verapamil in the absence of P-glycoprotein overexpression. *Br J Cancer* 1991, **64**, 1011–1018.
10. Bourhis J, Goldstein L, Riou G, Pastan I, Gottesman M, Benard J. Expression of a human multidrug resistance gene in ovarian carcinomas. *Cancer Res* 1989, **49**, 5062–5065.
11. Van der Zee A, Hollema H, de Jong S, *et al.* P-glycoprotein expression and DNA topoisomerase I and II activity in benign tumours of the ovary, before and after platinum/cyclophosphamide chemotherapy. *Cancer Res* 1991, **51**, 5915–5920.
12. Roninson IB. The role of *mdr*-1 (P-glycoprotein) gene in multidrug resistance *in vitro* and *in vivo*. *Biochem Pharmacol* 1992, **43**, 95–102.
13. Holzmayer T, Hilsenbeck S, Von Hoff D, Roninson I. Clinical Correlates of *mdr*-1 (P-glycoprotein) gene overexpression in ovarian and small cell lung carcinomas. *J Natl Cancer Inst* 1992, in press.
14. Bradley G, Naik M, Ling V. P-glycoprotein expression in multidrug-resistant human ovarian carcinoma cell lines. *Cancer Res* 1989, **49**, 2790–2796.
15. Ichikawa M, Yoshimura A, Furukawa T, Sumizawa T, Nakazima Y, Akiyama S. Glycosylation of P-glycoprotein in a multi-drug-resistant KB cell line, and in the human tissues. *Biochim Biophys Acta* 1991, **1073**, 309–315.
16. Benard J, Da Silva J, Teyssier J, Riou G. Overexpression of *mdr*-1 gene with no DNA amplification in a multiple-drug-resistant human ovarian carcinoma cell line. *Int J Cancer* 1989, **43**, 471–477.
17. Lau D, Lewis A, Ehsan M, Sikic B. Multifactorial mechanisms associated with broad cross-resistance of ovarian carcinoma cells selected by cyanomorpholino doxorubicin. *Cancer Res* 1991, **51**, 5181–5187.
18. Martin A, Clynes M. Acid phosphatase: endpoint for *in vitro* toxicity tests. *In Vitro Cell Dev Biol* 1991, **27A**, 183–185.
19. Clynes M, Redmond A, Moran E, Gilvarry U. Multiple drug-resistance in a human non-small cell lung carcinoma cell line DLKP. *Cytotechnology* 1992, **10**, 75–89.
20. Muller C, Ling V. P-glycoprotein stability is affected by serum deprivation and high cell density in multidrug resistant cells. *Proc Am Assoc Cancer Res* 1992, **33**, 452.

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Treatment Results, Survival and Prognostic Factors in 109 Inflammatory Breast Cancers: Univariate and Multivariate Analysis

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Between 1978 and 1987, 109 patients without metastatic disease were treated by induction chemotherapy for inflammatory breast cancer (IBC) or "neglected" locally advanced breast cancer (LABC): 62 patients had a clinical history of rapidly growing tumours (doubling time ≤ 4 months) and inflammatory signs; conversely, the 47 neglected patients had local inflammation with a longer history of LABC. 103 patients were fully evaluable. All patients received the same induction chemotherapy with doxorubicin, vincristine, cyclophosphamide and 5-fluorouracil. After six cycles, locoregional treatment was by radiotherapy if a complete or nearly complete response had been obtained, and total mastectomy, with pre or postoperative radiotherapy, in other cases. The chemotherapy after local treatment comprised of six cycles for LABC and 12 cycles for IBC (six without doxorubicin). With a median follow-up of 120 months, the median overall survival (OS) time was 70 months as against 45 months for disease-free survival (DFS). No difference was observed for OS and DFS between LABC and IBC. The regional recurrence rate was 24% (15% for radiotherapy alone). 20 factors of potential prognostic significance were evaluated by univariate and multivariate analysis. For DFS and OS, univariate analysis suggested a worse prognostic significance for "peau d'orange" appearance of the skin, clinical evidence of node involvement and poor response to chemotherapy after three cycles, on mammographic criteria. The cumulative dose of doxorubicin after three cycles seemed to have a significant effect on OS ($P < 0.03$) but was too closely correlated with age to draw definite conclusions. In the multivariate analysis, "peau d'orange", menopausal staus and clinical node involvement predicted DFS. "Peau d'orange" and clinical node involvement also predicted OS. Our results indicate that IBC and LABC do not behave differently when treated with our procedure.
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INTRODUCTION

INFLAMMATORY BREAST cancer (IBC) is an uncommon cancer constituting only 1–4% of breast cancer cases in western countries [1]; most of our knowledge comes from retrospective and prospective (single-armed) studies, devoid of control groups. IBC is characterised by a high rate of locoregional and mainly metastatic failures, which occur rapidly. With well-managed locoregional treatment (surgery and/or radiotherapy) alone the overall survival (OS) may not exceed 5% at 5 years [1, 2]. Therefore, IBC has been considered to be a systemic disease, i.e. with micrometastasis at the time of diagnosis, requiring systemic treatment with combination chemotherapy. This effectively improves OS to within the range of 30–50% at 5 years [2–5].

