Paclitaxel administration on days 1 and 8 every 21 days in anthracycline-pretreated metastatic breast cancer patients. A multicenter phase II trial

Abstract Paclitaxel is now included in second- and even first-line regimens in advanced breast cancer. The optimal dose and schedule of this drug, however, still remain a matter of investigation. A group of 57 consecutive patients with advanced breast cancer previously treated with anthracycline-containing regimens were submitted to treatment with single-agent paclitaxel administered at 130 mg/m² on days 1 and 8 every 21 days. Of the 57 patients, 56 were fully evaluable, and of these 25 had an absolute anthracycline resistance, 14 a relative resistance and 17 were potentially sensitive. The median age of the patients was 57 years (range 33–71 years), their median performance status was 1 (0–3), and 27 (47%) had liver involvement, 17 (30%) lung involvement, 30 (53%) bone involvement and 15 (26%) skin/lymph node involvement. Toxicity was recorded in 295 cycles. This scheme was well tolerated, the dose-limiting toxicities being hematological and neurological. Grade 3/4 leukopenia was observed in 20% of patients at nadir, while grade 3 leukopenia was observed in 3% of patients at recyle. Only one patient experienced febrile neutropenia. Grade 2/3 neurotoxicity was observed in 26% of patients, leading to drug withdrawal in three. The treatment was given on an outpatient basis in all patients and the median relative dose intensity of 86.6 mg/m² per week was 100% of the planned dose (range 75–100%). Three patients (5%) attained a complete clinical response and 12 (21%) a partial response for an overall response rate of 26% (95% confidence interval 18–38%), while 30 (53%) attained disease stabilization and 11 progressed (19%). Time to progression in responding patients was 10.3 months, and the median overall survival of the entire population was 15.4 months. To conclude, paclitaxel administration on days 1 and 8 every 21 days was active and manageable in advanced breast cancer patients previously treated with anthracyclines. The response obtained was durable.

Key words Paclitaxel · Breast cancer · Anthracyclines · Second-line chemotherapy

Introduction

Breast cancer still remains the leading cause of death from cancer among women in Italy [35]. There is no known treatment that appears to substantially prolong disease-free survival or overall survival of patients with advanced disease. The main goal of therapy is the palliation of symptoms [14]. Cytotoxic chemotherapy
has become established as a key element in multimodality treatment. To date anthracyclines, notably doxorubicin and epirubicin, are the most active agents, yielding excellent response rates both as single agents and in combination therapy [6, 8, 23, 34]. Objective response rates to second- or third-line therapy with other cytotoxic agents, such as cisplatin, mitomycin-C and mitoxantrone, in patients previously exposed to anthracyclines are rare (15–20% on average) and the median duration of response is generally very short [5, 21, 27]. Anthracyclines are now increasingly employed in an adjuvant setting and this represents a hindrance, leading to limitation of their use in relapsed patients. Patients who relapse or have progressive disease during or immediately after adjuvant anthracycline treatment have a poor prognosis and a low chance of achieving an objective response when treated with other cytotoxic agents [17, 21].

New active agents and strategies are therefore needed. Recent studies have suggested that a new class of drugs, the taxanes, have the ability to elicit responses in patients with anthracycline-resistant tumors. Paclitaxel is the prototype of these chemotherapeutic agents. It has a unique mechanism of action: promoting intracellular tubulin polymerization and stabilizing abnormal microtubule structures [19]. In phase I/II studies, this drug has shown significant activity in metastatic breast cancer, with a response rate of 30–62% in patients with no prior exposure to cytotoxic agents and 21–30% in heavily pretreated patients [1, 11, 15, 24, 29, 30]. Short paclitaxel infusion (3 h) has been found to be well tolerated using an appropriate premedication [18, 29, 30]. In the majority of the trials, the drug was delivered in a 1-day schedule of administration using various doses ranging from 135 to 250 mg/m² every 21 days. Randomized trials comparing different doses administered in a 3-week schedule, however, have failed to demonstrate a dose/response relationship, while higher doses have been associated with a greater degree of toxicity [24, 37].

