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Original article

Preliminary monocentric results of biological characteristics of pregnancy associated breast cancer

Silvia Michieletto [a,*], Tania Saibene [a], Laura Evangelista [b], Franco Barbazza [a], Raffaello Grigoletto [a], Giovanna Rossi [c], Cristina Ghiotto [c], Fernando Bozza [a]

[a] Surgery Oncology Unit, Istituto Oncologico Veneto IOV – IRCCS, Padova, Italy
[b] Radiotherapy and Nuclear Medicine Unit, Istituto Oncologico Veneto IOV – IRCSS, Padova, Italy
[c] Oncology 2 Unit, Istituto Oncologico Veneto IOV – IRCCS, Padova, Italy

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ABSTRACT

Purpose: We performed a mono-institutional study for evaluating the biological data, such as p53, Ki67 and BRCA mutations, as well as clinical characteristics of pregnancy associated breast cancer (PABC), its therapeutic management and the prognosis in a small cohort of patients.
Materials and methods: We retrospectively examined 26 patients with PABC. Clinical and histopathological characteristics along with Ki67, p53 and BRCA mutations were analysed. Information about chemotherapy, surgery and radiotherapy was recovered. Data about long-term prognosis was registered and computed by Kaplan–Meier analysis.
Results: Of 26 patients, 17 (65%) were considered as having a locally advanced breast cancer. The majority of them (65.4%) had a ductal invasive carcinoma. Oestrogen and progesterone receptors were positive in 13 (50%) patients, resulting both negative in four (15.4%) subjects. HER-2 was positive in 5 subjects (19.2%). Ten patients underwent conservative surgery treatment, and 14 were sent to radical mastectomy (38 vs. 54%) associated with axillary lymph node dissection in 18 cases. Many patients (65%) were further treated with adjuvant chemotherapy and/or hormone therapy. Eight out of 11 patients undergoing the evaluation of BRCA mutation were positive while only 2 out of 3 patients had a mutation of p53. After a median follow-up of 110 months (range: 8.2–1227 mo.), 18 women were still alive, six patients (25%) died and two were lost. Three patients showed a loco-regional recurrence, after a median period of 26 months (range: 2–42 mo.). Distant metastases verified in six patients after a median period of 12.5 months (range: 2–108 mo.). The prognosis was less favourable in BRCA mutated patients than no-BRCA mutated group, although not statistically significant.
Conclusions: In women with PABC, the initial stage of disease is more advanced requiring more aggressive treatment.

Introduction

Breast carcinoma is optimally treated when early diagnosed while its management is difficult for the advanced stages, particularly in pregnant patients because of the delay in its detection. Most modern studies reported a mean delay of 1 or 2 months in diagnosis in this particular population [1–3]. A pregnancy associated breast cancer (PABC) is defined as a breast cancer developed during pregnancy or within one year of delivery [4]. PABC is described as being particularly aggressive because of low hormone receptor positivity and high rate of HER2 overexpression [5]. Its pathogenic pathway is probably different from that of non-PABC [6,7], being accelerated by an altered hormonal state. Tumorigenesis in the breast is significantly influenced by hormonal factors, but the precise mechanisms of tumour induction and promotion are still poorly understood. Similarly, also the therapeutic approach is not completely clear in this subset of patients. Several case series have reported on the use of cytotoxic therapy in pregnancy, with no apparent increase in the risk of congenital malformation seen when therapy was initiated after the first trimester in the largest series [8,9]. In order to improve understanding of breast cancer diagnosed during pregnancy, we performed a mono-institutional study for evaluating the biological data, such as p53, Ki67 and BRCA

* Corresponding author. Surgery Oncology Unit, Istituto Oncologico Veneto IOV – IRCCS, Via Gattamelata, 64 35128 Padova, Italy. Tel.: +39 0498215550; fax: +39 0498215542.
E-mail addresses: silvia.michieletto@ioveneto.it (S. Michieletto), laura.evangelista@tin.it (L. Evangelista).

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mutations, as well as clinical characteristics of PABC, its therapeutic management and the prognosis in a small cohort of patients.

