Original Article

Tamoxifen Toxicity in Breast Cancer Radiation

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ABSTRACT

Objectives: To see any added toxicity of tamoxifen when prescribed during radiotherapy in breast cancer.

Design: Treatment, Randomized, Open Label, Parallel Assignment

Setting: Department of Clinical Oncology Allied Hospital Faisalabad.

Period: from February 2005 to June 2007.

Patient and Methods: 300 patients were enrolled, age ranging from 22 to 73 years. Stage-I, II and III breast cancer were included in study. Staging was done on AJCC staging system. All were hormone positive. All patients were divided into two arms. Arm A, 150 patients given tamoxifen during radiation and arm B, 150 patients were given tamoxifen after completion of radiotherapy. All patients were examined for skin reactions and lung toxicity (pneumonitis) weekly and at six weeks after completion of radiation.

Results: Most of patients in both arms show skin reactions in 3rd week and pneumonitis around the end of treatment. Only 2 % patients in each arm suffer from grade IV toxicity. Toxicity was manageable and comparable.

Conclusion: There was no significant additional toxicity of concurrent use of tamoxifen with radiation.

Key words: breast cancer, radiotherapy, concurrent tamoxifen, toxicity.

INTRODUCTION

Globally, breast cancer is the most common cancer among women[1,2]. Between 1975–1990, Asia and Africa have experienced a more rapid rise in the annual incidence rates of breast cancer than North America and Europe[1,3]. According to Karachi cancer registry reports, breast cancer is the most common cancer (34.6% of all cancer cases) among females. The age-standardized incidence rate (to the world population) was 69.1 per 100,000 averaged over the years 1998–2002, the highest recorded rate of breast cancer in Asia[4]. Similarly in Lahore breast cancer was the most common female cancer[5].

Pakistan faces a high burden of breast cancer disease with late stage presentation being a common feature. It has been seen that more than half of the patients present in advanced stages (stages III and IV) [6-7].

There are no national screening programs for breast cancer in Pakistan. About 75% of breast cancers are estrogen-receptor positive (ER+ve). About 65% of ER positive breast cancers are also progesterone-receptor positive (PR+ve). About 25% of breast cancers are ER-negative (ER–ve) and PR-negative (PR–ve) or of unknown status. About 10% of breast cancers are ER-positive and PR-negative. About 5% of breast cancers are ER-negative and PR-positive [8]. The ER positive /PR negative tumors are less sensitive to tamoxifen than ER positive/PR positive [9]. It was documented that a total hormone receptor expression of only 53.5% breast cancers in Indian patients as opposed to 75-80% reported in the western literature [10]. The treatment of early disease includes surgery, chemotherapy, radiation therapy and hormone therapy. Post operative radiotherapy improves disease free survival as well as over all survival and reduces the loco regional as well as distant metastasis [11,13]. Radiation therapy was delivered to the chest wall, including the surgical scar and regional lymph nodes. Hormone therapy contains different types of drugs one of them is tamoxifen which is gold standard for all ages. It reduces relative risk of recurrence by 25 % in ER positive, PR negative patients and 53% in ER positive, PR positive patients compared with ER negative and PR negative patients [12]. Patients with ER positive and PR negative tumor have a reduction in relative risk of death of 30% and 38% compared with ER negative /PR negative. The ER positive and PR positive tumors, the reduction of

risk of death is greater than 46%. The acute toxicity of breast radiation is skin reactions and pneumonitis.

In old practice the tamoxifen was prescribed after radiotherapy which has no rationale except it delays hormone therapy for six to eight weeks which is essential part of treatment. The purpose of study is to see any added toxicity of concurrent use of tamoxifen when given with radiation therapy.

Objectives: To see any added toxicity of tamoxifen when prescribed during radiotherapy in breast cancer.

Operational Definitions: Skin toxicity (on common toxicity criteria version 2.0 proposed by National Cancer Institute)

Table 1

Grade 0	No change in skin
Grade I	Blackening or discoloration of skin
Grade II	Dry desquamation of skin
Grade III	wet desquamation of skin
Grade IV	Necrosis or fibrosis of skin

Table 2
Lung toxicity

Grade 0	No lung symptoms
Grade I	Mild lung symptom needs no intervention
Grade II	lung symptoms need treatment and relieved by medication
Grade III	Symptoms not relieved despite of treatment
Grade IV	Life threatening conditions.

PATIENT AND METHOD

Study Design: Treatment, Randomized, Open Label, Parallel Assignment

Setting: Department of Clinical Oncology Allied Hospital Faisalabad.

Duration of study: From February 2005 to June 2007.

Sample Size: 300 patients

Sample Selection;

Inclusion Criteria:

1. Stage I, II and III breast cancer
2. All age groups
3. Performance status 0 and 1.
4. Female and male sex
5. Hormone positive
6. Patients reliable for follow up
7. Patients post mastectomy requiring radiotherapy because of nodal positivity.