Table 1. Clinical classification of patients according to TNM-UICC

Tumour size	N0	N1	N2	Supra clavicular node	Doubling time < 4 months (IBC) Pev 2	Doubling time < 4 months (IBC) Pev 3	LABC
< 2 cm		1			1	0	0
2–5 cm	3	12	1	3	10	2	7
> 5 cm	25	53	6	5	33	16	40

All patients were T4d, due to the presence of clinical inflammatory signs. However, more details are given as tumour size, clinical node status and Pev classification.

Our purpose was to define more clearly the factors related to the risk of recurrence in IBC treated by chemotherapy, to evaluate the effectiveness of a combined modality approach using neoadjuvant chemotherapy, and to compare our group of IBC patients with a group of locally advanced breast cancer (LABC) patients with inflammatory signs which appeared in the later stages of a "neglected" tumour, and constituting also a group of patients of bad prognosis with a high recurrence and metastasis rate.

PATIENTS AND METHODS

Between January 1978 and December 1987, 109 patients with IBC, or secondary inflammatory LABC participated in this study. This retrospective work included two groups: 62 patients (group I) treated for IBC, and 47 patients (group II) for "neglected" breast cancer. Group I included patients showing clinical evidence of IBC, i.e. all were T4d for TNM-UICC; they were classified according to Denoix [6]; Pev2 for erythema, with or without oedema, localised to the tumoral area and Pev3 for inflammatory signs (erythema, oedema, warmth, pain) enlarged to the whole breast, when associated with a clinical history of rapidly growing tumour (doubling time $\leq$ 4 months) [7–9]. Conversely, group II included patients with "neglected" tumour (doubling time from 4 months to a few years), all of whom presented secondary evidence of the same clinical inflammatory signs; all these patients could also be classified T4d according to TNM-UICC (Table 1).

Of the 109 patients, 103 were evaluable for response, 6 were excluded because of distant metastasis at referral (2 patients) and different treatments from the scheme proposed in this review—3 patients for primary surgery, and 1 patient for another combination chemotherapy.

Local malignancy was ascertained by breast biopsy for all patients. Tumour grading according to Scarff–Bloom–Richardson (SBR) was established for only 71 tumours, and hormonal receptor assays for 36 tumours (mostly at surgery).

We paid particular attention to "peau d'orange" appearance, but skin biopsy was deemed appropriate in only 12 cases: tumour emboli within the dermal lymphatic vasculature were noted in 7 of these 12 cases.

The staging was completed by general evaluation—bone scintigraphy, chest X-ray, and liver echography or scan.

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The median age of the patients was 53.7 (range 32–79 years); 47 patients were premenopausal and 63 postmenopausal. Clinical evidence of lymph node involvement was noticed in 82 patients, confined to the axillary area (N1, N2) in 74 and extended to the supraclavicular region (M1) in 8 cases. Median follow-up was 120 months as of 1 July 1992.

The patient- and tumour-related variables taken into account were inflammatory signs (Pev2, Pev3, and "neglected" tumours), age, menopausal status, initial tumour size, clinical nodal stage and pathological involvement of axillary nodes, "peau d'orange" appearance, tumour differentiation, oestrogen and progesterone receptors, primary mammographic criteria, and family history of breast cancer.

Treatment

All the patients were treated by the same first combination chemotherapy: doxorubicin, 30 mg/m^2 day 1 (D1); vincristine, 1 mg/m^2 D2; cyclophosphamide, 300 mg/m^2 and 5-fluorouracil, 400 mg/m^2 D3 to D6. Treatment was repeated on the 28th day after D1, which marked the first day of the next cycle. After three to six cycles (mainly six cycles) the patients received a locoregional treatment according to clinical response: radiotherapy alone, if a complete or nearly complete response had been obtained, and total mastectomy, with pre- or postoperative irradiation, in all other cases (Fig. 1). Chemotherapy was resumed for six cycles for LABC and 12 cycles for IBC (six without doxorubicin).

Irradiation of the breast and lymphatic area (axillary, supraclavicular and internal mammary) was effected by opposed tangential beam of ^{60}Co. The average dose was 50 Gy, given for 5–6 weeks (2 Gy/day, 5 days/week).

Patients whose local treatment consisted of radiotherapy alone received an additional 25 Gy boost to the residual breast mass, using a reduced tangential cobalt beam, and 5–15 Gy to the axillary region (according to the initial clinical lymph node involvement). For those treated by surgery, an additional 5 Gy on the skin and in the axillary area was effected by cobalt beam and electrontherapy.

Additional hormonal therapy (tamoxifen 20–30 mg/day orally) was used in the initial treatment or after surgery for 20 postmenopausal patients in whom hormonal receptors (E_2) were detected (of whom 12 belonged to group II).

Evaluation

Clinical and paraclinical responses. Patients were evaluated after three cycles of primary chemotherapy, and reviewed again after the end of treatment. Response criteria are given in Table 2.

Clinical responses were evaluated according to developments in the size of tumour, lymph node and inflammatory signs, and were classified in the following five classes: complete response (CR), partial response > 50% (PR), moderate response < 50% (MR), no change (NC) and progression of disease (PD). The same classification was used for mammographic responses.

The disappearance of inflammatory signs (oedema, erythema, pain) with persistence of warmth was considered as a PR, as was the persistence of "peau d'orange" appearance without the other signs. In this last case, when the thickening of the skin on mammogram was unchanged, the response was classed as MR. When the clinical tumour had disappeared, leaving a tumoral residue which was discovered only at surgery, the response was classified as PR.

