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ORIGINAL ARTICLE

Neoadjuvant chemotherapy followed by neoadjuvant concurrent chemoradiation for locally advanced breast cancer: a feasibility study and 10-year follow-up results

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Abstract

Purpose Locally advanced breast cancer (LABC) is best managed by neoadjuvant chemotherapy followed by surgery and radiotherapy. Recent reports suggest that complete pathological response is associated with improved survival. Major concern of using concurrent chemoradiation in LABC is toxicity and cosmesis, and only very few studies addressed this issue. This study is carried out to study the feasibility, toxicity profile, pathological response of neoadjuvant anthracycline-based chemotherapy followed by concurrent chemoradiation with biweekly paclitaxel in locally advanced breast cancer patients.

Methods Fourteen patients with LABC were enrolled into this prospective feasibility study during the period 2005–2006, but only 12 patients completed the study protocol. Patients were treated with four cycles of adriamycin + cyclophosphamide followed by concurrent chemoradiation with paclitaxel and then underwent surgery. Patient characteristics, toxicity during treatment, pathological response were all documented, and patients were followed up for a minimum of 10 years to assess the long-term survival and toxicity with this approach.

Results Most of our patients were in the high-risk biological group (ER, PR negative or HER 3+). Major toxicity reported was radiation-related acute grade ¾ cutaneous toxicity, in four patients leading to radiation treatment break. Two patients had delay in surgical wound healing. Regarding response to treatment four patients had complete pathological response (both primary and nodal), and two patients had complete nodal response with residual at primary. At the time of last follow-up, six out of 12 patients were alive without disease. Out of the alive six patients, four had pathological complete response and two had pathological nodal complete response. All the six patients having pathological complete response at the nodal site are alive without disease. No major toxicity has been reported at 10 years.

Conclusion Addition of radiation to neoadjuvant chemo is feasible with improved pathological response and overall good outcome in good responders, especially nodal complete responders. For patients with non-luminal type LABC, overall survival is poor but nodal pathological CR patients with non-luminal LABC are surviving even at 10 years with no additional late morbidity.

Keywords Neoadjuvant · Concurrent · Chemoradiation · Paclitaxel · LABC

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Introduction

Neoadjuvant or preoperative treatment is an approved approach for treatment of locally advanced breast cancer (LABC). The clinical advantages of neoadjuvant therapy are that it can make resection possible and in some cases

even breast conservation becomes feasible. Since the primary lesion is intact, it provides an in vivo estimation of treatment response. Recent reports suggest patients getting pathological complete response with neoadjuvant treatment have a better survival when compared to patients who have residual disease, and this pathological complete response is more in triple-negative tumors [1, 2]. Patients with HER2-positive tumors, who receive anti-HER treatment, also have increased pathological complete response. Radiotherapy (RT) is not usually considered as a neoadjuvant option in breast cancer, even though dramatic effects on large tumors can be achieved with radiotherapy. Concurrent neoadjuvant chemoradiotherapy is the standard in locally advanced rectal, esophageal and anal cancers, but in breast cancer its role has not been studied much. The proposed benefit of concurrent chemoradiation may be the increased pathological response, which in turn can lead on to some improvement in survival, especially in triple-negative breast cancers [3]. Concurrent chemoradiotherapy with paclitaxel is also explored in a few earlier studies based on its proven synergistic effect with radiation [4–7].

Aim

To study the feasibility of neoadjuvant anthracycline-based chemotherapy followed by concurrent chemoradiation with biweekly paclitaxel in locally advanced breast cancer patients.

To study the toxicity profile (both acute and late), pathological response and survival with neoadjuvant concurrent chemoradiation.

Materials and Methods

This was a prospective study conducted in our center to assess the feasibility, toxicity profile and pathological response to neoadjuvant concurrent chemoradiation. As our usual protocol for neoadjuvant was four cycles of adriamycin + cyclophosphamide (AC) followed by four cycles of Taxol, we decided on giving the 4 AC first and then combining biweekly Taxol with RT. Trastuzumab was not routinely being used during this period in our center, and hence, the HER2-Neu-positive patients were not offered trastuzumab. Patients with LABC who satisfy the inclusion criteria and gave consent for study were enrolled to the study protocol. Minimum sample size for this feasibility study was ten and we could enroll 14 patients, but only 12 patients could complete the study protocol. All patients alive were followed up for a minimum of 10 years to document any late toxicity.

