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REVIEW ARTICLE

Concurrent chemoradiotherapy for locally advanced breast cancer—time for a new paradigm?

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ABSTRACT

Background

In cases of locally advanced breast cancer (LABC), preoperative ("neoadjuvant") therapy was traditionally reserved to render the patient operable. More recently, neoadjuvant therapy, particularly chemotherapy, is being used in patients with operable disease to increase the opportunity for breast conservation. Despite the increasing use of preoperative chemotherapy, rates of pathologic complete response, a surrogate marker for disease-free survival, remain modest in patients with locally advanced disease and particularly so when the tumour is estrogen or progesterone receptor–positive and HER2-negative. A new paradigm for LABC patients is needed. In other solid tumours (for example, rectal, esophageal, and lung cancers), concurrent chemoradiotherapy (CCRT) is routinely used in neoadjuvant and adjuvant treatment protocols alike.

Results

The literature suggests that CCRT in LABC patients with inoperable disease is associated with response rates higher than would be anticipated with systemic therapy alone.

Conclusions

Ongoing trials in this field are eagerly awaited to determine if CCRT should become the new paradigm.

KEY WORDS

Breast cancer, concurrent chemoradiotherapy, neoadjuvant therapy, locally advanced disease

1. INTRODUCTION

Locally advanced breast cancer (LABC) was initially defined as a heterogeneous group of tumours deemed inoperable either by size or by location[1]. More recently, the definition has evolved to include tumours larger than 5 cm (T3N0 or T3N1) or the presence of bulky metastatic lymph nodes on physical exam (stage IIB–IIIC)[2]. Although the natural history of LABC often varies depending on biologic subtype [for example, hormone and HER2 (human epidermal growth factor receptor 2) status], staging criteria are still based on the anatomic features of tumour size and lymph node involvement.

Traditionally, preoperative ("neoadjuvant") systemic therapy has been used to downstage tumours in the hope of making inoperable disease operable. In recent years, neoadjuvant therapy has increasingly been used in patients with operable disease. The objectives in this setting include improving surgical choice (that is, the ability to choose breast-conserving therapy) and allowing for an assessment of the *in vivo* response to systemic treatment. A number of clinical studies have even made use of the *in vivo* response to conduct sequential tissue biopsies and assess a range of biomarkers of resistance and sensitivity to neoadjuvant treatment. It had been hoped that earlier introduction of systemic therapy in the neoadjuvant setting would be associated with a survival advantage over traditional postoperative adjuvant therapy. Sadly, however, such an advantage has not been seen in most studies[3–7], but its potential remains an area of great interest for tumours of specific molecular subtypes such as HER2-positive or triple-negative[7].

Several trials assessing neoadjuvant therapy in predominantly operable patients have shown that the amount of residual disease in breast and axilla is inversely related to survival and that pathologic complete response (pCR) is associated with a significantly better prognosis[3,7–13]. Indeed, pCR is frequently used in clinical trials as a surrogate endpoint on the assumption that it is predictive of disease-free survival (DFS)[14]. In the setting of operable disease, rates of pCR range from 3% to 29%[15]. Although patients with HER2-positive or triple-negative breast cancer achieve the highest rates of pCR (31% and 27% respectively),

relapse rates in the absence of pCR remain high[16]. In contrast, patients with estrogen receptor–positive disease have a better overall prognosis regardless of pCR[16].

