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Pathological response to preoperative concurrent chemo-radiotherapy for breast cancer: Results of a phase II study

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ABSTRACT

This study evaluated, in terms of pathological complete response (pCR) and acute toxicity, preoperative concurrent (5-fluorouracil (5-FU)-vinorelbine) chemoradiotherapy for large breast cancers. A total of 60 women were included in the study. Chemotherapy consisted of 4 cycles of 5-FU, 500 mg/m^2/d, continuous infusion (d1–d5) and vinorelbine, 25 mg/m^2 (d1; d6). Starting with the second cycle, radiotherapy delivered 50 Gy to the breast and 46 Gy to the internal mammary and supra/infra-clavicular lymph nodes. Breast surgery and axillary lymph node dissection were then performed. Four patients did not complete their chemotherapy. Breast conservation was possible in 69% of patients. The rate of pCR was 27%. Three factors were associated with pCR: histological grade 3, absence of hormonal receptors and high mitotic index. Grade 4 haematological toxicity occurred in 22% of patients. In conclusion, chemoradiotherapy demonstrated good efficacy, both in terms of pCR and in allowing breast conservation with acceptable tolerance.

1. Introduction

The standard treatment of breast adenocarcinomas larger than 3 cm is mastectomy with axillary lymph node clearance. Five randomised studies have compared neoadjuvant with adjuvant chemotherapy, the local treatment being either surgery or radiotherapy.[1–5] The principal clinical benefit of neoadjuvant chemotherapy was, in the case of good clinical response, to avoid mastectomy. There was no significant difference in terms of loco-regional control, overall or disease-free survivals.[6]

Radiotherapy is important in the treatment of locally advanced breast cancers.[7,8] It can single-handedly cure breast cancers.[9–12] It achieves complete clinical responses rates (6–41%) with doses compatible with planned secondary surgeries.[13–15] At the Institut Curie, Paris, France, the S6 trial randomised pre-menopausal women between chemotherapy and radiotherapy as first initial treatment for large breast cancers.

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There was no difference in 10-year overall survival.[2] Out of 69 tumours still palpable after four cycles of FAC (5-fluorouracil, adriamycin and cyclophosphamide), 42 (61%) achieved complete clinical response after 54 Gy. This supported the idea that combined treatment with radiotherapy and chemotherapy could improve the rate of breast conservation. We chose a concurrent setting in order to benefit from the additive or supra-additive interaction between the two treatments. This has been proven beneficial for a number of cancers.[16–19] Preoperative concurrent chemoradiotherapy has rarely been used for breast cancer[20,21] and, to our knowledge, assessed in just one randomised trial.[13] We chose chemotherapy with 5-fluorouracil (5-FU) and vinorelbine for two reasons. First, it had shown objective response rates for metastatic breast cancers similar to those achieved by anthracycline-based regimens (50–65%).[22–25] Secondly, vinorelbine, a semi-synthetic vinca-alkaloid, is a potent inhibitor of mitotic microtubule polymerisation with good radio-sensitising effect both *in vitro*[26] and *in vivo*.[27] The goals of this study were to evaluate this concurrent (5-FU-vinorelbine) chemoradiotherapy for breast cancer in terms of the pathologically assessed efficacy of the tumour response and of acute toxicity.

2. Patients and methods

2.1. Patients

S14 is a phase II study that recruited patients from November 2001 to September 2003 at the Institut Curie. Eligibility criteria included untreated, histologically confirmed, invasive adenocarcinoma of the breast not amenable to conservation breast surgery (tumour size relative to breast volume). Patients with metastases, inflammatory or bilateral breast diseases were excluded. Patients were women between 18 and 65 years old without a history of cancer (other than adequately treated carcinoma *in situ* of the cervix or basal cell carcinoma of the skin), who were fit for chemotherapy (Karnofsky performance score >80, no history of intestinal occlusion, no severe cardiovascular condition, no peripheral neuropathy, no reason that would jeopardise compliance with the treatment or follow-up) with adequate organ function (granulocyte count $\geqslant$1500/μl, platelets $\geqslant$100,000/μl, haemoglobin $\geqslant$10 g/dl, total bilirubin $\leqslant$2 N, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant$2.5 N and creatinine clearance $\geqslant$50 ml/min). Progesterone receptor status was assessed when the carcinoma was negative for oestrogen receptors. Pregnancy was an exclusion criterion. Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board and Ethics Committee and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice ICH guidelines and French regulatory requirements.

