Kyriakos P. Papadopoulos · Merrill J. Egorin
May Huang · Andrea B. Troxel · Elizabeth Kaufman
Casilda M. Balmaceda · Linda T. Vahdat
Charles S. Hesdorffer

The pharmacokinetics and pharmacodynamics of high-dose paclitaxel monotherapy (825 mg/m² continuous infusion over 24 h) with hematopoietic support in women with metastatic breast cancer

Received: 12 May 2000 / Accepted: 3 August 2000 / Published online: 7 November 2000
© Springer-Verlag 2001

Abstract Purpose: We evaluated the pharmacokinetics and pharmacodynamics of high-dose paclitaxel (HDP) monotherapy (825 mg/m² continuous infusion over 24 h) with peripheral blood progenitor cell (PBPC) and G-CSF support in 17 women with metastatic breast cancer. Methods: Pharmacokinetic and pharmacodynamic data were collected in 17 women entered in a phase II trial of sequential HDP, and high-dose melphalan and cyclophosphamide/thiotepa/carboplatin. Results: The maximal plasma concentration (Cmax), area under the plasma concentration time curve (AUC), apparent clearance (Clapp), duration of plasma concentration above 0.05 μM (t > 0.05 μM) for paclitaxel were (means ± SD): 9.11 ± 7.45 μM, 145 ± 88 μM·h, 8.06 ± 2.90 l/h per m² and 82.4 ± 31.2 h, respectively. There was a significant correlation between the plasma paclitaxel concentration at 1 h (r² = 0.87), 12 h (r² = 0.85) and 23 h (r² = 0.92) and the AUC (P < 0.0001). Duration of neutropenia was brief (median 3 days, range 0–5 days) and neutrophil recovery occurred earlier (median 6 days, range 0–7 days) than could be attributed to infused PBPC. Median nadir count for platelets was 66 × 10⁹/l (range 13–160 × 10⁹/l). Pharmacodynamic analysis showed no correlation between pharmacokinetic parameters (Cmax, AUC, t > 0.05 μM) and time to neutropenic nadir, duration of neutropenia, platelet count nadir and grades of neuropathy or mucositis. In ten patients in whom detailed neurologic and nerve conduction studies were performed, linear regression analysis showed a significant correlation between pre- and post-HDP treatment total neuropathy scores (r² = 0.46, P = 0.03). Conclusions: HDP (825 mg/m² continuous infusion over 24 h) did not appear to be myeloablative. The degree of neurotoxicity subsequent to HDP was associated with the degree of baseline neuropathy but was not predictable from pharmacokinetic parameters.

Key words Paclitaxel · Three-compartment nonlinear model · Neurotoxicity

Introduction

Paclitaxel has activity in a number of solid malignancies including breast cancer [1]. In patients undergoing multiple cycles of standard-dose paclitaxel, the dose-limiting toxicities have been both hematological and nonhematological, notably peripheral neuropathy [1, 2]. Although controversial, high-dose chemotherapy with progenitor cell support may improve outcome in some patients with advanced breast cancer and is currently under study [3]. Preclinical data in breast cancer cell lines and MCA-4 transplanted tumors in C3Hf/Kam mice support a dose-concentration/response effect for paclitaxel in breast cancer [4, 5]. High-dose paclitaxel (HDP) has thus been included in sequential and combination high-dose regimens with peripheral blood progenitor cell (PBPC) support [6, 7, 8] in women with breast cancer. The nonlinear pharmacokinetics and pharmacodynamics of single-agent paclitaxel have been
extensively studied at conventional doses [9, 10, 11], but are less well documented at doses above 450 mg/m².

In a phase I trial of sequential HDP, and high-dose melphalan and cyclophosphamide/thiotepa/carboplatin (CTCb) in women with metastatic breast cancer, the maximum tolerated dose of paclitaxel was determined as 825 mg/m² [7]. We report here the pharmacokinetics and pharmacodynamics of HDP (825 mg/m²) as a continuous infusion (CI) over 24 h with PBPC and G-CSF support in 17 women with metastatic breast cancer entered in a phase II trial of this sequential regimen.

Patients and methods

Complete paclitaxel pharmacological data were collected in 17 women with metastatic breast cancer enrolled in a phase II trial of sequential HDP, and high-dose melphalan and CTCb with hematopoietic cell and G-CSF support [12]. All patients had adequate hepatic (bilirubin not more than twice normal, transaminases not more than 1.5 times normal) and renal function (creatinine less than 1.5 times normal). Patients with central nervous system metastasis or pre-existing National Cancer Institute Common Toxicity Criteria (NCI-CTC) neuropathy of grade 3 or more were ineligible. Paclitaxel 825 mg/m² was administered as a CI over 24 h on day −4 with PBPC reinfusion on day 0. Patients were premedicated with dexamethasone 20 mg, cimetidine 300 mg and diphenhydramine 50 mg. G-CSF (5 μg/kg per day) was administered subcutaneously following PBPC reinfusion and continued until recovery from neutropenia (absolute neutrophil count > 1 x 10⁹/l). The next sequential treatment of melphalan, and then CTCb, each with PBPC and G-CSF support, was given following marrow recovery to a leukocyte count of at least > 2 x 10⁹/l, and platelets to > 20 x 10⁹/l [7]. This study was approved by the institutional review board and written informed consent was obtained according to institutional requirements.