Materials and methods

At our Institution, from January 2000 to December 2010, 26 PABC-women (median age 36 years, range 24–44 years) were evaluated. Only patients who have received a new diagnosis of invasive breast cancer during or within one year after pregnancy were considered for the endpoints of this study. The medical charts of all identified patients were comprehensively reviewed to confirm the diagnosis of PABC. Breast cancer was diagnosed during pregnancy in 12 cases and during 12 months post-partum in 14 cases. Data were recovered from the medical records of patients, including previous pregnancy history, tumour immunohistochemistry and pathologic features, treatment variables, and outcome measure including time and site of metastasis and overall survival. The analysed features included age, histology type, histoprognostic grade, mitotic index, hormone receptor status and HER2 status and in selected patients BRCA gene and p53 expression.

Definition

Tumour stage was coded using the seventh edition of the American Joint Committee on Cancer (AJCC) TNM classification system, and the pathological TNM was considered. Histologic type was defined as invasive and no-invasive cancer, and as a ductal or lobular cancer. Different histological type were defined as other. Grading was classified as well differentiated G1, moderately differentiated G2 and scarcely differentiated G3. BRCA gene expression was tested throughout specific genetic test. Hormone receptor status was defined positive when the expression of both oestrogen receptors (ER) and progesterone receptors (PR) was $\geq$10% by immunohistochemistry (IHC). HER-2 was considered positive when scored 3+ in IHC or positive for fluorescence in situ hybridization (FISH). In our Centre, determination of HER-2 status became standard procedure in 2001. Ki-67 was defined as low when IHC staining was present in <15% of tumour cells, as intermediate with staining in 16–30% of the cells, and as high with staining in >30%, according to St. Gallen guidelines [10].

p53 status and BRCA mutation analyses

Tumour samples from primary breast cancer were obtained before any treatment. Immunohistochemical analysis was performed on formalin-fixed tumour tissues using a mouse monoclonal antibody, clone DO-1 (Immunotech, Marseilles, France). Samples were examined for TP53 gene mutations by analysing exons 5 to 8, which include 94% of the mutations (p53 Soussi mutation database, http://p53.free.fr). Briefly, DNA isolated from formalin-fixed tumour tissues was subjected to polymerase chain reaction using primer pairs specific for each exon [11]. The amplified products were then sequenced by fluorescent capillary electrophoresis (ABI Prism 310 genetic analyzer; Applied Biosystems, Foster City, CA). BRCA1 and BRCA2 mutations were identified in the DNA extracted, according to standard procedures, from peripheral blood of patients, using a combination of different approaches including denaturing high performance liquid chromatography for identification of point mutations and multiplex ligation-dependent probe amplification for major genomic rearrangements [12,13].

Treatment management

Information about chemotherapy, surgery and radiotherapy was recovered. The type and doses of chemotherapy agents and the number of chemotherapy cycles carried out during pregnancy were recorded. HER2 positive tumours were treated also by trastuzumab, according to the current guidelines [14].

Clinical outcomes

Disease-free survival (DFS) was defined as the length of time from the date of breast cancer diagnosis to any relapse (local or distant recurrence, or contra-lateral breast), the appearance of a second primary cancer (other than squamous-cell or basal-cell carcinoma of the skin or carcinoma in situ of the cervix), whichever occurred first. Overall survival (OS) was defined as time from breast cancer diagnosis to death from any cause.

Statistical analysis

Continuous variables were expressed as median or mean $\pm$ standard deviation and categorical data as frequencies or percentage. Differences in distribution of categorical variables were assessed using chi-square test. Survival curves were constructed using the Kaplan–Meier method to account for censored survival times and were compared with the log rank test. Disease-free survival (DFS) and overall survival (OS) were defined as the length of time from the date of surgery to any relapse (local or distance recurrence or contra-lateral BC, or second cancer) and to death from any cause, respectively. A p value <0.05 was considered statistically significant.

Statistical analysis was made by SPSS software for Windows.

Results

Out of 26 patients, 24 were symptomatic for breast cancer, such as palpable nodule and mastitis. At initial diagnosis, one patient (4%) was in stage 0, four (15%) in stage I, 11 (42%) in stage II, six (23%) in stage III, three (12%) in stage IV and finally, one (4%) was not evaluable. Therefore, 17 (65%) patients were considered as having a locally advanced breast cancer (stage II–III). The stage IV patients ($n = 3$) showed bone, liver and contralateral axillary lymph node metastasis.