The initial work-up included a complete clinical assessment, bone scan, chest radiograph, breast and abdominal ultrasound scans, mammography and breast magnetic resonance imaging (MRI).

2.2. Treatment

After insertion of a central venous catheter, patients were treated with 5-FU, 500 mg/m^2/d, administered by continuous intravenous infusion over 5 consecutive days and vinorelbine, 25 mg/m^2, short intravenous infusion on d 1 and 6. Associated treatments included anti-emetic prophylaxis (ondansetron 8 mg and methylprednisolone 80 mg intravenous before vinorelbine) and anti-mucositis prophylaxis (sodium bicarbonate mouthwash). Courses were repeated every 3 weeks for a total of four courses. Weekly dose intensity was defined, for all patients, as the total dose (mg/m^2) divided by the total duration of the chemotherapy in weeks from day 1 of cycle 1 through one cycle length after the date of the last chemotherapy treatment.[28]

Radiotherapy (cobalt-60 or 4–6 MV) started on day one of the second course of chemotherapy. The whole breast was irradiated to 50 Gy (International Commission on Radiation Units; ICRU) in 25 daily fractions and 5 weeks.[29] The internal mammary chain (combination of photons and electrons) and the supra/infra-clavicular areas (lateral border of the field at the humeral head) were irradiated to 46 Gy in 23 daily fractions and 4.6 weeks. Thus only the third level of the axilla was irradiated.

Surgery was indicated in all cases at completion of the chemo-radiotherapy, after the healing of the epidermitis, i.e. a minimal interval of 6 weeks after radiotherapy. It consisted of an axillary lymph node dissection of the first two levels and, depending on the relative volumes of the residual tumour and of the breast as assessed both clinically and by the same breast imaging modalities as at inclusion, of either a tumourectomy or a modified radical mastectomy.

Adjuvant treatments were decided on according to age and pathological criteria with radiotherapy boost (young age or margins at risk), FEC (5-FU, epirubicin and cyclophosphamide) chemotherapy (absence of complete pathological response) and/or tamoxifen (presence of hormone receptors).

2.3. Evaluations

Clinical tumour response,[3,30] defined at the time of surgery, was reported as complete if there was no palpable tumour in the breast, partial if there was a reduction in tumour size (product of the two greatest perpendicular diameters) >50% and as progressive disease when there was an increase >50%. Tumours not meeting these criteria were considered to be stable disease.

Tumours with epithelial malignant residual component strictly *in situ* or representing less than 5% of the breast tumour mass without any mitosis were classified in the group of in-breast pathological complete response. This definition was the interpretation at the Institut Curie[31,32] of the concept, proposed by Sataloff and colleagues[33] of a 'total or near total therapeutic effect'. Because pathological complete response (pCR) did not take histological nodal status into account, patients with pCR could have positive axillary lymph nodes.

In the case of surgical margins involved by infiltrating or ductal carcinoma *in situ* (DCIS), distinction was made between minimal (<15 mm) and extensive involvement ($\geqslant$15 mm).

All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria. Patients were seen at inclusion, before each cycle of chemotherapy, on a weekly basis during radiotherapy and before surgery. Biological

verifications of blood counts were performed weekly and of liver and renal functions every 3 weeks.

2.4. Statistics

The main end-point was the rate of in-breast pCR according to Sataloff criteria of the breast tumour. This study was designed to detect a rate ranging from 20% to 45% with a two-sided 3% significance level and a statistical power of 98% and necessitated the enrolment of 50 women. To ensure an analysis of 50 patients, we planned to enlist 60 patients.

Secondary end-points included clinical tumour response, pathological axillary lymph node response, toxicity, breast conservation rate and predictive factors for in-breast pCR. Long-term results will be presented in due course.

Univariate logistic regression was performed to identify predictive factors of pCR according to the Institut Curie definition and estimate crude odds ratios (OR). A multivariate logistic regression analysis permitted the estimation of the OR of variables independently associated with pCR. A stepwise backward modelling algorithm was used, with a significance level of 0.10 for entering and 0.05 for removing risk factors. P values <0.05 were considered significant. Analyses were performed using SPSS statistical software package, version 11.5 (SPSS Inc., Chicago, Illinois, United States of America (USA)).

