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Neoadjuvant systemic therapy in breast cancer

KEYWORDS: Breast Neoplasms; Neoadjuvant Therapy; Antineoplastic Agents

Primary breast cancer is recognized as a systemic disease rather than a local disease. Acceptance of these views has led to two major changes in the management of breast cancer. The first is conservative surgery rather than mastectomy for patients with small cancers and the second is the use of adjuvant systemic therapy given immediately after surgery to try to control clinically undetectable micrometastases.

Neo-adjuvant systemic treatment is the next step in managing breast cancer as a systemic disease. In animal models, when systemic chemotherapy precedes the surgical resection of transplantable tumor, it prevents the kinetic perturbation associated with the tumor removal and survival is optimized. Thus, it is possible that neoadjuvant therapy may result both in better local and systemic disease control (1).

The main intentions of neo-adjuvant systemic therapy are: (a) to make non-operable tumors operable, (b) to achieve breast conservation or (c) to select sensitivity for specific treatment by using specific biomarkers.

RESULTS OF NON-RANDOMIZED STUDIES WITH CHEMOTHERAPY

During 1980's and 1990's, most neoadjuvant protocols included CMF or anthracycline - containing regimens. The median overall response rate was around 70-80%. However, a median clinical response was approximately 50% and pathological complete response 17% (2-6).

During the late 1990's and after the year 2000 a number of taxane-containing regimens appeared in the literature as neoadjuvant setting. From these trials, the clinical complete response rate was around 40% and the pathological complete remission rate was no more than 20% (Table 1) (7-11).

RESULTS OF NON-RANDOMIZED STUDIES WITH ENDOCRINE THERAPY

Early studies with tamoxifen involved small numbers of patients and were designed to avoid mastectomy in elderly or unfit patients with operable breast cancer. These trials showed that an overall objective response could be achieved in 33-67% of the patients. However, the time to achieve a response could be as long as nine months (12-16).

Third generation aromatase inhibitors (anastrozole, letrozole or exemestane) were tested in small non-randomized studies and all have resulted in rates of tumor regression higher than those previously seen with tamoxifen. Also, 59-67% breast conservation rates have been observed (Table 2) (17-19).

Table 1. Results of non-randomized studies with chemotherapy

Publication	Stage	No pts	Neoadjuvant Rx	cCR (%)	pCR (%)
1980's and 1990's					
JNCI, 1990(2)	T>3cm	161	CMF x3-4, FAC x3-4	17	4
EJC, 1995(3)	III	125	FACx3	10	3.5
JCO, 1995(4)	T>3cm	50	Ecis Fx8	66	NR
ASCO, 2000(5)	T>3cm	426	Ecis F or AC	34	NR
EJC, 1997(6)	High-risk	50	ACVF	51	30
Late 1990's and >2000					
Semin Oncol 1997(7)	T2-3, LABC	41	AT	NR	5
ASCO, 1999(8)	T2-3,	180	AT	14	16
	N0-1	67	AC	9	10
ASCO, 2002(9)	T>2cm	270	AT → CMF	27	23
EJC, 2002(10)	III	28	T	11	8
Ann Oncol, 2002(11)	III	232	AT	20	17

cCR=clinical complete response, pCR=pathological complete response, CMF=cyclophosphamide, methotrexate, fluorouracil, FAC=fluorouracil, adriamycin, cyclophosphamide, EcisF-epirubicin, cisplatin, fluorouracil, AC=adriamycin, cyclophosphamide, ACVF=adriamycin, cyclophosphamide, vinorelbine, fluorouracil, AT=adriamycin, taxol, LABC=locally advanced breast cancer

Table 2. Results of non-randomized studies with hormonal therapy

Publication	Age	Stage	No pts	cCR (%)	cPR (%)	cPR (%)
TAMOXIFEN						
Clin Oncol, 1983(12)	>70	T1-3	161	27	34	24
BMJ, 1983(13)	>70	T1-3	53	55	26	11
Eur J Surg Oncol, 1991(14)	>70	-	100	40	28	-
Br Ca Res Treat, 1995(15)	>75	-	85	14	23	46
Neoplasma, 1996(16)	>70	-	120	10	38	44
AROMATASE INHIBITORS						
Br Ca Res Treat, 2002(17)	-	LABC	83	-	78 (overall)	-
ASCO, 2003(18)	-	III A/B	112	54.5	28.6	17
ASCO, 2004(19)	-	T2-4α-b	55	2	48	48

cCR=clinical complete response, cPR=clinical partial response, SD=stable disease, LABC=locally advanced breast cancer

RESULTS OF RANDOMIZED NEOADJUVANT STUDIES COMPARING DIFFERENT CHEMOTHERAPY REGIMENS

The results from several randomized studies are listed in Table 3 (5,20-26).

