The Role of Hormonal Therapy for Premenopausal Women, WithEarly Stages Hormone Receptor Positive Breast Cancer

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Abstract
Aim: *To highlight Tamoxifen and ovarian suppression as effective adjuvant approaches for premenopausal steroid receptor-positive breast cancer. In addition to encourage surgeons toward breast-conserving surgery with this effective adjuvant approaches.*
Patients and Methods: *Premenopausal women with early stages, steroid hormone receptor–positive breast cancer, 100 selected patients, for retrospective study were randomly assigned to six or eight cycles of chemotherapy. Followed by two years of monthly Goserelin, and daily Tamoxifen for five years. The primary endpoints were time to recurrence (TTR) for Tamoxifen alone therapy versus combined Tamoxifen and Goserelin therapy.*
Results: *With two year follow-up, the combination of Tamoxifen and Goserelin show improved time to recurrence (TTR).*
Conclusion: *Combination of Tamoxifen and Goserelin improves outcome for premenopausal stage1, II and IIIA, hormone receptor-positive breast cancer.*

Key words: *Brest cancer, Tamoxifen, Goserelin*

Introduction:

Despite local treatment, up to 50% of women with early-stage breast cancer die of metastatic disease in the absence of adjuvant systemic therapy. Older trials conductedseveral decades ago suggested that ovarian ablation by surgery or radiation could reduce the risk of recurrence in premenopausal women younger than 50 years. Furthermore,

individual trials of adjuvant chemotherapy demonstrated improved recurrence-free and overall survival for premenopausal womenwith node-positive breast cancer. In 1985,the results from these initial trials were first combined in a meta-analysis of all randomized trials of adjuvant ovarian ablation or chemotherapy. This analysis unequivocally demonstrated the benefit of adjuvant chemotherapy in premenopausalwomen with node-positive breast cancer. This combined analysis also demonstrated improved outcome for younger women treated with ovarian ablation. Finally, in other studies, the equivalence of oophorectomy and chemical ovarian suppression by chronic administration of luteinizing hormone-releasing hormone agonists for treatment of premenopausalwomen with steroid receptor–positivemetastatic breast cancer wasdemonstrated.(1)

Premenopausal status was defined by any one of the following; less than 4 months since

last menstrual period, 4 to 12 months since last menstrual period with premenopausal FSH level, or less than 61 years of age with a previous ovary-sparing hysterectomy and premenopausal FSH level(2). Hormones play an important role in the development and progression of breast cancer. Estrogen and its metabolite and other steroid hormone like progesterone all have been shown to have an effect .breast cancer risk is related to estrogen exposure over time. Patients with hormone receptor- positive tumors survive (2-3 times longer than patients with hormonal receptor-negative tumors (3).

Patients with tumor negative for both

estrogen and progesterone receptor are not considered candidate for hormonal therapy. Tumor positive for both receptor have higher response rate (>50%) to endocrine therapy than those not expressed estrogen and progesterone receptor (<10%). Tumor positive for one receptor but not the other has an intermediate response rate of 33%.The determination of estrogen and progesterone receptor status used to require biochemical evaluation of fresh tumor tissue. Hormone receptor status should be ascertained for both premenopausal and postmenopausal patient to identify patients who are most likely to benefit from endocrine therapy. Hormones receptors are detectable in more than 90%of well differentiated ducal and lobular invasive breast cancer(3).Positive ER and PR were defined as (10 fm/mg) protein by biochemical assay or positive immunohistochemistry according to individual laboratory standards(4, 5).

Hormonal Therapy**;** Tamoxifen (Nolvadex®), is a competitive antagonist of the estrogen receptor in breast tissue via its active metabolite, Hydroxytamoxifen.Tamoxifen causes cells to remain in the G_0 and G_1 phases of the cell cycle. Because it prevents (pre)cancerous cells from dividing but does not cause cell death, tamoxifen is cytostatic rather than cytocidal. In other tissues such as the endometrium, it behaves as an agonist, and thus may be characterized as a mixed agonist/antagonist. Tamoxifen is the usual endocrine (anti-estrogen) therapyfor hormone receptor-positive breast cancerin pre-menopausal women, and is also a standard in post-menopausal women although aromatase inhibitors are also frequently used in that setting(6). Goserelin (Zoladex®)(6); is a synthetic analogue of a naturally occurring luteinizing-hormone releasing hormone (LHRH).It rapidly binds to the LHRH receptor cells in the pituitary gland thus leading to an initial increase in production of luteinizing hormone and thus leading to an initial increase in the production of corresponding sex hormones. Eventually,after a period of about 14–21 days, production of LH is greatly reduced due to receptor down regulation, and sex hormones are generally reduced to castrate levels.This drug is givenas (1to3) monthlysubcutaneous injection.

Patients and methods; this is a retrospective study implicating premenopausal women with operable invasive stage1, II and IIIA, estrogen and/or progesterone receptor (ER and/or PR) positive breast cancer. Involving no, one or more axillary lymph nodes by conventional histology were eligible for the study. For the period from January 2010 to January 2012,

100 patients in Marjan teaching hospital, oncology unit, in Al Hilla Province, wereenrolled. The staging of breast cancer is asin table (1).

