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Early Assessment of a New Anticancer Drug Analogue — are the Historical Comparisons Obsolete? The French Experience with Pirarubicin

P. Herait, N. Poutignat, M. Marty and R. Bugat

Data of all phase II studies of pirarubicin (THP-doxorubicin) have been analysed for toxicity or activity in breast cancer and compared with published reports on doxorubicin, epirubicin or mitoxantrone used as single drugs. A graph of the 95% confidence intervals for each event was used. The results suggest that pirarubicin is as effective as other intercalating drugs in breast cancer and grossly better tolerated than doxorubicin, especially alopecia and cumulative cardiotoxicity. The equimyelotoxic doses of each drug were also estimated. The methodology and the validity of such historical comparisons is discussed: they cannot replace prospective randomised phase III studies, and do not allow definitive conclusions. However, most comparative trials of anticancer drug analogues cannot answer the right questions because their objectives are not adequate (especially for equiefficacy). But early evaluation by historical comparisons can help the conception of phase III studies.
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INTRODUCTION

AFTER THE phase II trials have shown efficacy and described main toxicities, the development of a new anticancer drug reaches a pivotal point. It is necesary to compare it with the standard drugs, when they exist or to no specific treatment when such drugs do not yet exist. This comparison has to be done by mean of comparative, randomised phase III trials.

Such trials are time-consuming, costly and need a heavy organisation for collecting and treating data by the sponsor. That is the reason why, before starting the phase III trials, a thorough examination of the data available from the phase II studies should be recommended, to target the most adequate population of patients and to give the optimal dose of the drug, in order to ask the right questions and to give oneself the means to answer them, with the ethically acceptable price for the patients.

Historical comparisons, despite all statistical objections, are the only manner to place early the new drug. They cannot, obviously either substitute themselves to the phase III studies, or give definitive conclusions, but, on the other hand, they can valuably help their conception.

Pirarubicin (tetrahydropyranyl [THP] doxorubicin) is an anthracycline, selected on preclinical data which had shown an efficacy superior or equal to the mother compound doxorubicin with less toxicity [1]. We report here the methodology and the results of the early evaluation of THP, using phase II data of the drug, compared with historical data concerning DOX and other intercalating drugs effective in breast cancer (i.e. epirubicin and mitoxantrone).

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Table 1. Patients at risk from CHF according to the cumulative dose of pirarubicin (patients never given prior anthracycline or anthracenedione)

Cumulative dose of THP (mg/m²)	Mean dose of THP in mg/m² (range)	n	Cumulative no. of patients at risk	CHF	Mean follow-up in months (range)	n
0– 100	65.9 (27–100)	88	350	2	3.3 (3–10)	88
100– 200	154 (102–200)	127	262	0	4.8 (3–46)	127
200– 300	256.3 (202–300)	69	135	0	6.1 (3–53)	69
300– 400	349 (301–400)	31	66	0	5.1 (3–15)	31
400– 500	452.1 (405–495)	16	35	0	6.5 (3–13)	16
500– 600	558.9 (510–590)	9	19	0	10 (3–31)	9
600– 700	605	1	10	0	3	1
700– 800	742.3 (717–800)	5	9	1	10 (3–16)	5
800– 900	829	1	4	0	12	1
900–1000	1000	1	3	0	3	1
1000–1100	1080	1	2	0	14	1
1100–1200	1103	1	1	0	10	1
Total		350		3	5.4 (3–53)	350

None of the patients had ever previously received anthracycline or anthracenedione.

MATERIALS AND METHODS

Data concerning THP

576 patients were enrolled in the phase II studies using single-drug with an every −3 to −4 week schedule, at doses ranging from 45 to 75 mg/m², in 14 different tumour types [2]. WHO criteria of evaluation of efficacy and toxicity were used [3].

