

Pathological complete response in younger and older breast cancer patients

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Abstract

Introduction: Pathologic complete response (pCR) after neoadjuvant systemic treatment for inoperable locally advanced breast cancer is defined as complete microscopic disappearance of invasive cancer in both the breast and axilla in the postoperative specimen. The aim of the study was to characterize the groups of younger (≤ 40 years old) and older (≥ 70 years old) breast cancer patients who achieved a pCR.

Material and methods: One hundred thirty-eight consecutive patients aged between 30 and 78 years with locally advanced breast cancer, operated on after neoadjuvant systemic treatment between November 2007 and June 2010, were analyzed. In this group 9 women (6.5%) were 40 years of age or younger, and 12 patients (8.7%) were 70 years of age or older.

Results: In the younger group, pCR was achieved in 1 patient with triple negative, invasive ductal breast cancer, G3, BRCA 1 mutation, treated with cisplatin. A near pCR was achieved in 2 other patients, with triple negative, invasive ductal breast cancer, G3, treated with AT. The pCR in the breast was found in a HER2 positive patient. In older patients, pCR was achieved in 2 patients with triple negative, invasive ductal breast cancer, G3, treated with AT or FEC. Pathologic complete response in the axilla was achieved in 1 patient with triple negative, ductal carcinoma. The pCR rates were significantly higher in triple negative breast cancer in both groups ($p = 0.047$ and $p = 0.018$, respectively).

Conclusions: Pathologic complete response was significantly associated with receptor-based subtypes in both young and old women.

Key words: breast cancer, pathological complete response, young, elderly.

Introduction

Pathological complete response (pCR) after neoadjuvant systemic treatment for inoperable locally advanced breast cancer with intent to change tumour status to operable or allowing reduction of its size, permitting

breast conservation, is defined as complete microscopic disappearance of invasive cancer in both the breast and axilla in the postoperative specimen [1, 2]. The sequence of neoadjuvant systemic treatment and subsequent operation provides a unique opportunity to objectively determine *in vivo* cancer response to preoperative chemo- or endocrine therapy [1, 3]. The pCR predicts better survival, whereas a large residual cancer burden worsens disease-free survival prognosis [4, 5]. The age of the patient at diagnosis may influence these parameters [6-8].

The aim of our study was to characterize a group of younger (≤ 40 years) and older (≥ 70 years) breast cancer patients who achieved a pCR after neoadjuvant systemic treatment.

Material and methods

The Breast Cancer Database in the Departments of Chemotherapy, Proliferative Diseases and Surgical Oncology, Copernicus Memorial Hospital, Cancer Centre, Lodz, Poland was searched, and a consecutive series of 138 patients identified who had inoperable locally advanced breast cancer or resectable tumours suitable for downstaging, and treated with neoadjuvant chemo- or endocrine therapy then subsequently resected between November 2007 and June 2010.

Inclusion criteria

Breast cancer patients who had preoperative systemic therapy, 40 years of age or younger or 70 years of age or older, treated between November 2007 and June 2010, were included.

Before starting neoadjuvant systemic treatment, a diagnosis of invasive breast cancer was confirmed by core-needle biopsy of the breast tumour, although in some cases only results of fine needle aspiration with oestrogen (ER) and progesterone receptor (PR) concentrations were available. Dedicated breast pathologists from the Department of Pathology, Medical University of Lodz, reviewed all biopsy specimens. The ER and PR status was determined by immunohistochemistry (IHC) using the Allred score. Human epidermal growth factor receptor 2 (HER2) status was evaluated by immunohistochemistry or by fluorescence in situ hybridization. HER2-positive tumours were defined as 3+ receptor overexpression on IHC staining and/or gene amplification found on fluorescent in situ hybridization. TNM clinical staging was assessed by mammography, ultrasound of the breast, axilla and abdomen, and chest X-ray. In selected cases, MRI of the breast was performed. The following preoperative chemo- and endocrine therapy regimens were used: AT (doxorubicin 50 mg/m², docetaxel 75 mg/m²), FAC (5-fluorouracil 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²),

