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# Pirarubicin in Advanced Breast Cancer: A French Cooperative Phase II Study

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**79 patients with advanced breast cancer were given Pirarubicin 20–25 mg/m² during 3 consecutive days every 3 or 4 weeks. 78 were evaluable for response (41 without previous chemotherapy and 37 with only one previous regimen). The overall response rate was 35% (95% CI 24–45) and the complete response rate was 8%. In previously untreated patients, the response rate reached 41.5%. The limiting toxicity was a non-cumulative granulocystopenia, sometimes severe at these high doses, with a prompt recovery. The non-haematological toxicities were mild, and included 13% with grade 3 alopecia.**
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## INTRODUCTION

PIRARUBICIN (4'-0-tetrahydropyranyl-doxorubicin) has a higher preclinical therapeutic index than doxorubicin[1,2] with low cardiotoxicity in different animal models[3–5]. Pharmacokinetic studies show a half-life shorter than that of doxorubicin with an earlier cellular uptake and a higher cellular concentration of the drug[6,7]. Phase I studies have shown that the limiting toxicity was granulocystopenia and that the optimal dose was between 45 and 75 mg/m² every 3 weeks.

In Japanese phase II reports, the spectrum of activity of pirarubicin was close to that of doxorubicin with less toxicity, especially alopecia[8]. Mathe *et al.*[9] reported a response rate of 28% in 50 patients with advanced breast cancer, mostly heavily pretreated. They suggested that a 3 day schedule gave a better tolerance than bolus administration. We have done a cooperative phase II study of pirarubicin in non-heavily pretreated advanced breast cancer.

## PATIENTS AND METHODS

*Eligibility criteria*

All female patients with a pathologically proven advanced breast cancer (metastatic and/or with locoregional relapse), aged under 70, had been enrolled if they had at least one measurable or evaluable site of evaluation (except isolated bone disease), and either no previous chemotherapy or only one previous regimen containing less than 300 mg/m² doxorubicin (or equivalent) at least 1 year before inclusion. Performance status (ECOG) under 2 was required, as well as white cell counts over $4 \times 10^9$/l, platelets over $120 \times 10^9$/l, serum bilirubin under 35 μmol/l, and serum creatinine under 135 μol/l. All patients gave oral informed consent.

*Exclusion criteria*

Congestive heart failure, previous myocardial infarction, severe rhythm abnormalities or left ventricular ejection fraction

*Table* 1. *Dose adjustment*

| Nadir value (day 8 or 15) | | Value at 3 weeks* | | Further dose (% starting dose) |
|---|---|---|---|---|
| PMN | Plt | PMN | Plt | |
| ⩾ 0.5 | ⩾ 50 | ⩾ 2.0 | ⩾ 120 | 100% |
| — | — | 1.5–1.9 | 75–119 | 75% |
| < 0.5 | < 50 | Any value | Any value | 75% |

* When PMN < 1.5 or Plt < 75 at day 21, the following cycle was postponed for 1–2 weeks until recovery.
PMN = polymorphonuclear cells and Plt = platelets.

(LVEF) below 0.50, severe current infection, previous history of another cancer, and symptomatic central nervous system localization were exclusion criteria. Furthermore, at least one site of evaluation had to be outside a field of previous radiotherapy.

*Treatment*

Pirarubicin was provided by the Laboratoire Roger Bellon, Neuilly, as lyophilized red powder reconstituted with sterile water at 1 mg/ml. The drug was administered on 3 consecutive days as an intravenous bolus followed by washing of the vein. The starting dose was 25 mg/m$^2$ per day in the first 22 patients, then reduced to 20 mg/m$^2$ per day because of severe haematological toxicity. The cycles were repeated every 3–5 weeks according to the haematological recovery and a dose adjustment was planned as shown in Table I. Treatment was discontinued in cases of stabilization after at least 3 cycles or of objective disease progression whatever the cycle, patient's refusal, or severe toxicity.

*Assessments*

The initial assessment included physical examination, blood cell counts and differential, blood chemistry, electrocardiogram, chest *X*-ray, abdominal ultrasound or computed tomography, radionuclide cardiography, and bone scan. Blood counts were done every week and biochemistry at each cycle. LVEF was checked at the cumulative dose of 300 mg/m$^2$, then every cycle.

*Response and toxicity*

All patients achieving 2 complete cycles were adequately evaluated for response. Patients having an objective progression before the second cycle were classed as failures. All patients were evaluated for toxicity. WHO criteria[10] were used to evaluate efficacy and toxicity, except cardiotoxicity, which was assessed by criteria of Alexander *et al.*[11]. Special attention was given to alopecia and patients with scalp-cooling systems were not evaluable, except in case of complete (grade 3) hair-loss.

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*Table* 2. *Characteristics of* 78 *patients evaluable for response*

| | | |
|---|---|---|
| Age (yrs) | 54 | (30–70) |
| Time from diagnosis (yrs) | 4.2 | (0–26) |
| Post-menopause | 69 | (88%) |
| Previous therapies | | |
| Surgery | 64 | (82%) |
| Radiotherapy | 59 | (76%) |
| Hormonotherapy | 35 | (45%) |
| Chemotherapy | 27 | (35%) |
| Adjuvant | 10 | (13%) |
| Palliative | 25 | (32%) |
| with anthracycline* | | |
| Evaluable lesions ($N$ = 115) | | |
| Node | 21 | (27%) |
| Lung | 23 | (29%) |
| Liver | 27 | (35%) |
| Skin | 16 | (21%) |
| Breast | 14 | (18%) |
| Bone | 9 | (12%) |
| Others | 5 | (6%) |

* Mean cumulative dose of anthracycline 271 mg/m$^2$ (95–300).