The socio-demographic, histological and treatment features for any patients are resumed in Table 1. As shown, the majority of patients ($n = 17$) had a ductal invasive carcinoma, whereas only four subjects showed an invasive lobular carcinoma (65.4 vs. 15.4%, Chi-square test $p < 0.001$). The expression of HER-2 was available in 25 patients: five (19.2%) of them had a positive results and thus treated with Trastuzumab. Moreover, many of the involved women showed a luminal B breast cancer (rate: 30.8%).

Ten patients were treated by neoadjuvant therapy, in particular one of them during pregnancy. Ten patients (38%) underwent conservative surgery, whereas 14 had radical mastectomy (54%), and axillary lymph node dissection was required in 18 cases (69%). Patients received different chemotherapy regimen as follows: taxanes ($n = 1$), antracyclines ($n = 4$), cyclophosphamide plus methotrexate plus fluorouracil (CMF) regimens ($n = 3$), and the combination of some chemotherapies ($n = 9$). Among patients who received chemotherapy, one patient received taxanes, four antracyclines, three alone cyclophosphamide plus methotrexate plus fluorouracil (CMF) regimens and nine the combination of some chemotherapies. In our experience, five patients out of 26 (19.2%) were treated by trastuzumab and antracycline-based chemotherapy was employed more frequent (46.1%) than the other ones. No side effects were seen. Sixteen patients (61.5%) underwent adjuvant external beam radiotherapy after at least 6 months from the delivery; in particular six out of 14 patients after radical mastectomy and all subjects who performed a conservative therapy.

Table 1
Clinical and histopathological data from overall population.

Variables	*N* of patients, (%)
n	*26*
Age in years, median (range)	36 (24–44)
Familiarity for breast cancer, *n* (%)	
No	13 (50%)
Yes	12 (46%)
NA	1 (4%)
N of pregnancy,[a] median (range)	1 (1–3)
Symptomatic status, *n* (%)	
Yes	24 (92%)
NA	2 (8%)
Clinical TNM, *n* (%)	
cT1 N0-3 M0	7 (27%)
cT2 N0-3 M0	11 (41%)
cT3 N0-3 M0	3 (12%)
cT1-4 N0-3 M1	5 (20%)
Neoadjuvant chemotherapy, *n* (%)	
No	15 (%)
Yes	10 (%)
NA	1 (4%)
Type of surgery, *n* (%)	
No	1 (4%)
Conservative	10 (38%)
Mastectomy	14 (54%)
NA	1 (4%)
Pathological stage, *n* (%)	
Stage 0	3 (12%)
Stage I	6 (24%)
Stage II	7 (26%)
Stage III	5 (18%)
Stage IV	2 (8%)
NA	3 (12%)
Vascular invasion, *n* (%)	
No	14 (56%)
Yes	5 (18%)
NA	7 (26%)
Type of adjuvant chemotherapy, *n* (%)	
NO	7 (26%)
Adriamycin or FEC (fluorouracil, epirubicin and cyclophosphamide)	4 (15%)
Taxans	1 (4%)
Adriamycin and taxanes	4 (15%)
Adriamycin and CMF scheme	3 (12%)
Adryamicin, taxanes and CMF scheme	1 (4%)
Cyclophosphamide, methotrexate and florouracil (CMF)	3 (12%)
Vincristin and cyclophosphamide	1 (4%)
NA	2 (8%)
Trastuzumab, *n* (%)	
No	20 (78%)
Yes	5 (18%)
NA	1 (4%)
Hormone therapy, *n* (%)	
No	9 (35%)
Yes	16 (61%)
NA	1 (4%)
Hystology[a]	
Ductal	17 (65.4)
Lobular	4 (15.4)
Others	3 (11.5)
Intraductal	2 (7.6)
Grading[a]	
Grade1	4 (15.4)
Grade2	9 (34.6)
Grade3	11 (42.3)
Unknown	2 (7.7)
MIB-1[a]	
≤15%	9 (34.6)
16–30%	2 (7.7)
>30%	12 (46.2)
Unknown	3 (11.5)
Hormonal receptors[a]	
ER+ and/or PR+	13 (50)
ER− and PR−/+	8 (30.8)
Unknown	5 (19.2)
HER-2[a]	
Positive	5 (19.2)
Negative	20 (76.9)
Unknown	1 (3.9)
Molecular subtypes	
Luminal A (ER+ and/or PR+/Ki67 < 15%, HER2/neu−)	5 (19.2)
Luminal B (ER+ and/or PR+/Ki67 > 15%, HER2/neu−)	8 (30.8)
Pure HER2/neu (HER2/neu+, ER−, PR−)	1 (3.9)
Triple negative (ER−, PR−, HER2/neu−)	2 (7.7)
Unknown	10 (38.4)
Mutation of BRCA	
Positive	8 (30.8)
Negative	3 (11.5)
Unknown	15 (57.7)
Mutation of p53	
Positive	2 (7.7)
Negative	1 (3.8)
Unknown	23 (88.5)

