One-Hour Paclitaxel via Weekly Infusion: Dose-Density With Enhanced Therapeutic Index

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A preliminary report of a phase II trial of paclitaxel (Taxol) administered in a dose-dense manner as first- and second-line therapy for metastatic breast cancer is presented. Patients who had received one or two prior lines of chemotherapy were enrolled.

Inasmuch as the 1980s was the decade of platinum compounds, because of their significant therapeutic impact on the treatment of various solid tumors, the 1990s is clearly the decade of the taxanes. This designation is perhaps most valid in the context of systemic therapy for breast cancer. The efficacy and tolerability of paclitaxel (Taxol) has been established through numerous phase II and III clinical trials that mostly evaluated doses ranging from 135 mg/m² to 250 mg/m² and infusion durations of 3, 24, or 96 hours. No less than five large randomized trials will be completed by 1998 evaluating optimal dose and scheduling of paclitaxel as single-agent therapy for metastatic breast cancer (Table 1).

Much preclinical data demonstrate the schedule-dependent cytotoxicity of paclitaxel against various carcinoma cell lines (where longer is “better”) [1,2], and prolonged 96-hour infusions of paclitaxel can overcome resistance that has emerged after exposure to shorter 3-hour infusions. [3,4] Nevertheless, the infusional approach can be cumbersome in the clinic. To the extent that the efficacy linked to infusion duration relates to capturing a higher proportion of cells in the G²/M phase of the cell cycle, more frequent, shorter infusions should hypothetically accomplish the same. Motivated by the cytokinetic considerations of dose-dense therapy, [5] the demonstrated feasibility of 1-hour infusions [6,7] and the considerations of convenience of drug administration, we performed a phase II trial and pharmacologic investigation of weekly 1-hour paclitaxel infusion as first- and second-line chemotherapy for metastatic breast cancer.

Patient Criteria

Patients were required to have received one or two prior chemotherapy regimens, either for metastatic disease or in the adjuvant setting. Prior anthracycline was permitted, though not required, and prior taxane therapy was not allowed. All patients had to have bidimensionally measurable disease and preserved end-organ function (WBC > 3,000/µL, AGC >1,500/µL, hemoglobin > 8 g/dL, platelets > 100,000/µL, serum creatinine < 1.4 mg/dL, serum bilirubin < 1.5 mg/dL, serum calcium < 10.5 mg/dL, Karnofsky performance status > 60%, and anticipated survival > 12 weeks). Patients with a history of grade 3 or 4 peripheral neuropathy of any etiology were excluded. Patients with diabetes mellitus (type I and II) were initially included, but subsequently excluded after grade 3 neuropathy was noted in all of the first three such patients treated.

Treatment Plan

Paclitaxel was administered via 1-hour intravenous infusion at an initial dose of 100 mg/m² every 7 days without interruption. Treatment was administered in the outpatient clinic with a physician or chemotherapy nurse present during the first 15 minutes. Vital signs were monitored after the first 15 minutes. All patients received standard prophylactic antiallergic premedication before each paclitaxel infusion. This consisted of dexamethasone 20 mg, orally at 12 and 6 hours before paclitaxel administration and diphenhydramine 50 mg and cimetidine 300 mg, intravenously, 30 to 60 minutes before paclitaxel infusion. Treatment was planned to continue until disease progression or intolerable toxicity (Figure 1). Dose modifications were initially scheduled after every four infusions; however, after the first nine patients were treated, this was possible after every two infusions, as indicated in Table 2. Radiologic assessment of measurable disease was performed no less than every 8 weeks.
Pharmacologic evaluation
Pharmacologic studies were done during the first drug administration for 14 patients. Serum samples collected at 0.5, 1, 3, 6, 25, and 28 hours after initiation of paclitaxel infusion were analyzed by high-performance liquid chromatography (HPLC) as described previously.[8]

Results
Patient Population
Between February 1996 and June 1997, 30 patients were entered into this trial. This preliminary report describes mature data on the first 16 patients. The median age was 56 years (range 35-74 years); median Karnofsky performance status was 90% (70% to 100%). Twelve patients had received one prior chemotherapy regimen, and four had received two. Ten patients (63%) had received doxorubicin previously. One half of all patients had pulmonary or osseous metastases, 44% skin and/or lymph node metastases, and 31% hepatic metastases. Patients had a median of two organ-system sites of metastases (range one to three).

