GOCS

GRUPO ONCOLÓGICO COOPERATIVO DEL SUR

Sixteen years follow-up results of a randomized phase II trial of neoadjuvant FAC compared with CMF in stage III breast cancer.

A. O. Zwenger[1], J. Leone [1, 2], C. T. Vallejo[2], J. E. Perez[3], A. O. Romero[3], M. R. Machiavelli[3], L. Romero Acuña[4], M. E. Dominguez[5], M. Langui[4], H. M. Fasce[6], B. A. Leone[2], E. Ortiz[7], J. P. Leone[8], J. Iturbe[1, 2].

Poster # 22H
Abstract #1073

Background

Neoadjuvant chemotherapy (NAC) is a standard treatment for locally advanced and inflammatory breast cancer but it has also become an alternative option for early stages of disease. The preoperative use of chemotherapy has considerable advantages including the direct assessment of the tumor's sensitivity to therapy, the early eradication of systemic micrometastatic disease, and the possibility of performing breast conserving therapy in women who might otherwise need a mastectomy.

The management of locally advanced breast cancer remains challenging, with high rates of locoregional and distant recurrences and significant morbidity and mortality. Moreover, a subset of patients fails to respond or even show tumor progression to NAC.

The use of chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was first described by Bonadonna et al. in the adjuvant setting.[1] Another commonly used chemotherapy regimen consisted of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC).[2] A prospective randomized study described an objective response rate of 71% for CMF in the neoadjuvant setting,[3] whereas another study conducted at our institution showed similar results with the use of FAC.[4]

Based on this data, we developed a randomized phase II study to compare FAC vs CMF at doses intensity of equivalent activity in the neoadjuvant setting for patients with locally advanced breast cancer.

Objective

The aim of this study was to describe long-term results of FAC vs CMF neoadjuvant chemotherapy in stage III breast cancer patients (pts).

Primary endpoints were:

- Response rate.
- Toxicity.

Secondary endpoints were:

- Breast conservative surgery after NAC.
- Locoregional control rate.
- Disease-Free Survival (DFS).
- Overall Survival (OS).

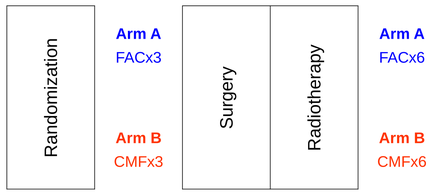
Materials and Methods

Patient selection

Elegiblility criteria:
- Histologic diagnosis of breast cancer by trucut needle biopsy.
- Stage III disease according to UICC criteria.
- Measurable disease.
- Performance-status (ECOG-Zubrod) ≤2.
- Adequate bone marrow, renal and liver function.

Ineligibility criteria:
- Inflammatory breast cancer.
- Prior systemic, radiation or surgical therapy.
- Synchronous bilateral breast cancer.
- Evidence of myocardial dysfunction.

Study design



Evaluation of treatment

Before treatment:
- Complete history and clinical examination.
- Histological diagnosis.
- TNM stage (UICC).
- Performance-status (ECOG-Zubrod).
- Menopausal status.
- Hormonal receptor status.
- Laboratory: complete blood count, liver and renal function, glycemia, kalemia, alkaline phosphatase, lactic dehydrogenase.
- Imaging: Bilateral mammography, chest X-ray, bone scan, hepatic ultrasound or computed tomography, echocardiogram.

During treatment:
- Monthly complete physical exam.
- Weekly CBC and complete biochemical profile before each cycle of CT.
- Tumor assessment every 3w.
- Repeated mammogram and ultrasound after the first 3 cycles for tumor assessment.
- Repeated echocardiogram every three treatment cycles in Arm A.

Follow-up:
- Complete history and physical exam every 3m for the first two years; and complete metastatic survey every 6m during the first two years; then patients were assessed at least twice a year to date.

Treatment modality*

		Dose mg/m2	Form	Days	Cycles every
Arm A	5-Fluorouracil	500	IV	1 and 8	21d
	Adriamycin	50	IV	1	
	Cyclophosphamide	500	IV	1	
Arm B	Cyclophosphamide	600	IV	1 and 8	28d
	Methotrexate	40	IV	1 and 8	
	5-Fluorouracil	600	IV	1 and 8	

*: after chemotherapy pts with hormone-sensitive tumors received tamoxifen 20mg/day for 5y in both arms. All pts received adjuvant radiation therapy.

Treatment results

Endpoint assessment:
- Patients were considered evaluable for response if they had received at least 3 cycles of CT.

Response criteria:
- Standard WHO response criteria were considered.

