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PROSTATE CANCER

New IL-11Rα drug is on target

Results of preclinical and early clinical evaluations of a novel therapy targeting IL-11 receptor α (IL-11Rα) in metastatic prostate cancer have been reported in the journal *Cancer*. Pasqualini and colleagues developed a ligand-directed agent—bone metastasis-targeting peptidomimetic-11 (BMTP-11)—containing the CGRRAGGSC peptide motif that has previously been found to bind to IL-11Rα in the tumour vascular endothelium, and a pro-apoptotic motif, $_{D}$(KLA-KLAK)$_{2}$, internalisation of which induces apoptosis of the cell in preclinical models of cancer.

The efficacy of BMTP-11 was analysed in two classic nude mice models of prostate cancer (an LNCaP-derived model and a DU145-derived model). A third model, which forms osteoblastic lesions in severe combined immunodeficient mice—MDA-PCa-118b—was also used. Tumour volumes were significantly reduced ($P=0.0001$) in mice bearing DU145-derived and LNCaP-derived tumour xenografts that received 10 mg/kg BMTP-11 once a week. In MDA-PCa-118b-derived xenografts, marked IL-11Rα expression and localization was observed and intravenous treatment with 10 mg/kg BMTP-11 once weekly had significant antitumour effects, with near-complete suppression of tumour growth.

Pharmacokinetic analysis in mice revealed that only approximately 25% of the circulating ^{125}I-labelled BMTP-11 was present in the whole blood after 15 min. Most of the radioactivity was in the kidneys, liver, spleen and heart 24 h after treatment. Pharmacokinetic analysis in cynomolgus monkeys showed that plasma levels of the drug decreased exponentially to background levels over 8 h. Area under the curve analysis indicated that clearance mechanisms for BMTP-11 were not saturated or concentration dependent at any of the tested doses.

Renal injury was the most frequent toxicity reported and concentration-dependent injury was observed in all preclinical experimental groups. Clinical chemistry parameters related to renal function returned to baseline levels after treatment discontinuation, indicating an adaptive and/or regenerative renal response, and no immunoreactivity against BMTP-11 was observed. Evaluation of the safety of BMTP-11 in monkeys showed no lethality from dose-dependent toxicity up to doses of 100 mg/kg and no irreversible toxicity at the highest repeat doses tested. A conservative starting dose of 18 mg/m^2 for humans was allometrically estimated for the first-in-man clinical trial.

The phase 0 clinical trial of BMTP-11 enrolled six patients with high-volume, castration-resistant bone metastases. Two patients treated at the lowest dose of 18 mg/m^2 showed no clinical toxicity. One patient who received the highest dose of 36 mg/m^2 experienced a grade 3 reduction in glomerular filtration and an increase in serum creatinine. Of the three patients who received the intermediate dose of 27 mg/m^2, one patient received all four doses with minimal renal toxicity. Another went off study after two doses, owing to disease progression, but had increases in serum creatinine and urine protein at day 15. The last patient received three doses but discontinued treatment after a large protein urine increase.

No treatment-related deaths or grade 4 adverse events were recorded and proteinuria and increased serum creatinine were the most prominent toxicities reported. Analysis of BMTP-11 localization showed accumulation at bone metastasis sites, consistent with preclinical data, and BMTP-11 colocalization with tumour apoptosis. No responses defined by the Prostate Cancer Working Group 2 criteria were observed and one patient on the intermediate dose regime had symptomatic improvement and declines in serum PSA; however, his tumour progressed rapidly after treatment with BMTP-11 finished.

Treatment options for metastatic castration-resistant prostate cancer are limited. The results reported in this study are promising and provide justification for further investigation of BMTP-11 as a targeted prototype therapy for this disease.

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Original article Pasqualini, R. *et al*. Targeting the interleukin-11 receptor α in metastatic prostate cancer: a first-in-man study. *Cancer* doi:10.1002/cncr.29344