Table 3. Results of randomized studies comparing different chemotherapy regimens (selected trials)

Publication	No pts	Regimens	Responses %		Mastectomy rates %
			pCR	Overall	
Proc ASCO, 2000(5)	210	AC	-	75	66
	211	EcisF	-	77	77
Proc ASCO, 2003(20)	205	VE	15	62	38
	206	AC	15	57	35
Proc ASCO, 2003(21)	111	FAC	-	67	-
		CMF	-	67	-
Ann Oncol, 2000(22)	247	FAC	-	No	-
		FTC	-	difference	
JCO, 1999(23)	174	T	8	80	80
		FAC	17	79	79
Proc ASCO, 1999(24)	180	AT	16	83	56
	67	AC	10	66	45
Br Cancer Res Treat,	103	FAC	9.6	82	26
2002(25)		AT	25.4 (p=0.003)	84	35 (p=0.08)
Proc ASCO, 2002(26)	286	AC	12	78	-
		AD	8 (NS)	88 (NS)	

AC=adriamycin, cyclophosphamide, EcisF=epirubicin, cisplatin, fluorouracil, VE=vinorelbine, epirubicin, FAC=fluorouracil, adriamycin, cyclophosphamide, CMF=cyclophosphamide, methotrexate, fluorouracil, FTC=fluorouracil, thiotepa, cyclophospamide, T=taxol, AT=adriamycin, taxol, AD=adriamycin, docetaxel.

Results of selected large studies comparing different chemotherapy regimens showed that the combination of anthracyclines and taxanes improve response rates and consequently breast conservative surgery rates. Nevertheless, the potential toxicity especially neutropenia should also be taken into account. However, the final impact on outcome remains largely unknown. For the time being it may be reasonable to restrict the use of anthracycline - taxane com-

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binations in selected patients such as young women with poor prognostic factors.

RESULTS OF RANDOMIZED NEOADJUVANT STUDIES WITH HORMONAL THERAPY

The results of selected randomized neoadjuvant trials comparing tamoxifen versus aromatase inhibitors are depicted in Table 4 (27-30).

Table 4. Results of randomized studies comparing tamoxifen versus aromatase inhibitors (selected trials)

Publication	Drug studied	No pts	Responses %		Surgery
			Clinical	U/S	feasibility %
Ann Oncol, 2001(27)	Letrozole	154	55	35	45
	Tamoxifen	170	36	25 (p=0.042)	35 (p=0.022)
JCO, 2001(28)	Anastrozole	113	37	24	46
	Tamoxifen	108	36	20	22
	Both	109	39 (NS)	28 (NS)	26
Breast Can Res Treat,	Anastrozole	87	70	44	-
2003(29) (ATAC STUDY)	Tamoxifen		44.4	30	-
	Both		44.9	32 (p=0.072)	-
Breast Can Res Treat,	Exemestane	36	NS	NS	38.7
2003(30) (IMPACT STUDY)	Tamoxifen	37			10.8 (p=<0.05)

U/S = ultrasound, NS=non-significant

RESULTS OF RANDOMIZED NEOADJUVANT VERSUS ADJUVANT CHEMOTHERAPY STUDIES

In a recent metanalysis, all eligible trials comparing preoperative to postoperative chemotherapy were reported (Table 5) (31).

Table 5. Results of randomized neoadjuvant versus adjuvant chemotherapy studies

Publication	No pts	Stage	Regimens	Responses %		
				cCR	cPR	pCR
Chirurgie, 1998(32)	272	T2-3, N0-1	EVM, MTV	33	30	-
Ann Oncol, 1994(33)	271	IIB, IIIA	TMF	12	57	29
Eur J Cancer, 1994(34)	390	T2-3, N0-1b	FAC	24	42	-
Ann Oncol, 1998(35)	293	T0-4, N0-1	MMM/TAM	22	61	7
JNCI, 2001(36)	1493	T1-3, N0-1	AC	36	43	13
Ann Oncol, 2001(37)	210	T1-4, N0-2	MMM/Gsr, Frm	25	26	-
JCO, 2001(38)	698	T1c-4b, N0-1	FFC	7	42	4
Ann Surg Oncol, 2003(39)	53	II	FLAC	65	12	20

cCR=clinical complete response, cPR=clinical partial response, pCR=pathological complete response, EVM=epirubicin,vincristine, methotrexate, MTV=mitomycin, thiotepa, vindesine, TMF=thiotepa, methotrexate, fluorouracil, FAC=fluorouracil, adriamycin, cyclophosphamide, MMM/TAM=mitroxantrone, mitomycin, methotrexate/tamoxifen, AC=adriamycin, cyclophosphamide, Gsz=goserelin, Frm=formestane, FEC=fluorouracil, epirubicin, cyclophosphamide, FLAC=fluorouracil, leucovorin, adriamycin, cyclophosphamide

In this report, it was found no statistically or clinically significant difference between neoadjuvant and adjuvant therapy arms associated with death (RR = 1.00), disease progression (RR=0.99) or distant disease recurrence (RR=0.94). However, neoadjuvant therapy was statistically significant associated with an increased risk of locoregional disease recurrences (RR=1.22) compared with adjuvant therapy, especially in trials where more patients in the neoadjuvant than the adjuvant arm received radiation therapy without surgery (RR=1.53) (32-39).

RESULTS OF TRASTUZUMAB INCORPORATION INTO NEOADJUVANT SETTING

The optimal neo-adjuvant regimen for treatment of HER2-amplified breast cancer has not yet been defined.
Promising results have been observed in patients who received neoadjuvant trastuzumab in combination with a taxane, although full evaluations from randomized studies are pending (40-42).

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