FEC (5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m²), AC (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²), EC (epirubicin 100 mg/m², cyclophosphamide 600 mg/m²), TAC (docetaxel 75 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²), cisplatin (75 mg/m²), CMF (cyclophosphamide 100 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m²), and anastrozole. The various regimens were in 21-day cycles, except for 28-day CMF cycles. Anastrozole was taken orally 1 mg daily. Upon completion of chemotherapy (4-6 cycles), dedicated breast surgeons performed mastectomy or breast conservation, with axillary dissection or sentinel node biopsy. Postoperative specimens were examined by dedicated breast pathologists. pCR was defined as postoperative microscopic absence of invasive carcinoma in breast tissue, and axillary lymph nodes after neoadjuvant systemic treatment. A near complete response with only minimal residual disease was described as scattered tumour cells in the primary tumour site or lymph node or minimal cellularity in the surgical specimen. pCR and near pCR were key points in statistical analysis.

As these procedures were routine diagnosis and treatment; ethical approval and informed consent were not required.

Statistical analysis

The computer package Statistica version 8.0 (StatSoft) was used for all statistical analyses. The two-tailed Fisher's exact test was used to compare variables with a *p* value of 0.05 established as the threshold of statistical significance.

Results

Young age group

Of 138 consecutive patients from our database, 9 women (6.5%) were between 30 and 40 years old, mean age 36.3 years, all with invasive ductal breast cancer; grade G2 – 2 patients, G3 – 6 patients, Gx – 1 patient; stage IIB – 1 patient, IIIA – 5 patients, IIIB – 2 patients, IIIC – 1 patient; ER(0)PR(0)HER2(0) (triple negative) – 4 patients, ER(+)PR(+)HER2(0) – 2 patients, ER(+)PR(+)HER2(+) – 2 patients, ER(0)PR(0)HER2(+) – 1 patient. Neoadjuvant regimens comprised: AT – 6 patients, TAC – 1 patient, AC – 1 patient, cisplatin – 1 patient. After completion of neoadjuvant chemotherapy, mastectomy was performed in 8 patients, and breast conservation in 1 patient. The pCR was achieved in 1 patient from this younger patient group (1/9, fraction = 0.11), with triple negative, invasive ductal breast cancer, G3, BRCA1 mutation, treated with cisplatin. Furthermore, a near complete response to preoperative chemotherapy was achieved in 2 other patients. These also had triple negative,

invasive ductal breast cancers, G3, treated with AT. One of these had a pCR in the axilla but scattered 2 mm cancer cells in the breast, in the mastectomy specimen. In the other, pCR was achieved in the breast but a 3 mm metastasis remained in the axillary lymph node after breast conservation. Additionally, pCR in the breast was found in a HER2 positive breast cancer patient, treated with AT. The characteristics of these young (≤ 40 years old) patients are shown in Table IA and II. Comparison of pCR according to receptor-based subtypes and grade with p values is summarized in Table III.

Older age group

Of 138 consecutive patients from our database, 12 (8.7%) were between 70 and 78 years old, mean age 72.3. Histopathological tumour type: invasive ductal carcinoma (9 patients), invasive lobular classical type (1 patient), invasive lobular pleomorphic type mixed with 5% invasive ductal cancer (1 patient), mucinous cancer (1 patient). Tumour grade: there were 1, 3 and 8 patients with grades Gx, G2 and G3, respectively. Tumour staging: stage IIA (1 patient), IIIA (4 patients), IIIB (6 patients), IIIC (1 patient). Receptors: ER(+)PR(+)HER2(0) in 4 patients, ER(0)PR(0)HER2(0) (triple negative) in 4 patients, ER(0)PR(+)HER2(0) in 1 patient, ER(+)PR(+)HER2-ambiguous in 1 patient, ER(0)PR(0)

