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4'-*O*-Tetrahydropyranyl-doxorubicin in advanced breast cancer: a phase II study

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Summary. In a phase II study, 35 patients with advanced breast cancer were treated with 4'-*O*-tetrahydropyranyl-doxorubicin (THP-DXR) (70 mg/m^2 i.v. on day 1); treatment was repeated every 3 weeks. Eight patients had failed prior chemotherapy for advanced disease. A total of 34 patients were evaluable for response. After a median of 10 treatment courses (range, 3–15), objective tumor response was seen in 59% (20 of 34 patients) (95% confidence limits, 42%–75%). In all, 17 partial remissions and 3 complete remissions were observed; stable disease occurred in 13 patients. The median duration of response was 42+ weeks (range, 21–77+ weeks). The dose-limiting side effects were leukopenia (26 patients, WHO grade III–IV) and thrombocytopenia (9 patients, WHO grade II–IV). Nausea/vomiting was experienced by 34 patients; in 18, it reached WHO grade II–III. Other treatment-related side effects included alopecia (WHO grade II–III) in 26 patients and stomatitis and diarrhea (WHO grade I–III) in 9 patients. At cumulative doses of THP-DXR of at least 700 mg/m^2 (range, 700–1,050 mg/m^2), no signs of congestive heart failure were observed. We conclude that THP-DXR is effective for first- and second-line chemotherapy in advanced breast cancer and that side effects are manageable.

Introduction

Doxorubicin-containing combination regimens are considered to be among the most active treatment regimens in breast cancer. However, the occurrence of cardiac toxicity and gastrointestinal side effects limits the use of doxorubicin. To increase the therapeutic index of this drug, new anthracycline analogs were recently developed by altering the chemical structure of doxorubicin [7, 23]. Pirarubicin is a semisynthetic derivative of doxorubicin with the chemical name 4'-*O*-tetrahydropyranyl-doxorubicin (THP-DXR) [22].

In in vitro screening, e.g. in the proliferation assay with L1210 leukemia or in the clonogenic assay with human tumors, THP-DXR has been shown to have an antitumor effect that is equivalent or superior to that of doxorubicin. Similar findings have also been reported in in vivo experiments, e.g. with L1210 and P388 leukemias, B16 melanoma and Lewis lung carcinoma [9, 19, 20, 22]. In its pharmacokinetics and tissue distribution, THP-DXR differs distinctly from doxorubicin and has, for example, a far greater distribution volume [12]. Data obtained in the golden hamster model of Dantchev has shown that the cardiotoxicity of THP-DXR is lower than that of doxorubicin, epi-doxorubicin or mitoxantrone [4].

Early clinical trials of THP-DXR have demonstrated objective remissions in patients with cervical and ovarian cancer, breast cancer, mesothelioma and malignant lymphoma [8, 15, 18]. These studies followed initial phase I dose recommendations in Japan of 35–50 mg/m^2 given every 3 weeks [11, 17]. A phase I trial conducted in Europe has indicated an MTD (maximally tolerated dose) of 70 mg/m^2. Differences in the study populations, including ethnic characteristics, are believed to have contributed to the difference in MTD [14]. Based on the results of this later dose-finding study, a phase II trial of THP-DXR in advanced breast cancer was initiated.

Patients and methods

Between October 1987 and November 1988 a total of 35 patients with histologically proven breast cancer were entered into the phase II study. All subjects except one were women who had locally advanced or metastatic breast cancer and measurable and/or evaluable progressive disease. The median disease-free interval was 116 weeks (range, 0–624 weeks). The median time from the first relapse to the start of THP-DXR therapy was 30 weeks (range, 0–241 weeks). Previous endocrine and/or cytotoxic therapy as an adjuvant or as treatment for metastatic disease did not exclude patients from entry, provided that therapy had been stopped for a minimum of 4 weeks. Prior to chemotherapy, 5 patients were treated

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Table 1. Patient characteristics