Only a handful of large-scale prospective neoadjuvant chemotherapy trials in patients with LABC or inflammatory breast cancer (IBC) have been published. An international, multicentre trial of epirubicin and cyclophosphamide in LABC and IBC, which compared neoadjuvant dose intensification (120 mg/m^2 epirubicin and 830 mg/m^2 cyclophosphamide on day 1 every 14 days for 6 cycles) with standard dosing (60 mg/m^2 epirubicin on days 1 and 8 and 75 mg/m^2 oral cyclophosphamide on days 1–14 every 28 days for 6 cycles), did not show an improvement in the rate of pCR (14% and 10% respectively)[17]. On the other hand, the SICOG trial showed that a weekly regimen of paclitaxel, epirubicin, and cisplatin improved the pCR rate in estrogen receptor–negative tumours (27.5% vs. 5.4%, $p = 0.026$) and in HER2-positive tumours (31% vs. 5%, $p = 0.037$)[18]. Results of the long awaited SWOG 0012 trial were recently published. It randomly assigned patients with IBC or LABC to treatment either with conventionally-dosed doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by weekly paclitaxel, or with metronomic doxorubicin 24 mg/m^2 weekly and cyclophosphamide 60 mg/m^2 daily followed by standard weekly paclitaxel. No overall differences in the pCR rate or survival were found between those regimens[19]. Clearly, the foregoing trials cannot directly compare response rates in operable and advanced disease, and the lower rates of pCR observed in patients with a LABC rather than with an operable breast cancer have therefore been assumed to reflect the increased bulk of disease.

A recent analysis by the GEPAR TRIO group looked at response rates in patients with operable breast cancer ($n = 1777$), LABC ($n = 193$), and IBC ($n = 94$). The pCR rate was observed to be lower in the LABC and IBC groups combined than in the operable group (10.5% vs. 17.7%, $p = 0.002$)[16]. When all patients were included, young age, non-lobular histologic type, grade 3 disease, and hormone receptor–negative status all were independent predictors of pCR. Tumour stage was not itself an independent predictor of pCR. The lower response rate seen in the LABC and IBC groups of the GEPAR TRIO trial might therefore be more reflective of the pathologic characteristics of LABC and IBC tumours than simply of an advanced stage at diagnosis[16].

Amplification of the gene encoding HER2 in breast cancer is a poor prognostic factor that is associated with advanced stage. However, the development of trastuzumab has dramatically changed the natural history of HER2-positive breast disease in the metastatic and adjuvant settings. It is not surprising that three large phase III trials—the MD Anderson Cancer Center neoadjuvant trastuzumab trial, the Neoadjuvant Herceptin (NOAH) trial, and the GeparQuattro trial—demonstrated that, compared with chemotherapy alone, neoadjuvant trastuzumab plus chemotherapy significantly increased pCR rates to as high as 65%[20–22]. Improvements in 3-year event-free survival (76% vs. 56% for the trastuzumab groups) were also reported in the NOAH trial[22].

Clearly, a need to optimize both local and systemic care for inoperable LABC remains. Improvements in chemotherapy regimens, such as the sequential addition of taxanes, have slightly improved pCR rates[23,24]. For patients with LABC who remain inoperable after neoadjuvant systemic therapy, the accepted approach is to treat with salvage radiation therapy in an attempt to convert to an operable state. In the largest reported series in that setting, more than 80% of patients were found to be able to proceed to mastectomy after moderate radiation doses, and 28% of them remained disease-free after 6 years of follow-up[25]. Furthermore, in patients entered into trials of neoadjuvant systemic therapy, adjuvant radiation appears to confer additional local control and DFS benefits, even after a pCR[26]. Those data suggest that the effects of radiation are complementary to those of chemotherapy in LABC and that combining those approaches might lead to improved outcomes.

In breast cancer, the approach since the advent of anthracycline-based regimens has been to sequentially deliver chemotherapy and then radiotherapy (RT). For other tumour sites (gastric, rectal, and lung cancers), concurrent treatment with chemotherapy and RT has improved local control, which has translated into survival benefits[27–31]. In nonoperable LABC, locoregional control remains a significant problem. Concurrent chemoradiotherapy (CCRT) might be an attractive approach to improve outcomes. Significant improvements in locoregional control and better conversion rates from a nonoperable to an operable state might translate into increased survival. The present review describes an experience of CCRT for inoperable LABC, addressing the use of CCRT in the adjuvant (that is, postoperative) setting and the results of completed and ongoing neoadjuvant trials in patients with LABC.