Table (1): staging of breast cancer

Stage	T	N	M
Stage 0	Tis	N 0	M 0
Stage I	T 1	N 0	M 0
Stage IIA	T 0	N 1	M 0
	T 1	N 1	M 0
	T 2	N 0	M 0
Stage IIB	T 2	N 1	M 0
	T 3	N 0	M 0
Stage IIIA	T 0	N 2	M 0
	T 1a	N 2	M 0
	T 2	N 2	M 0
	T 3	N 1	M 0
	T 3	N 2	M 0
Stage IIIB	T 4	N 0	M 0
	T 4	N 1	M 0
	T 4	N 2	M 0
Stage IIIC	*Any* T	N 3	M 0
Stage IV	*Any* T	*Any* N	M 1

All patients received appropriate local therapy with modified radical mastectomy and underwent axillary dissection. Womenwere excluded if they had bilateral breast malignancies, locally advanced breastcancer, pregnant, lactating, or metastases. Staging before random assignment included normal chest x-ray, abdominal ultrasound and blood studies for hematologic, hepatic and renal function. After stratification by number of positive axillary lymph nodes (1 to 3 or 4 to 9), hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR+), and time since primary surgery (6 weeks), patients were assigned to receive (6 or 8) cycle chemotherapy, followed by Goserelin and Tamoxifen. . Patients assigned to receive Goserelin, received a 3.6 mg depot subcutaneouslyevery4 weeks for 5 yearsbeginning on cycle 6 or 8, day 29 of chemotherapy. Patients randomly assigned to receive Goserelin plus Tamoxife also took Tamoxifen 10mg PO/ bid for 5 years beginning on cycle 6 or 8, day 29 of chemotherapy.

Statistical terms; Time To Recurrence (TTR); is defined as time from random assignment to disease recurrence or new breast cancer primary, where death without recurrence was censored(7).

Disease-Free Survival (DFS); is defined as time from random assignment to disease recurrence, new breast cancer primary, or death, whichever occurred first(7).

Overall Survival (OS)(7); is defined as time from random assignment to death.

Hazard ratio (HR); Measure of how oftena particular event happens in one group, compared to how often it happens in another group, over time. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio greater than one or less than one means thatsurvival was better in one of the groups(8).

RESULTS*:*

Patient Selection andCharacteristics; Between Jan. 2010 andJan. 2012,100 patients were selected. Thepatient's characteristics were distributedaccording to the following

tables:

Table (2): Demographic distribution.

	Number of patients
Age <40	39
>40 years	**61**
Marital status Married	**87**
unmarried	**13**
Parity status Para	**81**
Null Para	**6**

Table (3): General characteristics of tumors

	Number of patients
No. of LN N0(0)	**38**
N1(1-3)	**40**
N2(4-9)	**22**
Tumor size T1(<2cm)	**30**
T2(2-5cm)	**70**
Stages: Stage I	**14**
Stage II	**64**
Stage IIIA	**22**
Receptor status: ER+/PR+	**90**
ER-/PR+	**7**
ER-/PR-	**3**

Patient's characteristics were assigned across treatment groups (Table 4).

Table (4): characteristics of selected patients.

Patients characteristics	No. of Patients on Tamoxifen	%	No. of patients on Tamoxifen + Goserelin	%	l number of patients	%
No. of nodesN0(0)	25	37	13	38	38	38
N1(1-3)	27	40	13	38	40	40
N2(4-9)	14	21	8	23	22	22
Age=<40	18	27	21	61	39	39
>40	48	72	13	38	61	61
ER/PR Status	57	86	33	97	90	90

ER+/PR+						
ER-/PR+	6	9	1	2	7	7
ER+/PR-	3	4	0	0	3	3
Tumor size(cm)T1(<2)	17	25	13	38	30	30
T2(2-5)	49	74	21	61	70	70
Total	66		34		100	

Outcomes; With a follow-up for recurrence- free period of 6 months (as a minimum) to24 months (as a maximum) of patients still alive on January, 2012 there have been 5recurrences, no significant events and no deaths. Because there is no deaths in thispresented study, DFS and OS have excluded statistically from the outcome due to lack of comparison. Sites of and times to recurrence
in relation to patient characteristics are shown in Table 5.
The use of combination of Tamoxifen and Goserelin will significantly improve TTR, when compared with Tamoxifen alone treatment, especially when hazard ratio was adjusted for age, nodal status, ER/PR status, and tumor size. Table 6.