Plasma sampling and paclitaxel assay

Blood samples collected in heparinized tubes were obtained before the start of the paclitaxel infusion, and then at 1, 12, 23, 24.5, 25, 26, 28, 30, 48, 72 and 84 h. Samples were obtained from a well-flushed drug administration line, centrifuged, and the resulting plasma was stored in polypropylene cryovials at −20°C until analysis. Plasma paclitaxel concentrations were quantified using the high-performance liquid chromatography (HPLC) method of Vergnol et al. [13] as modified for paclitaxel analysis. Briefly, plasma extraction of paclitaxel was accomplished by adding 1 ml 30% acetonitrile and 50 μl docetaxel (2 ng/μl, as internal standard) to a 1 ml plasma sample. The mixture was vortexed and applied to a preconditioned 100 μg/ml C18 solid phase extraction cartridge (Varian, Harbor City, Calif.). The sample cartridge was preconditioned with 1 ml methanol followed by 1 ml deionized water (dH₂O). Immediately following the addition of the sample mixture, the column was washed with 1 ml dH₂O followed by 1 ml 50% methanol. The absorbed paclitaxel was eluted with 250 μl 90% methanol and 200 μl was loaded onto the HPLC column for analysis. The HPLC system consisted of a Hewlett Packard 1090 M liquid chromatograph, DR5 solvent delivery system (Hewlett Packard, Waldbronn, Germany), a Spheri-5 ODS 220 x 4.6 mm column (Applied Biosystems, Foster City, Calif.) and an RP-18 guard column (Perlin Elmer, Norwalk, Ct.). Samples were chromatographed with 67.5% methanol/32.5% H₃PO₄ (0.3%) at a flow rate of 1 ml/min, and the eluate was monitored at 228 nm with a UV diode array detector. The retention time of paclitaxel was 6.95 min. The intraassay and interassay coefficients of variation were below 10%.

Pharmacokinetics

A previously described three-compartment, nonlinear distribution and elimination model was fitted to the plasma concentrations of paclitaxel from each patient [14]. This was done with the ADAPT II program [15] and MAP Bayesian weighting. Individual patient parameters were then used to simulate complete concentration versus time courses from which were calculated AUC and the time that plasma paclitaxel concentration remained above 0.05 μM. Peak paclitaxel concentrations (Cmax), area under the concentration versus time curve (AUC), apparent clearance (Clapp) and time for which the concentration of paclitaxel was greater than 0.05 μM (t > 0.05 μM) were determined for each patient. Linear regression analysis was performed to determine the association between plasma paclitaxel concentration at 1 h, 12 h and 23 h versus AUC.

Neurologic studies

Before and after HDP infusion, motor and sensory neuropathy were graded according to the NCI-CTC. In ten patients detailed clinical and neurophysiological examinations were performed before HDP and these were repeated at approximately 4 weeks, prior to high-dose melphalan. Changes in sensory symptoms, strength, pin perception, vibration, tendon reflexes and nerve conduction studies (NCS) were scored from 0 (none) to 3 (severe) according to the total neuropathy (TN) score of Chaudhry et al. [16], modified to include changes in amplitude, velocity and latency of motor (unilateral median and peroneal) and sensory (unilateral median and sural) nerves (Table 1).

Hematologic studies

The number of days to neutrophil nadir, duration of neutropenia (absolute neutrophil count (ANC) < 0.5 x 10⁹/l) and days to ANC recovery > 0.5 x 10⁹/l following the nadir were recorded, with the day of PBPC reinfusion designated day 0. For platelets, days to platelet nadir, nadir platelet counts and percentage reduction in platelets were recorded.

Statistical analysis

Nonparametric Spearman’s coefficients were estimated. Univariate linear regression was performed using a significance level of 0.05.

Results

Pharmacokinetic data were assessed in 17 patients receiving paclitaxel 825 mg/m² as a CI over 24 h. Patient characteristics are shown in Table 2. Mean pharmacokinetic parameters estimated from the nonlinear model are shown in Table 3. A representative plasma paclitaxel concentration versus time curve is shown in Fig. 1. There was a significant correlation between the plasma paclitaxel concentration at 1 h (r² = 0.87), 12 h (r² = 0.85) and 23 h (r² = 0.92) and the AUC (P < 0.0001). No correlation between paclitaxel concentration or AUC and time above 0.05 μM was found.

There were no deaths or irreversible grade 4 toxicities following the HDP therapy. Pre- and post-HDP CTC grades and hematopoietic parameters were available in 16 patients. One patient refused further hematologic and neurologic testing following HDP and withdrew from the protocol. A blood count obtained from this patient on day +8 following HDP showed full hematologic recovery.