All patients were evaluable for toxicity. Concerning the cumulative cardiac toxicity of THP, all congestive heart failures (CHF) have been reported, whatever their assumed cause (which is probably non-toxic, especially for low cumulative doses). In order to avoid unknown late CHF in patients lost to follow-up, only patients without cardiac event and with a clinical follow-up of at least 3 months after the last THP administration have been considered evaluable for risk of CHF. The actuarial risk has been calculated by intervals of dose of 100 mg/m². Table 1 shows the number of patients, never given prior anthracycline or anthracenedione, at risk from CHF, according to the cumulative doses of THP, and the number of observed CHF.

Efficacy in breast cancer was documented among 197 patients from four different studies, one of which was multicentric, including 15 different cancer centres. Stratifications were done according to main prognostic factors.

Data concerning doxorubicin and other intercalating agents

A review of the literature upto August 1989 found 82 publications concerning either doxorubicin, epirubicin or mitoxantrane as single drug, with an every −3 to −4 week schedule in advanced solid tumour patients in either a phase II study or in one-arm of a phase III study. 77 references were relevant for toxicity [4–80] and 28 for efficacy in advanced breast cancer [7, 8, 10, 11, 17–19, 22, 26, 30, 31, 42, 43, 46, 52, 57, 59, 60, 66, 67, 69, 72, 78, 81–85]. Special attention has been drawn to avoid mentioning the same patient twice if mentioned in more than one publication.

Method of comparison

All comparable data for one given item were compiled either for THP or for other compounds. For THP, the raw data were directly available at the Laboratoire Roger Bellon [2]. For the other compounds, each item concerning the efficacy in breast cancer or the toxicity was used, provided that explanations in the text showed clearly they were comparable (e.g.: WHO grade of nadir—and not of recovery—of leucocytes per patient or per cycle). The number of events and the number of patients (or cycles) evaluable for this event were merely added. The overall rate of this event was then calculated with its 95% confidence interval (95 CI) obtained by:

$$\sqrt{\frac{pq}{n}} \times 1.96, \text{ where } p \text{ is the frequency of the event} \times 100,$$

$q = 100 - p$ and

n = the number of subjects at risk for the event.

The confidence intervals were graphically compared for each item on the figures. The risk of CHF was calcualted by the actuarial method [86] according to the cumulative dose of either THP or doxorubicin, using for this latter drug the raw data given in ref. [80]. Confidence limits of both curve have been calculated by the method of Rothman [87].

The results were presented to a panel of medical oncologists, to ensure that they did not radically differ from their own experience, and compared with published general reviews on epirubicin [13] or mitoxantrone [44, 68].

RESULTS

Efficacy

Figure 1 shows the response rates, in advanced breast cancer, achieved with doxorubicin, epirubicin, mitoxantrone or THP (single drugs). Objective response rates (CR + PR) are given separately for patients without prior chemotherapy (front-line) and for patients given chemotherapy previously. The former subgroup is more homogeneous regarding the likelihood of response to any chemotherapy, whereas the latter includes heterogeneous patients heavily or not heavily pretreated, and with different kinds of drugs. It must be emphasised that the rate of patients pretreated with other anthracyline or anthracenedione varies widely from one group to another: none of the 479 pretreated patients receiving doxorubicin, 42 out of the 219 (19%) receiving epirubicin, 209 out of the 509 (41%) receiving

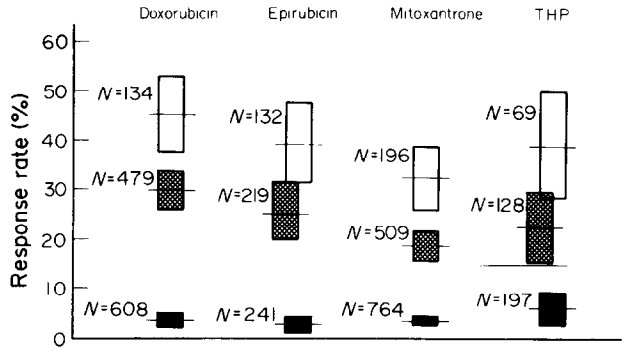

Fig. 1. Response rate in breast cancer patients and 95% confidence limits. □ = CR + PR (patients not previously given chemotherapy), ▩ = CR + PR (patients given prior chemotherapy; either without or with anthracycline and/or anthracenedione), ■ = CR (all patients). *N* = Number of evaluable patients.