Table 1 – Patient and tumour characteristics

Characteristics		*n*	%
Age (years) (mean)	50		
Menopausal			
Yes		24	41
No		35	59
Tumour maximal diameter – mm (mean)	47		
Clinical stage			
T2N0		24	41
T2N1		19	32
T3N0		8	14
T3N1		8	14
Infiltrating carcinoma			
Ductal		41	69
Lobular		12	20
Undifferentiated		4	7
Mucinous		1	2
Mixed epithelial / mesenchymal		1	2
Histological grade			
1		13	22
2		29	49
3		15	25
Unknown[b]		2	3
Number of mitoses / 10 HPF			
0		7	12
<11		34	58
11–22		4	7
>22		12	20
Unknown[b]		2	3
HER2 over-expression			
Yes		8	14
No		49	83
Unknown[b]		2	3
Ductal carcinoma *in situ* component			
Yes		11	19
No		43	73
Unknown		5	8
Oestrogen/progesterone receptors[a]			
ER+/PR unknown		37	63
ER−/PR+		4	7
ER−/PR−		16	27
ER unknown/PR unknown[b]		2	3

HPF, high-power field.
a Progesterone receptor was assessed only if ER−.
b Two patients had insufficient core biopsy material for these items to be studied.

3. Results

3.1. Patients' characteristics

Sixty patients were enrolled, but 1 withdrew her consent, leaving 59 assessable patients. Patients' characteristics (Table 1), in summary, were: median age 49 years (range 31–65 years); 41% menopausal (50% on hormone replacement therapy); clinical T stage (T2, 73%; T3, 27%); median maximal diameter, 45 mm (range 21–80 mm); 54% clinical N0 and 46% N1.

Histological details were: 41 (69%) ductal, 12 (20%) lobular and 6 (10%) other types of infiltrating carcinomas. Histological grade (Ellis Elston[34]) was scored 2 for 49% of patients. The median number of mitoses per 10 high-power fields (HPF)[32] was 4 (0–115). A component of DCIS was observed in 19%, hormonal receptors (HR) were positive in 70%. Eight tumours (14%) were HER2 over-expressed as they showed a membranous staining in more than 60% of cells by

Table 2 – Acute toxicity (grade 3–4 according to NCI) during concurrent chemo-radiotherapy

	Number of patients (%)			
	Grade 3		Grade 4	
	n	%	*n*	%
Haematological	14	24	13	22
Anaemia	1	2	–	
Neutropaenia	14	24	12	20
Neutropaenia with fever (grade 3/4)	1	2	2	3
Neutropaenia with infection (grade 3/4)	–		1	2
Thrombocytopaenia	–		1	2
Infection without neutropaenia grade 3/4	1	2	–	
Gastrointestinal system	7	12	1	2
Nausea/vomiting	1	2	–	
Mucositis	4	7	1	2
Constipation	2	3	–	
Cardiac				
Ischaemia	2	3	–	
Thrombembolia	1	2	–	
Alopecia	1	2	–	
Skin toxicity	8	14		

immuno-histochemistry, either of strong or moderate intensity, which was confirmed by gene amplification assessed by fluorescence *in situ* hybridisation.[35]

3.2. *Treatment compliance*

Fifty-three patients (90%) completed their four cycles of chemotherapy without delay (>7 d) or toxicity-related dose-diminution (>25%). Four patients (7%) had to stop chemotherapy because of toxicity (2 had angina, 1 had deep venous thrombosis and 1 had febrile neutropaenia). One patient (2%) postponed her third chemotherapy cycle for 10 d because of grade 2 constipation. One patient (2%) had a 33% dose reduction of 5-FU because of febrile neutropaenia after the first cycle. From a total of 225 courses, the median weekly dose intensities were 814 mg/m^2 (504–932), i.e. 98% of the theoretical one (61–112) for 5-FU, and 16 mg/m^2 (8–17), i.e. 98% of the theoretical one (50–105) for vinorelbine.

Fifty-four patients (92%) underwent radiotherapy without interruption. Median total dose to the breast was 50 Gy (range 46–52 Gy). Five (8%) had to have their treatment interrupted with a median duration of 2 d (range 2–15 d) because of haematological toxicity in 3, skin toxicity in 1 and gastrointestinal toxicity in 1. No patient had reduced dose because of toxicity.

