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CLINICAL TRIAL REPORT

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A phase I/II study of 4′-*O*-tetrahydropyranyl-doxorubicin, 5-fluorouracil, and high-dose leucovorin as first-line therapy in advanced breast cancer patients

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Abstract A total of 50 patients were treated weekly with 5-fluorouracil (FU), leucovorin (LV), and 4′-*O*-tetrahydropyranyl-doxorubicin (THP) as first-line chemotherapy for advanced breast cancer (ABC). In phase I the doses of LV (500 mg/m^2, day 1) and FU (350 mg/m^2, day 1) were held constant, while the dose of THP (day 1) was escalated, from the initial dose of 10 mg/m^2 up to the maximum tolerated dose (MTD). Twenty-eight patients entered phase I, and MTD for THP was defined as 35 mg/m^2 in this combination. Dose-limiting toxicities were myelosuppression and hepatotoxicity. In phase II, another 22 patients were treated with THP at a dose level of 30 mg/m^2. Including 4 patients already treated at this dose in the first part, 25 patients were evaluable for response: 1 patient obtained a complete response (CR) and 13 showed a partial response (PR), giving an objective response rate of 56%. The median duration of response was 9.1+ months and median survival, 15.5+ months. Side effects were generally mild, with ECOG grade I and II leukopenia in 51% of all cycles and grade III in 3% of the courses. Other toxicity included nausea and vomiting (54% and 8%, respectively) and alopecia (24%), all restricted to ECOG grade I and II. Our results suggest that weekly THP/LV-FU represents an active regimen for first-line treatment of ABC with relative low toxicity.

Key words Breast cancer · 4′-*O*-Tetrahydropyranyl-doxorubicin · Fluorouracil/Leucovorin · Weekly schedule

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Introduction

The palliative management of advanced breast cancer (ABC) with various combination chemotherapies produces an objective remission of the disease in 40–70% of cases [2]. It is, however, disturbing for both the patient and the clinician when toxicity detracts from the quality of survival while objective disease regression is occurring. Clinical research has concentrated its efforts on improving treatment modalities, by development of new cytotoxic drugs, by manipulations of doses, schedules and combinations or by 'modulation' of known cytotoxic drugs. Doxorubicin is regarded as one of the most active single agents for the treatment of ABC [3, 10, 21]. The acute dose-limiting factor is myelosuppression, in particular, leukopenia [3]. Other side effects are varying degrees of nausea and vomiting and a high rate of total alopecia. The most important drawback is cumulative dose-dependent cardiotoxicity [3, 24]. To increase the therapeutic index, new anthracycline analogues were developed by altering the chemical structure of doxorubicin [23]. 4′-*O*-Tetrahydropyranyl-doxorubicin (THP), also known as pirarubicin, is a semisynthetic derivative of doxorubicin [23]. With regard to pharmacokinetics and tissue distribution, THP differs distinctly from doxorubicin: for example, it has a far greater distribution volume [5, 13]. Data obtained in the golden hamster model of Dantchev showed that the cardiotoxicity of THP was lower than with doxorubicin or 4′-epi-doxorubicin [4]. Early clinical trials of THP have demonstrated objective remissions in patients with cervical and ovarian cancer, breast cancer, mesothelioma, and malignant lymphoma [11, 17]. Based on the results of a phase I study conducted in Europe, which indicated a maximum tolerated dose (MTD) of 70 mg/m^2 for a 3-weekly schedule [15], phase II trials with THP in ABC demonstrated remission rates between 30% and 50%, with leukopenia as the dose-limiting factor [18, 19].

5-Fluorouracil (FU) remains a standard part of combination programs applied to the therapy of ABC [7, 9]. One potential method of enhancing the efficacy of FU is

biochemical modulation with leucovorin (LV) [12, 16]. The combination of FU and LV has also been used in the treatment of metastatic breast cancer, and has shown activity both in previously untreated and in heavily pretreated patients [1, 14, 20].

Since the main side effects of this combination were diarrhea, oral mucositis, and conjunctivitis, while hematological toxicity was reported to be very mild, it appeared it might be useful to combine this regimen with drugs characterized by a different pattern of toxicity, e.g., THP. In an attempt to reduce toxicity while maintaining dose intensity, weekly treatment courses were chosen to diminish dose per single course.

