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Original Research

Phase I results of a phase I/II study of weekly *nab*-paclitaxel in paediatric patients with recurrent/refractory solid tumours: A collaboration with innovative therapies for children with cancer

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Abstract ***Background:*** *nab*-Paclitaxel has demonstrated efficacy in adults with solid tumours and preclinical activity in paediatric solid tumour models. Results from phase I of a phase I/II study in paediatric patients with recurrent/refractory solid tumours treated with *nab*-paclitaxel are reported.

Patients and methods: Patients with recurrent/refractory extracranial solid tumours received *nab*-paclitaxel on days 1, 8 and 15 every 4 weeks at 120, 150, 180, 210, 240, or 270 mg/m^2 (rolling-6 dose-escalation) to establish the maximum tolerated dose (MTD) and recommended phase II dose (RP2D).

Results: Sixty-four patients were treated. Dose-limiting toxicities were grade 3 dizziness at 120 mg/m^2 and grade 4 neutropenia >7 days at 270 mg/m^2. The most frequent grade 3/4 adverse events were haematologic, including neutropenia (36%), leukopenia (36%) and lymphopenia (25%). Although the MTD was not reached, 270 mg/m^2 was declared non-tolerable due to grade 3/4 toxicities during cycles 1–2 (neutropenia, $n = 5/7$; skin toxicity, $n = 2/7$; peripheral neuropathy, $n = 1/7$). Of 58 efficacy-evaluable patients, complete response occurred in one patient (2%; Ewing sarcoma) and partial responses in four patients (7%; rhabdomyosarcoma, Ewing sarcoma, renal tumour with pulmonary metastases [high-grade, malignant] and sarcoma not otherwise specified); all responses occurred at ≥210 mg/m^2. Thirteen patients (22%) had stable disease (5 lasting ≥16 weeks) per RECIST.

Conclusions: *nab*-Paclitaxel 240 mg/m^2 qw3/4 (nearly double the adult recommended monotherapy dose for this schedule in metastatic breast cancer) was selected as the RP2D based on the tolerability profile, pharmacokinetics and antitumour activity. Phase II is currently enrolling patients with recurrent/refractory neuroblastoma, rhabdomyosarcoma and Ewing sarcoma.

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1. Introduction

Cancer is a leading cause of childhood death in developed countries [1]. Despite a relatively high combined survival rate for childhood cancers, recurrent/refractory disease is common in paediatric patients with certain solid tumour types, such as metastatic sarcoma and high-risk neuroblastoma, and long-term outcomes are poor [2–6]. Therefore, effective treatment options are needed.

Solvent-based taxanes have demonstrated antitumour activity in children with refractory solid tumours. However, their use has been compromised by dose-limiting toxicities (DLTs) that, in some cases, may result from the solvent-based formulation of these agents [7–9]. In a phase I trial, paclitaxel treatment resulted in DLTs, including acute neurological toxicities such as coma and possibly severe allergic toxicity, as well as delayed peripheral neurotoxicity potentially attributable to both the ethanol and polyethoxylated castor oil or polysorbate 80 components of solvents [7]. In a phase I study, docetaxel treatment resulted in dose-limiting neutropenia in heavily and less-heavily pretreated children with refractory solid tumours [8]. Similarly, in 2 phase I trials of >60 paediatric patients with refractory solid tumours, docetaxel administration resulted in dose-limiting neutropenia and desquamative dermatitis [9].

nab-Paclitaxel, an albumin-bound form of paclitaxel, is ethanol free and may be a feasible treatment option for paediatric patients with refractory/relapsed solid tumours because it was designed to increase antitumour activity and reduce toxicities, including hypersensitivity reactions [10,11]. Further, compared with conventional paclitaxel, *nab*-paclitaxel has demonstrated enhanced transport across endothelial cell monolayers, faster and deeper tissue penetration and slower elimination of paclitaxel [11,12]. Regimens containing *nab*-paclitaxel have demonstrated safety and efficacy in adults with various solid tumour types [10,11,13–16]. *nab*-Paclitaxel has been approved in the United States and Europe for the treatment of metastatic breast cancer after failure of prior treatment, for the treatment of advanced non–small cell lung cancer in combination with carboplatin, and for the treatment of metastatic pancreatic cancer in combination with gemcitabine [10,17]. *nab*-Paclitaxel received its first indication as a single agent in metastatic breast cancer at a dose of 260 mg/m^2 every 3 weeks [10]. In adults with early-stage breast cancer, *nab*-paclitaxel monotherapy has also demonstrated efficacy at 125 mg/m^2 weekly (3 of 4 weeks; qw3/4) [18]. Single-agent *nab*-paclitaxel has displayed dose-dependent cytotoxicity in several paediatric solid-