ER: Oestrogen receptors; PR: progesterone receptors.
[a] In patients who performed neoadjuvant therapy, biopsy or histology specimen was used as reference.

Eight out of 11 patients undergoing the evaluation of BRCA mutation were positive. Moreover, no difference between patients with and without BRCA and/or p53 mutation was found in respect to tumour characteristics, ER/PR/HER2-neu/Ki67 staining and molecular subtypes (Table 2).

After a median follow-up of 110 months (range: 8.2–1227 mo.), 18 women were still alive, six patients (25%) died and two were lost. Three patients showed a loco-regional recurrence, after a median period of 26 months (range: 2–42 mo.); among patients who performed postoperative radiotherapy, one had a mastectomy and one a conservative surgical approach. Distant metastases verified in six patients after a median period of 12.5 months (range: 2–108 mo.), in particular five patients had both visceral and no-visceral (skeletal or lymph node site) spread of disease, while one had a skeletal involvement. Therefore, about 1/4 of patients had a risk of loco-regional and distant recurrence after a median period of three years from surgical treatment (estimated likelihood of recurrence in 5 years: 45%). Two patients had a contralateral breast cancer after a median period of 22 months (range: 11–33 mo.). The distant metastases were equally represented in patients with positive ER and negative ER, independently from the PR expression. The Kaplan–Meier curves for DFS and OS of all patient population are shown in Fig. 1. As demonstrated, after 9-year follow-up the DFS and OS were 48.9 and 47.6%, respectively. A trend for poorer survival in patients with BRCA mutations was found both for DSF and OS, although they did not result statistically significant ($p = 0.051$ and $p = 0.068$, respectively). These results could be associated to the small number of adverse events during the follow-up period.

Discussion

Breast cancer during pregnancy is a rare clinical situation and it poses several clinical conflicts: the standard regimens are not always possible and tailored approaches should be considered. Pregnancy has traditionally been thought to decrease a woman's lifetime risk of developing breast cancer, but the actual situation is more complex. This physiological condition, actually confers a transient increased risk of breast cancer as compared to nulliparous women.

Many authors have concluded that pregnancy must cause a period of promotion before it eventually produces its protective effect [15,16]. Pregnancy clearly has multiple complex effects on breast tissue, which may have profound effects on both normal

Table 2
Comparison between patients with BRCA and/or p53 mutations and patients without any mutations.

	BRCA mutation and/or p53 mutation ($n = 10$)	No BRCA mutation and/or p53 mutation ($n = 4$)	*p Value*
Grading			
1	1 (10%)	1 (25%)	*0.435*
2	3 (30%)	0	
3	4 (40%)	1 (25%)	
NA	2 (20%)	2 (50%)	
Hystology			
DCIS	0	1 (25%)	*0.505*
IDC	5 (50%)	2 (50%)	
ILC	3 (30%)	1 (25%)	
Others	1 (10%)	0	
NA	1 (10%)	0	
Hormone receptors			
ER−PR−	1 (10%)	0	*0.522*
ER and/or PR+	7 (70%)	2 (50%)	
NA	2 (20%)	2 (50%)	
HER2neu receptor			
Negative	8 (80%)	2 (50%)	*0.533*
Positive	1 (10%)	1 (25%)	
NA	1 (10%)	1 (25%)	
MIB-1			
<15%	2 (20%)	1 (25%)	*0.088*
>30%	6 (60%)	0	
NA	2 (20%)	3 (75%)	
Molecular subtypes			
Luminal A	1 (10%)	1 (25%)	*0.593*
Luminal B	5 (50%)	0	
Pure HER2/neu	0	0	
Triple negative	1 (10%)	0	
NA	3 (30%)	3 (75%)	

NA: not available; DCIS: ductal cancer in situ; IDC: invasive ductal cancer; ILC: invasive lobular cancer; ER: oestrogen receptors; PR: progesterone receptor.

