A phase 1 study of the polymeric nanoparticle containing docetaxel to patients with advanced solid tumors

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ABSTRACT SUMMARY

The taxanes have been widely used in cytotoxic treatment of many solid tumors as a family of very efficient anticancer drugs, but the current commercial formulation for the two main taxanes - Taxol for paclitaxel and Taxotere for docetaxel (DTX) - have shown dramatic side effects. DTX has been known to be superior to paclitaxel in clinical efficacy against many cancers, but it also exhibits severe side effects. Taxotere, the most famous commercial formulation of DTX contains the non-ionic surfactant Tween 80 (polysorbate 80) and 13% ethanol; the side effects caused by DTX and the solvent have significantly limited its clinical use. We have developed polymeric nanoparticles (PNP) in which taxanes were incorporated to reduce the side effects and improve the therapeutic efficacy. The novel polymeric drug delivery system comprised of ionically fixed polymeric nanoparticles (IFPN) was fabricated using a monomethoxypolyethylene glycol-polylactide (mPEG-PLA) diblock copolymer and a sodium salt of d,l-poly(lactic acid) (d,l-PLACONOa) upon the addition of CaCl2. The IFPN formulation containing DTX was highly kinetically stable in aqueous medium compared to the polymeric micelle formulation. We recently finished its phase 1 clinical study. In this presentation we introduce the result of the phase 1 clinical trial of DTX-PNP including side-effect profile, pharmacokinetics, and document any observed antitumor activity.

INTRODUCTION

Docetaxel (DTX) is the antineoplastic agents widely used for chemotherapy and chemoradiotherapy to treat various tumors. DTX is a synthetic analog prepared from European yew (1). It has been well known that the principle mechanism of DTX is acting as mitotic spindle inhibitors through the promotion of microtubule assembly and stabilization of the spindle (2). Cells exposed to the drugs exhibit profound cell cycle arrest at the G2/M phase (3). Mitotic catastrophe has been also reported as a typical pattern of cell death induced by DTX in breast cancer cells. Although taxanes have a broad spectrum of anticancer activity against a number of tumors, typical toxicities such as toxic dermatitis and hypersensitivity reaction have been reported (4). To reduce the toxicities, taxanes have been designed to be slowly infused into patients for several hours and taken with the pre-treatment of corticosteroids, diphenhydramine, or H2 receptor antagonists. Nonetheless, most cancer patients administered with taxanes are still suffered by severe side effects that limit the further application.

EXPERIMENTAL METHODS

PNP was prepared by using polylactic acid monovalent salt (PLA-COONa) and an amphiphilic block copolymer (mPEG-PLA) as described previously. To incorporate drugs into PNP, ethanol-solubilized taxanes were combined with polymeric matrix of PLA-COONa and mPEG-PLA in ethanol. After addition of calcium chloride to fabricate the PNP-taxanes, the solution was filtered through a 0.22 µm filter and lyophilized under aseptic condition. The PNP-taxanes in degassed bottles were stored in a container at 4°C until being used for experiment. The PNP-taxanes were reconstituted in sterile water immediately in use.

Patients and Methods

Adult patients with refractory solid tumors were enrolled. Progressive disease with development of new lesions or an increase in preexisting lesions or standard therapy in order to provide clinical benefit does not exist or is no longer effective. A Previous anti-cancer therapies must be completed before 21 days of first study dose and Patient must have recovered from any previous therapy. (5)

RESULTS AND DISCUSSION

Nineteen patients having sold tumor were treated in cohorts of three or six patients each with escalating DTX-PNP dose (20, 30, 45, 60 and 75 mg). The most
common adverse events were neutropenia and edema. Dose escalation was to be halted when the MTD was reached; MTD (maximum tolerated dose) was defined as one dose level below that at which DLT (dose-limiting toxicity) was observed in one-third or more of the patients.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th># Patient</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/m²</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>30 mg/m²</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>45 mg/m²</td>
<td>3</td>
<td>-</td>
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<tr>
<td>60 mg/m²</td>
<td>6</td>
<td>PR in 1</td>
</tr>
<tr>
<td>75 mg/m²</td>
<td>1</td>
<td>PR in 1</td>
</tr>
</tbody>
</table>

Table 1. Clinical trial of DTX-PNP
Superior Pharmacokinetics to DTX Partial response in 2 patients by 60 mg/m²

Blood samples were collected for pharmacokinetic analysis of atrasan concentrations before the initial dose on days 1 and 28 and at the following intervals thereafter: 15, 30, and 45 min and 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 30, 36, and 48 h. DTX-PNP plasma concentrations were determined using a validated liquid chromatography method.

Figure 1. Pharmacokinetic analysis of DTX-PNP
The drug effect of Taxotere 75 mg/m² and DTX-PNP 35 mg/m² are almost identical.

Intriguingly, among the patients treated with DTX-PNP, two patients having pancreatic or breast cancer showed partial remissions, at a dose of 65 or 75 mg.

Figure 2. Clinical trial of Partial remission in pancreatic cancer
The arrow indicated a reduced tumor after a treatment of DTX-PNP.

CONCLUSION
DTX-PNP could effectively inhibit growth of tumor with less volume and less frequency of a dosage compared to Taxotere. This indicates DTX-PNP could reduce side-effect that are caused from the treatment of Taxotere.

REFERENCES

ACKNOWLEDGMENTS
Supported by a grant of the Korean Health Technology R&D Project, Ministry for Health and Welfare, Republic of Korea (A062254 and A102059).