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Objective Response to a TKI in Metastatic Renal Cell Cancer Is Substantially Improved with Individualized Dose Schedules

Madrid - Optimal response to a tyrosine kinase inhibitor (TKI) employed first line in metastatic renal cell carcinoma (mRCC) appears to be achieved by individualizing the dose and schedule in order to sustain dose intensity, according to objective data from a prospective study. In a phase 2 multicentre trial, this method was associated with an 89.2% rate of disease control (objective response plus disease stabilization) and a 55.4% rate of objective responses (complete and partial responses). These rates are up to 70% greater than those reported in previously published phase 3 trials. The modification of the dosing schedule is guided by specific grades of toxicity when evaluated at prespecified intervals after initiating therapy. The data, which define a new model for managing mRCC with TKIs, are preliminary but are consistent with other evidence that the pharmacokinetics (PK) of TKIs are highly variable between patients, encouraging individualized dosing strategies.

TKIs that target the vascular endothelial growth factor (VEGF) pathway have become a standard of care in the treatment of mRCC, but new data indicate that response rates with sunitinib can be substantially improved relative to those reported in previous trials when dosing is adjusted to toxicity. In a study that tested a scheme for modifying both the schedule and the dose based on specific grades of adverse events (AEs), objective response rates increased substantially over those previously reported.

"The data from this study challenges the one-size-fits-all approach to using TKIs," reported Dr. Georg A. Bjarnason, Sunnybrook Odette Cancer Centre, Toronto, Ontario. "A high variability in the PK of TKIs has been established previously, but these data provide clear evidence that this variability is clinically meaningful. Individualized dosing appears to be a safe and effective way to boost response rates over those seen with fixed dosing schedules."

The sunitinib dosing scheme, which in many cases reduces the consecutive days on treatment from the conventional 28 days to 14 or 7 days, was tested in a phase 2 trial. Sunitinib established TKIs as the standard for mRCC when it almost doubled progression-free survival (PFS) relative to interferon in a previously published phase 3 trial (Motzer et al. *N Engl J Med* 2007;356:115-24).

Toxicity Guides Dose Intensity

In the dosing scheme, all patients initiate sunitinib on the standard 50-mg, once-daily dose and are then reassessed after 14 days when adjustments are guided by toxicity. The results of the study, which has enrolled 91 patients so far, appear to validate the relatively simple scheme, which is based on two major decision points.

Specifically, this scheme achieved a 55.4% objective response rate (ORR), which includes 4.6% rate of complete responses (CR). In past studies, CR with any therapy in mRCC has been extremely rare. In comparison, the ORR was 31% in the initial phase 3 trial with sunitinib, 31% with pazopanib in a non-inferiority comparison to sunitinib (Motzer et al. *N Engl J Med* 2013;369:722-31), and 32% with axitinib when used second-line in mRCC therapy (Motzer et al. *Lancet Oncol* 2013;14:552-62). The ORR in the new dosing scheme is approximately 70% greater than each of these.

First Assessment at 14 Days

In the relatively straightforward stepwise approach, the first of two key decision points occurs 14 days after patients have initiated sunitinib on the 50-mg dose. In those who have developed a grade 2 or higher toxicity at this point, the dose is reduced and the schedule is individualized with most patients taking sunitinib for 14 days followed by 7 days off (14/7) to maintain dose intensity, but longer or shorter on-treatment periods are possible even though the 7-day off period is a constant in all cases.

In those who tolerate 50 mg at 14 days, the next decision point occurs at 28 days. If there is no toxicity, the dose is escalated but, again, the schedule is individualized although most are treated on the 14/7-day regimen. Those with grade 2 toxicity typically remain on the conventional 50-mg dose in a 28/7-day schedule.

"This is a very practical approach that improves dose intensity while reducing adverse events," Dr. Bjarnason reported. "It's another important step toward personalized treatment."