Statistical evaluation. In spite of only 103 out of 109 patients being evaluable for response, our analysis was performed on the

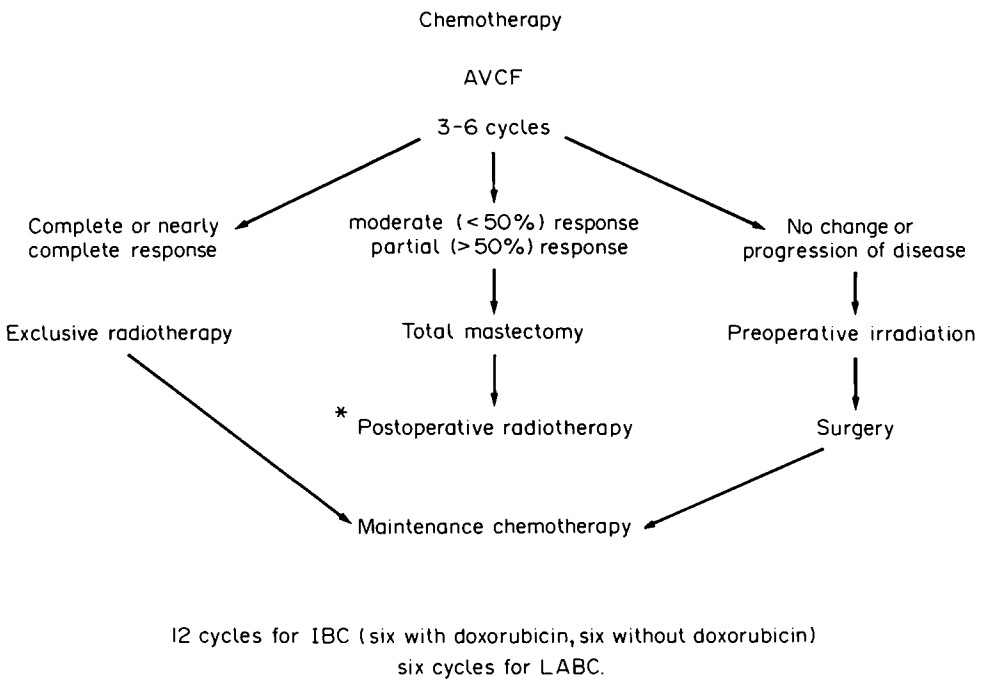

Fig. 1. Scheme of treatment. * In the case of massive axillary lymph node involvement, irradiation was performed at the end of chemotherapy. Number of all cycles of chemotherapy: 18 for IBC, 12 for LABC.

whole group. 20 variables were analysed (Table 2) in a univariate analysis using the Kaplan–Meier method [10] for calculating curves of OS and disease-free survival (DFS).

The time to failure or death was calculated from the date of the first examination, which was rapidly followed by chemotherapy (within 5 days). Comparisons between curves were made using the log rank test. The relative importance of prognostic factors on OS and DFS was estimated according to the Cox model [11].

A few patients were excluded for some particular parameters when lacking in the patient survey. Actual numbers for each statistical analysis are indicated in the text.

RESULTS

Patient and disease-related factors

Doubling time and inflammatory signs (Pev2, Pev3, LABC). The median OS for all patients was 70 months; at 5 years the actuarial survival rate was 55%. The median DFS was 44.9 months; at 5 years the actuarial disease-free survival rate was 44% (Fig. 2).

There was no significant difference in DFS and OS between the two groups of IBC (62 patients) and LABC (47 patients), nor in the subgroups Pev2 (44 patients) and Pev3 (18 patients) (Fig. 3).

As no difference in prognosis was observed between groups 1 and 2, both groups were studied together to assess the importance of other factors.

Age and menopausal status. Age was a significant factor in OS ($P < 0.03$) and DFS ($P < 0.02$) when the patients were separated into two groups (under 55 and over 55), with a significantly worse survival in older patients. Menopausal status was also significant for decreased DFS ($P < 0.02$) and OS ($P < 0.02$).

Tumour size. Tumour size is often difficult to estimate precisely in inflammatory breasts; Table 1 shows a predominance of large tumours. However, patients presenting with a small tumour (T1, T2) showed a significantly better overall survival rate ($P < 0.04$) and DFS ($P < 0.04$) than those with a larger tumour (Table 2), but, in the multivariate analysis, the Cox model did not retain it.

"Peau d'orange" as a main prognostic factor? Patients presenting a "peau d'orange" appearance (45 patients) showed a worse OS ($P < 0.0001$) and DFS ($P < 0.0001$) than patients devoid of this clinical sign (60 patients) (Fig. 4).

Lymph node involvement. A significant difference in OS ($P < 0.05$) was seen after grouping patients by no involvement (NO) versus evidence of clinical node involvement (N1b, N2, N3). DFS appeared to be significantly affected by this categorisation ($P < 0.03$). The lymph node involvement after chemotherapy was a significant factor on OS ($P < 0.02$) and DFS ($P < 0.01$).

Criteria on primary mammography. Together with clinical signs inflammatory signs were also considered: thickening of the skin (which corresponds with "peau d'orange" appearance), oedema, and hyperdensity of the whole gland. Thickening of the skin had no significant effect on overall survival ($P < 0.09$), and on DFS ($P = 0.30$); the other signs were insignificant.

