PROSTATE CANCER

Targeting prostate tumour angiogenesis with cediranib

Results of a phase II trial of cediranib in men with docetaxel-refractory metastatic castration-resistant prostate cancer (CRPC) not only demonstrate clinical response, but also indicate that dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) might be used to predict clinical outcome. “Identifying predictive biomarkers that can determine response and select patients for antiangiogenic therapy remains an area of need in this era of personalized cancer medicine,” William Figg, corresponding author of the study, told *Nature Reviews Urology*.

Cediranib is a potent inhibitor of vascular endothelial growth factor receptors (VEGFR1–3) that has shown promise in preclinical studies of prostate cancer. Although other antiangiogenic agents (including bevacizumab and sunitinib) have failed to show any clinical benefit in phase III trials of men with CRPC, cediranib seems to tell a different story.

For this single-centre study, 36 men with metastatic CRPC who had progressed on docetaxel chemotherapy were administered 20 mg cediranib daily (the maximum tolerated dose according to phase I data) for 28-day cycles. Median progression-free survival (PFS) for 35 patients (one man was removed from

the trial owing to spinal cord compression) was 3.6 months. Median overall survival was 10.9 months.

DCE-MRI (using T1-weighted gradient echo images with low-molecular-weight gadolinium chelates) was performed to determine changes in tumour vascularity during treatment. Increased vascular permeability is indicative of angiogenesis, and vice versa, so contrast transfer coefficient (K_{trans}) and initial area under the gadolinium curve measured over 60 s ($iAUC_{60}$) were evaluated at various time points after the patients started taking cediranib. Both parameters decreased within 24 h to the degree of 17.65% for K_{trans} and 14.50% for $iAUC_{60}$. Using a >30% drop in K_{trans} to indicate a positive pharmacodynamic response to antiangiogenic therapy, Figg and colleagues found that 60% of patients responded to treatment after one cycle. Notably, high baseline K_{trans} was found to be significantly associated with PFS, suggesting DCE-MRI might be used to select patients for antiangiogenic therapy.

In terms of toxicity, hypertension (43%), fatigue (33%), anorexia (31%) and weight loss (27%) were the most commonly reported adverse effects. Consequently, investigators recruited a second cohort of men with docetaxel-refractory CRPC ($n = 23$) who were given prednisone (10 mg

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daily) alongside cediranib. Accordingly, reported rates of fatigue, anorexia and weight loss were reduced to 17%, 26% and 17%, respectively.

So what next for cediranib? “We will go back to the laboratory and see if we can combine cediranib with other nonangiogenic agents to develop novel combination regimens to treat CRPC,” explains Figg. “We will also look at patient samples from this trial to determine if there are germ-line DNA predictive markers that might identify a subset of individuals who responded better and experienced fewer adverse effects to cediranib.”

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