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CLINICAL INVESTIGATION **Breast**

CONCOMITANT RADIATION THERAPY AND PACLITAXEL FOR UNRESECTABLE LOCALLY ADVANCED BREAST CANCER: RESULTS FROM TWO CONSECUTIVE PHASE I/II TRIALS

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Purpose: The management of unresectable locally advanced breast cancer (ULABC) remains a major challenge because of the necessity both to treat local disease and to prevent distant disease. Two consecutive Phase I/II trials of concomitant chemotherapy and radiation (CRT) were performed to attempt to address both local and distant disease control in ULABC. This analysis focuses on rates of locoregional control and radiation-associated acute and late complications.

Methods and Materials: Thirty-three patients with unresectable locally advanced or inflammatory breast cancers (T4N0-3M0-1) or locally recurrent disease were treated with CRT on two consecutive Phase I/II trials. Radiotherapy consisted of 60–70 Gy to the breast or chest wall and 60 Gy to draining lymphatics in a week-on/week-off (WO/WO) schedule. Chemotherapy consisted of either continuous infusion or bolus paclitaxel ± vinorelbine. A subset analysis of 16 patients with nonmetastatic ULABC Stage IIIB–C (T4N0-3M0) was performed. Among this cohort, 13 patients (81%) underwent planned mastectomy after CRT.

Results: Of the 16 patients with Stage IIIB–C disease, acute toxicity included moist desquamation ($n = 8$) and Grade 3–4 neutropenia ($n = 3$). Late toxicity included breast reconstruction loss, decreased range of arm motion, lymphedema, and skin toxicity, although none was life-threatening. Of 15 assessable patients, 14 had a clinical response, 7 had a pathologic complete response (pCR) including 6 of 13 patients undergoing mastectomy. With a median follow-up for living patients of 43.8 months, the 4-year actuarial locoregional control, disease-free survival, and overall survival were 83%, 33%, and 56% respectively.

Conclusions: Concurrent WO/WO radiation therapy and paclitaxel ± vinorelbine is effective locoregional therapy for ULABC with an acceptable toxicity profile. Further investigation of concurrent chemoradiotherapy in ULABC is warranted. **© 2005 Elsevier Inc.**

Locally advanced breast cancer, Concomitant radiation and chemotherapy.

INTRODUCTION

Although less common in the era of mammographic screening, unresectable locally advanced breast cancer (ULABC) remains a significant therapeutic challenge. Results of treatment with surgery, radiotherapy (RT), or both have been disappointing because of high rates of local and distant failures, with 5-year survival rates of 0–30% (1–5). The most promising results for this subset of patients have been achieved with multimodality therapy consisting of surgery, RT, chemotherapy, and hormonal therapy, to address local, regional, and distant disease (4, 5). Currently, most treatment approaches for Stage IIIB–C breast cancer involve sequential delivery of chemotherapy, surgery, and radiation therapy with 5-year survival rates of 30–55%, disease-free survival of 30–50%, and 5-year local control of 70–90% (4–7). However, many patients who present with far advanced local disease or chemotherapy-resistant disease may benefit from immediate local therapy with radiation with concurrent chemotherapy to address clinically undetectable systemic disease. The benefits of concomi-

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tant therapy include synergism between chemotherapy and RT and eliminating the delay of chemotherapy or RT, which may adversely affect outcome (8, 9).

The role of concomitant chemoradiation therapy (CRT) for ULABC is not well defined. For locally advanced head-and-neck, cervical, and lung cancers, concomitant CRT results in superior local control and overall survival compared with sequential CRT (10–12). A preliminary report from a randomized trial suggested that local control is improved with concomitant CRT in comparison to sequential chemotherapy and RT for resectable node-positive breast cancer (13). Standard chemotherapeutic regimens used for breast cancer include doxorubicin and cyclophosphamide (AC) with or without a taxane, and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (14). For node-negative, estrogen receptor (ER) negative breast cancer, concomitant methotrexate-based adjuvant chemotherapy and full-dose RT improved local control compared with RT alone but resulted in increased rates of pneumonitis and skin toxicity (15, 16). Concomitant administration of anthracyclines with RT is generally not undertaken due to concerns of significantly increased normal tissue toxicity, particularly cardiac, if full RT and chemotherapy doses are employed (17).