The median time-lapse was 43 d (range 24–73 d) between the end of radiotherapy and surgery and 123 d (range 106–162 d) from the date of the initial biopsy.

Table 3 – Pathological details of the 51 tumours with residual invasive carcinoma after concurrent chemo-radiotherapy[a]

	n	%
Maximal dimension of the infiltrating carcinoma (mm)		
Median		22
Range		1–85
Lympho-vascular invasion		
Absent	39	76
Present	12	24
Necrosis		
Absent	45	88
Present	6	12
Component of invasive epithelial cells		
⩽5%	10	20
[5–20%]	13	25
>20%	27	53
unknown	1	2
Number of mitoses/10 high-power fields		
0	28	55
1–10	22	43
11–22	1	2
Final surgical margin (infiltrating or ductal carcinoma *in situ*)		
Minimal involvement	7[b]	14
Extensive involvement	1[c]	2
No involvement	43	84

a Out of a total 59 tumours, 8 showed no sign of residual invasive carcinoma (pCR). Of the 51 tumours with residual invasive carcinoma, 8 had less than 5% of invasive epithelial cells with no mitosis and thus also qualified as pCR.
b All these patients had minimal involvement of their final surgical margins by infiltrating carcinoma and underwent high-dose boosts to the tumour bed.
c This patient had an involvement of the surgical margin by infiltrating carcinoma. She refused mastectomy and was therefore treated with a 26 Gy boost to the tumour bed.

3.3. *Treatment toxicity*

There was no toxic death. All toxicities considered, 21 patients (36%) experienced a grade 3 toxicity and 13 (22%) a grade 4 (Table 2). Three patients had cardiovascular toxicity scored grade 3 (5%), all before start of radiotherapy. Skin toxicity in the irradiated field was scored grade 2 in 11 patients (19%), grade 3 in 8 (14%). No neurological, pulmonary, hepato-biliary, or renal toxicity was recorded.

Neither per-operative nor immediate (first 24 h) complications occurred. The median duration of postoperative hospitalisation was 7 d (range 3–12 d). Five patients had wound infections after tumourectomy, which, for 2, needed surgical drainage. Two patients had voluminous haematoma after tumourectomy: 1 underwent surgical drainage, whereas the other could not have postoperative radiotherapy because of it. Twenty-patients had aspirations of lymphoceles.

3.4. *Response*

Twelve patients (20%) had clinical complete response, 20 (34%) partial response, 17 (29%) stable disease, and 2 (3%) progression. Eight tumours (14%) were un-assessable, 7 of which were treated by tumourectomy.

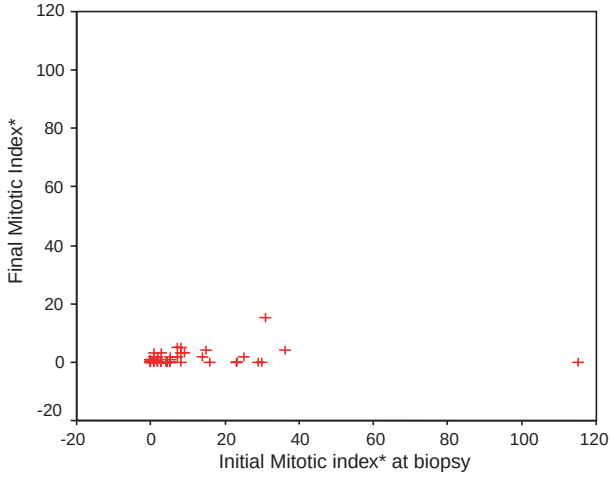

Fig. 1 – Histograms of the number of mitoses per 10 high-power fields (HPF) at initial biopsy (before chemoradiotherapy) and at surgery (after chemoradiotherapy). *Mitoses /10 high power fields. NB: in the case of pathological complete response at surgery, the tumours were considered as having no mitosis. The patient who had 15 mitoses/10 HPF at final surgery had 31 mitoses at biopsy and had stopped her chemotherapy during the first cycle because of angina.

Breast-conserving surgery was performed in 41 patients (69%), and required re-excision in 2 patients. Mastectomy was performed in the remaining 18 patients (31%). Axillary lymph node dissection was performed in all 59 patients.