The aspect of the tumour mass was also analysed (nodular, radial, or absence of tumour) as well as the uni- or plurifocality, and the presence of microcalcifications. All these criteria had no significant effect on OS or DFS.

Treatment-related factors

Response to induction chemotherapy after three cycles. Clinical response, measured by changes in tumour size had no significant impact on DFS or OS, although DFS was better for those in whom inflammatory signs resolved ($P < 0.04$). Mammographic response, which was evaluable in 89 patients did, however,

Table 2. Univariate analysis according to Kaplan–Meier's method

Factor	No.	Overall survival			Relapse-free survival		
		5-year (%)	Median (months)	*P*	5-year (%)	Median (months)	*P*
Inflammatory signs							
Pev2	44	61.4	74.6		54	—	
Pev3	18	55.6	70.2	0.75	39	37	0.20
LABC	47	48.9	64.6		36	38.3	
Age							
< 55	56	62	—		55	70	
⩾ 55	53	47	76.7	< 0.03	32	36.2	< 0.02
Menopausal status							
Pre-	47	66	—		57	73.4	
Post-	62	47	53	< 0.02	34	35.5	< 0.02
"Peau d'orange"							
Yes	45	38	41.8		29	25.5	
No	60	70	—	< 0.0001	58	83.5	< 0.0001
Tumour							
T1	1	N/A	—		N/A	—	
T2	13	77	—		69	—	
T3	29	69	103.2	< 0.05	52	61.2	< 0.02
T4	66	44	45.9		35	31	
N stage (clinical)							
N0	28	75	112.4		61	81.2	
N1	66	51	65.4	< 0.05	41	38.7	0.20
N2	7	29	38		29	21	
N3	8	37	41.5	< 0.05	25	30	< 0.03
N1, N2, N3	82	47	53.8		37	36.6	
Grading (SBR)							
1	3	66	52.5		33	32	
2	43	53	67.7	0.80	39	40	0.90
3	25	56	69.2		48	45	
N involvement (pathology)							
Positive	52	46	52.9		31	34	
Negative	23	78	—	< 0.01	70	—	< 0.001
Oestrogen receptor							
Positive	22	64	75.9		45	51	
Negative	14	61	—	0.81	50	52	0.90
Progesterone receptor							
Positive	12	91	—		58	—	0.16
Negative	24	54	65.9	< 0.05	46	46	
Response after three cycles of induction chemotherapy based on mammographic criteria							
CR + PR	19	84	125.5		68		
MR, NC, PD	70	49	55.4	< 0.02	38	36.2	< 0.01
Clinical criteria							
Tumour							
CR + PR	21	65	89		52	56.2	
MR, NC, PD	68	54	70	0.14	42	41	0.17
Inflammatory signs							
CR + PR	51	64	93.7		49	55	
MR, NC, PD	43	46	51.5	0.22	39	27	< 0.04
Adjuvant chemotherapy							
Yes	84	65	100		51	64.5	
No	11	27	39	0.04	27	22	< 0.03
Criteria on primary mammography							
Inflammatory signs							
Skin thickening							
Yes	40	45	58.5		32	34	
No	23	65	80	< 0.09	48	54.5	0.30
Oedema							
Yes	32	47	51		40	35	
No	31	58	74	0.87	35	45	0.71
Hyperdensity							
Yes	31	51	63.4		36	35	
No	30	53	61.4	0.94	40	39	0.36

Continued overleaf

Table 2. Continued

Factor	No.	Overall survival 5-year (%)	Overall survival Median (months)	Overall survival P	Relapse-free survival 5-year (%)	Relapse-free survival Median (months)	Relapse-free survival P
Tumour mass							
Radial	50	58	69.6		48	52	
Nodular	12	58	73	0.50	50	39	0.30
Absence	35	51	62		34	37.2	
Plurifocality	17	53	63		47	46.5	
Unifocality	80	54	66.9	0.89	41	38.9	0.88
Microcalcifications							
Yes	45	53	68.2		40	41.5	
No	49	57	69.2	0.57	45	44	0.67
Family history of breast cancer (present)	38	62	75.6		52	60.9	
First degree relative (present)	29	60	71.4	0.60	47	52.3	0.27
No family antecedent	72	49	56.6		38	37.2	
Relative dose intensity of doxorubicin after three cycles							
≤ 0.70	24	37	37		29	29	
≥ 0.71	76	62	81.5	< 0.02	49	52.9	< 0.05
Total dose of doxorubicin (mg)							
≤ 450	37	43	51.5		35	35.5	
> 450	59	71	105.5	< 0.03	56	71.5	< 0.03

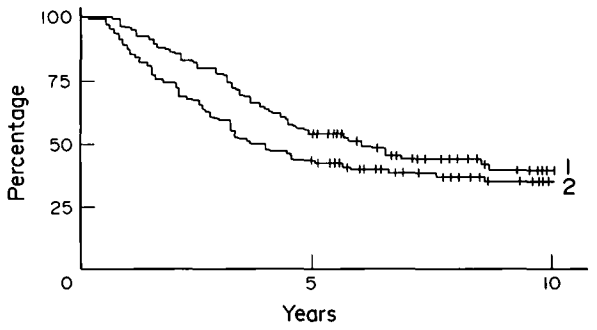

Fig. 2. Disease-free survival (DFS) and overall survival (OS) of the 109 patients on 1 July 1991, according to Kaplan–Meier method. Curve 1: OS mean 65.6 months; median 71.2 months. Curve 2: DFS mean 55.6 months; median 44.9 months.