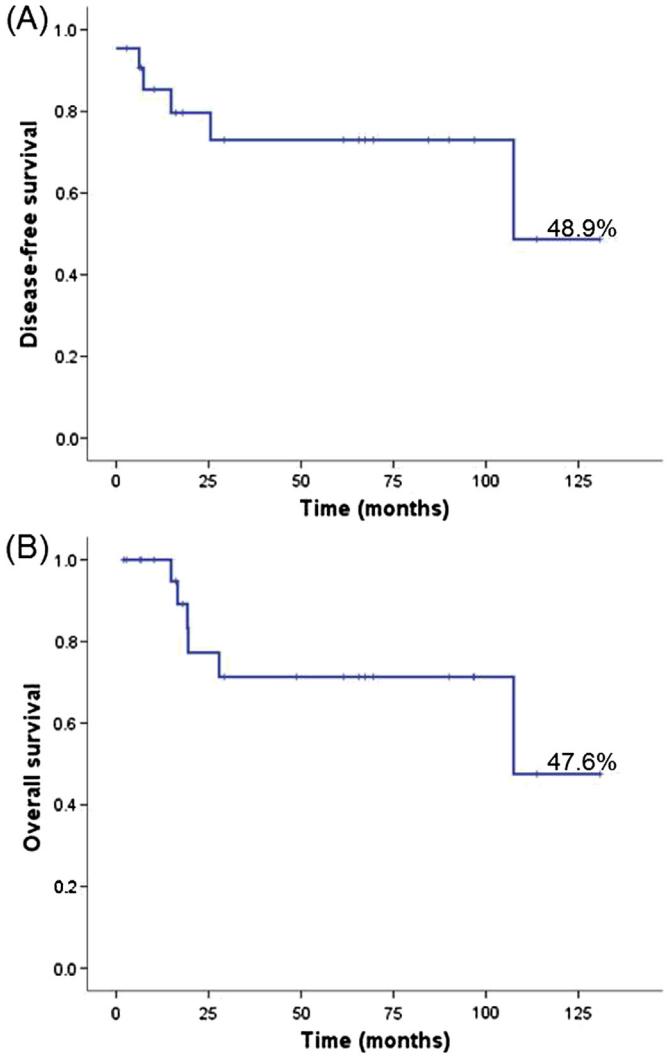

Fig. 1. Survival curves in all patient population. (A) Disease-free survival curve; (B) overall survival curve.

tissue and developing tumours. A potential mechanism for increased aggressiveness of breast cancer diagnosed or treated in the post-partum period is facilitation of metastasis through the wound-healing and or pro-inflammatory microenvironment of the involuting breast [16]. We retrospectively analysed 26 patients with PABC for better identifying the correlations among demographic data, histology, hormone expression and prognosis. According to Lyons et al. [16] and Guidroz et al. [17], 35 is thought to be critical age when a first pregnancy causes a permanently increased risk of breast cancer. In the present report, the subset of enrolled patients showed a median age of 36 years, respectively 36 for pregnant and 35 for breast-feeding patients. According to the Europeans register on PABC, the median age of PABC is 33 years, compared to 60 in non-PABC, and the mean gestational age at diagnosis is 21 weeks [15]. Breast cancer in this young age group is associated with a positive family history in up to 50% of cases and risk of gene mutation (BRCA1/BRAC2) in up to 30% of the women [18]. In accordance with this latter concept, one third (30%) of our study populations had a BRCA abnormality, while 8% a mutation of p53.

