Biomarker identified in relation to drug response in refractory urothelial cancer

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The antiangiogenic drug pazopanib has demonstrated clinically meaningful activity in patients with refractory urothelial cancer, according to results presented at the AACR Annual Meeting 2012, held here March 31 - April 4. The results also revealed that increases in interleukin-8 levels early after treatment with pazopanib may predict a lack of tumor response to the therapy.

"Historically, prognosis of patients with relapsed or refractory urothelial cancer is quite dismal," said Andrea Necchi, M.D., faculty member in the department of medicine at Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy. "Patients who fail to be cured after multiple chemotherapy regimens have a poor survival estimate, and palliative care is a reasonable trade-off."

Data from the phase II proof-of-concept trial identified pazopanib as the first targeted compound to have clinically meaningful activity in patients with refractory urothelial cancer, according to Necchi.

"Our data indicate that pazopanib seems to be a legitimate drug in this disease," said Necchi. "Most interestingly, our biomarker analysis clearly pointed out the role of rising levels of circulating interleukin-8 as an early and potentially practice-changing indicator of tumor resistance and poor survival."

The researchers assigned 41 patients with relapsing or progressing urothelial cancer between 2010 and 2011 to 800 mg once-daily pazopanib. All patients had at least one prior chemotherapy regimen for metastatic disease.

At follow-up, seven patients had a partial response to therapy and 24 patients had stable disease - an overall clinical benefit of 76 percent. Median progression-free survival was 2.6 months, and median overall survival was 4.7 months. However, 10 percent of patients had a long-term cure after a median follow-up of 19 months.

The researchers examined blood samples for predictive biomarkers at baseline and every four weeks. They found that early rising levels of interleukin-8 (e.g., after four weeks of pazopanib) were associated with tumor progression and shorter overall survival.

"This trial gave a clear proof of concept that will require confirmation on a larger number of patients," Necchi said. "However, the preliminary findings, mainly regarding the role of interleukin-8 levels, have the potential to change at least the concept of new trial design with antiangiogenic agents in this disease."

Necchi served as an adviser and consultant for GlaxoSmithKline Inc. The current study was sponsored by Fondazione IRCCS Istituto Nazionale dei Tumori. GlaxoSmithKline Inc. provided the drug supply and granted independent radiologic review, which was performed at Columbia University Medical Center.

More information: Biomarker analysis and final results of INT70/09 phase II proof-of-concept study of Pazopanib (PZP) in refractory urothelial cancer

Abstract

Introduction: Discouraging results have been achieved with standard and novel compounds in refractory urothelial cancer (UC). Promising interim results with PZP, a multitargeted drug with distinct anti-angiogenic activity, were recently reported (ESMO 2010, ASCO 2011). The final results corroborated by biomarker analysis is presented. Material and Methods: Eligible pts relapsing or progressing after at least 1 chemotherapy regimen for metastatic disease underwent PZP 800 mg once daily until disease progression or unacceptable toxicity. Whole-body contrast-enhanced CT scan with densitometric analysis of

target lesions and PET scan were planned at baseline and q4weeks thereafter. Independent review of all CT scans was made. ?5 RECIST complete + partial responses (CR+PR) were required overall to declare drug activity according to Simon's Optimal 2-stage design. 50 mL of EDTA blood samples were collected at baseline and q4wks (concurrently with CT-PET scans) in all pts to analyze drug-induced changes in the amount of plasma VEGF, sVEGFR-1,-2 and -3, c-Kit, IL-6, 8 and 12 by multiplex ELISA plates.
Results: 41 pts were enrolled from 02/2010 to 07/2011. Median age was 67 yrs (40-84). 15 pts (37%) had UC of the upper urinary tract. 20/41 pts were treated in 3rd line or beyond. 19 pts (46%) were CDDP-refractory and 22 (54%) had hepatic metastases. 27 (66%) had ECOG PS 1-2. 7 pts (17%) had a confirmed RECIST-defined PR, 24 had a stable disease (76% clinical benefit). 20 pts (49%) had a clear necrotic evolution of multiple metastases and/or a decreased SUV at PET consistent with PR. Median progression-free (PFS) and overall survival (OS) were 2 (1-14) and 4 mos (2-19), respectively but 7 pts (17%) had long-term cure for >10mos (4/7 beyond 2nd line). 4 cases of cavitation-fistulization of large tumor masses were observed. G3 hypertension occurred in 2 pts, G1-2 asthenia in 11, diarrhoea in 5, anemia and hand-foot syndrome in 3 pts each. No discontinuations/dose reductions were needed. Significant increase from T0 (baseline) to T1 (+4wks) level was observed for VEGF (p