Survival:
- **Diseases-free survival** was recorded from the start of therapy until the date of local or distant recurrence.
- **Overall survival** was estimated from the start of therapy until death, or date of last follow-up for those that continue alive. Comorbid death was handled as if patients were withdrawn alive.

Toxicity evaluation:
- Toxicity was evaluated according to WHO criteria.

Statistical methods

Differences in proportions were assessed by means of the Chi square test and exact Fisher's test was used when it was appropriate. Distribution of disease free survival and overall survival were estimated by the method of Kaplan and Meier, and differences between treatment groups evaluated by the logrank test.

Results

Between August 1995 and April 2004, 131 patients with stage III breast cancer were accrued, five of these patients were randomized but subsequently excluded from analysis because of major violation of protocol. The remaining 126 patients were fully eligible to evaluate the efficacy of neoadjuvant treatment with FAC or CMF. The median of age was 52 years (range: 24-75) and median follow-up was 6.4y (95%CI: 4.5-8.6).

Patients Characteristics

		Arm A (%) n=64	**Arm B** (%) n=62
Age (years)		51.2±1.4	54.5±1.5
Menopausal Status	Pre	28 (44)	17 (27)
	Post	36 (56)	45 (73)
Breast Surgery	Conservative	9 (14)	8 (13)
	Mastectomy	51 (80)	52 (84)
	No surgery	4 (6)	2 (3)
Average Number of LN Resected		16.0	15.4
Mean Number of Positive LN		4.9	6.0
Tumor Grade	1	1 (2)	5 (8)
	2	23 (36)	19 (31)
	3	30 (47)	29 (47)
	Unk	10 (16)	9 (14)
HistologicType	Ductal	52 (81)	52 (84)
	Other	12 (19)	10 (16)
Mean Tumor Diameter (mm)		37.1±3.0	40.7±2.9
ER Status	Pos	38 (59)	38 (61)
	Neg	20 (31)	19 (31)
	Unk	6 (10)	5 (8)
PR Status	Pos	31 (48)	25 (40)
	Neg	27 (42)	32 (52)
	Unk	6 (10)	5 (8)
TNM	IIIA	28 (44)	31 (50)
	IIIB	36 (56)	31 (50)

Haematological toxicity (WHO grade 3-4 toxicity)

	Arm A (%)	**Arm B** (%)	P
Anemia	1 (2)	3 (6)	NS
Leukopenia	16 (28)	24 (44)	NS
Neutropenia	26 (45)	30 (56)	NS
Thrombocytopenia	4 (7)	13 (24)	0.0114

Non-haematological toxicity (WHO grade 3-4 toxicity)

	Arm A (%)	**Arm B** (%)	P
Nausea/vomiting	4 (7)	11 (20)	0.0364
Alopecia	32 (55)	9 (17)	<0.0001
Diarrhea	-	2 (4)	NS
Cardiac	-	-	-

Clinical Response (%)

		Arm A IIIA	IIIB	Total	**Arm B** IIIA	IIIB	Total	P
CR		4 (14)	3 (8)	7 (11)	1 (3)	2 (6)	3 (5)	NS
Histologic response	Negative pathology (pCR)	2 (7)	2 (6)	4 (6)	-	-	-	
	DCIS	1 (4)	-	1 (2)	1 (3)	-	1 (2)	
	Invasive cancer	1 (4)	1 (3)	2 (3)	-	2 (6)	2 (3)	
PR		15 (54)	17 (47)	32 (50)	17 (57)	20 (64)	37 (61)	
SD		6 (21)	15 (42)	21 (33)	12 (37)	9 (29)	21 (33)	
PD		3 (11)	1 (3)	4 (6)	1 (3)	-	1 (2)	
OR (CR+PR)				39 (61)			40 (66)	NS

Pathological Tumor down staging

Arm A Clinical Tumor Status **Before** NAC	N pts	Pathological Tumor Status **After** NAC **pT0-pTis**	**pT1**	**pT2**	**pT3**	**Arm B** Clinical Tumor Status **Before** NAC	N pts	Pathological Tumor Status **After** NAC **pT0-pTis**	**pT1**	**pT2**	**pT3**
cT1-2	3	0	0	3	0	**cT1-2**	7	0	2	4	1
cT3	27	**4**	**7**	**10**	6	**cT3**	32	**2**	**3**	**18**	9
cT4	30	**1**	**5**	**19**	**5**	**cT4**	21	**0**	**4**	**15**	**2**