Patients with PABC usually are found to have more advanced disease at diagnosis. This is generally attributed to delay in diagnosis. It has been reported that the average delay in diagnosis in pregnant patients is 5–10 months as compared to 1–4 months in no-pregnant patients [15,19,20]. The majority of abnormalities found in women's breasts during pregnancy and lactation are benign. Since usually these lesions can grow and cause pain and cannot be clinically be distinguished from malignancy, further investigation is required. Physicians must be vigilant of breast masses occurring during pregnancy to avoid delay in the diagnosis of breast cancer.

The histopathological and immunohistochemical findings of breast cancer in pregnancy are similar to those in non-pregnant women who are younger than 35 years. Similar to the general breast cancer population, invasive ductal carcinoma is the most prevalent type of cancer in PABC. Previous reports reported a high prevalence of invasive ductal cancer ranged between 71 and 100% [3,4,21–25]. However, these patients tend to have higher grade disease than their non-pregnant peers. Tumour is typically larger and has associated lymphatic and vascular invasion as well as positive axillary lymph nodes. Hormone receptors are more likely to be negative, i.e. Elledge et al. [23] found that 67% of PABC had a negative ER than the counterpart of no-PBCA who showed a prevalence of 48%. Herein, we found that 65% of patients had an invasive ductal cancer (vs. 15.4% of invasive lobular cancer); 42.3% of subjects demonstrated a poorly differentiated cancer; and 19.2% had a both negative ER and PR tumour. Furthermore, we reported that 46.2% of women had a MIB-1 >30%, an indirect sign of tumour aggressiveness. Moreover, as recently reported by Turkoz et al. [24], women with first-full term pregnancy at age ≥30years also had significantly elevated risk of luminal breast cancer, when compared to hormone receptor negative cases, as well as emerged from our findings. At our knowledge, no data about the association of different molecular subtypes and PABC is described in literature. A wide collection of data from literature about prognosis in PBCA is shown in Table 3.

Table 3
A collection of data from literature (from 1969 to today).

Author, (Ref)	Study design	N° of subjects		Histology results[a]		Nuclear grade[b]		ER− and PR−		Positive ER2		Prognosis	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Mausner et al., [27]	Retrospective cases	73	647	–	–	12.3%	3.6%	–	–	–	–	48.4% (OS – 5yrs)	61.6% (OS – 5yrs)
Wallgren et al., [28]	Retrospective cases	15	58	100%	100%	–	–	–	–	–	–	53%[d]	52%[d]
Nugent et al., [29]	Case-control series	19	157	–	–	–	–	71%	–	–	–	56% (OS – 5yrs)	56% (OS – 5yrs)
Greene [30]	Case-control series	8	36	–	–	–	–	–	–	–	–	87.5% (OS – 14yrs)	–
Petrek et al., [4]	Retrospective cases	56	159	78%	75%	–	–	–	–	–	–	–	–
Zemlickis et al., [31]	Case-control series	102	269	–	–	–	–	–	–	–	–	–	–
Ishida et al., [21]	Case-control series	192	191	92%	88%	–	–	62% (ER-) 83% (PR-)	59% (ER−) 58% (PR−)	–	–	55%[d]	79%[d]
Elledge et al., [23]	Case-control series	15	411	–	–	–	–	67% (ER−) 53% (PR−)	48% (ER−) 57% (PR−)	58%	16%	–	–
Anderson et al., [32]	Retrospective cases	22	205	91%	89%	–	–	–	–	–	–	44%[d]	71%[d]
Ezzat et al., [33]	Case-control series	28	84	86%	82%	39%	39%	1/7 (ER+)	7/21 (ER+)	–	–	57% (OS – 7yrs)	61% (OS – 7yrs)
Bonnier et al., [3]	Case-control series	154	308	88.2%	87.6%	40%	36.1%	41.9%	21.3%	–	–	50%[c]	70%[c]
Shousha et al., [25]	Case-control series	14	13	71%	69%	80%	33%	50% (ER−) 70% (PR−)	9% (ER−) 36% (PR−)	44%	18%	–	–
Ibrahim et al., [34]	Case-control series	72	216	–	–	60%	60%	33% (ER+)	43% (ER+)	–	–	32% (OS, Stage IV)	23% (OS, Stage IV)
Murphy et al., [22]	Case-control series	99	186	–	–	84%	65%	59% (ER−)	31% (ER−)	20%	19%	n.d.	n.d.
Middleton et al., [26]	Prospective cases	39	–	100%	–	84%	–	28%	–	28%	–	23% (median FUP: 32 mo)	–
Siegelmann-Danieli et al., [35]	Case-control series	22	192	n.d.	n.d.	68%	32%	53%	25%	–	–	71.5% (OS – 5yrs)	81.2% (OS – 5yrs)
Aziz et al., [36]	Case-control series	24	48	–	–	–	–	71% (ER−PR−)	42% (ER−PR−)	42%	44%	54% (OS – 5yrs)	44% (OS – 5yrs)
Reed et al., [5]	Retrospective cases	122		82%	–	95%	–	66% (ER−)	–	44%	–	–	–
Mathelin C et al., [2]	Case-control series	40	61	82.5%	92%	55%	41%	52.5% (ER−)	31% (ER−)	–	–	70%[d]	97%[d]
Beadle et al., [37]	Case-control series	104	564	93.3%	93.1%	51%	36.9%	49% (ER−)	39.5% (ER−)	–	–	64.6%[d]	64.8%[d]
Halaska et al., [38]	Case-control series	32	32	97%	97%	47%	47%	59% (ER−)	34% (ER−)	62,5%	62.5%	38%[d]	70%[d]
Moreira et al., [39]	Case-control series	87	252	90.8%	92.1%	25.3%	32.1%	13.8%	15.5%	–	–	19.2%[d]	34.8%[d]
Johansson et al., [40]	Case-control series	1110	14,611	–	–	–	–	–	–	–	–	54% (OS – 15yrs)	66% (OS – 15yrs)
Loibl et al., [41]	Retrospective and prospective cases	447	–	97%	–	75%	–	52%	–	36%	–	60%[d]	–

