Use of a targeted oncolytic poxvirus, JX-594, in patients with refractory primary or metastatic liver cancer: a phase I trial

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Summary

Background JX-594 is a targeted oncolytic poxvirus designed to selectively replicate in and destroy cancer cells with cell-cycle abnormalities and epidermal growth factor receptor (EGFR)-*ras* pathway activation. Direct oncolysis plus granulocyte-macrophage colony-stimulating factor (GM-CSF) expression also stimulates shutdown of tumour vasculature and antitumoral immunity. We aimed to assess intratumoral injection of JX-594 in patients with refractory primary or metastatic liver cancer.

Methods Between Jan 4, 2006, and July 4, 2007, 14 patients with histologically confirmed refractory primary or metastatic liver tumours (up to 10·9 cm total diameter) that were amenable to image-guided intratumoral injections were enrolled into this non-comparative, open-label, phase I dose-escalation trial (standard 3×3 design; two to six patients for each dose with 12–18 estimated total patients). Patients received one of four doses of intratumoral JX-594 (10^8 plaque-forming units [pfu], 3×10^8 pfu, 10^9 pfu, or 3×10^9 pfu) every 3 weeks at Dong-A University Hospital (Busan, South Korea). Patients were monitored after treatment for at least 48 h in hospital and for at least 4 weeks as outpatients. Adverse event-monitoring according to the National Cancer Institute Common Toxicity Criteria (version 3) and standard laboratory toxicity grading for haematology, liver and renal function, coagulation studies, serum chemistry, and urinalysis were done. The primary aims were to ascertain the maximum-tolerated dose (MTD) and safety of JX-594 treatment. Data were also collected on pharmacokinetics, pharmacodynamics, and efficacy. Analysis was per protocol. This study is registered with Clinical Trials.gov, number NCT00629759.

Findings Of 22 patients with liver tumours who were assessed for eligibility, eight patients did not meet inclusion criteria. Therefore, 14 patients, including those with hepatocellular, colorectal, melanoma, and lung cancer, were enrolled. Patients were heavily pretreated (5·6 previous treatments, SD 2·8, range 2·0–12·0) and had large tumours (7·0 cm diameter, SD 2·7, range 1·8–10·9). Patients received a mean of 3·4 (SD 2·2, range 1·0–8·0) cycles of JX-594. All patients were evaluable for toxicity. All patients experienced grade I–III flu-like symptoms, and four had transient grade I–III dose-related thrombocytopenia. Grade III hyperbilirubinaemia was dose-limiting in both patients at the highest dose; the MTD was therefore 1×10^9 pfu. JX-594 replication-dependent dissemination in blood was shown, with resultant infection of non-injected tumour sites. GM-CSF expression resulted in grade I–III increases in neutrophil counts in four of six patients at the MTD. Tumour responses were shown in injected and non-injected tumours. Ten patients were radiographically evaluable for objective responses; non-evaluable patients had contraindications to contrast medium (n=2) or no post-treatment scans (n=2). According to Response Evaluation Criteria in Solid Tumors (RECIST), three patients had partial response, six had stable disease, and one had progressive disease.

Interpretation Intratumoral injection of JX-594 into primary or metastatic liver tumours was generally well-tolerated. Direct hyperbilirubinaemia was the dose-limiting toxicity. Safety was acceptable in the context of JX-594 replication, GM-CSF expression, systemic dissemination, and JX-594 had anti-tumoral effects against several refractory carcinomas. Phase II trials are now underway.

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Introduction

Targeted treatments with new mechanisms of action are needed to treat cancer. Replication-selective oncolytic viruses (also known as virotherapeutics) replicate selectively in cancer cells, resulting in virus progeny production, tumour-cell necrosis, and release and spread in tumour tissues.[1–3] Some oncolytic viruses can also be engineered to express therapeutic transgenes. However, these viruses have not yet been shown to be clinically potent,[3] including having inefficient intratumoral spread and intravenous delivery. We postulated that these limitations could be overcome with a new poxvirus pharmacophore. Poxvirus replication and spread is rapid, motile (actin tail-dependent), and driven by the epidermal growth factor receptor (EGFR)-*ras* pathway activation present in most cancers. Poxviruses also have efficient intravenous spread and stability, including resistance to complement and antibodies. Their large transgene-encoding capacity allows

expression of multiple therapeutic transgenes. The vaccinia poxvirus has been used in smallpox vaccination programmes and antiviral agents are available (cidofovir and vaccinia immunoglobulin).

