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A COMPARATIVE STUDY TO EVALUATE THE CONCURRENT CHEMORADIOTHERAPY VERSUS RADIOTHERAPY ALONE IN THE MANAGEMENT OF BREAST CANCER

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Abstract
Background: We designed a study to compare radiotherapy alone in sandwich set up with concurrent chemo radiotherapy in the management of breast cancer.
Methods: This study was conducted on 30 patients suffering from advanced breast carcinoma who visited Department of Radiotherapy and Clinical Oncology, S. N. Medical College, Agra. All these patients were referred from Department of Surgery, S.N. Medical College or from other nearby centers. Out of 30 patients 25 patients completed the treatment and were enrolled for analysis.
Results: 84.61% of patients had no evidence of disease and were alive without disease in arm A vs 100% in arm B. The overall survival at 1 year was 100% in both the arms. The disease free survival at 1 year was 84.61% in arm-A and 100% in arm-B.
Conclusion: The overall adverse effects were higher in ARM-B (concurrent arm) as compared to ARM-A but it was acceptable without any drop out during the treatment.
Keywords: Breast cancer, concurrent chemoradiotherapy, neoadjuvant therapy, locally advanced disease.

Introduction:

Cancer is a group of diseases that cause cells in the body to change & grow out of control. Most types of cancer cells eventually form a lump or mass called a tumor, and are named after the part of the body where the tumor originates. Global breast cancer incidence increased from 641,000 (95% confidence intervals 610,000-750,000) cases in 1980 to 1.643,000 (1,421,000-1,782,000) cases in 2010, an annual rate of increase of 3.1%. The health care burden related to breast cancer in India has been steadily mounting. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta and Trivandrum where it constitutes > 30% of all cancers in females. [1]

Radiotherapy is important modality in the treatment of breast cancer. Role of adjuvant radiotherapy has been analyzed in 20000 patients in 40 trials. The most recent analysis found that use of radiotherapy reduces the incidence of local recurrence at 20 years of the follow-up. Benefit is most evident in patients with involved lymph nodes. [2]

The optimum sequencing of radiotherapy and chemotherapy is controversial

The main advantages of CCRT are delivering both two treatments modalities of Chemotherapy and Radiotherapy at same time. Adjunction of chemotherapy to radiotherapy produces a Biological synergistic effect that can increase the efficacy of the treatment.

Kim et al compared the outcome of concurrent versus sequential administration of cyclophosphamide, methotrexate, and 5-flurouracil (CMF) chemotherapy and

radiotherapy after breast conserving surgery in early breast cancer. 156 patients were included in the study. Concomitant administration of chemotherapy and whole breast irradiation resulted in improved loco regional control over sequential administration, without an increase in significant toxicity.[3]

In the ACROSEIN study the authors identified a significant decrease in the risk of loco-regional recurrence by 39% with Concurrent Radiotherapy and Chemotherapy for node-positive patients. Rouessé et al showed that Concurrent treatment has a significantly better loco regional control in node-positive breast cancer after conservative surgery.[4]

After reviewing the above trials, we designed a study to compare radiotherapy alone in sandwich set up with concurrent chemo radiotherapy in the management of breast cancer.

MATERIAL & METHODS

This study was conducted on 30 patients suffering from advanced breast carcinoma who visited Department of Radiotherapy and Clinical Oncology, S. N. Medical College, Agra. All these patients were referred from Department of Surgery, S.N. Medical College or from other nearby centers. Out of 30 patients 25 patients completed the treatment and were enrolled for analysis.

Selection of the patients

There were certain criteria that we laid down for the patients in order to qualify for this study. These criteria were as following:

- Females in the age group 35-69 yrs
- Pathologically confirmed breast cancer
- Stage pT1-T4/pN0-3 without evidence of metastasic disease.
- All patients were previously operated and required treatment in the form of chemotherapy and radiotherapy.
- Informed consent prior to the treatment
- Additional eligibility criteria were – adequate renal, hepatic and bone marrow function.
- No history of previous exposure to chemotherapy or radiotherapy.
- No history of previous or concomitant cancer.
- In post operative case adjuvant radiotherapy improves local control. Adjuvant Chemotherapy is equally mandatory for diminishing metastasis and recurrence.
- The optimal sequencing of chemotherapy and radiotherapy remain controversial. The delivery of radiotherapy was planned before or after chemotherapy, concurrently or within cycle of Chemotherapy (sandwich therapy).
- Patients were randomized into two groups :
- Arm-A – 4 cycle of Cyclophosfamide (500 mg/m^2), Adriamycin (50mg/m^2) and 5-flurouracil (500 mg/m^2) given intravenously on day D1 every 3 weeks followed by Radiotherapy followed by CMF (CMF-cyclophosphamide 600 mg/m^2, mtx 40 mg/m^2, 5-flurouracil 600 mg/m^2) on D1 and D8 with a interval of 4 weeks.
- Arm-B – 4 cycle of Cyclophosfamide (500 mg/m^2), Adriamycin (50mg/m^2) and 5-flurouracil (500 mg/m^2) given intravenously on day D1 every 3 weeks. Followed by Concurrent Chemotherapy and Radiotherapy with Cyclophosfamide, Methotrexate and 5-Fluorouracil regimen on D1 and D8 with a interval of 4 weeks.
- Radiotherapy was given to internal mammary chain, supraclavicular fossa and axillary region by direct anterior field and to the chest wall by two tangential fields to a total dose of 45 Gy/20#/5 weeks/2.25Gy/#/4F by Co60 teletherapy. Half beam block were used in tangential fields irradiation. Head of the humerus and common field of IMC and supraclavicular field were shielded.
- Before starting chemotherapy a complete haemogram and complete biochemical test were performed. Anti emetics were given prior to chemotherapy. Chemotherapeutic agents were given by slow intravenous bolus or by intravenous infusion. Adequate hydration was maintained during chemotherapy. Patients were observed closely for the side effects or toxicity of the drugs and were treated symptomatically.
- All the patients were also given general supportive treatment in the form of antibiotics, analgesics, appetizers, haematinics and multivitamins.