ER: oestrogen receptor; PR: progesterone receptor; OS: overall survival, n.d.: no difference.
[a] Ductal invasive cancer.
[b] Grading 3.
[c] 5-year metastases-free survival.
[d] 10-year survival rate.

There is no epidemiological, clinical or prognostic evidence to suggest that pregnancy, or its terminations, will alter the natural history of breast cancer or improve survival [42]. We cannot forget that pregnancy by itself need not compromise effective breast cancer treatment, although the selection of and order of modalities will need to consider fetus safety. Therapeutic strategies are determined by tumour biology, tumour stage, and the patient's and her family's wishes. Counselling is crucial because of the complexity of the issue. A multidisciplinary team with all involved specialities should assess the medical (obstetric, oncological, paediatric end genetic), ethical, psychological and religious issues. Surgery in all trimesters, chemotherapy in the second and third trimester, and post-partum radiotherapy are considered safe therapeutic options for the majority of patients with PABC. However, few patients who present with advanced stage disease (stage III and IV) during the first trimester, termination is usually recommended, as chemotherapy and/or radiotherapy at this stage is likely to damage the fetus (*NCCN guidelines 2011*, 43).

The main stay of treatment in breast cancer is surgery. It has been shown by many authors that surgery and the use of general anaesthesia can be safely performed with little risk to the fetus during any stage of pregnancy. Physicians involved should take extra precautions with monitoring and be aware of the physiologic changes of pregnancy including increased cardiac output, decreased peripheral vascular resistance, increased blood volume, and a physiologic dilutional anaemia. Breast cancer surgery should follow the same guidelines as for non-pregnant women. Mastectomy and breast conservation surgery followed by radiation are the two surgical options for breast cancer patients. In our population, 38% of patients underwent conservative procedures and 54% performed a radical mastectomy. Radiation is contraindicated during pregnancy except in extremely special circumstances, and hence in our PABC population, mastectomy was favoured. Breast conservation is a valid surgical option for many, although limited by the postoperative radiotherapy given to optimize local control, which is contraindicated during all trimesters of pregnancy. Postoperative radiotherapy should be deferred until after delivery. In our cases, 16 patients underwent radiotherapy after at least 6 months for the delivery, in particular six out of 14 patients after radical mastectomy and all subjects who performed a conservative therapy. Moreover, according to the follow-up results, among patients who performed postoperative radiotherapy, only two loco-regional recurrences occurred, one in mastectomy and one in conservative approach.