Inclusion Criteria

1. Biopsy proven locally advanced breast cancer patients stage IIIA (T0N2, T1N2, T2N2, T3N1) and stage III-B (T4 N0-2, T3N2) and those with any T and Supraclavicular nodes.
2. Measurable disease required.
3. Adequate laboratory values: Hb > 10; ANC > 1500; platelets >1,50,000; creatinine <1.5; liver functions 3 × normal.
4. Patient >18 years age.
5. Medically and psychologically able to comply with all study requirements.
6. ECOG performance status 0–I.

Exclusion Criteria

1. Breast cancer patients with stage 0, stages I and II.
2. Presence of distant metastasis documented clinically or radiographically.
3. Previous XRT or chemotherapy, previous history of malignancy.
4. Pregnancy.
5. Inflammatory breast cancer.
6. Patients on immunosuppressive or hormonal medications.

Study Protocol

Baseline Evaluation

- Core biopsy for confirmation of diagnoses and receptor studies (ER, PR, HER2-Neu).
- Staging evaluation including baseline blood tests (CBC, RFT, LFT, ECG, ECHO), CT scan of chest, USG Abdomen and pelvis, bone scan, baseline mammogram.
- Consultation with medical, surgical and radiation oncologist.

Treatment Schedule

1. Adriamycin 60 mg/m^2 Day 1 Q 3 weeks.
2. Cyclophosphamide 600 mg/m^2 Day 1 Q 3 weeks for four cycles followed by concurrent chemotherapy with twice a week paclitaxel 30 mg/m^2 (Monday and Thursday) and radiotherapy. Concurrent chemoradiation started after 3 weeks of 4th cycle of AC.
3. Dexamethasone 8 mg and ondansetron 8 mg as premedication were used before chemotherapy.

Radiation Dose Schedules and Protocol

Three-dimensional conformal radiation (3DCRT) with tangent fields for breast and AP SCF, PA axillary fields for SCF and axilla were used.

CT simulation was done with patient positioned in a breast board, ipsilateral arm abducted to more than 90° and head turned to opposite side. Thermoplastic masks used in case of large pendulous breasts.

Treatment planning was done using Xio planning system with standard medial and lateral tangents of appropriate gantry angles to cover the breast tissue adequately, and half-beam technique for *X* axis is used to avoid divergence to lungs. Axilla and supraclavicular fossa were treated using 10°–15° angled AP SCF fields to avoid dose to trachea, esophagus and spinal cord, and humeral heads were shielded with multileaf collimators. PA axillary fields were used to cover the deeper part of the axilla. Monoisocentric technique was used, and isocenter was placed at the level of caudal edge of the clavicle. Dose prescribed was 45 Gy/25 Fr, to the SCF, axilla and breast followed by boost to the primary tumor 14 Gy/7 Fr.

Dose inhomogeneity allowed was maximum +10% and minimum −5% for 2 cc of volume. Radiation was delivered one fraction/day, 5 days a week, using 6 MV linear accelerator, and port film verification was done on day 1 and then weekly once.

Treatment Modifications

For patients on radiation experiencing more than grade 2 radiation reaction, treatment was interrupted for a few days and with chemotherapy, for recurrent grade two toxicity, dose was reduced by 25% and for grade three dose was reduced by 50%.

Toxicity assessment was done using RTOG and NCICTC acute toxicity scoring criteria.

Surgery

Surgery was modified radical mastectomy or breast conservation surgery after 4 weeks of completion of chemoradiation.

Response Assessment

Clinical Response

Clinical response was measured by the following criteria

Complete response (CR) complete disappearance of all known tumor masses and the appearance of no new lesions.

Partial response (PR) greater than 50% reduction in the product of perpendicular measures of all measurable tumor masses and the appearance of no new lesions.

Stable disease (SD) less than a 50% decrease or less than 25% increase in the product of perpendicular measures of tumor masses and the appearance of no new lesions.

Progressive disease (PD) greater than a 25% increase in the product of perpendicular measures of tumor masses or the appearance of new lesions.

Pathological Response

Specimens were processed and sectioned to identify residual tumor. Accurate measurements were performed for quantification of pathologic response. Residual tumor measurements were carried on at pathology and classified as:

Complete pathological response (pCR) absence of residual invasive tumor cells in both the removed breast and axillary contents specimens (persistent DCIS is accepted).