2. STANDARD ADJUVANT THERAPY

Surgery, systemic chemotherapy, and RT all have integral roles in the multimodal treatment of breast cancer. The current standard treatment approach is surgical excision of the primary breast tumour, if technically feasible, by lumpectomy or mastectomy. After surgery, various systemic therapies and radiation are considered based on the pathologic features of the tumour, with the objective of maximizing DFS and overall survival (OS). In higher-risk disease the standard approach is to deliver chemotherapy first, followed by RT. Although that approach is widely accepted and practiced, the optimal sequence of delivery is unclear. In the adjuvant setting, chemotherapy and RT can be given sequentially (that is,

systemic therapy followed by RT), concurrently, or in a sandwich approach (that is, RT sandwiched between cycles of chemotherapy).

Data supporting sequential treatment derives mostly from studies in early-stage breast cancer. From pooled data of 10 retrospective studies, delaying RT in favour of chemotherapy increased the risk of local relapse to 16% from 6%[32]. Furthermore, RT given more than 8 weeks after surgery has been shown to double the local recurrence rate[32]. The only prospective trial designed to answer the questions concerning sequential treatment in early breast cancer demonstrated that patients initially given RT had higher rates of distant relapse; in contrast, patients initially given chemotherapy had higher rates of local relapse[33]. The differences were no longer apparent at 10 years of follow-up[34]. A major limitation of the sequential studies is that the systemic treatments in use at the time are not comparable to modern chemotherapy regimens, which typically include taxanes or targeted agents such as trastuzumab. It is therefore possible that the differences in local relapse rates seen in the foregoing studies might overestimate the clinical reality today.

3. CONCURRENT CHEMORADIOTHERAPY

Chemotherapy concurrent with radiation has the potential to offer patients the combined benefits of improved local and distant disease control. In early breast cancer, CMF (cyclophosphamide–methotrexate–5-fluorouracil)–based adjuvant CCRT has been studied in several trials. Although that treatment had an acceptable toxicity profile and a shortened overall treatment time, clinical benefit in terms of OS or DFS has not consistently been shown[35–38]. Anthracycline-based CCRT has been associated with serious skin toxicity, including recall reactions and cardiac toxicities. In the multicentre randomized Arcosein trial, CNF (mitoxantrone 12 mg/m^2, in combination with cyclophosphamide 500 mg/m^2 and fluorouracil 500 mg/m^2) every 21 days for 6 cycles, with RT starting during cycle 1, was compared with sequential CNF and RT; concurrent treatment was shown to improve local control in lymph-node-positive patients[39,40]. Unfortunately, the concurrent regimen failed to show any benefit in 5-year DFS and OS. Similar results were seen in a French multicentre trial comparing concomitant CNF and RT with CEF (cyclophosphamide–epirubicin–5-fluorouracil) and sequential RT[41]. A benefit in local control and a decline in the local recurrence rate by a factor of 2.8 was seen in the concurrent treatment arm, with no significance difference in OS and DFS being observed. Unfortunately, mitoxantrone has been associated with high rates of leukemic transformation; it is therefore now rarely used.

Anthracyclines and taxanes are the backbone of most modern breast chemotherapy regimens in North America. Because anthracycline-based CCRT has been associated with serious skin and cardiac toxicity, the use of taxane-based CCRT has been investigated in patients with operable breast cancer. Taxane-based CCRT has been shown to carry significant toxicity—for example, pneumonitis when paclitaxel was given at weekly and every-three-weeks doses of 60 mg/m^2 and 175 mg/m^2 respectively[42]. Although other studies have shown such regimens to be safe, apart from mild skin toxicities (see Table I), they are not recommended in the early (operable) breast cancer population because of the increased risk of toxicity from taxane-based CCRT.