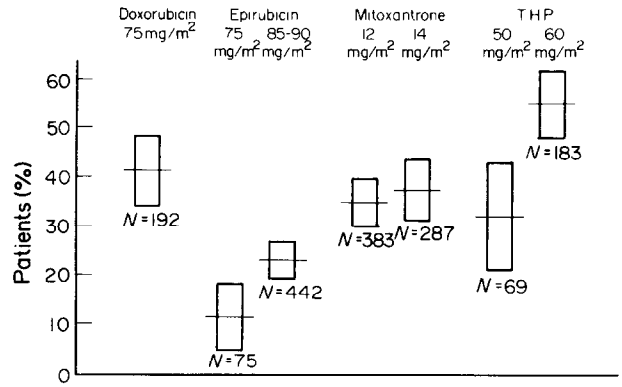

Fig. 3. Severe (WHO grade 3 + 4) leukopenia: lowest nadir values per patient incidence and 95% confidence limits according to the dose. *N* = Number of evaluable patients. THP = pirarubicin.

mitoxantrone, and 98 out of 128 (77%) receiving THP. The data concerning doxorubicin come from refs 7, 19, 52, 67 and 85, that of epirubicin from refs 7, 8, 10, 11, 17, 18, 19, 22, 26, 30, 31, 81, 82 and that of mitoxantrone from refs 42, 43, 46, 52, 57, 59, 60, 66, 67, 69, 72, 78, 83, 84. The 197 THP patients were treated with a starting dose ranging from 45 to 75 mg/m² and finally received a median dose of 57 mg/m². No clear dose–activity relationship between low and high doses was demonstrated in this range of dose [2], wherein a clear dose–toxicity relationship does exist.

Concerning the duration of the response the median duration with THP was 52 weeks [2]; that reported with doxorubicin ranged from 18 to 56 weeks [7, 19, 52] that with epirubicin from 30 to 52 weeks [7, 17, 19, 82] and that with mitoxantrone from 19 to 48+ weeks [42, 43, 52, 69, 72, 83].

Toxicity

Leukopenia is the acute limiting toxicity of all four drugs. It is reported more often than granulocytopenia. Only references where the lowest value between the cycles were reported, using at least a weekly blood count, have been taken into account. Some publications report the toxicity per cycles and others per patients. The former appears to be always milder than the latter because of dose adjustment following toxicity observed at the first cycle. Therefore leukopenia per cycles is not comparable with that per patient. Figure 2 shows the incidence of severe (WHO grade 3 + 4) nadir values, reported per cycles and according to the planned dose.

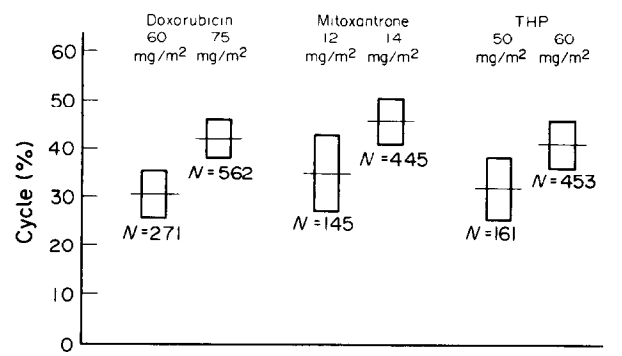

Fig. 2. Severe (WHO grade 3 + 4) leukopenia at the nadir per cycle incidence and 95% confidence limits according to the dose. *N* = Number of evaluable cycles. THP = pirarubicin.