More recently, the administration of paclitaxel in a weekly or biweekly schedule has been shown to be very active in the treatment of advanced breast cancer [9, 31]. The rationale of such an approach is found in Norton’s concepts of cell kinetics and tumor growth [26]. These suggest that reducing the interval between treatments should minimize the appearance of drug-resistant cell clones and regrowth, providing a greater opportunity for log tumor cell kill. The delivery of lower, more frequent doses of paclitaxel has been found to alter the toxicity profile. Sensory neuropathy has proven to be the dose-limiting toxicity, whereas myelosuppression is modest [7, 28, 31]. The optimal dose and schedule for delivering the drug on a substantial weekly schedule is still a matter of investigation. In this multicenter phase II trial we evaluated the activity and the safety of single-agent paclitaxel administered on days 1 and 8 every 21 days in anthracycline-pretreated breast cancer patients.

Patients and methods

Eligibility criteria

To be eligible for this study, patients had to meet the following criteria: age more than 18 years and less than 75 years; histologically confirmed breast cancer with clinical evidence of progressive metastatic disease; presence of measurable disease; previous exposure to an anthracycline regimen, either in an adjuvant setting (providing that they had relapsed within 12 months of completion of chemotherapy) or for advanced disease, or as a contraindication to further anthracycline therapy for a prior cumulative doxorubicin dose of 550 mg/m² or for a prior cumulative epirubicin dose of 1000 mg/m²; ECOG performance status of 0–3; estimated life expectancy 12 weeks or more; adequate bone marrow function (absolute neutrophil count ≥2000 cells/μL, hemoglobin count ≥10 g/dL and platelet count >100,000/μL); normal hepatic and renal function (total serum bilirubin <1.5 mg/dL and serum creatinine <1.5 mg/dL).

All patients were allowed to have received prior radiotherapy if it had been completed 4 weeks or more before study entry. An assessable target lesion should not have been irradiated. Hormonal agents, either as adjuvant treatment or as therapy for metastatic disease were allowed, but they had to have been discontinued at least 4 weeks before study entry.

Exclusion criteria were the presence of symptomatic brain metastases; history of primary malignant neoplasm other than curatively treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix surgically cured; history of myocardial infarction within the past 6 months; documented coronary artery insufficiency; chronic congestive heart failure; severe infections; previous history of grade 2–3 peripheral neuropathy of any etiology; previous treatment with taxanes. Each patient provided informed consent to the treatment.

Assessment of response and toxicity

Pretreatment evaluation included a complete medical history and physical examination, hematological tests and blood biochemistry, electrocardiogram and a baseline echocardiogram, chest radiograph, bone scan, liver ultrasound. A computed tomographic scan was performed only when indicated to evaluate bidimensionally measurable disease (i.e. liver metastases). A complete blood count was performed before every paclitaxel administration (on days 1 and 8) but was optional on the 15th day. A repeat history and physical examination with documentation of toxicity were performed before each cycle. Baseline laboratory studies as earlier were repeated on day 1 of each cycle.

Antitumor activity was evaluated every three courses on all measurable lesions and all patients were scheduled for at least two cycles in order to be eligible for assessment of tumor response. In patients with tumor response or stable disease, the treatment was continued up to a maximum of six cycles. Tumor response was classified according to the WHO criteria [22] and documented with appropriate scan or examinations by two investigations 6 weeks a part. Response was defined as complete response (CR, disappearance of all measurable disease), partial response (PR, ≥50% reduction in the sum of the products of two perpendicular diameters of all measurable disease), stable disease (SD, <25% change in measurable disease) or progressive disease (PD, ≥25% increase in any measurable disease site or the appearance of new lesions). In cases of multiple measurable lesions, response assessment was limited to the four or five best indicator lesions. Toxicity was recorded according to WHO criteria [22].

The level of resistance to anthracyclines was classified according to the definitions listed in Table 1. Time to disease progression was defined as the period between the first day of treatment and the date at which disease progression was documented or death occurred for whatever reason. Overall survival was defined as the period from the first day of chemotherapy to the patient’s death.