Sixteen tumours (27%) showed pCR (3 with and 13 without residual DCIS). Of these 16 tumours, 8 (14%) had no residual invasive carcinoma and 8 had less than 5% of invasive carcinoma without any mitosis. Fifty-one tumours had residual invasive carcinoma (8 still complied with pCR). Table 3 gives more pathological details.

The number of mitoses per 10 HPF before preoperative chemoradiotherapy and at surgery is shown in Fig. 1.

In univariate analysis, three factors were associated with pCR according to Sataloff definition (Table 4): histological grade 3 (60% in grade 3 versus 17% in grade 1–2; $P = 0.003$), negative hormone receptor (HR) status (56% in HR– versus 17% in HR+; $P = 0.005$) and high number of mitoses per 10 HPF (50% in $\geqslant 11$ versus 19% in <11; $P = 0.03$). In multivariate analysis only histological grade 3 was associated with pCR (OR = 7.1 (1.9–26.4); $P = 0.004$).

Table 4 – Predictive factors for in-breast pathological complete response (univariate and multivariate analyses) according to Sataloff and colleagues

	Univariate analysis				Multivariate analysis		
	pCR (%)	OR raw	95% CI	P	OR adjusted	95% CI	P
Age							
<50 years	26	1					
⩾50 years	28	1.1	[0.3–3.4]	0.9			
Menopause							
No	26	1					
Yes	29	1.2	[0.4–3.8]	0.8			
Clinical stage							
T2	23	1					
T3	38	2.0	[0.6–6.8]	0.3			
N0	25	1					
N1	30	1.3	[0.4–4.0]	0.7			
Histological type							
Ductal	22	1					
Lobular	31	1.5	[0.4–6.1]	0.5			
Other	50	3.4	[0.6–20.1]	0.2			
Histological grade[a]							
Grade 1 or 2	17	1					
Grade 3	60	7.5	[2.0–27.9]	0.003	7.1	[1.9–26.4]	0.004
Hormone receptors[a]							
Positive	17	1					
Negative	56	3.8	[1.7–22.2]	0.005			
Mitoses /10 HPF							
<11	19	1					
⩾11	50	4.1	[1.2–14.4]	0.03			
HER2 over-expression							
No	23	1					
Yes	50	3.5	[0.7–16.1]	0.1			
Time from RT to surgery							
<44 d	28	1					
⩾44 d	26	0.8	[0.3–2.6]	0.7			
CT dose (/theoretical)							
⩾95%	28	1					
<95%	25	0.8	[0.2–2.9]	0.8			
Completion of CT							
Yes	27	1					
No	25	0.9	[0.1–9.2]	0.9			

HPF, high-power field; CT, chemotherapy; RT radiotherapy; 95% CI, 95% confidence interval; OR, odds ratio; pCR, pathological complete response.

a Factors entered in the multivariate analysis (NB: the mitotic index was not entered into the model as it was highly correlated with the histological grade).

Table 5 – Predictive factors for in-breast pathological complete response (univariate and multivariate analyses) according to Chevalier and colleagues (grade 1–2)

	Univariate analysis				Multivariate analysis		
	pCR (%)	OR raw	95% CI	*P*	OR adjusted	95% CI	*P*
Age (years)							
<50	18	1					
⩾50	8	0.4	[0.1–2.2]	0.3			
Menopause							
No	17	1					
Yes	8	0.44	[0.08–2.4]	0.3			
Clinical stage							
T2	12	1					
T3	19	1.8	[0.4–8.4]	0.5			
N0	9	1					
N1	19	2.2	[0.5–10.2]	0.3			
Histological type							
Ductal	15	1					
Lobular	8	0.5	[0.05–4.3]	0.5			
Other	17	1.1	[0.1–11.5]	0.9			
Histological grade[a]							
Grade 1 or 2	5	1					
Grade 3	40	13.3	[2.3–77.2]	0.004			
Hormone receptors[a]							
Positive	2	1					
Negative	44	31.1	[3.4–250]	0.002	17	[2–175]	0.015
Mitoses /10 HPF							
<11	7	1					
⩾11	31	5.8	[1.2–28]	0.03			
HER2 over-expression							
No	9	1					
Yes	60	6.7	[1.2–39.2]	0.05			
Time from RT to surgery							
<44 d	16	1					
⩾44 d	11	0.6	[0.1–2.9]	0.5			
CT dose (/theoretical)							
⩾95%	13	1					
<95%	15	1.2	[0.3–5.6]				
Completion of CT							
Yes	15	1					
No	0	NA	NA				

HPF, high-power field; CT, chemotherapy; RT, radiotherapy; NA, not applicable; 95% CI, 95% confidence interval; OR, odds ratio.
a Factors entered in the multivariate analysis (NB: the mitotic index was not entered into the model as it was highly correlated with the histological grade).