	Patients (*n*)
Entered	35
Inevaluable	1
Evaluable for response	34
Median age in years (range): 61 (39–79)	
Sex:	
Women	34
Men	1
Menopausal status:	
Premenopausal	8
Postmenopausal	26
Hormone receptor status (fmol):	
Estrogen receptor positive (≥ 10)	13
Estrogen receptor negative (0–9)	10
Estrogen receptor unknown	12
Karnofsky index (%):	
50– 60	4
70– 80	10
90–100	21
Dominant site of disease:	
Soft tissue/nodes	11
Bone	8
Visceral	15
Advanced primary lesion	1
Number of metastatic sites:	
1	17
2	14
≥3	4
Prior chemotherapy	14
Adjuvant:	
without anthracyclines	2
containing anthracyclines	4
For metastases:	
without anthracyclines	5
containing anthracyclines	3

with adjuvant endocrine therapy (tamoxifen, 30 mg/day) and 14 patients with positive estrogen-receptor status and/or other good prognostic factors had endocrine therapy for metastatic disease (10 patients, 1 agent; 4 patients, 2 consecutive agents). Estrogen receptors were analysed by the dextran-coated charcoal method, and a concentration of ≥ 10 fmol/mg cytosol protein was considered to be a positive value. In patients previously treated with anthracyclines or anthracycline derivatives, this therapy had to be finished at least 6 months before the start of THP-DXR treatment.

Prior to starting treatment, all patients had to have a Karnofsky index [5] of >40%. Other entry criteria included a white blood cell count (WBC) of >3,500/μl, a platelet count of >100,000/μl and bilirubin and creatinin values of <1.5 mg/dl. A history of myocardial infarction within the previous 6 months, heart failure requiring regular medication, severe arrhythmia or the pattern bundle-branch block or a left ventricular ejection fraction of <50% excluded patients from the trial. Patients with central nervous system metastases or with second malignancies, except skin cancer and cervical cancer of stage 0, were also excluded. The study was conducted according to the ethical standards described in the Helsinki declaration. Informed consent was required for starting THP-DXR therapy.

Before the beginning of treatment, a complete history and physical examination, an ECG, a chest X-ray (CXR), an abdominal sonogram, a bone scan, and, where appropriate, a skeletal survey, computerised tomographic scan(s), and a liver scan were obtained. Pretreatment laboratory tests included hemoglobin determinations, leukocyte and platelet counts, liver and renal function tests, a coagulation profile, measurement of serum electrolytes and urinanalysis. Leukocyte and platelet counts and hemoglobin determinations were undertaken at least once between days 10 and 14 after treatment as well as prior to every new treatment cycle (together with a biochemical profile). Cardiac function was monitored by serial estimations of the left ventricular ejection fraction (LVEF) using multigated analysis. The lower limit of normal for this investigation was 50%. For patients with bone or visceral metastases, CXRs and/or abdominal sonograms were repeated every 3 months together with all other scans that were used for disease evaluation in such individuals.

THP-DXR was given i. v. at a dose of 70 mg/m^2 every 3 weeks. As an antiemetic, patients received 20 mg i. v. metoclopramide prior to treatment. In case of drug-induced myelosuppression, as indicated by leukocyte and platelet counts evaluated on day 21, the dose of THP-DXR was adjusted as follows: the dose was reduced to 75% if the WBC count was between 3,000 and 3,500/μl and/or the platelet count was between 75,000 and 100,000/μl. Treatment was postponed for at least 1 week when WBC and/or platelet counts fall below these values (WBC <3,000/μl; platelets, <75,000/μl). More than 3 weeks' postponement represented interruption due to toxicity. Treatment was discontinued after the administration of a maximum of 15 treatment courses, or if the patient refused further treatment, or if disease progression or severe toxicity occurred.

Tumor response was assessed according to International Union Against Cancer (UICC) [6] and WHO criteria [13], and drug toxicity was graded according to WHO criteria [13]. The duration of objective response was defined as the time from the start of treatment until disease progression. Survival was measured from the 1st day of treatment with THP-DXR until the day of death. An adequate treatment trial was defined as at least two cycles of chemotherapy. Patients who showed progression were removed from the study but continued to be followed for survival.

