2459 Risk of CNS relapse following pathological complete response to neoadjuvant chemotherapy

L. M. Leite[1], G.R. de Almeida[1], M.C. Tavares[1], M.G. Cesca[1], F.B. Campos[1], F.A. Oliveira[1,2], D.M. Dornellas[1,3], E.F. Saldanha [1,4], P.T. Guimarães[1], D.D. Arruda[1], M.S. Held[1], R.L. Viana[1], F.G. Moura[1], S.K. Loose[1], S.F. Silva[1], R. Pirolli[1], C.A. Fogassa[1], B.R. Mattos[1], S.M. Sanches[1], V.C. Cordeiro de Lima[1]

[1] Department of Medical Oncology, A.C. Camargo Cancer Center, São Paulo, SP, Brazil, [2] Department of Medical Oncology, Instituto do Câncer de São Paulo (ICESP), São Paulo, SP, Brazil, [3] Department of Medical Oncology, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil, [4] Division of Medical Oncology and Hematology, Princess Margaret Cancer Center, University Health Network, University of Toronto, Toronto, Canada.

Contact: Luciana.leite@accamargo.org.br

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Introduction

Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) improved outcomes in breast cancer. However, systemic therapy has limited central nervous system (CNS) penetration, and pCR may not predict reduced risk of brain metastases. We evaluated CNS recurrence patterns in patients with or without pCR following NAC.

Methods

We conducted a retrospective study including all consecutive stage I-III breast cancer patients treated with NAC and surgery between 2007 and 2018 at A.C. Camargo Cancer Center. Breast cancer subtypes were defined by hormone receptor (HR) and HER2 status from pretreatment biopsies and pCR was defined as ypT0/is ypN0. The primary objective was the impact of pCR on the risk of CNS recurrences across breast cancer subtypes. The secondary objectives were patterns of CNS recurrence (brain/leptomeningeal only versus synchronic systemic and CNS metastasis), CNS recurrence-free survival (CNS-RFS) and overall survival after CNS metastasis. Fisher`s Exact test and Pearson's Chi-square test were used to evaluate differences in CNS across pCR status. Kaplan-Meier and regression analyses were performed. Two-tailed p-values<0.05 were considered significant.

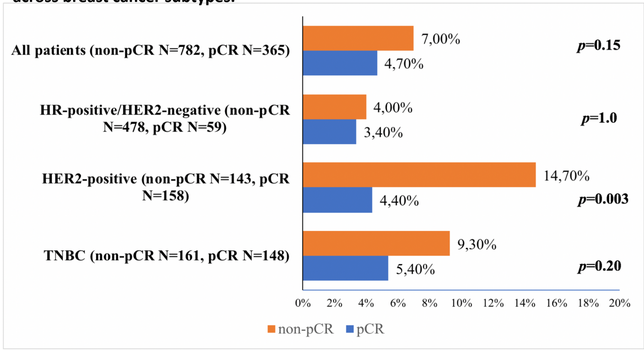
Results

Among 1147 patients treated with neoadjuvant chemotherapy, 537 patients had HR-positive/HER2-negative, 301 HER2-positive, and 309 triple-negative (TNBC) breast cancer. Median age was 45, most had ductal histology (84.7%), grade III (42.9%), and stage III (59.2%) carcinomas. 365 (31.8%) achieved pCR - 59/537(11%) HR-positive/HER2-negative, 158/301(52.3%) HER2-positive, 148/309(47.9%) TNBC. CNS recurrences according to pCR are shown in figure 1 and patterns of brain recurrence in figure 2. CNS-RFS was improved in HER2-positive patients with pCR but not in other subtypes (Figure 3A-D) . Median overall survival after CNS relapse was 12 months, and was highest in HER2-positive patients. Multivariate analysis identified HER2-positive and TNBC subtypes and cN2–3 status as independent predictors of CNS recurrence.

Table 1. Baseline characteristics of patients in the entire cohort and each immunohistochemical subgroup.