For comparison with the literature we have added Table 5, which gives rates of in-breast pCR according to Chevallier grade 1–2.

In univariate analysis only histological grade 3 was associated with breast-conserving surgery (Table 6).

When analysing clinical tumour response as a 'test' of pCR, the sensitivity and specificity of complete clinical response were 46% and 85%, the positive and negative predictive values were, respectively, 50% and 82%.

The median number of examined axillary lymph nodes was 11 (3–23). No involved lymph node was found in 33 patients (56%). The number of positive lymph nodes was between 1 and 3 in 13 patients, between 4 and 9 in 11 and more than 9 in 2. The rate of patients with pCR in the breast and negative axillary lymph nodes was 19% (11/59). Of the 8 patients with no residual invasive carcinoma, 6 (10%) had no positive axillary lymph node.

4. Discussion

This phase II study examined the rate of pathological response and early toxicity of preoperative concurrent chemoradiotherapy with 5-FU and vinorelbine for women with large breast cancers. Its efficacy was satisfactory in terms of pCR (27%) and breast conservation rate (69%). The latter compared favourably with that of preoperative chemotherapy alone in

Table 6 – Type of surgery according to patients' and tumours' characteristics

	Tumourectomy (%)	Mastectomy (%)	P
Age (years)			
<50	71	29	0.8
⩾50	68	32	
Menopause			
No	66	34	0.4
Yes	75	25	
Clinical stage			
T2	67	33	0.8
T3	75	25	
N0	72	28	0.7
N1	70	30	
Histological type			
Ductal	65	35	NA
Lobular	77	23	
Other	83	17	
Histological grade[a]			
Grade 1 or 2	60	40	0.02
Grade 3	93	7	
Hormone receptors[a]			
Negative	88	12	0.1
Positive	63	37	
Mitoses/10 HPF[a]			
<11	61	39	0.05
⩾11	88	12	
HER2 over-expression			
No	71	29	0.6
Yes	75	25	
Time from RT to surgery			
<44 d	74	26	0.4
⩾44 d	64	36	
CT dose (/theoretical)			
⩾95%	67	33	0.5
<95%	75	25	
Completion of CT			
Yes	71	39	0.6
No	50	50	

HPF, high-power field; NA, not applicable; RT, radiotherapy; CT, chemotherapy.
a Factors entered in the multivariate analysis (NB: the mitotic index was not entered into the model as it was highly correlated with the histological grade).

women who had planned mastectomy (23% in the European Organisation for Research and Treatment of Cancer (EORTC)-10902 study,[5] 27% in the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B18 study[36] and 61% in the Institut Bergonié Bordeaux Groupe Sein (IBBGS) study,[37] 66–69% in the Trial of Preoperative InfusionalChemotherapy (TOPIC) study[38]) which did not seem to be improved by the addition of taxanes.[30] Our rate of breast conservation was of the order of that achieved by radiotherapy alone with doses (45–50 Gy) compatible with secondary surgery (54–77%).[14,15]

As others have already shown,[20,21,30,39] complete clinical response is not an accurate test for pCR. We found poor sensitivity (50%) and rather good specificity (85%). The possible relevance of additional data obtained from imaging modalities such as ultrasound scans, mammography and magnetic resonance imaging (MRI) to assess response will be reported elsewhere.

The rate of in-breast pCR according to the interpretation at the Institut Curie of Sataloff's definition was 27% (14% if defined as no invasive tumour in the breast or Chevalier grade 1–2).[40] This rate is difficult to compare with those from the literature given the diversity of definitions of pCR, the inter-observer variability[41] and the discrepancy in the selection of tumours. The rate of pCR with radiotherapy alone ranged from 11% to 19%.[13,42] Most trials of chemotherapy alone achieved rates ranging from 4% to 26%.[4,5,30,36,38,39,41,43–46] It ranged from 21% to 30.5% with the addition of taxanes.[30,47] However, the trials that addressed the role of taxanes did not exclude patients with T1 tumours.[30,47] Semiglazov and colleagues compared in a phase III trial of 271 patients, a concurrent combination of chemotherapy (1 or 2 courses of thiotepa, methotrexate and 5-FU) and radiotherapy (60 Gy) with the same radiotherapy alone. All patients underwent a mastectomy after completion of the radiotherapy. The addition of chemotherapy improved both the pCR rate (29% versus 19%; $P = 0.06$) and the 5-year disease-free survival (81% versus 72%; $P < 0.05$).