Pathological LN down staging

Arm A Clinical LN Status **Before** NAC	N pts	Pathological LN Status **After** NAC **pN0**	**pN1**	**pN2**	**pN3**	**Arm B** Clinical LN Status **Before** NAC	N pts	Pathological LN Status **After** NAC **pN0**	**pN1**	**pN2**	**pN3**
cN0	8	0	6	1	1	**cN0**	5	3	1	1	0
cN1	31	**12**	7	5	7	**cN1**	31	**8**	10	7	6
cN2	21	**4**	**6**	6	5	**cN2**	24	**3**	**6**	9	6

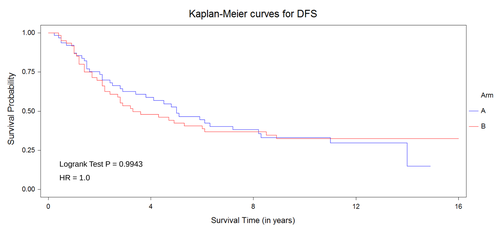
Correlation between Primary Tumor and LN response

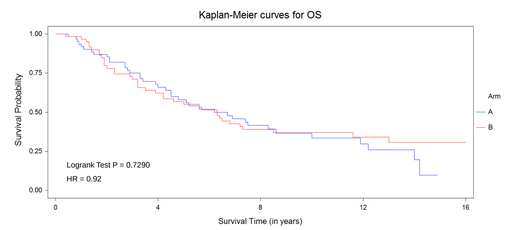
Arm A Pathological Response of **Primary Tumor**	N pts (%)	Pathological **LN** Status **N pts LN-**	**MeanLN+**	P	**Arm B** Pathological Response of **Primary Tumor**	N pts (%)	Pathological **LN** Status **N pts LN-**	**MeanLN+**	P
MRPT*	4 (7)	3	2.2	0.047	**MRTP**	-	-	-	NS
mRPT# (CR + PR)	33 (57)	10	3.3		**mRPT** (CR + PR)	40 (68)	9	6.2	
mRPT (SD)	19 (34)	3	6.9		**mRTP** (SD)	19 (32)	5	5.6	

*MRPT: Maximal Response Primary Tumor (pCR).
#mRPT: minimal Response Primary Tumor.

Summary of Results

		Arm A (%)	**Arm B** (%)	p
Locoregional Recurrence	No	57 (89)	56 (90)	NS
	Yes	7 (11)	6 (10)	
Contralateral Breast Cancer	No	63 (98)	58 (93)	NS
	Yes	1 (2)	4 (6)	
Distant Recurrence	No	35 (55)	27 (43)	NS
	Yes	29 (45)	35 (57)	
	Soft tissue only	3 (5)	11 (18)	NS
	Bone only	10 (16)	11 (18)	
	Visceral only	7 (11)	5 (8)	
	Multiple sites	9 (14)	8 (13)	
Median DFS (years)		5.1	3.3	NS
Median OS (years)		6.7	6.3	NS
Status	Alive	28 (44)	25 (40)	NS
	Dead	36 (56)	37 (60)	
Cause of Death	Tumor progression	30 (79)	32 (84)	NS
	Other causes	6 (21)	5(16)	





Conclusions

To the best of our knowledge, this is the first study to report long-term outcomes of FAC and CMF in the neoadjuvant setting. Within the sensitivity of our study, both regimens showed similar OR, long-term toxicity, DFS and OS rates at 16 years. After 5 years of follow-up, the hazard of death seems to decline (nearly 40% of pts are still alive), a finding that is similar to what has been reported for other regimens.

Bibliography

1. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-10, 1976.
2. Buzdar AU, Blumenschein GR, Smith TL, et al: Adjuvant chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide, with or without Bacillus Calmette-Guerin and with or without irradiation in operable breast cancer. A prospective randomized trial. Cancer 53:384-9, 1984.
3. Cocconi G, di Blasio B, Bisagni G, et al: Neoadjuvant chemotherapy or chemotherapy and endocrine therapy in locally advanced breast carcinoma. A prospective, randomized study. Am J Clin Oncol 13:226-32, 1990.
4. Machiavelli MR, Romero AO, Perez JE, et al: Prognostic significance of pathological response of primary tumor and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. Cancer J Sci Am 4:125-31, 1998.

[1]Hospital Provincial Neuquén, [2]Unidad Oncológica del Neuquén, [3]Centro Radioterapéutico de Excelencia Oncológica de Bahía Blanca, [4]Centro Oncológico del Litoral de Santa Fe, [5]Centro Oncológico de Tres Arroyos, [6]Hospital Alejandro Korn de La Plata, [7]Centro Oncológico Infinito de La Pampa, [8]University of Pittsburgh, Department of Medicine.