Characteristics	Total (N=1.147)	HR+/HER2- (N=537)	HER2+ (N=301)	TNBC (N=309)
Median age (range)	45 (23 – 90)	46 (24 – 82)	46 (23 – 82)	44 (24 – 90)
Menopausal status (%)				
Premenopausal	707 (61.6)	342 (63.7)	174 (57.8)	191 (61.8)
Postmenopausal	392 (34.1)	178 (33.1)	110 (36.6)	104 (33.7)
Perimenopausal	45 (4)	15 (2.8)	16 (5.3)	14 (4.5)
Male	3 (0.3)	2 (0.4)	1 (0.3)	0
cT (%)				
T1	33 (2.9)	13 (2.4)	5 (1.7)	15 (4.9)
T2	425 (37.1)	171 (31.9)	111 (36.9)	143 (46.3)
T3	339 (29.6)	166 (30.9)	89 (29.6)	84 (27.2)
T4	350 (30.4)	187 (34.8)	96 (31.8)	67 (21.6)
cN (%)				
N0	343 (29.9)	164 (30.5)	73 (24.3)	106 (34.3)
N1	538 (46.9)	255 (47.5)	153 (50.8)	130 (42.1)
N2	189 (16.5)	88 (16.4)	55 (18.3)	46 (14.9)
N3	77 (6.7)	30 (5.6)	20 (6.6)	27 (8.7)
Neoadjuvant therapy (%)				
Anthracycline/taxane	1090 (95)	519 (96.6)	270 (89.7)	301 (97.4)
Dose dense AC	379 (33)	149 (27.7)	67 (22.3)	163 (52.8)
Carboplatin	206 (18)	17 (3.2)	28 (9.3)	161 (52.1)
Trastuzumab	188 (16.4)	0	188 (62.5)	0
Trastuzumab + Pertuzumab	104 (9.1)	0	104 (34.5)	0
Radiotherapy (%)	1089 (94.9)	515 (95.9)	280 (93)	294 (95.1)
Surgery (%)				
Mastectomy	827 (72.1)	416 (77.5)	214 (71.1)	197 (63.8)
Breast conserving	320 (27.9)	121 (22.5)	87 (28.9)	112 (36.2)
Axillary dissection (%)	779 (67.9)	392 (73)	200 (66.4)	187 (60.5)

Figure 1. CNS recurrences by the degree of pathological response (pCR vs. non-pCR) across breast cancer subtypes.

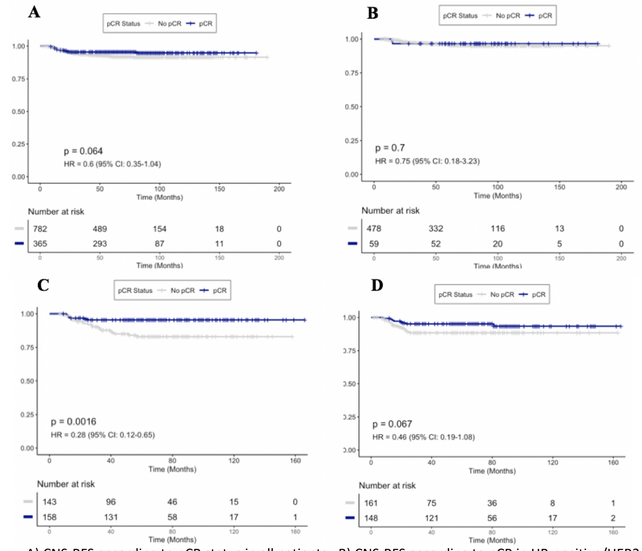


CNS recurrence occurred in a total of 72 patients. Twenty-one patients had HR-positive/HER2-negative tumors (pCR N=2 vs. non-pCR N=19), 28 patients had HER2-positive tumors (pCR N=7 vs. N=21 in non-pCR) and 23 TNBC patients (pCR N=8 vs. N=15 in non-pCR). pCR was defined as no invasive carcinoma in the breast and in axillary lymph nodes at the time of surgery. Frequencies were compared with Fisher's exact test or Chi-square test.

Figure 2. Patterns of brain recurrence according to breast cancer subtype and pCR (N=72).

Subtype		Isolated CNS recurrence	CNS plus systemic recurrence	Total CNS recurrences	*p*-value
All patients	pCR	14 (82.4%)	3 (17.6%)	17 (100%)	0.006
	non-pCR	24 (43.6%)	31 (56.4%)	55 (100%)	
HR-positive/HER2-negative	pCR	1 (50.0%)	1 (50.0%)	2 (100%)	1.0
	non-pCR	10 (52.6%)	9 (47.4%)	19(100%)	
HER2-positive	pCR	7 (100%)	0 (0.0%)	7 (100%)	0.007
	non-pCR	8 (38.1%)	13 (61.9%)	21 (100%)	
TNBC	pCR	6 (75.0%)	2 (25.0%)	8 (100%)	0.19
	non-pCR	6 (40.0%)	9 (60.0%)	15 (100%)	

Figure 3. CNS-RFS according to breast cancer subtype and pCR status.



A) CNS-RFS according to pCR status in all patients; B) CNS-RFS according to pCR in HR-positive/HER2-negative; C) HER2-positive; and D) TNBC.

Conclusion

Pathological complete response was not associated with reduced CNS recurrence overall, but was linked to a lower risk of CNS relapse in HER2-positive breast cancer. Isolated CNS relapse was the predominant pattern, suggesting a sanctuary effect.

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