OBSERVATIONS

This study was conducted in Radiation Oncology Department of S.N. Medical College, Agra from January 2013 to December 2014. 25 biopsy proven cases of advanced postoperative breast carcinoma

were analysed in this study. All cases were categorized in two groups according to the treatment regimen. Patients were assessed for signs and symptoms with duration. Pathological staging of all patients were done. This study included premenopausal as well as postmenopausal patients.

All patients were checked for adequate haematological status before starting of chemotherapy and assessed after each cycle of chemotherapy for acute GI toxicities, myelosuppression and skin toxicities. The patients were assessed for acute toxicities like nausea / vomiting /diarrohea/ myelosuppression and skin toxicities weekly during radiation and at interval of one month after completion of treatment.

After that patients were followed up monthly for 1st year. General, physical and local examination of all patients was done during follow-up. Blood investigations / X-ray chest / ultrasound abdomen were done at six months interval. Patients were advised for the physical exercise in order to prevent lymph edema and improve pulmonary functions.

Recurrent breast cancer without any treatment were also included in this study. All the statistical data were calculated on the computer and statistician was consulted.

In Arm A no patients were in the age group of 30-39 years but in Arm B 8.33% of patients were in that age group. In both the arms, maximum number of patients were in the age group of 40 – 49 years (Arm A - 61.54% & Arm B - 66.66%). 15.38% & 25% of patients were in the age group of 50-59 years in Arm A & Arm B respectively. 23.07% of patients were seen in the age ≥60 years in Arm A and no patients in Arm B were seen in that age group. In arm A 3 patients (23.07%) were premenopausal and 10 patients (76.92%) were postmenopausal whereas in arm-B there were 5 premenopausal (41.66%) and 7 post menopausal (58.33%) patients. It was seen that maximum number (68%) of total patients were in post menopausal state. In both the arms maximum number of patients (total 15/25, 60%) presented with lump in upper outer quadrant of breast, followed by central quadrant (total 5/25, 20%). 16% of total patients had lump in lower outer quadrant while 4% of total patients in upper inner quadrant of breast. In the study the presentation of lump preoperatively were upper outer quadrant, central quadrant, lower outer quadrant, upper inner quadrant. No patients had lump in lower inner quadrant.

Table 1: DISTRIBUTION OF PATIENT AS COMPLETED PLANNED TREATMENT:

Concurrent chemoradiotherapy with CMF	ARM A n=13		ARM B n=12	
	No.	%	No.	%
D1 & D8 of 1st cycle	-	-	2	16.66
D1 , D8 of 1st cycle & D1 of 2nd cycle	-	-	8	66.66
≥ 2 cycles	-	-	2	16.66

The patients in arm B received concurrent chemoradiotherapy. It was seen that 66.66% of the patients received ≥1 cycle of CMF regimen (i.e. D1, D8 of 1st cycle of CMF & D1 of 2nd cycle of CMF regimen) while 16.66% of patients received D1, D8 of Ist cycle and same percentage (16.66%) of patients received 2 cycles (i.e. D1, D8 of Ist cycle & D1, D8 of 2nd cycle).

TABLE 2: COMPLICATION DURING CHEMOTHERAPY

Effects	ARM-A n=13		ARM-B n=12	
	No.	%	No.	%
Nausea/vomiting	7	53.8	5	41.66
Anaemia (grade II & grade III)	5	38.46	3	25
Neutropenia (grade II & grade III)	3	23.07	3	25
Thrombocytopenia	1	7.69	1	8.33
Alopecia	10	76.92	8	66.66
Mucositis	1	7.69	1	8.33
Cardiotoxicity	-		-	
Neurotoxicity	-		-	
Nephrotoxicity	-		-	
Lethargy & somnolence	-		-	

More GI toxicity in the ARM-A as compared with the ARM-B. Other toxicities like haematological, alopecia and mucositis were reported equally in both the arms. None of the patients developed cadiac toxicity, neuro toxicity or nephrotoxicity.