For doxorubicin 60 mg/m² the only data available came from one literature review [68]; for doxorubicin 75 mg/m² more data were available by compiling refs 29 and 52. For mitoxantrone 12 and 14 mg/m² more data are available from ref. 68. No data are available for epirubicin.

Figure 3 shows the incidence of severe nadir values of leukopenia per patient. Only 28 patients were evaluable for doxorubicin 60 mg/m² with 18 severe leukopenia (results not shown). For doxorubicin 75 mg/m², 192 patients were evaluable from refs 29, 52, 79. For epirubicin 75 mg/m², results came from refs 29, 33, 36 and for epirubicin 85–90 mg/m² from refs 12, 16, 19, 20, 22, 24, 26, 27, 31.

The quality of the reported results is likely to vary from one publication to another. For example in the study of Kolaric *et al.* [22], no severe leukopenia is reported among 92 patients. This result is surprising because other studies report 10–64% among smaller samples of patients and suggests that only recovery values were reported instead of nadir values. However there are clear explanations in the text that nadir values are reported; thus although this publication has been taken into account, it should be emphasised that it could improve the overall results.

For mitoxantrone 12 mg/m² results came from refs 40, 45, 48, 62–66, 75, 76, 83 and for mitoxantrone 14 mg/m² from refs 42, 49, 50, 52, 56, 69, 77.

Alopecia is a common toxicity of anthracyclines. It is reported in the literature as overall incidence and/or as severe alopecia. Considering that WHO grade 4 (irreversible) alopecia does not exist with chemotherapy, we have reported for THP patients both WHO grade 2 (partial) and 3 (complete) alopecia as severe because such patients may need a wig. In the literature, we have selected as severe alopecia, those reported as severe, or as grade 2 and 3 or as needing a wig. Figure 4 shows the comparative incidence of alopecia for doxorubicin [7, 19, 29, 52, 67, 73, 79]; epirubicin [4–11, 14–24, 26–31, 33–35]; mitoxantrone [39, 41–43, 46–48, 51, 52, 54–61, 63, 66, 67, 69, 70, 72, 73, 76–78, 83, 84] and THP [2]. The 73% rate (95% CI [70–76]) for epirubicin is comparable with that reported by Ganzina *et al.* [13] as well as the 52% rate of severe alopecia.

The rates shown for doxorubicin and mitoxantrone are slightly higher than that reported by Crossley [44] and Posner *et al.* [68] but they are calculated among a greater number of patients.

Figure 5 shows the incidence of nausea–vomiting and stomatitis. The data come from refs 7, 19, 29, 52, 67, 73, 79 for doxorubicin, 4–11, 14–27, 29–37 for epirubicin and are compar-

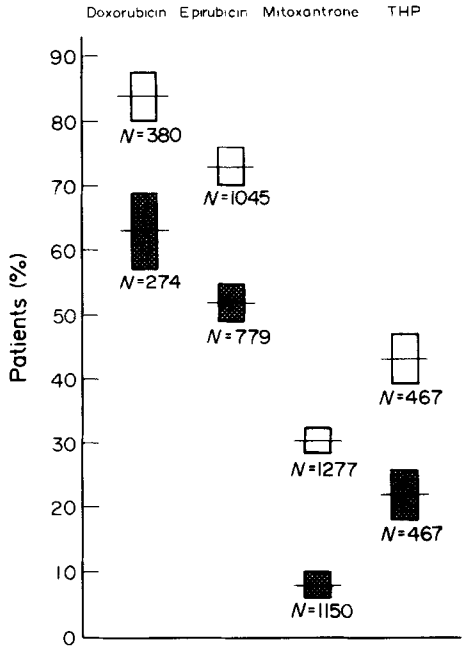

Fig. 4. Incidence of alopecia (and 95% confidence limits). □ = All grades (WHO 1–3). ■ = Severe alopecia (WHO grade 2 and 3) requiring a wig. *N* = number of evaluable patients. THP = pirarubicin.

able with that reported by Ganzina *et al.* [13], from refs 38–40, 42, 46–56, 58–67, 69–78, 83, 84 for mitoxantrone. The results are slightly lower than that reported by Crossley [44] and Posner *et al.* [68].