Partial pathological response (pPR) persistent microscopic foci of invasive cancer cells in either the breast or nodal specimens in less than $\leq$10 high power field (HPF).

No pathological response (pNR) microscopic confirmation of persistence of invasive tumor >10 HPF.

Survival Analysis

Overall survival is calculated from the date of diagnosis to date of death due to any cause, and patients were censored at last follow-up date. Kaplan–Meier method was employed for survival analysis.

Results

This study was started in the year 2005–2006 and enrolled 14 patients, but only 12 patients could complete the study protocol. One patient withdrew consent for chemoradiation after four cycles of AC, and the second patient could not take concurrent chemoradiation due to personal reasons. Median age of our patients was 58 (23–69) years. Twelve patients were evaluable for response, and patient characteristics were as shown in Table 1.

Most of our patients were in the high-risk biological group (ER, PR negative or HER 3+), and one patient had supraclavicular node at presentation. In one patient, the ER and PR status was not done due to technical reason.

Patients were expected to start CTRT at 84 days of starting AC chemotherapy, and expected duration of RT

Table 1 Patient characteristics, response and status at last follow-up

No.	Initial T size CM	Initial nodal status *N*	ER	HER2	Clinical response	Path response (*p*)	Path T CM	Nodes	FU in years	Status
P1	6 × 4	2	NEG	NEG	CR	pCR	–	0/19	11.74	NED
P2	6 × 5	1	NEG	NEG	CR	pCR	–	0/15	11.45	NED
P3	6 × 5	2	NEG	NEG	DP	pNR	6 × 4	16/21	0.94	DIED
P4	3 × 2	1	POS	NEG	PR	pPR	1 × 1	0/16	11.08	NED
P5	6 × 4	2	NEG	NEG	PR	pNR	3 × 2	7/13	2.85	DIED
P6	7 × 4	1	POS	NEG	PR	pNR	0.3 × .2	3/13	4.8	DIED
P7	4 × 3	2	NEG	NEG	CR	pCR	–	0/9	10.8	NED
P8	4 × 3	2	NEG	POS	PR	pNR	2 × 2	9/14	4.8	DIED
P9	3 × 2	1	POS	POS	PR	pPR	<1 × 1	0/28	10.8	NED
P10	8 × 5	1	NEG	NEG	CR	pCR	–	0/4	10.8	NED
P11	7 × 6	2			PR	pPR	<1	1/3	0.75	DIED
P12	14 × 10	3	POS	POS	PR	pNR	17 × 8	46/54	1.6	DIED

CR complete response, *PR* partial response, *DP* disease progression, *NED* no evidence of disease, *NR* no response