Table (5): Sites &times of recurrence and patients characteristics

No.of patient	Site(s)	Age (years)	Stage	Grade	ER/PR Status	Tamoxifen alone	Tamoxifen + Goserelin	TTR /mon
1	Local+liver	25	T2N0	2	ER^+/PR^-	Yes	No	6
1	Lt.pleural effusion	37	T2N2	1	ER^+/PR^+	Yes	No	12
1	Rt. pleural effusion	46	T2N2	2	ER^+/PR^+	Yes	No	12
1	Ipsilateral axillary and supraclavicular LN	43	T2N1	2	ER^+/PR^+	Yes	No	8
1	Local	43	T2N2	2	ER^+/PR^+	Yes	Yes	6

Table (6): Treatment effect and patient characteristics

Patient characteristics	Tamoxifen + Goserelin vs.Tamoxifen HR	CI
Age<40TTR	*	0
Age>40TTR	1.85	(0.85- 3.99)
NodesN0TTR	*	0
N1TTR	*	0
N2TTR	0.88	(0.105- 7.308)
ER/PR Status ER+/PR+TTR	0.58	(0.199- 5.014)
ER-/PR+TTR	**	
ER+/PR-TTR	***	
Tumor sizeT1TTR	**	
T2TTR	0.58	(0.07_4.77)

*No recurrence at Tamoxifen–Goserelin group (combined treatment is the best).
**No recurrence in both treatment groups.
***For patients with ER+/PR-, there is no patient took the Tamoxifen-Goserelin treatment (nonumber).The landmarks (*, **) mean HR for TTR cannot be adjusted for patient characteristics; however,TTR is significantly improved with combined treatment.

limitations; Unfortunately, this study lacks the real and accurate statistics about the patient compliance and side effects of treatment because of the difference and irregularity in time and places of patient attendance and lack of documentation, especially with Tamoxifen which is given as an outpatient treatment. However, in general, the compliance was accepted and there were no serious adverse effects of treatment.

Discussion; The role of the hormonal therapy is evaluated through a randomly assigned study of Tamoxifen alone and combined Tamoxifen –Goserelin treatment in premenopausal women with stage 1,II and IIIA, steroid hormone receptor-positivebreast cancer.

The results obtained from this study showed that combined Tamoxifen-Goserelin therapy significantly improved TTR when compared with Tamoxifen therapy alone, especially in women lessthan 40 years, while those more than 40 years show no benefit from the addition of Goserelin. Similar results were obtained from Davidson et al(7),where addition of combined Tamoxifen-Goserelin therapy following full course of chemotherapy will significantly improve outcome(hazard ratiofor TTR=0.75 for those patient less than 40years and hazard ratio for TTR=1 for those more than 40 years). Therefore, the selection of premenopausal women was the major strength of this study as those patients are most likely to get benefit from this treatment modality. The selection was restricted to the patients with steroid hormone receptor positive tumors as they are most likely to benefit from the hormonal therapy. This is supported by results of trial of Bardou V, Arpino G. et al.(5),where patients with ER+ve / PR+ve breast cancer had great benefit from adjuvant endocrine therapy(hazard ratio for TTR =0.78).In our current study, there is one of five recurrences, which is ER+ve / PR-ve disease on Tamoxifen only therapy, which heralded the prognostic significanceof progesterone receptors as this is shown by trial of Fernoet al studies involving patients with ER+/PR+ breast cancer which show significant improvement with Tamoxifen therapy for 5 years, compared with those have ER+/PR- tumor.

Further, all patients randomly assigned for axillary lymph nodes status; whether they are negative(N0), or positive (N1 or N2), a subset group of patients has higher recurrence rate show significant improvement in TTR. By comparing with trial of Davidson etal(7)study showed no difference in improvement of TTR for patients with N0 disease given Tamoxifen alone treatment (HHR= 1), while patients with N1 and N2 disease given Tamoxifen alone showed noimprovement in TTR (HR=1.57 , 3.52 respectively).

In this trial, patients with T1disease
show good improvement regarding TTR for both modalities; but there is significant inTTR with combined treatment (HR=0.58) for patients with T2 disease. Bardou V., Arpino G.et al trial (1) showed no difference in TTR in patients with T1 disease givenTamoxifen alone treatment (HR=1), and also those with T2 disease given Tamoxifenalone treatment showed no improvement in TTR(HR=1.29).

Tamoxifen and Goserelin were used for 5years and2 year respectively and were given after completion of chemotherapy, a strategy that seems to be optimal based on oncological guidelines1(6).

Major drawbacks of this presented study are; Lack of real and accurate statistics concerning patient's compliance and side effects of treatment. However, Patients compliance was accepted and no serious complications of treatment weredocumented. And short duration of the follow up, and the treatment strategy is 5years, so the duration of the follow up should be

longer in order to perform a better evaluation of the hormonal therapy in termof improve TTR.DFS &OS. And pick up more serious side effect and toxicities of treatment modality.
3. Both treatment groups are not equal, however statistically the results can be compared between them.

Conclusion:

1. Combined Tamoxifen-Goserelintreatment is significantly effective for a patient less than forty years, but it is not for the ages more than forty years.
2. Breast cancers of ER+/PR+ status are highly responsive to Tamoxifen- Goserelin treatment.
3. Patients with N0, N1 and N2, and those with T1 and T2 breast cancer are a good candidate for receiving combined Tamoxifen –Goserelin treatment.

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