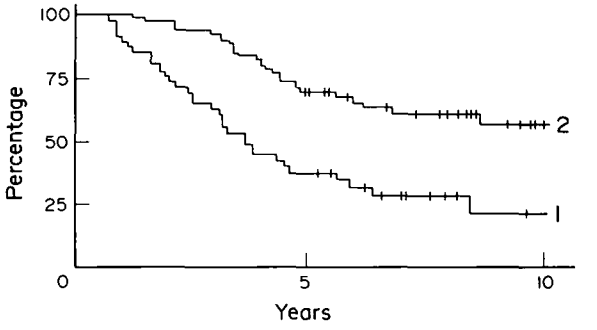

Fig. 4. Overall survival of patients with "peau d'orange" appearance (curve 1) or absence (curve 2). 1: 45 patients, mean 51.1 months; median 41.8 months. 2: 60 patients, mean 78.3 months; median 119.1 months. $P < 0.0001$ (Mantel–Haenszel test $\in = 4.1$).

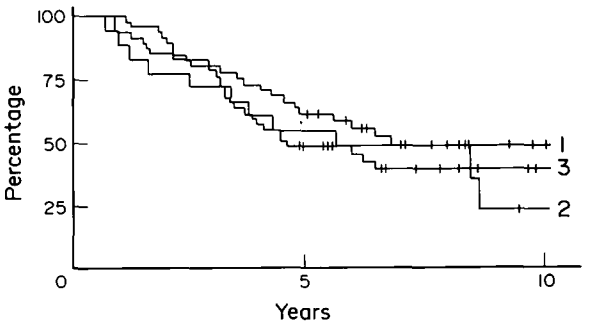

Fig. 3. Overall survival in three subgroups of patients (15 February 1991). 1: 44 patients classified PEV2, mean 69.9 months; median 78.9 months. 2: 18 patients classified PEV3, mean 67.1 months; median 67 months. 3: 47 patients classified LABC, mean 60.9 months; median 53 months. n.s. (log rank test $\chi^2 = 1.92$).

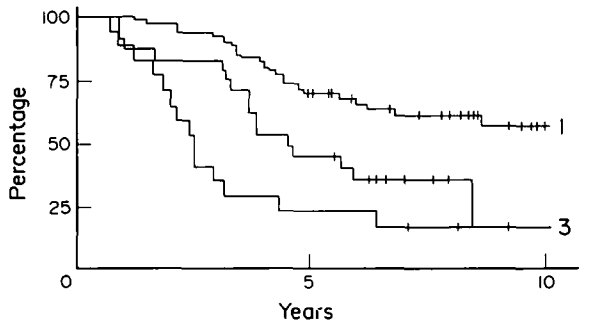

Fig. 5. Overall survival in patients presenting before treatment: Curve 1: (60 patients) without "peau d'orange", mean 78.3 months; median 119.1 months. Curve 2: (24 patients) "peau d'orange" without microcalcifications on mammogram, mean 57.4 months; median 53 months. Curve 3: (17 patients) "peau d'orange" and microcalcifications, mean 41.7 months; median 28.2 months. $P < 0.001$ according to Kaplan–Meier test ($\chi^2 = 24.8$).

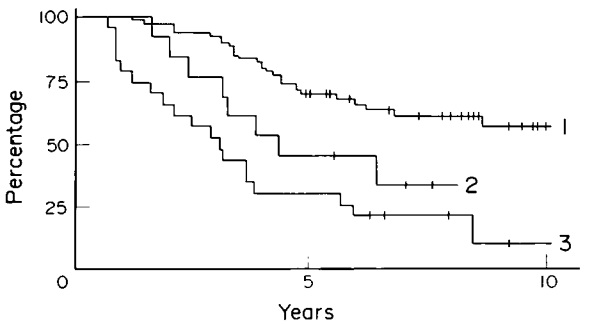

Fig. 6. Overall survival in patients presenting before treatment: Curve 1: (60 patients) without "peau d'orange", mean 98.3 months; median 119.1 months. Curve 2: (13 patients) "peau d'orange" without skin thickening on mammogram mean 56 months; median 48 months. Curve 3: (23 patients) "peau d'orange" and skin thickening, mean 44.2 months; median 35 months. $P < 0.001$ according to Kaplan–Meier test ($\chi^2 = 21.25$).

have a significant influence on both DFS ($P < 0.01$) and S ($P < 0.02$).

Dose intensity and total dose of doxorubicin. According to the method of Hryniuk and Bush [12], we calculated the dose intensity really received (DIRR) of each drug for each patient at three and six cycles as well as the relative dose intensity (RDI) for each drug, ratio: theoretical dose intensity (defined as 1)/actual days of treatment.

Doxorubicin DIRR at three cycles was the only drug with significant effect on OS ($P < 0.02$) and on DFS ($P = 0.05$); doxorubicin RDI was also significant for OS at six cycles ($P < 0.05$).

We analysed the patients in two groups, above and below a given doxorubicin RDI at three cycles (≤ 0.70 or ≥ 0.71). The group which received RDI ≥ 0.71 (76 patients) had a better survival curve ($P < 0.02$) than the group with RDI ≤ 0.70 (24 patients).

The total dose of doxorubicin administered was significant for OS ($P < 0.03$) and DFS ($P < 0.03$) by considering two groups with a given cumulative dose ($\leq$450 mg and $\geq$ 451 mg).