Statistical methods. The data were analysed for category, mean and standard deviation or the median, minimum and maximum, interquartile range and an approximated 95%, confidence interval for the median. For the analysis of categories a chi-square test was used and for low categories Fisher's exact test was used. The survival function was estimated by the Kaplan-Meier product-limit method and survival was compared using Gehan's and Peto-Peto's generalized Wilcoxon test [10].

Results

Efficacy

Patient data are listed in Table 1. Of the 35 patients entered into the study, 1 was considered to be inevaluable: severe leukopenia (WHO grade IV) after course 1 caused a postponement of treatment for >3 weeks, which had to be recorded as interruption due to toxicity.

A total of 34 patients received at least two cycles of THP-DXR treatment and were evaluable for response. A median of 10 courses (range, 3–15) were given. In all, 3 patients achieved a complete remission (CR), 17 achieved a partial remission (PR), 13 showed no change (NC) and 1 had progressive disease (PD). The overall response rate (CR + PR) for all 34 evaluable patients was 59% (95% confidence limits, 42%–75%) (Fig. 1).

The median duration of response from the 1st day of treatment until the detection of progressive disease was 42+ weeks (range, 21–77+ weeks; 95% confidence limits, 38–46 weeks). Response to THP-DXR therapy was not found to be related to menopausal status, performance

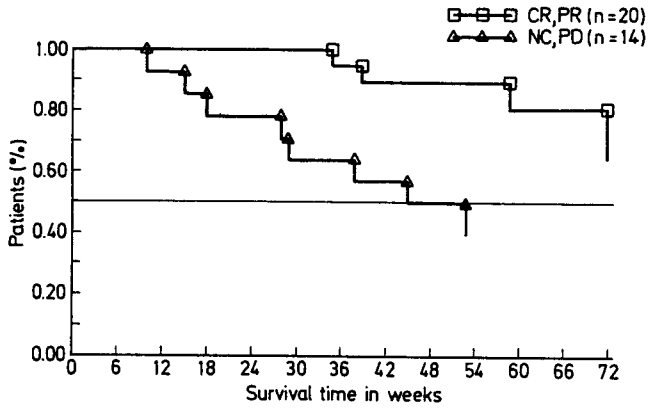

Fig. 1. Survival time of patients receiving at least two cycles of THP-DXR treatment

Table 2. Toxic effects of THP-DXR

Toxic effect	Number of patients WHO grade[1]:				
	0	I	II	III	IV
WBC count nadir	0	2	7	20	6
Platelet count nadir	21	5	6	2	1
Hemoglobin concentration (g/dl) nadir	4	8	18	2	3[2]
Nausea and vomiting	1	16	10	8	0
Stomatitis	26	2	5	2	0
Diarrhoea	26	3	6	0	0
Hair loss	2	7	17	9	0
Infection	18	10	4	3	0
Cardiac abnormality	30	5[3]	0	0	0

[1] Maximal grade per patient for all cycles
[2] One hemolytic episode in one patient
[3] Temporary sinus tachycardia

status at entry, length of disease-free interval or estrogen receptor (ER) status. Responses were seen at all sites of metastatic involvement, with no significant differences. Patients who received THP-DXR after having failed prior chemotherapy for advanced disease had a 29% overall response rate (2 responses among 7 patients) as compared with a 67% response rate (18 responses among 27 patients) in those receiving THP-DXR as first-line palliative treatment; the difference was not significant. The median time from the 1st day of treatment until the first detection of progressive disease for the 34 evaluable patients was 38+ weeks (range, 9–77+ weeks; 95% confidence limits, 33–43 weeks).

The median duration of survival of all patients entered onto the trial has not yet been reached but will be in excess of 76 weeks. Survival was not found to be correlated to prognostic factors existing before the start of THP-DXR therapy, such as menopausal status, performance status, disease-free interval, ER status, sites of metastatic involvement and prior treatment.

Toxic effects

All 35 patients entered into the study were evaluated for toxic effects. The total number of courses given was 285. There were no treatment-related deaths. Side effects detailed in Table 2 were primarily hematologic and gastrointestinal.