HER2(+) in 1 patient, ER(+)PR(0)HER2(+) in 1 patient. The following neoadjuvant chemotherapy regimens were used: AT – 4 patients, FEC – 4 patients, FAC – 1 patient, CMF – 1 patient, EC – 1 patient; in 1 patient neoadjuvant endocrine therapy (anastrozole) was used. After completion of systemic therapy, mastectomy with axillary dissection was performed in all patients. pCR was achieved by AT or FEC in 2 patients (2/12; fraction = 0.16) with triple negative, invasive G3 ductal cancer. Additionally, pCR in the axilla was achieved with neoadjuvant FAC in 1 other patient with triple negative, G3 invasive ductal cancer. Characteristics of the older (≥ 70 years old) breast cancer patient group are shown in Table I B and II. Comparison of pCR according to receptor-based subtypes, grade and histopathological tumour type with p values is summarized in Table III.

In both young and old groups, higher rates of pCR were observed in patients with triple negative receptor status ($p = 0.047$ and $p = 0.018$, respectively; Table III). No statistical differences were found in terms of ER, PR, or HER2 receptor status in both groups (Table III). The tumour grade showed no statistically significant influence on pCR both in young and old patients ($p = 0.46$ and $p = 0.49$). In women aged 70 years and above, no differences in pCR were shown in terms of histopathological cancer type ($p = 0.5$; Table III).

Table I A. Pathological response after neoadjuvant chemotherapy in younger breast cancer patients (≤ 40 years old)

Patient	Age [years]	Cancer type	ER	PR	HER2	G	cTN	ypTN	CHT	Surgery	BRCA mutation	pCR
1	30	Inv ductal	0	0	+	G3	cT4N3	ypT2N3	TAC	Mastectomy	No	No
2	35	Inv ductal	0	0	0	G3	cT4N2	ypT1aN0 (scattered 2 mm cancer cells in breast)	AT	Mastectomy	No	Very good response (near pCR)
3	35	Inv ductal	+	+	0	G3	cT2N2	ypT1cN1	AC	Mastectomy	No	No
4	36	Inv ductal	+	+	+	Gx	cT2N2	ypT1cN2a	AT	Mastectomy	No	No
5	36	Inv ductal	+	+	0	G2	cT3N2	ypT1cN1a	AT	Mastectomy	No	No
6	37	Inv ductal	0	0	0	G3	cT2N2	ypT0N0	Cis-platin	Mastectomy	Yes	pCR
7	39	Inv ductal	+	+	+	G2	cT3N2	ypT0N2	AT	Mastectomy	No	pCR in breast
8	39	Inv ductal	0	0	0	G3	cT2N1	ypT0N1 (scattered 3 mm cancer cells in one axillary node)	AT	BCT	No	Very good response (near pCR)
9	40	Inv ductal	0	0	0	G3	cT4N0	ypT4bN1 (3 months later lung metastases)	AT	Mastectomy	No	Progression

Inv ductal – invasive ductal, G – grading, cTN – clinical staging (tumour and nodes), ypTN – pathological staging (tumour and nodes), CHT – chemotherapy, BCT – breast conserving therapy, pCR – pathological complete response

Table I B. Pathological response after neoadjuvant chemo- and endocrine therapy in older breast cancer patients (≥ 70 years old)