Maintenance chemotherapy. Adjuvant postlocal treatment chemotherapy was significantly beneficial on DFS ($P < 0.03$) and on OS ($P = 0.04$). 11 patients (8 of whom refused) did not receive adjuvant treatment.

The total number of chemotherapy cycles (12 vs. 18) did not appear to be significant for OS. However, maintenance chemotherapy improved the DFS period (deferring relapse), although the difference was insignificant.

Treatment tolerance. Treatment tolerance was generally good, and there were no toxic deaths. Haematological tolerance of chemotherapy was generally good, except for 1 case of severe aplasia. In 3 cases, doxorubicin was discontinued due to the occurrence of electrocardiographic changes, but no congestive heart failure was observed. All patients developed alopecia. Nausea and vomiting were mild and controlled with antiemetics. We observed two pulmonary embolisms after surgery.

Locoregional treatment. Exclusive radiotherapy was carried out on 23 patients (7 CR, 10 PR, 4 MR, and 2 NC in mammographic criteria), for whom there was a clinical response consisting of the disappearance of inflammatory signs and no clinical tumoral residue.

Surgery was performed for 74 patients (absence of inflammatory signs, but with persistence of a tumour mass) and consisted of a modified radical mastectomy with axillary section, followed by radiotherapy.

6 patients had preoperative irradiation for progression or persistence of the tumour despite chemotherapy. Their survival was not significantly different. 3 other patients presented evidence of metastatic disease at 6 months and did not undergo any local treatment.

Local treatment failure and metastasis. 68 patients (62%) have relapsed, of whom 26 (24%) had a locoregional recurrence. This last figure represents 15% (4/26) of the patients treated by exclusive irradiation and 27% (21/69) of those treated by radiotherapy and surgery in conjunction. The median survival from the relapse was 16.9 months.

Systemic metastases were observed in 55 patients; located in the pleura and lung (16/54, 30%), bone (11/54, 20%), the brain (1/54, 2%), the liver (5/54, 9%), the ovaries (1/54, 2%) or at multiple sites (22/54, 41%) (associated sites of skin, bone, brain, lung and/or liver). Brain metastasis appeared to be frequently associated with other sites of metastasis in our study (19%). There was no significant difference between Pev2, Pev3, or LABC on the occurrence of metastasis or local failure.

DISCUSSION

IBC is the most agressive form of primary breast cancer, and should be differentiated from LABC on natural history parameters. The natural course of IBC is completely different from that of LABC. Inflammatory signs appear rapidly in a previously healthy breast with a short delay between the observation of the first symptom and the seeking of medical attention ($\leq$ 4 months) [7–9]; the tumour doubling time is short, ($\leq$ 6 months by definition) [6].

In this report, the diagnosis of IBC is based on clinical criteria (T4d) as in other recent reports [4, 9, 16], but in accordance with the Pev classification [6], inflammatory signs were limited to the tumour area (Pev2) or extended to the whole breast (Pev3).

Our results suggest that Pev2 and Pev3 may not be differentiated, despite the fact that Pev2 is clinically less severe (or because of the small size of the Pev3 group). The clinical characteristics proposed by Haagensen [8], including redness and oedema of more than 33% of the mammary surface, could be used.

Conversely to IBC, LABC concerns "neglected" locally advanced breast cancers, with secondary appearance of inflammatory signs.

However, in spite of clinical and biological differences, IBC and LABC have similarities: the high incidence of failures in distant sites indicates that disseminated micrometastasis have already taken place at the time of diagnosis [8, 13, 14]. Therefore, they often receive the same type of treatment with induction chemotherapy. Our results with primary chemotherapy did not show significantly different behaviour between IBC and LABC in terms of DFS and OS, as previously suggested by some authors [14, 15].

The introduction of chemotherapy in the management of IBC had led to a significant improvement in patient outcome [1, 4, 5, 7, 23, 27]. In this study, median OS was 70 months with a DFS of 44.9 months. The 5-year survival rate appeared to be lengthened (55%) compared to most published treatments [4, 9, 24], but it is uncertain whether a plateau is obtained, and the survival curve may still decrease progressively.

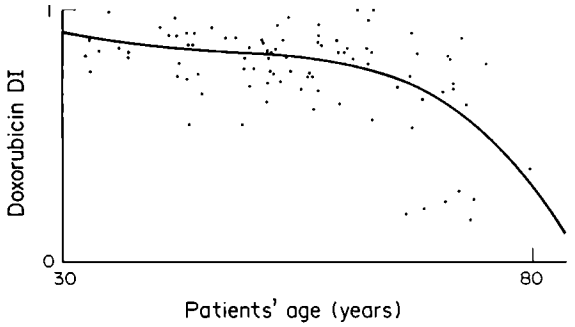

Fig. 7. Doxorubicin dose intensity at three cycles as a function of patient's age (correlation coefficient: $r = 0.528$; $P < 0.00001$).

The presence of "peau d'orange" was of negative prognostic significance for OS and DFS, as suggested in previous studies [25]; this sign is a major element in the current UICC-AJC staging system, but without practical consequences in staging; our results are in favour of considering it as a possible factor for subclassification.

Patients with clinically involved nodes (N1b, N2, N3) had a worse prognosis than those without (N0). Similar results have been reported by some authors [4, 25, 26], but not found by others [22, 27].