Table 3: COMPLICATIONS DURING RADIOTHERAPY:

COMPLICATION	ARM A n=13		ARM B n=12	
	No.	%	No.	%
Skin				
Grade 1	7	53.84	8	66.67
Grade 2	-	-	-	-
Grade 3	1	7.69	1	8.33
Grade 4	1	7.69	1	8.33

It was seen that equal number of cases reported with grade 3 & grade 4 skin reactions. These patients developed haemorrhagic ulcerations at irradiated area during the last few fractions which healed within 2-3 weeks. Nearly all the patients had developed hyperpigmentation of skin at irradiated site. The overall toxicity during the treatment were seen more in arm-B.

Table 4: COMPLICATIONS DURING CONCURRENT CHEMORADIOTHERAPY:

Complications	ARM A n=13		ARM B n=12	
	No.	%	No.	%
GI toxicity: nausea/vomiting	-	-	3	25.00
Neutropenia	-	-	1	08.33
Skin reaction: grade III/IV	-	-	2	16.66

3 patients (25%) had complaints of nausea/vomiting with every cycle of chemotherapy when given concurrently with radiation.

1 patient (08.33%) had developed grade 3 neutropenia in concurrent regimen. 16.66% of patient had grade 3-4 skin reaction in concurrent arm. It was seen that overall GI toxicities and haematological toxicities were slightly higher in arm B (i.e. 66.66% Vs. 53.8% and 41.66% Vs 23.07% respectively) but the concurrent chemoradiotherapy regimen was well tolerated by the patients and there were no drop outs during the treatment.

TABLE 5: EVENTS SEEN DURING FOLLOW UP AT 1 YEAR:

DURING FOLLOW UP	ARM-A n=13		ARM-B n=12	
	No.	%	No.	%
NED (no evidence of disease)	11	84.61	12	100
AWD (Alive with disease)	1	07.69	-	-
Progression of disease	1	07.69	-	-
Overall survival at 1 year	13	100	12	100
Disease free survival at 1 year	11	84.61	12	100

84.61% of patients had no evidence of disease and were alive without disease in arm A while 07.69% was alive with progressive disease in arm A. 100% of patients had no evidence of disease and were alive without any disease in arm B. The overall survival at 1 year was 100% in both the arms. The disease free survival at 1 year in arm B & arm A was 100% Vs 84.61%. One patient developed metastases to bone (lumbar L4-5) within 6 months of completion of treatment in arm A. There was no relapse and metastases in Arm B.

DISCUSSION

In substantial proportion of women breast cancer is diagnosed in an advanced stage, at the time of presentation. The surveillance epidemiology and end results (SEER) data, which include incidence from 1975 to 1980 revealed a 6.7% incidence of T_3N_0 &

7.3% incidence of T_4 disease. This total data of about 14% represent approximately 27,000 cases per year in U.S.A. of advance cases. This incidence is considerably higher in India around 25 – 50% of cases in advanced stage as large amount of population is illiterate and has poor health services.[5]

CCRT has advantages of prompt radiotherapy and of a possible radiation sensitization effect (Kyobo Kim, Wonshik Han et al (2007). Thus, CCRT has been considered as an alternative, and even superior option to SCRT. Concurrent administration of chemotherapy and radiotherapy, however, can enhance not only treatment efficacy but also increase toxicity. CCRT with full-dose CMF chemotherapy was shown to be well tolerated. As regards to cardiac toxicity, there was no patient with related symptom. This might be due to the insufficient duration of follow-up to detect possible late cardiac toxicity, which may develop more than 10 years after radiotherapy. In conclusion, concurrent administration of CMF chemotherapy and whole breast irradiation is a safe and effective option as an adjuvant treatment after modified radical mastectomy, with increased local-regional control compared to sequential administration. Concurrent CMF chemo-radiotherapy may serve as a viable option for patients at high risk for local-regional relapse not suitable for anthracycline or taxane-based chemotherapy. CCRT with full dose of CMF chemotherapy was shown to be well tolerated.[3]

A randomised trial from Italy (ACROSEIN trial 2007) revealed that CMF based CCRT resulted in local control similar to that of SCRT.[4] Two French randomised (Alain Toledano et al, 2007, the French multicenter phase III) studies reported superior local-regional control with CCRT, but they used mitoxantrone-based chemotherapy, which is no longer in use due to a possible leukemogenic effect. A retrospective study from Yale University showed increased local control with the use of CCRT using various chemotherapeutic regimens over SCRT.

At present the study was conducted to see the outcome of CCRT during the follow up. No evidence of disease was seen in 84.61% of patients in arm A while in arm B all patients had no evidence of disease. 7.69% of patient had progressive disease in arm A while none patients presented with progressive disease in arm-B. In our study the overall survival at 1 year was equal in both arms. Disease free survival was higher in arm-B compared to arm-A i.e. 100% Vs. 84.6%.

Toxicities were slightly higher in arm-B as compared to arm-A and were well tolerated - upper GI toxicities (66.66% Vs. 53.80%), skin reaction (16.66% vs. 7.69%) neutropenia (33.33% vs. 23.07%). It was seen that concurrent CMF chemoradiotherapy was well tolerated.

CONCLUSION

The overall adverse effects were higher in ARM-B (concurrent arm) as compared to ARM-A but it was acceptable without any drop out during the treatment.

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