The initial findings of this study appear to validate toxicity as a surrogate of PK. Dr. Bjarnason reported that 60% of patients had improved dose intensity versus the standard dose criteria. About 40% of patients remained on the standard 50-mg daily dose but for fewer days, demonstrating the advantage of the 14/7-day schedule for a substantial proportion of patients who might otherwise have had a dose reduction.

Maximum VEGF Suppression Sought

Sunitinib, sorafenib, and pazopanib are all approved in the first-line setting of mRCC, which represents about 25% to 30% of all RCC at presentation. Although each TKI targets a slightly different array of molecular pathways, their ability to suppress VEGF is considered the most important mechanism of action in mRCC. As a treatment, suppression of this pathway remains viable even after resistance develops to first-line VEGF inhibitors. Alternative TKIs that inhibit the VEGF pathway, such as axitinib, tivozanib, and cabozantinib, have all demonstrated activity as second-line therapies in patients previously exposed to first-line agents.

In these studies, such as one presented at ESMO by Dr. Pablo Maroto, Hospital de la Santa Creu, Barcelona, Spain, the data consistently suggest a correlation between ORR and disease control. In the study presented by Dr. Maroto, "real world" outcomes were evaluated in a compassionate use program for axitinib that enrolled 241 patients. In this study, only 16.7% of patients required a dose reduction but "a longer PFS [14.2 vs. 7.49 months; P=0.004] was seen in patients that achieved an objective response compared to those with disease stabilization," regardless of dose intensity.

However, reintroducing a first-line TKI in patients who have progressed on additional lines of therapy appears to yield new clinical benefit, according to data from the RESUME study. In this study, presented at ESMO by Dr. Stéphane Oudard, European George Pompidou Hospital, Paris, France, response to a rechallenge with third-line sunitinib was evaluated in 51 patients. In this group, 15% achieved an objective response and 46% had stable disease even though all had received sunitinib as first-line therapy. The median PFS for sunitinib rechallenge was 7.9 months, and Dr. Oudard credited the median overall survival of 55 months to the activity of third-line sunitinib.

Alternative Second-Line Strategies Tested

While such studies reinforce the importance of providing mRCC with optimal VEGF inhibition by focusing on dose intensity in first-, second-, and possibly third-line therapy, other options are being pursued in advanced disease. In addition to on-going studies with mTOR inhibitors such as temsirolimus and everolimus, significant attention was drawn to the activity of nivolumab, an antibody targeted at the programmed death-1 (PD-1) checkpoint. Checkpoint inhibitors like nivolumab are being evaluated in a variety of advanced and challenging cancers. At ESMO, phase 2 data were presented for 168 patients with clear-cell mRCC who had received prior VEGF receptor TKI. The majority had received at least two. About one third of patients had also received an mTOR inhibitor.

Despite multiple lines of previous therapy, nivolumab achieved an ORR of 21%, according to Dr. Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York City. While he characterized these data as "encouraging," he suggested that the duration of disease control in those who achieved an objective response was perhaps the most impressive finding. Of the 35 patients with an objective response, the response persisted for at least 12 months in 19 (54%). A small number of patients continue to have a response two years after initiating therapy.

Treatment discontinuations due to side effects considered to be nivolumab-related occurred in fewer than 10% of patients, and grade 3 or higher adverse events were observed in fewer than 20% of patients. On the basis of the activity of nivolumab and its "acceptable" level of safety, Dr. Motzer concluded larger trials are warranted.

Conclusion

The introduction of TKIs active against VEGF has dramatically improved the prognosis of mRCC. However, optimal disease control appears to depend on individualized therapy that compensates for the variability in how these drugs are metabolized. Fixed doses of sunitinib and potentially other TKIs pose a risk of both over-exposure and inadequate drug intensity. Titrating therapy on the basis of toxicity appears to offer an important opportunity to substantially increase ORR, a predictor of PFS. Sequential use of VEGF inhibitors, such as sunitinib and axitinib, offers an opportunity for extended periods of disease control with low and acceptable rates of adverse events. □

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