Menopausal status and age appeared to be significant for OS and DFS. But in the multivariate analysis, we found a higher risk of relapse for menopausal patients, as did Rouessé *et al.* [5]. Other authors [4, 16], have found that these factors do not influence prognosis.

Response to initial chemotherapy measured clinically was a poor indication of long-term outcome in our series, unlike several other studies [4, 13, 29]. However, mammographic response to chemotherapy at three cycles had a very important prognostic significance for DFS and OS, as reported elsewhere [4, 9, 20, 26, 29–31].

As for the dose intensity delivered at three and six cycles, doxorubicin dose intensity appeared to be the only significant drug factor at three cycles on OS and DFS. However, when separating patients under and over 55 years of age, it did not show any statistical significance. To eliminate this age effect (Fig. 7), we studied the doxorubicin DIRR with patients whose age was ≤ 65 years. Among them, patients receiving ≥ 0.70 of projected doxorubicin doses had a better OS with borderline significance ($P < 0.08$). We could conclude that dose intensity may be important, but its relationship with age makes interpretation difficult.

A multivariate analysis with a Cox model allowed classification of prognostic factors according to their significance: (1) "peau d'orange"; (2) microcalcifications; (3) thickening of the skin; (4) menopausal status; and (5) N stage. "Peau d'orange" associated with skin thickening worsened the prognosis (Fig. 6) ($P < 0.001$). The presence of breast microcalcifications also added a worse prognostic element when associated with "peau d'orange" (Fig. 5) ($P < 0.001$). Microcalcifications, which are known to correspond with tumoural necrosis, might be a factor of worse prognosis in this form of tumours, like necrosis in sarcoma [35].

This retrospective study confirmed the effectiveness of primary chemotherapy to obtain a longer survival in both LABC and IBC. Nowadays, several trials in this field use intensive chemotherapy, alone or associated with G/GM.CSF, or followed by bone marrow autografting.

1. Grace WR, Cooperman AM. Inflammatory breast cancer. *Surg Clin North Am* 1985, **65**, 151–160.
2. Chauvergne J, Durand M, Dilhuydy MH, *et al.* Traitement des cancers du sein inflammatoires. Etude contrôlée d'un programme d'association thérapeutique. *Rev Fr Gyn Obstét* 1981, **76**, 227–235.
3. Hagelberg R, Jolly PC, Anderson R. Role of surgery in the treatment of inflammatory breast carcinoma. *Am J Surg* 1984, **148**, 125–131.
4. Chevallier B, Asselain B, Kunlin A. Inflammatory breast cancer. Determination of prognostic factors by univariate and multivariate analysis. *Cancer* 1987, **60**, 897–902.
5. Rouessé J, Spielman M, Le Chevalier T, *et al.* Chimiothérapie première dans le traitment des cancers du sein inflammatoires: 230 observations. *Presse Méd* 1987, **16**, 475–478.
6. Denoix P. Treatment of malignant breast tumors. *Recent Results in Cancer Res.* Berlin, Springer, 1970, 6–10.
7. Hortobagyi GN. Progress in inflammatory breast cancer: cause for cautious optimism. *J Clin Oncol* 1986, **4**, 1727–1729.
8. Haagensen CD. Inflammatory carcinoma of the breast. In *Diseases of the Breast.* Philadelphia, Saunders, 1971, 576–584.
9. Fastenberg NA, Buzdar AU, Montague ED. Management of inflammatory carcinoma of the breast. A combined modality approach. *Am J Clin Oncol (CCT)* 1985, **8**, 134–141.
10. Kaplan EL, Meier P. Non parametric estimation from observations. *J Am Stat Assoc* 1958, **53**, 457–481.
11. Cox DR. Regression models and life tables. *J R Stat Soc B* 1972, **34**, 187–202.
12. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984, **11**, 1281–1288.
13. Delarue JC, May-Levin F, Mouriesse H, *et al.* Oestrogen and progesterone cytosolic receptors in clinically inflammatory tumors of the human breast. *Br J Cancer* 1981, **44**, 911–916.
14. Delena M, Zucalli R, Ziganotti G, *et al.* Combined chemotherapy-radiotherapy approach in locally advanced T3 B-T4 breast cancer. *Cancer Chemother Pharmacol* 1978, **1**, 53–59.
15. Kokal WA, *et al.* Inflammatory breast carcinoma: a distinct entity? *J Surg Oncol* 1985, **30**, 152–155.
16. Israel L, Breau JL, Morere JF. Two years of high dose cyclophosphamide and 5 fluorouracil followed by surgery after 3 months for acute inflammatory breast carcinomas. A phase II study of 25 cases with a median follow-up of 35 months. *Cancer* 1986, **57**, 24–28.
17. Leicht A. "Peau d'orange" in acute mammary carcinoma. Its cause in diagnostic value, 1909.
18. Meyer AC, Dockerty MD, Harrington SW. Inflammatory carcinoma of the breast. *Surg Gyn Obstet* 1948, **87**, 417–424.
19. Saltzstein SL. Clinically occult inflammatory carcinoma of the breast. *Cancer* 1974, **34**, 382–388.
20. Levine PH, Steinhorn C. Inflammatory breast cancer: the experience of the surveillance. Epidemiology and end results. *J Natl Cancer Inst* 1985, **74**, 291–297.
21. Lucas FV, Perez Mesa C. Inflammatory carcinoma of the breast. *Cancer* 1978, **41**, 1595–1605.
22. Fields JN, Kuske RR, Perez CA, *et al.* Prognostic factors in inflammatory breast cancer. Univariate and multivariate analysis. *Cancer* 1989, **63**, 1225–1232.
23. Ferrière JP, Hanin A, Kwiatkowski F, *et al.* Inflammatory breast cancer. The experience of the Centre Jean Perrin. In Ragaz J, Ariel L, eds. *High Risk Breast Cancer Therapy.* Berlin, Springer 1991, 334–345.
24. Fowble BW, Glover D, Rosato EF, *et al.* Combined modality treatment of inflammatory breast cncer. *Int J Radiat Oncol Biol Phys* 1986, **12** (suppl), 151–152.
25. Sarrazin D, Mouriesse H, Arriagada R, *et al.* Les facteurs cliniques de pronostic dans les cancers du sein. *Bull Cancer* 1977, **64**, 477–486.
26. Pouillart P, Palangie T, Jouve M, *et al.* Cancer du sein métastasé: rôle d'une immunothérapie par le BCG et durée de la phase de chimiothérapie intensive. *Bull Cancer* 1981, **68**, 171–186.
27. Zylberberg B, Salat-Baroux J, Ravina JH, *et al.* Inflammatory cancer of the breast. Assessment after 6 years of 16 patients treated by primary immunochemotherapy. *J Gyn Obstet Biol Reprod* 1985, **14**, 615–621.
28. Contesso G, Friedman S, Mouriesse H, *et al*, for the Breast Cancer Committee. The importance of histoprognostic grading as a factor in long term survival in breast carcinoma. *ASCO Proc* 1987, **6**, 50, abstract 194.
29. Buzdar AU, Montague ED, Barker JL, *et al.* Management of