Exclusion Criteria:

1. Hormone negative
2. previously treated patients
3. Stage IV disease
4. Skin disease

Data Collection Procedure: After selection of patients and written informed consent complete medical history was taken. Three hundred patients (298 females and 2 males) were enrolled with hormone positive disease. The age range was from 22 to 73 years for females and 56 to 62 years for male patients. All patients received standard chemotherapy and then divided into two arms. Arm A 150 patients were given concurrent tamoxifen with radiotherapy and arm B 150 patients in which tamoxifen was prescribed after completion of radiotherapy.

The dose of tamoxifen was 20 mg daily in both arms and radiation was given on Cobalt 60 to chest wall and supraclavicular area in node positive patients $\pm$ axilla. Dose of radiation was 50 gy in 25 fractions to chest wall with 10 gy boosts to primary or scar and 46 Gy in 23 fractions to supraclavicular area.

Patients were examined clinically on weekly basis for skin reactions and pneumonitis for six weeks and at six weeks after completion of radiation as first follow up. The common toxicity criteria of National Cancer Institute (NCI) version 2.0 were used. The data was entered in specified proformas.

Data Analysis: Data collected on proformas was entered in statistical package of social sciences (SPSS) version 10, software. Skin and lung toxicities were allotted grades o to 4. For each grade of toxicity percentage was calculated.

RESULTS

Among three hundred patients only two were males. 98% patients presented in Department with modified radical mastectomy majority belong to villages. 20-22% in stage I and II and rest of patients were in stage III.

The skin reactions were more than pneumonitis.

68 % patients in arm A show Grade I skin reaction versus 71 % in arm B

25 % patients developed Grade II skin reaction in arm A versus 23% in arm B and 5 % had Grave III skin reaction versus 4 % in arm B.

Grade IV skin reaction was 2% in both arms.

Pneumonitis was seen in Grave I only in both arms. No treatment modification was needed.

Table 3
Total number of patients in each Arms=150

Stage	Arm A	Arm B
I and II	22% (n=33)	20% (n=30)
III	78% (n=117)	80% (n=120)

Table 4
Skin Reactions

GRADE	A	B
I	68% (n=102)	71% (n=106)
II	25%(n=37)	23% (n=35)
III	5 % (n=8)	4% (n=6)
IV	2% (n=3)	2 %(n=3)

Table 5
Pneumonitis

GRADE	A	B
I	18.66% (n=28)	16.66%(n=25)
II	2.66% (4)	2% (n=3)
III	---	-----
IV	-----	------

DISCUSSION

Breast cancer is a big problem for the society. In early days it was treated with mastectomy and ovarian ablation then chemotherapy and hormone therapy came in clinical practice. Hormone therapy is important part of treatment. About 75% of breast cancers are estrogen-receptor-positive. About 65% of ER-positive breast cancers are also progesterone-receptor-positive. About 25% of breast cancers are ER-negative and PR-negative or of "unknown" status. About 10% of breast cancers are ER-positive and PR-negative. About 5% of breast cancers are ER-negative and PR-positive. If cells have receptors for both hormones or receptors for one of the two hormones, the cancer is considered hormone-receptor-positive [8]. The ER positive /PR negative tumors are less sensitive to tamoxifen than ER positive/PR positive [9]. 10% hormone negative patients respond to hormone therapy and vice versa. It was documented that a total hormone receptor expression of only 53.5% breast cancers in Indian patients as opposed to 75-80% reported in the western literature [10]. Usual presentation is lump in breast and in our setting most of patients presented in advanced stage. Postoperative radiotherapy improves disease free survival as well as over all survival and reduces the loco regional as well as distant metastasis [11, 13].

Hormone therapy contains different types of drugs of which one is tamoxifen which is gold standard for all ages. It reduces relative risk of recurrence by 25 % in ER positive, PR negative patients and 53% in ER positive, PR positive patients compared with ER negative and PR negative patients [12]. Patients with ER positive and PR positive tumor have a reduction in relative risk of death of 30% and 38% compared with ER negative/PR negative. The ER positive and PR positive tumors, the reduction of risk of death is greater than 46%. Harris EE conducted a retrospective study to assess the impact of sequencing of tamoxifen and radiation therapy on outcomes in early-stage breast cancer. He concluded that concurrent use of tamoxifen had good impact on survival and tolerance was good. Results of this study were comparable with our study [14]. The concurrent use of tamoxifen is very feasible and helpful to save the treatment time by six to eight weeks. A study was discussed in Principle and Practice of Radiation Oncology in which after modified radical mastectomy patients were randomized into three arms the maximum survival and acceptable toxicity was seen in radiation plus tamoxifen group [15]. The dose of Tamoxifen and protocol of radiotherapy was same as we did. This shows a better care and cure for breast cancer patient. In old days it was a practice that tamoxifen was given to patients after completion of radiotherapy due to the risk of additional toxicity of concurrent use of both modalities but there is no such proof. It simply delays an important part of treatment for six to eight weeks.

CONCLUSION

Toxicities were comparable and manageable. There was no significant difference in toxicity in both arms.

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