Figure 6 shows the actuarial risk of CHF according to the cumulative dose of doxorubicin [80] or THP (data of the Table 1)

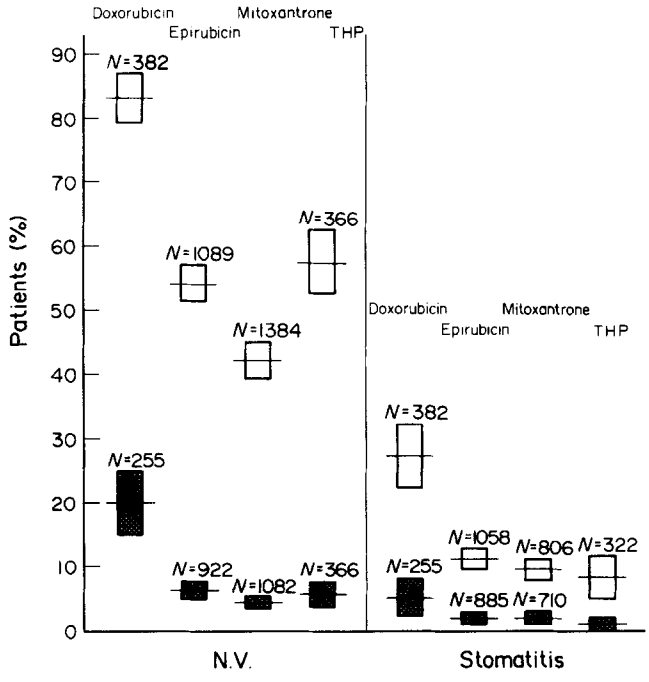

Fig. 5. Incidence of gastro-intestinal toxicities. Nausea–vomiting (N.V.) and stomatitis, and 95% confidence limits. □ = All grades (WHO 1–4). ■ = Severe (WHO 3 and 4). *N* = Number of evaluable patients. THP = pirarubicin.

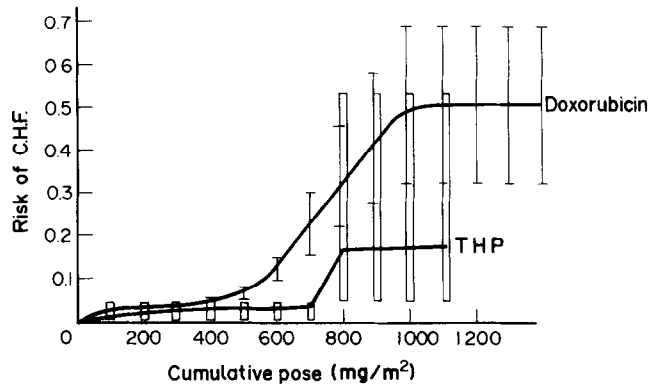

Fig. 6. Actuarial risk of CHF in patients given pirarubicin (THP) (*N* = 350) or doxorubicin, *N* = 3941; ref 80, and 95% confidence limits, according to the cumulative dose. I = confidence limits of the doxorubicin curve. □ = confidence limits of the THP curve.

and the confidence limits of the curves. The curve of THP is not interpretable over 700 mg/m² (width of the confidence limits) because the number of evaluable patients is too low and only one event exists.

Figure 7 shows the actuarial risk of CHF for doxorubicin [80], epirubicin [13], mitoxantrone [44, 68] and THP according to the putative number of cycles at the usually recommended dose as single drug. (i.e.: doxorubicin 60 mg/m²; epirubicin 75 mg/m²; mitoxantrone 12 mg/m² and THP 50 mg/m²). This graphic figuration takes into account the equimyelotoxicity for doxorubicin, mitoxantrone and THP (see Fig. 2) and the usually reported dose as single drug for epirubicin. However at the equimyelotoxic dose of 90 mg/m² of epirubicin (see Fig. 3), the inflexion point would be at 10 cycles.