inflammatory carcinoma of the breast with combined modality approach. An update. *Cancer* 1981, **47**, 2537–2542.
30. Buzdar AU, Hortobagyi GN, Montague E, *et al.* Short-term chemotherapy, surgery and radiotherapy in the management of inflammatory breast cancer. *Proc Am Soc Clin Oncol* 1986, 5, 61.
31. Hollender LF, Calderoli H, Bieber S, *et al.* Chimiothérapie pré et post-opératoire deans les cancers inflammatoires du sein. Analyse d'une série de 41 cas. *Chirurgie* 1986, **112**, 84–86.
32. Ackland SP, Bitran JD, Dowlatshahi K. Management of locally advanced and inflammatory carcinoma of the breast. *Surg Gyn Obstet* 1985, **161**, 399–408.
33. Sherry MM, Johnson DH, Page DL, *et al.* Inflammatory carcinoma of the breast. Clinical review and summary of the Vanderbilt experience with multimodality therapy. *Am J Med* 1985, 3, 355–364.
34. Burton V, Cox B, Leight S. Inflammatory breast carcinoma. Effective multimodal approach. *Arch Surg* 1987, **122**, 1329–1332.
35. Leyvraz S, Costa J. Issues in the pathology of sarcomas of the soft tissue and bone. *Sem Oncol* 1989, **16**, 273–280.

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Goserelin Acetate With or Without Flutamide in the Treatment of Patients with Locally Advanced or Metastatic Prostate Cancer

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From March 1987 to December 1990, 373 patients with stage C and D prostate cancer were randomized to receive either goserelin acetate alone or goserelin acetate plus flutamide. At a median follow-up time of 24 months, there was no significant difference in the response rate, progression-free and overall survival between the two treatment groups. In particular, median time to progression was 18 months in the goserelin arm and 24 months in the combined treatment arm ($P = 0.09$). However, median time to progression in stage D patients was 12 months in both treatment groups. Median time to death was 32 and 34 months, respectively. The combination regimen produced a more rapid normalisation of prostatic acid phosphatase levels and a more prompt relief of bone pain. However, significantly more patients in the combination arm experienced treatment-related side-effects such as diarrhoea and increases in transaminase levels. The concurrent use of goserelin acetate and flutamide does not seem to significantly improve the results that can be achieved with goserelin acetate alone.
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INTRODUCTION

HORMONOTHERAPY IS THE most common treatment offered to patients with locally advanced or metastatic prostate cancer. This treatment is beneficial for more than two thirds of patients and induces no significant side-effects. This is particularly true for treatment with luteinizing hormone releasing hormone (LH-RH) analogues that can achieve a chemical castration by interfering with the release of LH at pituitary level. These compounds are well tolerated, require only monthly administration and have been shown to be at least as effective as surgical castration or diethylstilboestrol treatment [1–3]. Therefore, they represent the treatment of choice for prostate cancer patients in many countries.

The main goal of endocrine therapy is to achieve androgen deprivation in order to neutralise androgen stimuli at the prostate cancer cell level. Gonadal ablation, while suppressing most of the circulating levels of testosterone, does not affect adrenal steroidogenesis. Therefore, it is not able to interfere with the biological action of the dihydrotestosterone which is produced at the prostate level through the peripheral metabolic conversion of weak adrenal androgens [4]. For this reason the simultaneous use of gonadal ablation and pure anti-androgens has been suggested [5]. In particular, these investigators reported on the high therapeutic activity of combined treatment with LH-RH analogues and flutamide both in patients with stage D and in those with stage C prostate cancer [6, 7]. In order to test prospectively the therapeutic value of such an approach, an

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