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Original Research

First-in-man phase I study assessing the safety and pharmacokinetics of a 1-hour intravenous infusion of the doxorubicin prodrug DTS-201 every 3 weeks in patients with advanced or metastatic solid tumours

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Abstract ***Purpose:*** DTS-201 is a doxorubicin (Dox) prodrug that shows encouraging data in experimental models in terms of both efficacy and safety compared with conventional Dox. The purpose of this phase I study was to assess the safety profile, to establish the recommended dose (RD) for clinical phase II studies and to assess potential anticancer activity of the compound.

Experimental design: DTS-201 was administered as a 1-hour infusion every 3 weeks in eligible patients with advanced solid tumours according to common clinical phase I criteria. Dose escalation was performed according to a modified Fibonacci schema.

Results: Twenty-five patients with a median age of 58 years (range, 30–72) were enrolled in the study. The median number of treatment cycles was 2 (range, 1–8). DTS-201 was administered at four dose levels (DLs) ranging from 80 to 400 mg/m^2, which is equivalent to 45–225 mg/m^2 of conventional Dox. No dose-limiting toxicity (DLT) occurred at the first two DLs. Three DLTs were observed at DL3 and DL4 (diarrhoea for DL3, vomiting and

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neutropenia for DL4). DL4 (400 mg/m^2) was considered the maximum tolerated dose. Myelosuppression was the main toxicity, and NCI-CTC grade III–IV neutropenia was common at RD. Non-haematological adverse reactions were mild to moderate and included nausea, anorexia, asthenia and alopecia. No treatment-related severe cardiac adverse events were observed.

Conclusions: DTS-201 is well tolerated and safe in heavily pretreated solid tumour patients. A high equivalent dose of Dox could be delivered without severe drug-related cardiac events. DTS-201 showed evidence of clinical activity with a confirmed partial response in a patient with soft-tissue sarcoma. The recommended phase II dose is 400 mg/m^2.

1. Introduction

Doxorubicin (Dox) is among the most widely used cytotoxic agents for the treatment of various types of cancer, but the clinical benefit brought by this agent is limited due to its toxicity profile, which includes not only reversible acute adverse events such as myelosuppression, nausea, vomiting and alopecia but also irreversible cumulative cardiac damage [1]. Second-generation anthracyclines such as epirubicin showed some safety improvement, but the risk of inducing cardiomyopathy remains high [2]. During the last few decades, to improve the therapeutic index, a tremendous effort has been done to develop safer anthracyclines, focussing on analogues and tumour-targeted formulations [3].

DTS-201 (or CPI-0004Na), *N*-succinyl-β-alanyl-L-leucyl-L-alanyl-L-leucyl-Dox, is a peptidic prodrug of Dox that remains stable and inactive in its cell-impermeable prodrug form (Fig. 1). The drug has been developed by the late Trouet *et al.* [4]. In 2003, Diatos S.A. licensed from Medarex certain European rights to develop and commercialise DTS-201. Later Medarex (now a subsidiary of Bristol-Myers Squibb) granted full European commercialisation rights for DTS-201 to Diatos S.A.

In the vicinity of a tumour, the tetrapeptide portion of the DTS-201 prodrug is cleaved by endopeptidases that are released extracellularly in the tumour environment. This yields the metabolites *N*-L-alanyl-L-leucyl-Dox (Ala-Leu-dox) and *N*-L-leucyl-Dox (Leu-dox), which can enter cells and are then converted to the active drug Dox. This results in an increased concentration of Dox in the tumour cells and reduced Dox levels in normal tissues [4].

Two tumour-specific endopeptidases have been identified, which cleave DTS-201: neprilysin (CD10, EC3.4.24.11) and thimet oligopeptidase (TOP, EC3.4.24.15). These endopeptidases are released in the extracellular space of solid tumours by stromal, tumour and neoangiogenic endothelial cells or expressed on their cell surface. The extracellular localisation of these enzymes permits to cleave and activate DTS-201 [4–8].

A significant therapeutic advantage of DTS-201 as an endopeptidase activated prodrug compared with free Dox has been demonstrated in a number of different tumour models including breast, colon, prostate and lung cancers. Pharmacokinetic and tissue distribution studies in normal and tumour-bearing mice have confirmed that an improved therapeutic index of the prodrug results in a tumour-selective release of Dox and a significant decrease in Dox levels in all normal tissues.

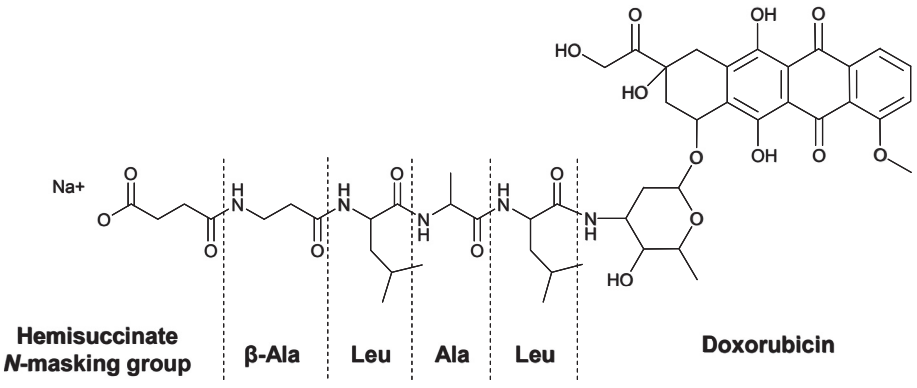

Fig. 1. Chemical structure of DTS-201.