JX-594 is a targeted and transgene-armed oncolytic poxvirus modified by insertion of human granulocyte macrophage colony-stimulating factor, GM-CSF (*CSF2*), and *LacZ* genes into the thymidine kinase (*TK*) gene region, thus disrupting the *TK* gene.[4] Vaccinia is inherently tumour-selective because of its dependency on the EGFR-*ras* pathway[5,6] and tumour-resistance to interferons.[7,8] Its inherent therapeutic index is amplified by the *TK* inactivation; JX-594 replication is therefore dependent on cellular TK, the concentration of which is increased by cell-cycle abnormalities in cancer cells.[9] GM-CSF stimulates anti-tumoral immunity[6,10] and in augmenting the intratumoral vascular shutdown induced by oncolytic vaccinia.[11] JX-594 has anti-tumoral efficacy after intravenous and intratumoral administration in immunocompetent rat and rabbit tumour models.[12]

In a phase I pilot trial of a JX-594 prototype, seven patients with melanoma of the skin received escalating doses injected into superficial skin metastases.[4] No maximum-tolerated dose (MTD) was reported (up to 8×10^7 plaque-forming units [pfu]), and regressions of small superficial tumours were noted. To extend these preliminary findings, in the current study we aimed to define: safety and MTD at substantially higher doses without pre-immunisation (as was done in the pilot study), specifically after treatment in a solid organ; pharmacokinetics, including replication-dependent shedding of JX-594 into the blood over 3 weeks; and efficacy against a broad spectrum of cancer types. In this phase I trial we therefore enrolled a population of patients with a broad spectrum of solid liver cancers (primary and metastatic) to understand the safety, MTD, and activity in the context of many tumour types and intratumoral administration in the liver. The reason for this choice was that the replication, gene expression, and tumour destruction caused by JX-594 treatment could vary substantially between different cancer types.

	Mean, SD (range), or n
Mean age, years	56·1, 8·2 (37·0–66·0)
Sex, n	
Men	11
Women	3
Mean number of previous treatments	5·6, 2·8 (2·0–12·0)
Tumour size, cm	7·0, 2·7 (1·8–10·9)
Cycles of JX-594 received	3·4, 2·2 (1·0–8·0)
Tumour types	
Colon	4
Hepatocellular carcinoma	3
Melanoma	2
Renal-cell carcinoma	1
Squamous cell carcinoma—thymic	1
Squamous cell carcinoma—lung	1
Gastric	1
Extragonadal germ cell	1

Table 1: **Characteristics of patients (n=14)**

Methods

Patients

Between Jan 4, 2006, and July 4, 2007, 14 patients were enrolled. Inclusion criteria were at least one unresectable, injectable solid tumour in the liver (primary or metastatic) that had progressed despite standard treatment, normal haematological function (leucocyte count $>3\times10^9$ cells/L, haemoglobin >100 g/L, platelet count $>75\times10^9$ cells/L), and organ function (including creatinine ≤132·6 µmol/L, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ≤2·5 of upper normal limit, and Child-Pugh class A or B), life expectancy ≥16 weeks, and Karnofsky Performance Status (KPS) of 70 or over. Exclusion criteria were increased risk of vaccination complications (eg, immunosuppression or eczema), treatment with immunosuppressive or cancer drugs in the previous 4 weeks, pregnancy, or breastfeeding.

All patients gave written informed consent according to the principles of Good Clinical Practice. The study protocol and the consent forms were approved by the Korean Food and Drugs Administration, and the Institutional Review and Infection Control Committees at Dong-A University, Busan, South Korea. An independent data-safety monitoring board reviewed all dose-escalation decisions and major safety assessments.

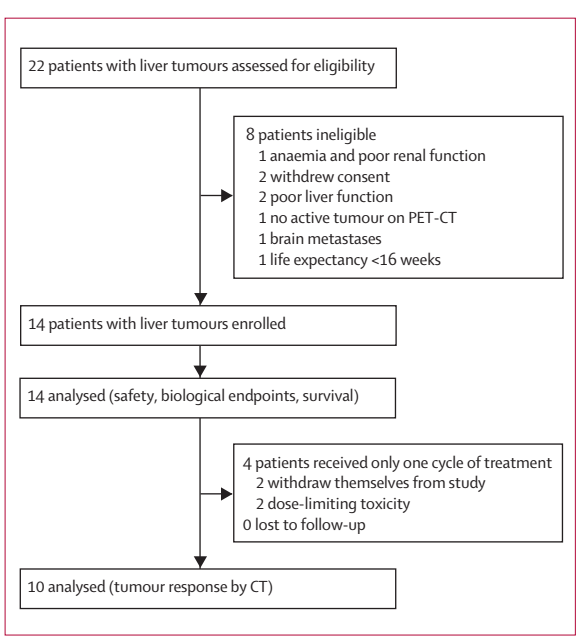

Figure 1: **Trial profile**