We therefore conducted a disease-oriented phase I–II trial in patients with ABC to define the MTD of THP in combination with FU and LV in a weekly schedule and to investigate the antitumor activity and the safety of this regimen.

Patients and methods

Eligibility criteria

To be eligible for this study, patients were required to have histologically proven ABC. Previous chemotherapy for metastatic disease excluded patients from participation, whereas adjuvant cytotoxic therapy did not, provided that the therapy had been stopped for a minimum of 12 months before entry. Further eligibility requirements included the presence of progressive measurable and/or evaluable disease (objective measurable disease was mandatory for the phase II trial), an age $\leq$70 years, an ECOG performance status $\leq$2, a white blood cell count of $\geq$3500/mm^3, a platelet count of $\geq$100,000/mm^3, adequate liver and renal function, and a normal left ventricular ejection fraction (LVEF). All patients entering this study were informed of the investigational nature of the treatment protocol and had signed an informed consent in accordance with the standards of the local institutional ethical committee.

Treatment plan

In the first part of the study, the MTD of THP in the combination with fixed doses of FU and LV had to be defined. Courses were scheduled in 7-day intervals on day 1, 8, 15, etc, consisting of LV 500 mg/m^2 i.v. over 2 h, and FU 350 mg/m^2 i.v. push at the 1-h point of the LV infusion, followed by THP i.v. over 15 min immediately after the LV administration. THP was generously provided by Behringwerke, Marburg, Germany. All cycles were given on an outpatient basis. A standardized metoclopramide schedule (10 mg i.v., 20 min prior to therapy, then 10 mg p.o. three times daily) was administered for antiemetic prophylaxis.

Cycles were repeated as scheduled, provided that the patients had recovered from toxicity. If recovery was not complete by day 8, i.e., white blood cell count $<$3500/mm^3, platelet count $<$100,000/mm^3, or in the case of persistent mucositis or gastrointestinal toxicity, chemotherapy was withheld and the patient reevaluated weekly.

The dose of THP was escalated in 5-mg/m^2 increments beginning at 10 mg/m^2 until the MTD was reached. There was no intrapatient dose escalation. A minimum of 4 patients was to be entered at each dose level. If none of these 4 patients experienced: (a) toxicity ECOG grade III or IV (alopecia was not regarded as a dose-limiting toxicity), (b) toxicity that caused postponement of planned treatment course for more than 2 weeks, or (c) a decrease of LVEF by more than 10% from the patient's baseline value and/or a value lower than 50% during the first six treatment courses, the next patients enrolled were entered at the next THP dose level. Whenever toxicity as detailed above was present in at least 1 of the 4 patients, another 4 patients were required to be treated at the same dose level. MTD for the regimen was defined as being that dose at which $\geq$50% of these 8 patients had developed the toxicity specified above.

In the second part of the study, it was planned that patients be treated at a THP dose one level below the defined MTD. In the absence of progressive disease (PD), a total of 18 treatment courses was scheduled for each patient; then, patients were to be followed up without any form of maintenance therapy until PD occurred.

Assessment of response

Evaluation of response took place every six cycles of therapy, and UICC criteria were used for this purpose [6]. Patients completing at least six cycles of therapy were considered evaluable for response.

Results

Patient characteristics

From June 1989 to February 1993, a total of 50 patients were entered into this trial (phase I, n = 28; phase II, n = 22). The main patients' characteristics are summarized in Table 1.

Phase I – assessment of MTD

All the 28 patients entered in the dose-finding procedure were evaluable for toxic effects. The number of patients and toxicity observed at each dose level is shown in Table 2. Remarkably little toxicity was observed at the first five dose levels. Although myelotoxicity was eventually seen at all dose levels, toxicity remained restricted to ECOG grades I and II. At the sixth dose level (THP 35 mg/m^2), 1 patient developed grade III and 1 patient, grade IV leukopenia. In another patient, persistent grade II leukopenia caused postponement of the planned course for more than 2 weeks. In 1 patient treated at the 35-mg/m^2 dose level, treatment was complicated by grade IV hyperbilirubinemia for which no other reason than ongoing chemotherapy could be found. Neither mucosal toxicity nor gastrointestinal side effects became a problem at the dose levels tested. Nausea and vomiting did not exceed grade II toxicity, but there were increasing numbers of toxic events at the higher dose levels. The MTD of weekly THP in the combination with FU 350 mg/m^2 and LV 500 mg/m^2 was determined as 35 mg/m^2.