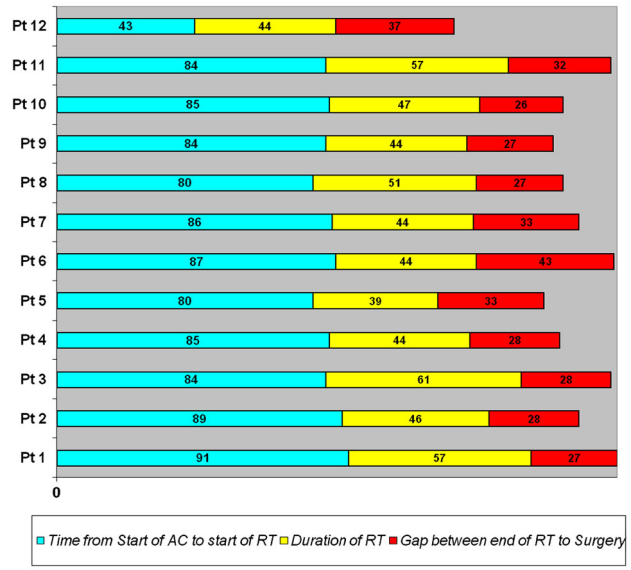

Fig. 1 Duration of treatment

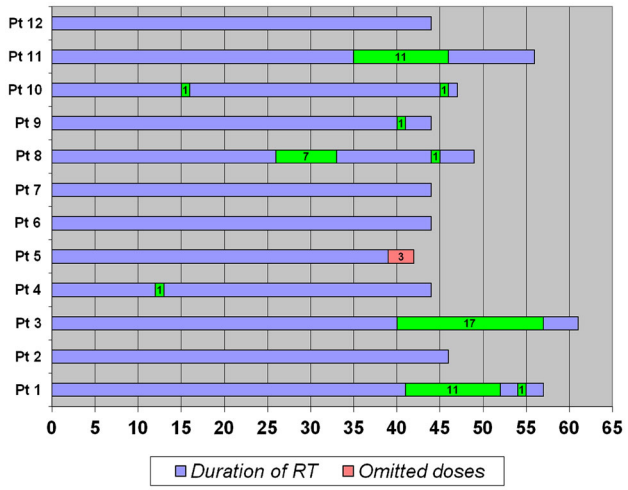

Fig. 2 Duration of RT, omitted doses and unplanned break in RT

was 32 Fractions over 44 days. Interval between CTRT and surgery was 4–5 weeks (28–35 days). Most of our patients were able to complete the treatment protocol as planned. One patient received CTRT after two cycles of AC because of bleeding from the ulcerated lesion and after CTRT underwent MRM with chest wall resection and reconstruction. Treatment characteristics are shown in Figs. 1 and 2. Four patients had radiation treatment break of more than 4 days, and only in one patient this break occurred before 28 days of radiation start (due to herpes zoster infection). Major toxicity reported was radiation-related acute grade ¾ cutaneous toxicity, in four patients leading to radiation treatment break. Two patients had delay in surgical wound healing. Treatment-related toxicities are listed in Table 2. At 10 years of follow-up, there was no grade 3 or 4 toxicity in the survivors.

Regarding response to treatment, four patients had complete pathological response (both primary and nodal), and two patients had complete nodal response with residual at primary.

At the time of last follow-up, six out of 12 patients were alive without disease. There was no locoregional alone recurrence.

The four patients having radiation break due to cutaneous toxicity is a matter of concern.

However, in three of these patients, the break occurred after 25 fractions; that is, during the boost part of the radiation. The whole breast radiation was given uninterrupted in these three. Only in one patient was the radiation break of 1 week in the third week of RT due to an attack of herpes. As to how these patients fared: two of these patients fared badly; one with progressive disease soon after completion of therapy and another with metastatic disease

Table 2 Showing chemo-RT acute toxicities and surgical morbidity

	Chemo-RT acute toxicities	
1	Confluent moist dermatitis (grades III/IV)	4
2	Radiation pneumonitis?	1
3	Cutaneous herpes	1
4	Fever	3
5	Neutropenia (grade 3)	1
	Surgical morbidity	
1	Wound infection and non-healing	2
2	Seroma, increased drainage	2
3	Collection at primary site	1

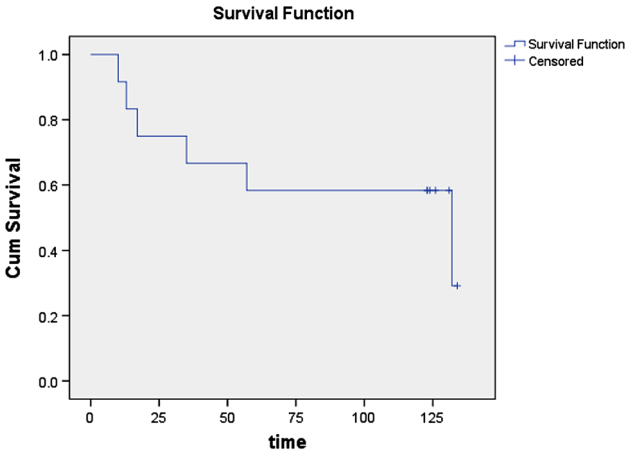

Fig. 3 Kaplan–Meier survival curve for overall survival with follow-up in months

2 years after treatment. Both have succumbed to their disease. Two other patients with breaks have fared well, one is alive and well after 10 years and the other died after 4.8 years due to metastatic disease.

Out of the alive six patients, four had pathological complete response and two had pathological nodal complete response. All the six patients having pathological complete response at the nodal site are alive without disease. Patients with no pathological response according to the response evaluation criteria progressed faster with metastatic disease, and their survival was poor. Receptor status, pathological response and survival are given in Table 1, and Kaplan–Meier survival curve in Fig. 3.