DISCUSSION

Historical comparisons of efficacy in breast cancer and toxicity have been performed between THP, doxorubicin, epirubicin and mitoxantrone from a review of the literature. The method has allowed to add a high number of patients and/or cycles of chemotherapy and to compare the 95% confidence limits of either the response rates or the incidence of toxic events.

The results show that: (1) The reponse rate in advanced breast cancer seems in the same confidence interval for the four compounds, especially the overall response rate (CR + PR) in non-pretreated patients and the CR rate (Fig. 1). (2) The limiting toxicity (leukopenia) at the nadir for THP at the recommended

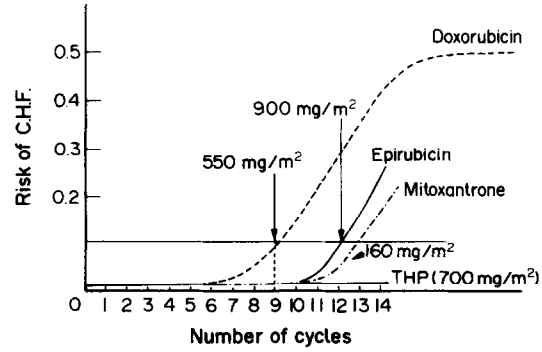

Fig. 7. Actuarial risk of CHF according to the putative number of cycles. Doxorubicin = 60 mg/m², epirubicin = 75 mg/m², mitoxantrone 12 mg/m², pirarubicin 50 mg/m².

dose of 50 mg/m² [2], seems comparable with that of doxorubicin 60 mg/m², that of mitoxantrone 12 mg/m² and that of epirubicin 85–90 mg/m² (Figs 2 and 3). (3) Alopecia of THP seems significantly lower than that of other anthracyclines (doxorubicin or epirubicin) and slightly higher than that of the anthracenedione mitoxantrone (Fig. 4), either for overall alopecia (THP and mitoxantrone are the two compounds that give less than 50% alopecia) or for severe alopecia. (4) The digestive toxicities of THP appear comparable with those of epirubicin or mitoxantrone and lower than those of doxorubicin (Fig. 5). (5) The cumulative clinical cardiac toxicity of THP is probably significantly lower than that of doxorubicin between 550 and 700 mg/m² (Fig. 6) and might be even lower than that of epirubicin or mitoxantrone when the number of cycles at either the recommended or equimyelotoxic doses are compared (Fig. 7).

These conclusions, though non-definitive before the results of phase III trials, suggest that THP is an anthracycline with an efficacy close to that of doxorubicin or other intercalating compounds in breast cancer, and grossly better tolerated than doxorubicin.

An advantage in terms of alopecia is suggested as compared with other anthracyclines and perhaps in terms of cumulative cardiac toxicity as compared to epirubicin or mitoxantrone.

These facts let us expect that an ideal phase III study should answer to an equivalence hypothesis. In other words, whereas it might be easy to prove the advantage in term of tolerance, as compared with doxorubicin, this advantage would have a clinical relevance only if the drugs shared the same efficacy at the recommended dose. Thus it will be necessary to prove the equiefficacy. In practice, that means that, for demonstrating only that THP does not give less than 35% response rate (assuming that the response rate of doxorubicin is 40%), 3.206 patients will have to be included for an α risk 0.05 and a β risk 0.10 or 4.054 patients for a β risk 0.05 [88]. Obviously a phase III trial will give additional information, such as survival time, disease-free survival, or time to treatment failure. Nevertheless the differences between two drugs that give the same response rate may be expected very small and thus need roughly the same number of patients to be detected.