Hematologic toxicity consisted of reversible depression of the leukocyte count and, to a lesser extent, of the hemoglobin concentration and platelet count. The nadir levels generally occurred 10–14 days after treatment, with recovery at 3–4 weeks after therapy. According to the protocol, leukopenia and/or thrombocytopenia required a THP-DXR dose reduction in 17% of the courses given and therapy had to be delayed because of prolonged myelosuppression to enable recovery of peripheral blood cell counts in 13% of the courses given. Leukopenia was the major toxicity in 26 patients (74%), associated with a WHO grade of III–IV. There was no evidence of cumulative hematologic toxicity.

Among treatment-related, non-hematologic toxicities, nausea/vomiting was observed in 34 of 35 patients (97%), with a median WHO grade of II. Stomatitis and diarrhoea were observed in 9 patients (26%), with a median WHO grade of II. In 17 patients (49%), infections with a median WHO grade of I were documented. Of these 17 patients, 2 presented with a herpes zoster syndrome. Two episodes of leukopenia-related sepsis occurred in two patients with a WBC count of <1,000/μl. Hair loss was observed in 33 patients (94%), with a median WHO grade of II. Otherwise, non-hematologic toxicity was mild and infrequent: six patients suffered from taste alteration and one showed onycholysis.

Cardiac abnormalities developed in five patients who demonstrated temporary sinus tachycardia immediately after receiving THP-DXR. To date, 19 patients have been treated with cumulative doses of at least 700 mg/m^2 (range, 700–1,050 mg/m^2). Serial estimations of the left ventricular ejection fraction by multigated analysis are available for 14 of these patients: the median pretreatment ejection fraction measured 70% (range, 50%–93%) and the median posttreatment value was 66% (range, 50%–85%). The posttreatment value represents the average recorded after a median of 10 (range, 10–15) trearment cycles. Thus far we have observed no signs of congestive heart failure.

Discussion

This study indicates that THP-DXR is of therapeutic value in both pretreated and previously untreated patients with advanced breast cancer. The overall response rate (CR and PR) was 59% and the median duration of response was 49+ weeks. These results suggest that the activity of THP-DXR is at least comparable with that achieved using other anthracyclines and their derivatives. Published data on the response rate for doxorubicin monotherapy on a 3-week schedule in previously untreated breast cancer patients vary between 38% and 47%; a median duration of response of between 17 and 30 weeks was reported in these patients [2, 21]. In several randomized trials comparing the re-

sponse rates for doxorubicin with those for mitoxantrone, values for duration of response and survival did not differ significantly, although there was a trend toward a lower rate of remission with mitoxantrone [1, 3, 16].

In classifying the observed high response rate of 59% and the median response duration of 49+ weeks with THP-DXR monotherapy in our study, the limited number of patients evaluated (34 patients) as well as the prognostic values of subgroups must be considered. On the one hand, only 8 (24%) of the 34 evaluable patients had received prior chemotherapy for metastatic disease, 21 (62%) patients had a Karnofsky index of at least 90% at the time of entry and 11 (32%) patients demonstrated soft-tissue and/or lymphnode metastases as their dominant site of disease. On the other hand, there was a poor-risk subgroup of patients in this study, since 18 (53%) patients had $\geqslant 2$ sites involved in metastases and 15 (44%) patients had viscerally dominant disease.

In agreement with the reports of previous phase I trials [11, 14, 17, 24], the dose-limiting toxicity of THP-DXR in our study was leukopenia. Other systemic side effects, such as nausea, emesis and hair loss, were frequent but usually of moderate degree. These toxic effects of THP-DXR monotherapy observed in our study appear to be similar to data reported for doxorubicin [6] but may be more severe than those reported in patients receiving mitoxantrone monotherapy [1, 3, 6]. In spite of cumulative doses of up to 1,050 mg/m^2, to date we have observed no signs of congestive heart failure. Due to relatively short observation periods, no definitive statement can be made regarding the possibly lower cardiotoxicity of THP-DXR as compared with that of other anthracyclines.

In summary, THP-DXR is an effective drug for first- and second-line chemotherapy in advanced breast cancer. The treatment is generally well tolerated, although therapy had to be delayed in some instances due to hematologic toxicity as well as to nausea and vomiting

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