The factors associated with pCR were, in univariate analysis, those already found in the literature, i.e. a histological grade 3,[43,48,49] absence of hormone receptors[30,32,43,48–51] and a high mitotic index.[32,52] The only independent factor was histological grade 3. However, caution in interpreting the multivariate test is required considering the small number of patients and the intertwinement of these factors. It is also worth noticing that in our series, more than two-thirds of the patients had less than 10 mitoses per 10 HPF. This could be interpreted as resulting from a bias towards recruiting patients whose tumours had low proliferation rate. The fact that their mitotic index plummeted (Fig. 1) has been reported as a prognostic factor of good outcome.[32] Frozen samples from fine-needle aspiration are available from 43 patients of our series. This will enable us to perform DNA-micro-arrays and real-time quantitative polymerase chain reaction to look for new predictive factors for pCR.[50,53]

The proportion of patients with negative axillary lymph nodes was 56% (after four cycles of 5-FU-vinorelbine without irradiation of the axilla). This was in the order of that found in the NSABP-B27, which showed an improvement in the rate of negative nodes by the addition of taxanes (51% after four cycles of doxorubicin (adriamycin) cyclophosphamide (AC) versus 58% after four cycles of AC followed by four of docetaxel, $P < 0.001$). The efficacy of our chemotherapy regimen seems satisfactory when one considers that the patients in NSABP-B27 differed from ours in terms of prognostic factors, with more than 48% of tumours amenable to initial tumourectomy and over 69% of clinical N0, compared with 54%, in our series. However, there is an incentive to look for more efficient chemotherapy regimens, such as those using taxanes, and to irradiate the axilla. A phase II study by Formenti and colleagues of 44 patients with stage IIB–III breast cancers treated by preoperative twice-weekly paclitaxel and concurrent radiotherapy (45 Gy at 1.8 Gy/fraction) to the breast and all lymph node regions achieved a rate of pCR in the breast of

34%, with 16% of patients with no evidence of invasive cancer in the breast or in the axilla, and seemed to be relatively well tolerated.[21] Another promising path is the association with targeted treatments, such as trastuzumab. Buzdar and colleagues studied a series of 42 patients treated for HER2-positive operable breast cancer, randomised between neoadjuvant treatment with either chemotherapy alone (four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin and cyclophosphamide) or with concurrent trastuzumab. The trial was stopped early because of the superiority of trastuzumab plus chemotherapy in terms of pCR, defined as the absence of residual disease both in the breast and the axilla (26% in the chemotherapy arm versus 65.2% in the trastuzumab plus chemotherapy arm, $P = 0.016$).[46] Interestingly, *in vitro* studies also showed that trastuzumab enhanced the radiosensitivity of cells overexpressing HER2.[54]

The toxicity that our patients encountered was deemed acceptable, with 14% of moist desquamation. The rate of febrile neutropaenia (5%) was of the order of that found during four preoperative cycles of AC (7%) according to Bear and colleagues.[30] The rate of wound infection in our study was 8% (5/59), equivalent to that found (8%, 27/348) in the postoperative chemotherapy group of the EORTC-10902 study.[5]

The use of concurrent chemotherapy with four cycles of 5-FU-vinorelbine with breast, internal mammary and supra/infra-clavicular radiotherapy for breast cancers considered too large for tumourectomy is effective, both in terms of pCR (27%) and in allowing breast-conserving surgery (69%). We will report, in due course, long-term follow-up to assess whether these good pathological results bode well for patient outcome[3,55–57] both regarding the sequelae and cosmetic results. These results also prompt us to consider more effective preoperative approaches combining other chemotherapy regimens and radiotherapy with the irradiation of the axilla and targeted therapies. Ultimately, a randomised study between preoperative chemoradiotherapy and chemotherapy alone will be required.

Conflict of interest statement

None declared.

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