Phase II – response data

Including 4 patients already treated at the THP 30-mg/m^2 dose level in the dose-finding part of the study, 26 patients were considered for the phase II evaluation. A median of 18 cycles (range, 3–18 cycles) was administered, with a median treatment time of 5.3 months. Ultimately, 25 of these 26 patients were evaluable for response; 1 patient was

Table 1 Patients' characteristics No.[a]

	Total	Phase I	Phase II
Entered	50	28	26[b]
Median age in years (range)	53 (33–71)	56 (41–69)	52 (33–71)
Menopausal status			
Premenopausal	15	9	6
Postmenopausal	35	19	20
ECOG performance status			
0	31	18	18
1	14	9	6
2	2	1	2
Hormone receptor status			
Positive	27	12	15
Negative	13	9	7
Unknown	10	7	4
Relapse-free interval			
>2 years	17	10	11
<2 years	33	18	15
Dominant site of disease			
Soft tissue	7	5	3
Bone	4	3	2
Visceral	34	16	20
Advanced primary lesion	5	4	1
Number of organ systems involved			
1	26	20	9
2	11	3	10
>3	14	5	7
Prior hormonal therapy			
Adjuvant	14	8	6
For metastatic disease	11	4	7
Prior adjuvant chemotherapy	11	4	9
FU-containing	9	2	9
Anthracycline-containing	2	2	–

[a] Unless otherwise specified, values = number of patients
[b] Four patients treated at the 30 mg/m² THP dose level in the phase I study included

lost to therapy after three courses because of a pathologic bone fracture that caused postponement of treatment for more than 3 weeks, and was therefore considered not evaluable for response. In all, 1 (4%) patient obtained a CR and 13 (52%) reached a PR, giving an overall response rate of 14/25 (56%) with a 95% confidence interval of between 31% and 77%; 6 (24%) patients achieved stabilization of their disease (NC), and in 5 (20%) patients the disease progressed during the treatment. Response according to dominant site of disease and number of involved organ systems is shown in Table 3.

One patient responding to the regimen had an advanced primary lesion for which she underwent surgery, and she was therefore considered not to be evaluable for duration of response. The median duration of response for the remaining patients was 9.1+ months (range, 4.9–21.5+ months),

Table 2 Phase I: side effects per dose level

THP dose level (mg/m²)	10		15		20		25		30		35			
No. of patients	4		4		4		4		4		8			
Side effects[a]														
ECOG grade	I	II	I	II	I	II	I	II	I	II	I	II	III	IV
Anemia	2	–	4	–	5	–	2	–	10	–	23	3	–	–
Leukopenia	2	–	10	4	10	2	9	3	12	4	18	17	1	1
Thrombopenia	–	–	–	–	–	–	–	–	–	–	3	–	–	–
Infection	3	–	1	–	1	1	4	–	2	2	3	–	–	–
Nausea	10	–	19	–	16	2	15	9	14	7	25	6	–	–
Vomiting	7	1	–	–	1	2	3	–	3	–	1	2	–	–
Stomatitis	–	–	2	–	1	–	2	1	1	–	–	–	–	–
Diarrhea	1	–	1	–	–	4	1	–	4	–	–	–	–	–
Bilirubin	–	–	–	–	–	–	–	–	–	–	–	–	–	1
Alopecia	–	–	2	–	1	–	5	–	6	1	12	11	–	–

[a] Values = no. of events with the first six treatment courses per dose level

Table 3 Phase II: response[a] according to dominant site of disease and number of organ systems involved (*DSD* dominant site of disease; *V* visceral; *O* osseous; *ST* soft tissue; *OSI* organ systems involved)

	DSD			No. of OSI		
	V	O	ST	1	2	<3
CR	1/20	–	–	1/8	–	–
PR	10/20	–	3/4	4/8	4/10	5/7
NC	5/20	–	1/4	2/8	3/10	1/7
PD	4/20	1/1	–	1/8	3/10	1/7

[a] Figures displayed are no. of patients/no. of patients in collection

and the median time to disease progression for the patients with NC accounted to 9.1+ months (range, 4.4–16+ months). The median survival was 15.5+ months (range, 2.7–31.7+ months) for all patients entered and 16.2+ months (6.2–21.1+ months) for responders. The median survival of the patients with PD was 3.9 months.