The indication for systemic chemotherapy are the same in PABC as in non-pregnant breast cancer patient. In fact, according to International recommendations, the treatment of PABC should

adhere closely to standardized protocols for patients without concomitant pregnancy. Chemotherapy has established an important role in improving the survival of patients with early stage breast cancer: if it can be administered during pregnancy, the choice of the neoadjuvant setting remains a strategic one with the risk (even if low) of disease progression. As recently reported by Loibl et al. [41], the adjusted survival analysis indicates that women who received chemotherapy during pregnancy might have a better survival outcome. However, the data should not be over interpreted and certainly do not suggest that initiation of treatment should be delayed.

In the present study, 17 patients had a locally advanced breast cancer, and 10 out of them performed neoadjuvant treatment, in particular one of them before delivering. Chemotherapy should not be administered in the first trimester of pregnancy as there is a 14–19% risk of fetal malformations and an increased risk of spontaneous abortion [31]. Furthermore, it should not be given after week 35 of pregnancy or within 3 weeks of planned delivery to avoid potential haematologic complications at the time of delivery. The greatest experience in pregnancy has been with anthracyclines and alkylating agents [20,43,44]. There is limited data on the use of taxanes and its use is not recommended during pregnancy but, if indicate, may be used after delivery [45]. Endocrine therapy is not recommended during pregnancy and tamoxifen is known to cause spontaneous abortions, birth defects and fetal demise. The use of trastuzumab has been linked with anhydromnios which resolved slowly with the discontinuation of the drug. In our experience, five patients out of 26 (19.2%) were treated by trastuzumab and antracicline-based chemotherapy was employed more frequent than the other ones (46.1 vs. 19.2%). No side effects were reported in our cases, probably due to the small number of patients undergoing chemotherapy during the pregnancy period.

Overall, the prognosis for PABC is poor. Firstly, because to higher stage at diagnosis. Secondly, the delay in diagnosis that allows the tumour more time to grow and in turn, increasing the metastatic potential of the disease. Moreover, a more favourable microenvironment created during pregnancy and lactation could favour the poor prognosis, because during this time, there is considerable cell proliferation, tissue remodelling, and angiogenesis which has been found conducive for oncogenesis. Finally, treatment delays to reduce fetal exposures to possible toxins also portend a worse prognosis [17]. Based on these concepts, we reported a high rate of distant relapse (23%) within one year. Moreover, about 1/4 of patients had a risk of loco-regional and distant recurrence after a median period of three years from surgical treatment (estimated likelihood of recurrence in five years: 45%). Furthermore, 25% of patients were died after about 5-year of follow-up. Old reports from literature [i.e. Ishida et al. [21] and Bonnier et al. [3]], demonstrated a low survival rate or metastases-free survival in PABC patients, probably justified by few therapeutic opportunities. Recently, a meta-analysis of 30 studies by Azim et al. [46] concluded that patients diagnosed with PABC are independently associated with poor overall survival; this is particularly obvious in patients diagnosed in the 1-year post-partum period than those diagnosed during pregnancy [HR: 1.81 (95% CI: 1.34–2.46) vs. 1.30 (95% CI: 0.95–1.39)].

The major limitations of the study are firstly the small number of patient population and secondly the absence of some results about genetic mutations or the follow-up data. Due to a small number of patients, the Kaplan–Meier analysis should be interpreted with caution.

Conclusion

In conclusion, in women with PABC, the initial stage of disease is more advanced requiring more aggressive treatment. A tailored therapy based on biological features of PABC should be evaluated even if the options are limited. Moreover, the special hormone environments during pregnancy and lactation may accelerate cancer growth and progression, leading to the poor therapeutic results. There is no marked difference in the prognosis among early stage cases, but once lymph node metastasis occurs the surgical results may become worse in correlation with the extent of rapid metastatic spread. In many cases, a multidisciplinary approach can help in decision of correct therapeutic regimen facing to improve both quality of life or long-term prognosis.

Authorship statement

Concept and design of data: Silvia Michieletto, Tania Saibene.

Analysis and interpretation of data: Silvia Michieletto, Tania Saibene, Laura Evangelista.

Writing of the manuscript: Silvia Michieletto, Tania Saibene, Laura Evangelista.

Revision of the manuscript: Fernando Bozza, Cristina Ghiotto.

Conflict if interest statement

None.

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