For locally advanced T3–4 breast cancer, Formenti *et al.* achieved a promising 20% pathologic complete response (pCR) rate with concomitant 5-fluorouracil (5-FU) and RT despite limiting RT to a total dose of 50 Gy due to concerns about skin toxicity (18). Taxanes have been observed to produce response rates of 50–60% when used as single agents for untreated metastatic breast cancer. Taxanes also have documented activity in anthracycline-resistant breast cancer (19). For operable breast cancer, single agent neoadjuvant paclitaxel has produced a similar response rate to that achieved with the combination of 5-FU, doxorubicin, and cyclophosphamide (20). There are also preclinical data suggesting that taxanes result in greater radiosensitization of tumor than normal tissue, suggesting a favorable therapeutic ratio for concurrent CRT (21, 22). Our institution has significant experience with aggressive concurrent CRT protocols for head-and-neck cancer employing taxanes, and the results have been quite promising (23). The combination of vinorelbine and paclitaxel demonstrated a 60% response rate as first-line chemotherapy for metastatic breast cancer (24), and vinorelbine has also been demonstrated to sensitize non–small-cell lung cancer cells to radiation *in vitro* (25). Therefore, patients with Stage IIIB–IV ULABC were enrolled on two consecutive Phase I/II trials investigating concurrent RT and paclitaxel ± vinorelbine using a novel week on/week off (WO/WO) treatment schedule.

METHODS AND MATERIALS

Eligibility criteria and pretreatment evaluation

Between November 1995 and March 2003, 33 patients with unresectable T4N0-3M0-1 American Joint Committee on Cancer 2003 Stage IIIB–IV breast cancer or unresectable chest wall recurrences were enrolled as part of two consecutive Phase I/II trials evaluating the safety of concurrent radiation and paclitaxel-based chemotherapy. The 16 patients with Stage IIIB–IIIC, T4N0-3M0 disease are the primary focus of this investigation. The patient characteristics are shown in Table 1. Patients were evaluated and prospectively staged by a multidisciplinary team consisting of surgical, radiation, and medical oncologists and were deemed to be unresectable. Patients underwent a standardized staging workup consisting of complete medical history and physical examination, complete blood count, differential, comprehensive metabolic profile, chest radiograph, computed tomographic (CT) scan of the chest and upper abdomen, bilateral mammogram, and bone scan.

Patients eligible for protocol enrollment were required to have histologically proven adenocarcinoma of the breast. Exclusion criteria included prior treatment with nitrosoureas, mitomycin, high-dose chemotherapy or prior ipsilateral breast or chest wall RT. Other eligibility criteria were: age greater than 18 years, Cancer and Leukemia Group B performance status <3, life expectancy ≥ 12 weeks, absolute neutrophil count $>1500/mm^3$, platelet count $>100{,}000/mm^3$, creatinine ≤ 2.0 mg/dL, bilirubin ≤ 1.5 mg/dL, and alanine aminotransferase ≤ 3 times upper limit of normal. Hormonal therapy was not allowed during treatment on protocol. All patients provided institutionally approved written informed consent.

Table 1. Patient characteristics

Parameters	Stage IIIB–C (n = 16)	Stage IV or recurrent (n = 17)
Age	range (26–69)	range (37–72)
<50	4	4
≥50	12	13
Race		
Non-Hispanic white	10	6
Black	6	10
Other	0	1
Performance status		
CALGB 0	10	9
CALGB 1	6	8
CALGB 2	0	0
Clinical node stage		
N0	7	7
N1	6	5
N2	2	4
N3	1	1
Inflammatory		
Yes	9	8
No	7	9
Pathologic grade		
1	0	0
2	6	4
3	8	11
Not available	2	2
ER status		
Positive	4	6
Neg but PR-positive	2	0
Neg and PR-negative	9	9
Not available	1	2
Prior chemotherapy		
Yes	5	9
No	11	8

Abbreviations: CALGB = Cancer and Leukemia Group B; ER = estrogen receptor; PR = progesterone receptor.