This high number of patients could not be easily reached, for practical and ethical reasons (only to prove that a new drug is not less effective than a standard treatment). Furthermore, the most standard chemotherapy for breast cancer is a 3-drug combination more effective than a single drug; it is ethically difficult to undertake a large trial with a single drug therapy. On the other hand, a comparative trial with a 3-drug regimen, in which only one drug is replaced by another in each arm raises new problems: if a small difference does exist between the new drug and the standard one, this difference may be shadowed by the two effective other drugs of the combination, which are the same in both arms of the trial.

Many comparative trials with anticancer analogues cannot answer to the equi-efficacy, properly because the number of patients is not adequate to detect a small difference in efficacy, especially within a drug combination [7, 17, 67, 89, 90].

One solution to resolve these difficult problems is to undertake several phase III trials with smaller numbers of patients and individual, limited objectives and thereafter to perform a meta-analysis [91–93] which could answer to the equi-efficacy.

Another dilemma is that of the optimal dose of a new drug in a phase III trial. Two different drugs, even structurally close, do not share the same toxicity at equimolar dose. In a phase III trial, if the optimal dose of the new drug is underestimated, that can lead to an erroneous conclusion of lower toxicity, whereas the new compound might also be less effective, a difference only apparent with a very large number of patients (see supra). If the drug had been used at the right, equiefficient dose, the toxicity would perhaps be the same. With our historical comparisons, we have an early evaluation of the equimyelotoxicity of the drugs (Figs 2 and 3). This indication is of great interest to choose the dose of THP in phase III trials. On the contrary, no indication can be obtained about the equiefficient dose. First because no clear dose–effect relationship dose exist for THP on response rates between 45 and 75 mg/m², a range of dose where there is a clear dose-related toxicity; secondly because the planned dose reported in the literature can be radically different than the dose effecitvely delivered to the patient, after dose adjustment.

In conclusion, we would like to emphasise the fact that many randomised studies in cancer chemotherapy, especially in the field of drug analogues, cannot answer to the question, is the new drug less toxic at a dose as effective as the standard one? The main reason is the small number of patients who can be reasonably enrolled in a phase III study. Historical comparisons, though they are unable to replace randomised studies may be relevant for an early evaluation of the drug and can lead to further decisions on the development of phase III studies.

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Prognostic Value of Progesterone Receptor After Long-term Follow-up in Primary Breast Cancer

M.F. Pichon, C. Pallud, K. Hacene and E. Milgrom

In a previous study of a series of 105 patients with primary breast cancer we found that the progesterone receptor (PgR) status was an important prognostic factor for early recurrences. 95 patients from the same series were followed-up for a median of 9.5 years and reassessed for the prognostic value of PgR status by univariate and multivariate statistical methods. In univariate analysis, the disease-free interval was only related to the lymph-node status. For overall survival, PgR and combined PgR–ER (oestradiol receptor) status had a prognostic value ($P = 0.035$ and 0.05, respectively). Moreover, PgR status was found to be discriminant for the survival of the node-negative patients ($P = 0.017$). In multivariate analysis, ER and PgR status were not significant, indicating that receptor status is not a powerful predictor of the course of breast cancer.
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INTRODUCTION

In 1980, we published a study of 105 patients with primary breast cancer, followed-up for an average duration of 2 years showing that progesterone receptor was a potent indicator of prognosis in these tumours [1]. Other studies subsequently published have either concurred with this result [2–9] or presented opposite conclusions [10–13]. One of the reasons for such discrepancies might have been the variable time of observation of the patients. Moreover, recent studies of prognosis in breast cancer have been complicated by the use of adjuvant chemotherapy.

It thus appeared interesting to re-examine the outcome of this cohort of patients, of whom only 10 dropped out of the study, who have now been followed-up for an average of 9.15 years, received no adjuvant therapy and in whom the natural history of the disease could be observed.

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PATIENTS AND METHODS

Patients

From the initial series of 105 patients, 95 were retained in this study. They were treated and followed-up at the Centre René Huguenin (Saint Cloud, France) between January 1975