	Age [years]	Cancer type	ER	PR	HER2	G	cTN	ypTN	CHT	Surgery	pCR
P1	70	Inv ductal	+	+	0	G2	cT4N2	ypT2mN1	AT	Mastectomy	No
P2	70	Inv ductal	+	+	amb	Gx	cT4N1	ypT2N3	FEC	Mastectomy	No
P3	70	Inv ductal	0	0	0	G3	cT4N1	ypT2N0	FAC	Mastectomy	pCR in axilla
P4	70	Inv ductal	+	+	0	G2	cT3N1	ypT2N1	AT	Mastectomy	No
P5	71	Inv ductal	0	0	0	G3	cT3N1	ypTON0	FEC	Mastectomy	pCR
P6	71	Inv ductal	0	0	0	G3	cT2N0	ypT2N1	CMF	Mastectomy	Progression
P7	71	Inv ductal	0	0	0	G3	cT4N1	ypTON0	AT	Mastectomy	pCR
P8	73	Inv lobular	+	+	0	G3	cT4N2	ypT3N3	AT	Mastectomy	No
P9	73	Inv ductal	+	+	0	G2	cT3N1	ypT2N1	EC	Mastectomy	No
P10	74	Pleom. lobular 95%, inv ductal 5%	0	0	+	G3	cT4N2	ypT3N2	FEC	Mastectomy	No
P11	77	Inv ductal	0	+	0	G3	cT3N2	ypT1N2b	Anastrozole	Mastectomy	No
P12	78	Mucinous	+	0	+	G3	cT2N3	ypT2N2	FEC	Mastectomy	No

Inv ductal – invasive ductal, Inv lobular – invasive lobular, Pleom. lobular – pleomorphic lobular, amb – ambiguous, G – grading, cTN – clinical staging (tumour and nodes), ypTN – pathological staging (tumour and nodes), CHT – chemotherapy, pCR – pathological complete response

Discussion

Scientific studies have shown that age of breast cancer patients is inversely related to tumour aggressiveness and outcome [6-9]. Both age groups younger than 40 years and older than 70 years are outside the upper and lower age limits in screening programmes in the majority of countries in the world [9]. We have therefore focused attention on patients in both of these age groups, and in particular with respect to pathological remission after neoadjuvant systemic treatment. Several articles have shown that the highest rate of pCR occurs in triple negative and HER2 positive breast cancer subtypes in comparison with ER(+) tumours, but no age stratification has been demonstrated [10-13]. Consistently, in our study pCR or a near complete pathological response to neoadjuvant chemotherapy was achieved in the younger cohort of patients in triple negative breast cancer, which was statistically significant ($p = 0.047$), and pCR solely in the breast in an HER2 positive tumour. Similarly, in the older age group (≥ 70 years old) we observed pCR and pCR in the axilla in the triple negative breast cancer subtype ($p = 0.018$). Indeed, surgeons from the Netherlands Cancer Institute have stated that among various variables such as menopausal status, tumour stage, nodal involvement, and histology, the receptor-based subtype was the only significant predictor of pCR, with triple negative patients being more chemosensitive [10]. Recently a new surrogate, the residual cancer burden (RCB), has been proposed to measure chemosensitivity as a continuous variable derived from the primary

Table II. Summary characteristics of the two study groups

Parameter	≤ 40 years	≥ 70 years
Age (mean ± SD)	36.3 ± 3.0	72.3 ± 2.8
Cancer type (ductal/other types)	9/0	9/3
ER (positive/negative)	4/5	6/6
PR (positive/negative)	4/5	6/6
HER2 (positive/negative)	3/9	3/9
Triple negative vs. ER, PR and/or HER2 positive	4/5	4/8
G (G3/G2 or Gx)	6/3	8/4
pCR/no pCR	3/6	3/9

tumour dimensions, cellularity of the tumour bed, and axillary nodal burden. The RCB is a significant predictor of distant relapse-free survival and can be used to more precisely determine the response to chemotherapy [11]. Peintinger *et al.* have stated that minimal residual disease (RCB-I) carries comparable prognosis as pCR (RCB-0) [5]. In contrast, extensive residual disease (RCB-III) is associated with poor prognosis [5, 10-12]. In view of the small sample size, in our study pCR and near pCR were combined in the statistical analysis. This can be justified in the light of research conducted by pathologists, surgical oncologists, medical oncologists and biologists from the University of Texas M.D. Anderson Cancer Center and Vall d’Hebron University Hospital, Barcelona [5, 10-12].