Phase II – toxicity

All 26 patients who entered the phase II part of the study were evaluable for toxic effects. The therapy was completed as scheduled in 23 of the 26 patients. Besides the 1 patient lost to therapy after three courses, 1 patient who had presented with soft tissue metastases and who achieved PR refused further therapy because of global intolerance after 12 cycles. In another patient, treatment had to be stopped after 12 courses because of cardiotoxicity (see below). The toxic events experienced with a total of 369 cycles given are outlined in Table 4. The principal toxic effect encountered with this regimen was myelosuppression. Of all courses delivered in the second part of this trial, 54% were associated with leukopenia, 53% with anemia, and 10% with thrombocytopenia. However, hematotoxicity remained restricted mainly to ECOG grades I and II. Grade III leukopenia was observed in 3% of cycles only, and anemia grade III in 1% of all cycles. Observed thrombocytopenia was limited to ECOG grade I. As anticipated, moderate (ECOG grades I and II) nausea and vomiting were encountered in 54% and 8% of all courses, respectively. Other toxic effects encountered included diarrhea and stomatitis, each seen in 2% of all courses and only classified as ECOG grade I. No case of treatment-related hyperbilirubinemia was observed. One patient experienced an asymptomatic decrease in the LVEF by more than 10% of baseline after 12 courses of therapy. Treatment was discontinued in this patient, and the decrease in the LVEF proved to be reversible after an observation period of 4 weeks.

Alopecia, grades I and II, was reported in 24% of treatment cycles, and necessitated wearing a wig in only 2 patients. Grade I and II thrombophlebitis at the site of administration appeared in 4% of the cycles, without any accidental extravasation. No other unique or unusual toxic effects were reported.

Discussion

The present study was conducted in the course of the search for therapies that combine effectiveness with acceptable toxicity in the treatment of ABC. The most frequent dose-limiting toxic effect of THP in combination with LV-FU was myelosuppression, while in 1 patient transient grade IV hyperbilirubinemia was the dose-limiting toxicity.

The overall response rate of 56% obtained in this investigation indicates the activity of the THP/LV-FU regimen in ABC. The response rate seems quite interesting, especially considerating that in 66% of the patients two or more organ systems were involved and 12/26 (46%) patients had liver metastases. The median duration of response, 9.1+ months, appears to be comparable to those achieved with other first-line drug regimens, especially when the high proportion of visceral involvement of the disease and the median treatment time of only 5.3 months are borne in mind [8, 22]. Another important observation recorded in this study is the lack of severe (grade III or IV) diarrhea and stomatitis, which are frequently experienced with the conventional 4-weekly (days 1–5) high-dose LV-FU regimens; this milder toxicity is probably related to the lower and shorter plasmatic peak drug exposure due to the weekly schedule [1, 14, 20].

With a THP dose of 30 mg/m^2, the toxicity observed was in general mild to moderate. Except for a reversible asymptomatic decrease of the LVEF in 1 patient, no signs of cardiotoxicity occurred. From a psychological point of view, in addition to the low incidence of acute side effects,

Table 4 Phase II: toxicity of treatment[a]

ECOG grade	I	II	III	IV
Anemia	161 (44)	28 (8)	3 (1)	–
Leukopenia	130 (35)	59 (16)	9 (3)	–
Thrombocytopenia	35 (10)	–	–	–
Infection	22 (6)	17 (5)	–	–
Stomatitis	6 (2)	–	–	–
Diarrhea	8 (2)	–	–	–
Nausea	143 (39)	56 (15)	–	–
Vomiting	17 (5)	9 (3)	–	–
Cardiotoxicity	1[b]	–	–	–
Alopecia	55 (15)	33 (9)	–	–
Thrombophlebitis	10 (3)	2 (1)	–	–

[a] Values are the number of toxic events (%) experienced with all the 369 treatment courses administered

[b] Therapy was discontinued after assessment of cardiotoxicity in this patient according to the protocol

the very low incidence of hair loss was important to the patients treated with this schedule.

In summary, we have demonstrated that these three agents can safely be combined, with acceptable and manageable toxic effects, and have defined the MTD for THP as 35 mg/m^2 in with the weekly schedule investigated. At a THP dose of 30 mg/m^2, THP/LV-FU provides an active regimen for first-line treatment of advanced breast cancer with relatively low toxicity.

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