (92%). The prognostic Heng score was good in 32% of patients, intermediate in 44% of patients, and poor in 24% of patients.

After a median follow-up of 40.3 months (95% CI, 11.1-66.6 months), 60% of patients receiving the 50-mg dose had a partial response and 16% had stable disease as best response, for a median duration of 11.4 months (95% CI, 3.0-20.7 months). After progression and subsequent dose escalation of sunitinib, 36% of patients had a partial response and 28% of patients had stable disease, for a median duration of 7.8 months (95% CI, 6.3-12.4 months). Three patients whose best response was progressive disease with the 50-mg dose achieved stable disease (2 patients) or a partial response (1 patient) after dose escalation.

The median PFS1 (the time between the start of sunitinib and first progression) was 6.1 months (95% CI, 2.3-19.4 months), the median PFS2 (the time between dose escalation and second progression) was 6.7 months (95% CI, 3.1-8.4 months), and the median OS was 63.6 months (95% CI, 26-not reached). Following dose escalation, the most common adverse events were fatigue (56%), diarrhea (40%), and skin toxicity (28%).

The authors concluded that patients with mRCC who progress on a 50-mg dose of sunitinib could still derive a clinical benefit and prolonged survival with dose escalation. This treatment strategy can overcome drug resistance and delay the change in systemic therapy. The toxicity profile of dose escalation appeared to be acceptable.

An ongoing, phase 2, single-arm study of 110 patients is prospectively examining the use of individualized sunitinib as first-line therapy in patients with metastatic clear cell RCC (NCT01499121).

Raphael J, Thawer A, Bjarnason GA, et al. Sunitinib dose escalation after disease progression in metastatic renal cell carcinoma [ASCO GU abstract 458]. *J Clin Oncol*. 2017;35(suppl 6).

Study Supports Individualized Approach to Sunitinib Use in mRCC

An individualized approach to sunitinib use—rather than using standardized sunitinib or standardized pazopanib (Votrient, Novartis)—was associated with better OS and time to treatment failure in first-line treatment of mRCC, according to a recent analysis that was presented as a poster.

For the analysis, Naveen S. Basappa, MD, of the University of Alberta in Edmonton, Alberta, Canada, and colleagues reviewed data from the Canadian Kidney Cancer information system, a prospective database. The researchers identified 598 patients who were diagnosed with clear cell mRCC and treated with first-line sunitinib or pazopanib between January 2011 and December 2015. Treatment was categorized as individualized sunitinib (355 patients), standardized sunitinib (151 patients), or standardized pazopanib (92 patients). Individualized treatment referred to therapy that included alterations to dose and schedule based on toxicity, whereas standardized treatment referred to therapy given as per the product monograph. The arms were well balanced for IMDC prognostic criteria and baseline characteristics except for age; patients were slightly older in the standardized pazopanib group.

The researchers found that median OS was significantly better in the individualized sunitinib group (37.9 months) than in the standardized sunitinib group (22.3 months) or the standardized pazopanib group (19.6 months). The time to treatment failure also was significantly better with individualized sunitinib (12.9 months) than with standardized sunitinib (5.6 months) or standardized pazopanib (7.0 months). Median OS and time to treatment failure were not significantly different between the standardized sunitinib group and the standardized pazopanib group.

Dr Basappa and his colleagues wrote that the results of this study further support the growing body of evidence for individualized therapy with sunitinib.

Basappa NS, Lalani A-K, Li H, et al. Individualized treatment with sunitinib versus standard dosing with sunitinib or pazopanib in patients with metastatic renal cell carcinoma (mRCC): results from the Canadian Kidney Cancer information system (CKCis) [ASCO GU abstract 468]. *J Clin Oncol*. 2017;35(suppl 6).

Delaying Dose Escalation of Axitinib Feasible in mRCC

When axitinib (Inlyta, Pfizer) is used as a second-line treatment in mRCC, physicians generally escalate the dose if the patient can tolerate it. Now, a retrospective review suggests that escalating the dose only after disease progression also may be an effective strategy. This approach has the potential to reduce treatment toxicity by reducing exposure to the agent.

Gary Doherty, MD, of the University of Cambridge in Cambridge, the United Kingdom, presented the results of his group's study as a poster. The study began by identifying all patients at a Cambridge tertiary referral center who had received more than 2 weeks of axitinib for mRCC over a 40-month period. Electronic health records revealed that 42 patients had received axitinib according to the strategy under study. A total of 29 of these patients had experienced 1 or more dose-escalation events. The median number of dose-escalation events was 2, for a total of 58 such events.

Dose escalation of axitinib led to disease control in 68.8% of cases after the first event and 70.0% of cases after the second event. The median OS from administration of axitinib was 19.9 months for patients who were dose-escalated and 6.7 months for patients who were not dose-escalated. The mean dose of axitinib for all patients at 90 days after starting treatment was 5.92 mg.

Standard axitinib dosing is based on the results of the AXIS trial (Axitinib As Second-Line Therapy For Metastatic Renal Cell Cancer) that was published in the *Lancet* in 2011, in which the initial dose of 5 mg twice a day increased at 2-week intervals to 7.0 mg and then 10.0 mg twice a day if tolerated. The authors concluded that postponing dose escalation of axitinib until disease progression may be an effective dosing strategy for patients with mRCC.

Doherty G, Lynskey D, Matakidou A, Fife K, Eisen T. A novel strategy for axitinib dosing in the treatment of metastatic renal cell carcinoma [ASCO GU abstract 464]. *J Clin Oncol*. 2017;35(suppl 6).