Table III. Comparison of pCR according to receptor subtypes, tumour grade and histopathological type in younger and older breast cancer patients (Fisher's 2-tailed exact test)

pCR according to receptor subtype	pCR/no pCR (in women aged 40 years and below)	Value of <i>p</i> in women aged 40 years and below	pCR/no pCR (in women aged 70 years and above)	Value of <i>p</i> in women aged 70 years and above
ER(-) vs. ER(+)	3/2 vs. 0/4	0.16	3/3 vs. 0/6	0.18
PR(-) vs. PR(+)	3/2 vs. 0/4	0.16	3/3 vs. 0/6	0.18
HER2(-) vs. HER2(+)	3/3 vs. 0/3	0.46	3/6 vs. 0/3	0.51
ER(-)PR(-) HER2(-) triple negative vs. other subtypes	3/1 vs. 0/5	0.047	3/1 vs. 0/8	0.018
pCR according to grade	pCR vs. no pCR (in women aged 40 years and below)	Value of <i>p</i> in women aged 40 years and below	pCR vs. no pCR (in women aged 70 years and above)	Value of <i>p</i> in women aged 70 years and above
G3 vs. G2, Gx	3/3 vs. 0/3	0.46	3/5 vs. 0/4	0.49
pCR according to histopathological type	pCR vs. no pCR (in women aged 70 years and above)		Value of <i>p</i> in women aged 70 years and above	
Invasive ductal vs. other types (lobular, mixed, mucinous)	3/6 vs. 0/3		0.5	

With respect to histological subtypes, it has previously been demonstrated that the pCR rate after primary chemotherapy is significantly lower in invasive lobular carcinoma, frequently characterized by high expression of steroid hormone receptors, when compared with the invasive ductal histotype [3, 13]. In our cohort of patients, both younger (≤ 40 years old) and older (≥ 70 years old), pCR in the breast and/or in the axilla was achieved in patients with invasive ductal breast cancer, which is in accordance with the literature [3].

Measures of high cell proliferation such as high grade also correlate with good response to neoadjuvant chemotherapy [14, 15]. In our study, all younger and older patients who achieved pCR or good partial response had G3 tumours. Our previous research on the characteristics of 101 breast cancer patients across the complete age range (30-78 years, median: 56.1 years), treated in our institution, also showed the highest rate of pCR in triple negative breast cancer patients, G3, with invasive ductal carcinoma [16]. These results mirror the characteristics of younger (≤ 40 years old) and older (≥ 70 years old) age groups in the present article. Although published breast cancer models stratified by age have shown disparities between younger and older women, with more favourable tumour biology in the latter [6, 7], the association of receptor-based subtypes (triple negative) with pCR rates was comparable in both age groups in our study. However, in view of the small sample size, we plan to study a more extensive cohort with special emphasis on the impact of pCR on survival in young and elderly patients. This is particularly important because, despite the highest rate of pCR in triple negative and HER2 positive tumours, those

with residual disease after neoadjuvant systemic treatment carry the worst overall survival, with a high relapse rate [17, 18]. One of the studied patients from the younger group, aged 40 years, with triple negative breast cancer, with a large residual tumour burden after completion of chemotherapy (AT) and mastectomy, developed massive lung metastases 3 months later (Table I). In view of this observation, it is vital to differentiate triple negative breast cancer patients with defective DNA repair similar to BRCA1-associated tumours that are sensitive to anthracyclines and resistant to taxane-based chemotherapy [19, 20].

In conclusion, we have concluded that pCR was significantly linked to receptor-based subtype in both young (≤ 40 years) and old (≥ 70 years) women. pCR rates were statistically significantly higher in triple negative breast cancer in both groups. Further studies are needed to incorporate multigene signatures within the receptor-based classification to predict chemosensitivity in the adjuvant setting [21] and to design targeted therapies in the genomic and proteomic era [22-24].

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