*Quality control*

All clinical report forms were checked by the monitor of the Laboratoire Roger Bellon. Every 6 months a meeting of investigators took place to confirm observed responses, discuss equivocal data, and complete missing data.

## RESULTS

*Patients*

From December 1986, to June 1988, 82 patients were enrolled. 3 were ineligible (1 with a non-cancer site of evaluation, 1 with a performance score of 3, and 1 with isolated bone metastases). 79 patients were evaluable for toxicity and 78 for efficacy.

41 patients were never given previous chemotherapy and 37 had been pretreated : 27 with adjuvant chemotherapy and 10 with only one palliative regimen (Table 2). Out of these 10, 6 had received an anthracycline. The mean number of involved organs per patient was 1.5 (1–3).

*Treatment*

Patients received an average of 4.7 cycles (2–13) and a mean cumulative dose of 274 mg/m$^2$ (120–825). The 25 patients previously treated with an anthracycline finally received a cumulative dose of 518 mg/m$^2$ (325–780) of anthracycline.

*Efficacy*

6 complete responses (8%) and 21 partial responses (27%) were observed, giving an overall response rate of 35% (95% CI 24–45%). There were 32 with no change (41%) and 13 with progressive diseases (17%), 5 early deaths and 1 non-lethal severe early haematological toxicity.

In previously untreated patients, there were 4 CRs and 13 PRs (41%, 95% CI 22–57), whereas in pretreated patients, there were 2 CRs and 8PRs (27%, 95% CI 13–41%). 4 out of 6 patients previously given an anthracycline for advanced disease and

*Table 3. Acute toxicities**

| | WHO grade | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Granulocytopenia (nadir) (n = 78) | 15 | 4 | 12 | 21 | 26 |
| Thrombocytopenia (nadir) (n = 77) | 57 | 7 | 5 | 6 | 2 |
| Anaemia (n = 77) | 37 | 10 | 15 | 12 | 3 |
| Nausea vomiting (n = 75) | 27 | 23 | 12 | 12 | 1 |
| Stomatitis (n = 75) | 66 | 2 | 4 | 2 | 1 |
| Diarrhoea (n = 75) | 69 | 3 | 2 | 0 | 1 |
| Infection (n = 78) | 62 | 4 | 4 | 3 | 5† |
| Haemorrhage (n = 78) | 76 | 0 | 0 | 0 | 2† |
| Alopecia (n = 73)‡ | 24 | 23 | 8 | 8 | — |

* n = total no. of evaluable patients. † related to severe haematological toxicity.
‡Grades 2 and 3 alopecia were considered as severe (needing a wig).

having achieved a first response responded again to pirarubicin.

The response rate according to the site of disease was node 44%, skin 41%, breast 26%, lung 22%, liver 18%, and bone 11%.

The median duration of the responses was not reached at 12 months. CR occurred after 2–6 cycles (mean 4.3).

*Acute toxicity*

The limiting toxicity was granulocytopenia, which was maximal at day 15 and responsible for 2–4 early deaths (Table 3). 2 early deaths were obviously toxic (septic shock during aplasia) and 2 others were questionable because septic shock occurred after complete haematological recovery. Another patient died early from thromboembolism. All 5 patients with severe haematological toxicity had liver metastases. The maximal toxicity always occurred in the first cycle even without any dose reduction, suggesting a lack of cumulative toxicity.

Thrombocytopenia was mild except in patients with severe leucopenia. Anaemia, in exceptional cases, required transfusions and was mainly related to disease rather than treatment. Recovery was prompt since 61% patients gained a normal granulocyte count at day 21 and 83% at day 28, and 100% regained a normal platelet count at day 21.

The acute non-hematological toxicities were marginal. Alopecia was mild for an anthracycline with 13% complete and 13% partial hair loss; 26% of patients with partial or complete alopecia might have needed a wig. This toxicity did not increase with the number of cycles.

*Cardiac toxicity*

1 patient died after only 1 cycle and a total dose of 60 mg/m$^2$ from septic shock (after haematological recovery) with congestive heart failure and multivisceral failure. In the absence of necropsy, any responsibility of the drug cannot be assessed.

28 patients were evaluable for change in LVEF. Among these, 3 had a grade 3 toxicity (with decrease of 15–42% from control values of 0.37–0.45), without any clinical symptoms, but needing withdrawal of drug. These patients were given cumulative doses of anthracyclines of 225, 390, and 480 mg/m$^2$, respectively. 7 additional patients had a grade 2 toxicity (with decrease of 12–26% of initial value and control values of 0.49–0.70) and they could continue the treatment under repeated assessments which did not confirm toxicity[11].

## DISCUSSION

Pirarubicin was effective in advanced breast cancer with a 35% response rate in 78 patients not heavily pretreated. The response rate in 41 patients without previous chemotherapy was 41% (95% CI 26–56%) and was therefore in the same range as that of doxorubicin[12–15, 17] or epirubicin [13,16,17].

The only limiting toxicity was granulocytopenia which may be severe at the dose of 60–75 mg/m$^2$ per cycle. These doses have to be considered as high doses for the drug and the dose of 50 mg/m$^2$ should be further evaluated for efficacy. Other toxicities were mild, especially alopecia since about 25% patients might need a wig. Cardiac toxicity cannot be evaluated in this small series of patients. Pirarubicin is a candidate for further evaluation in breast cancer, especially in terms of quality of life.


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