Drug delivery/toxicity
For the first 215 weekly drug infusions, the median number of infusions per patient was 13 (range 7-22). There were only four instances where a weekly infusion was held. The median delivered dose intensity was 95 mg/m²/week (range 80 to 108 mg/m²/week). As we encountered minimal myelosuppression, the weekly paclitaxel dose was increased to 110-120 mg/m²/week initially (Table 2). This resulted in grade 3 sensorimotor neuropathy in five of nine patients; hence, dose escalation beyond 100 mg/m²/week was subsequently abandoned.

Most strikingly, despite the delivery of 95 mg/m²/week of paclitaxel, neutropenia was either mild or non-existent for the vast majority of patients (Table 3). Grade 3/4 neutropenia has been noted in 14% of patients and no episodes of febrile neutropenia have been encountered. There has been a lack of cumulative neutropenia with up to 22 consecutive weekly administrations of paclitaxel (Figure 2). Three patients without a prior history of diabetes mellitus developed hyperglycemia after weekly dexamethasone administration and were managed with oral hypoglycemic agents. Acute hypersensitivity reactions warranting treatment discontinuation have not been noted. The complete toxicity profile is illustrated in Table 3.

Antitumor activity
To date, 6 of 15 evaluable patients have responded (40%; 95% confidence interval 16% to 68%). One complete remission in a patient with extensive cutaneous and subcutaneous chest-wall disease continues after high-dose consolidation 11 months later. Partial responses have been observed in liver[2], lungs, lymph nodes, and skin. Three responses have been noted in patients with prior anthracycline, two within three months of disease progression on doxorubicin. Four additional patients have experienced minor responses (25% to 49% reduction in bidimensionally measurable disease). One patient with extensive hepatic metastases died of autopsy-proven pulmonary microvascular carcinomatosis 18 hours after a first paclitaxel infusion.

Pharmacologic Analysis
Plasma paclitaxel concentration assayed by HPLC revealed a median Cₘₐₓ of 4.75 µM (range 2.73-6.76), a median AUC of 17.23 µM-h (range 9.34-22.35), t₁/₂ 12.23h (8.3-25.0). These parameters are well within the range necessary for in vitro cytotoxicity and are not very dissimilar from those seen with slightly higher doses (eg, 135 mg/m²) administered via 3-hour infusion.[9]

Discussion
This preliminary report is notable for significant activity and a very favorable toxicity profile for the weekly administration of paclitaxel via 1-hour infusion at ≤ 100 mg/m²/week. Despite the higher delivered dose intensity than with standard paclitaxel at 175 mg/m² (3 hours) every 3 weeks (95 mg/m²/week vs 58.3 mg/m²/week), less myelosuppression appears to occur with the present regimen. The resilience of myeloid precursors to repeated exposure to paclitaxel at this dose and schedule suggests that it is possible to uncouple drug delivery from bone marrow suppression. The complete absence of febrile neutropenia and relatively shallow leukocyte nadirs permitted chronic weekly therapy without treatment interruption or growth factor support. Neurotoxicity became dose-limiting when the weekly dose was increased above 100 mg/m², but it was rarely significant at doses ≤ 100 mg/m². Dose reduction to 80 mg/m² allowed the continuation of therapy in three responding patients who experienced significant neurosensory dysesthesia. Recent data from Breier et al have shown a lack of significant neurologic toxicity with weekly dosing of...
paclitaxel at 80 mg/m² via 1-hour infusion.[10] Cellular cytokinetic considerations imply that the shorter intertreatment intervals characteristic of dose-dense therapy should allow less opportunity for the emergence of drug-resistant clones.[5] However, emerging data also suggest that antiangiogenic[11] and proapoptotic effects[12] of paclitaxel may be exploitable by this novel drug administration schedule. Laboratory investigations are actively studying this issue. The preliminary safety and high therapeutic index of paclitaxel via 1-hour weekly infusion increases therapeutic options for patients with breast cancer. Whether as monotherapy or in combination, this strategy deserves further exploration in the treatment of breast cancer.

References:


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