Discussion

The contemporary management of LABC consists of preoperative systemic chemotherapy to facilitate the surgical removal of the tumor and to address early systemic treatment of distant micro-metastasis [1, 2]. This is followed by further chemotherapy, radiotherapy and hormonal treatment where appropriate. Evidence is emerging that pathological response after primary chemotherapy can be used as a surrogate endpoint for survival [3]. In spite of the differences in the criteria adopted to measure and report the pathological findings after primary noninvasive treatment, most groups have shown a similar correlation between residual disease found at surgery and patient outcome [8–11]. It has thus become clear that therapeutic attempts to improve pathological response to primary therapy are likely to reflect on patient outcomes. In addition, pathological response as a surrogate for outcome provides a much quicker method to evaluate treatments while also offering the opportunity to explore its association with biological correlates [4–6, 8–10, 14]. In this sense, LABC offers an ideal opportunity to expedite clinical research on how to best "tailor treatment" based on specific tumor characteristics. Moreover, original primary chemotherapy trials reported pathological complete response rates of less than 10% [1, 10]. These facts give us the impetus to investigate the combination of chemotherapy with radiation to increase the proportion of patients who might derive a potential survival benefit associated with a good pathological response.

The two consecutive chemo-RT phase I–II studies by Dr. Formenti's group proved the feasibility of concurrent chemotherapy and radiation as primary treatment for LABC, and the pathological complete response rates reported were 5–15% higher than pathological response rates reported in contemporary studies of preoperative chemotherapy alone [4, 8, 12].

The first trial by Formenti's group was continuous infusion 5 FU with concurrent radiation, and they were able to demonstrate a pathological response rate of 34%. With a median follow-up of 5 years, overall survival of the entire group of 38 patients is 74% and disease-free survival is 58%, which compares favorably with neoadjuvant chemotherapy. The patients who achieved a pathological response (pCR + pPR) to 5 FU/RT have both better DFS and OS than non-responders ($p = 0.023$ and $p = 0.08$, respectively). The second study looked into the benefit of concurrent chemo-RT with paclitaxel, which also showed a favorable pathological response rate of 33% [4].

Our results also demonstrated a good pathological response with a complete response rate of over 30% similar to the reported chemoradiation studies [4, 8]. Patients who had pCR continued to remain disease-free even after 10 years of treatment, indicating the impact of pCR on long-term survival. Six out of 12 patients are still alive, of which four had pathological complete response and two had pathological complete response in the nodes with some residual at the primary site. Thus, complete response in the nodes is possibly a stronger indicator of long-term survival than CR at the primary [11]. Ten-year results of a similar study also reported good co-relation with complete pathological response and survival [13].

Our toxicities were acceptable, but radiation dermatitis was a major concern and two patients had wound healing issues after surgery. Twelve out of 14 enrolled patients completed the treatment protocol. There was no major protocol violation except in one patient, who underwent chemoradiation after two cycles of AC due to bleeding from the local breast ulcer. Quality of life was not documented, but there was no significant long-term toxicity at 10 years of follow-up in the surviving patients.

Conclusion

The current management of LABC consists of preoperative systemic chemotherapy to facilitate the surgical removal of the tumor and to address early systemic treatment of distant micro-metastasis [1, 2]. This is followed by further chemotherapy, radiotherapy and hormonal treatment where appropriate. Evidence is emerging that pathological response after primary chemotherapy can be used as a surrogate endpoint for survival. Our study proves that addition of radiation to neoadjuvant chemo is feasible with improved pathological response and overall good outcome in good responders, especially nodal complete responders. For patients with non-luminal type LABC, overall survival is poor but nodal pathological CR patients with non-luminal LABC are surviving even at 10 years with no additional late morbidity. Hence, in operable LABC, CCRT can offer a valuable opportunity to improve outcomes with shortest possible treatment time. The optimal chemotherapy agent, and its dose and administration schedule, is not known. Promising results with acceptable toxicity of concurrent twice-weekly paclitaxel and RT emphasize the need for larger prospective studies. Careful management of acute skin toxicities is the key in reducing the overall treatment time.

In addition, pathological response as a surrogate for outcome provides a much quicker method to evaluate treatments while also offering the opportunity to explore its association with biological correlates [2, 4, 6, 9, 11, 12]. In this sense, LABC offers an ideal opportunity to expedite clinical research on how to best "tailor treatment" based on specific tumor characteristics.

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Compliance with Ethical Standards

Conflict of interest Authors disclose that they have no conflict of interest.

Ethical Approval Institutional review board and ethical committee cleared the study.

Human and Animal Rights All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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