In exploring the role of CCRT in breast cancer, the use of pCR as a surrogate for an increase in survival has its limitations. The correlation of survival with pCR achieved after systemic therapy has been well established. That correlation could be attributable to the sterilization of micrometastases if the systemic therapy were capable of achieving a complete response in the primary tumour and lymph nodes. In that setting, pCR would therefore be a reflection of the effect of the treatment on all cancer cells, including disseminated disease. The value of achieving a pCR with CCRT is not known. In fact, if, in a minimalist fashion, RT is viewed as a locoregional treatment, then achieving a pCR might not reflect systemic benefit. However, some authors have proposed an antitumour systemic effect of local breast radiation[14].

4. CCRT IN LABC

Patients with LABC are, by definition, at high risk of both local and systemic relapse and might therefore derive greater benefit from the concomitant use of chemoradiotherapy. The benefit of CCRT has made that treatment modality the standard of care in a range of malignancies (Table II). Surprisingly, in breast cancer, only a handful of small prospective studies have addressed the question of benefit from concurrent treatment. Small phase I/II studies looking at 5-fluorouracil infusion-based chemotherapy in LABC have shown some benefit in the pCR rate and in local control without added toxicity[52,53]. Capecitabine-based CCRT has also been shown to be beneficial in second-line neoadjuvant (salvage) treatment in anthracycline-resistant LABC[54]. Although 5-fluorouracil or capecitabine were shown to potentiate RT with an acceptable toxicity profile in other malignancies, those agents are generally not considered the most active in breast cancer.

The use of taxanes with concurrent RT is controversial. Two studies, one by Skinner *et al.*[55] and the second by Kao *et al.*[48], showed, in phase I/II prospective trials in 39 and 33 patients with LABC and IBC respectively, a benefit from concurrent paclitaxel and RT, especially in locoregional control. Unfortunately, toxicity was seen in more than 41% of patients (Table III).

It has been proposed that toxicities can be significantly reduced if paclitaxel is administered twice weekly at 30 mg/m^2 instead of weekly at 80 mg/m^2 or as a continuous infusion at 20–30 mg/m^2 daily[47]. A recent 5-year update of 105 patients showed high pCR rates without any cases of pneumonitis or rate-limiting toxicities with the use of CCRT containing twice-weekly paclitaxel. Overall, the pCR rate was 34%, with the highest rates achieved in the triple-negative and HER2-positive, hormone receptor–negative subgroups, at 54% and 50% respectively[14].

A possible explanation for the different toxicity profile reported by Formenti *et al.*[47] could be the timing of the anthracycline chemotherapy relative to CCRT and the twice-weekly dosing regimen. In the Formenti study, anthracycline-based chemotherapy was administered to all patients postoperatively. It is possible that the high toxicity rates were a result of synergy between the taxanes, anthracycline, and RT[45]. More prospective trials addressing the toxicity of CCRT and the proper timing and doses of chemotherapy relative to RT are needed.

TABLE I Concurrent paclitaxel and radiotherapy in breast cancer

Reference	*Pts (n)*	*Paclitaxel*		*Radiotherapy dosing (cGy)*	*Toxicity*
		Dose (mg/m^2)	*Schedule*		
Elmongy *et al.,* 1999[43]	32	175–225	Every 3 weeks	5040–6300	Grade 3 skin toxicity: 9
Bellon *et al.,* 2000[44]	8	20–35×4 days	Every 3 weeks	4680–5040	Acute skin toxicity requiring
	9	135–175	Every 3 weeks	plus boost	delay exceeding 5 days: 6
Taghian *et al.,* 2001[45]	7	175	Every 3 weeks	4000–4600	Pneumonitis: 3 of the 21
	14	60–100		plus 600–2000 boost	
Hanna *et al.,* 2002[46]	20	175	Every 3 weeks ×3	BCS: 4500 plus 1600 MAST: 5040 plus 1000	Grade 3 skin toxicity: 7 Pneumonitis: 4
Formenti *et al.,* 2003[47]	44	30	Twice weekly	4500 plus 1800	Grade 3 skin toxicity: 3
Kao *et al.,* 2005[48]	16	20–30×4 days	Every 2 weeks	6000	Greater than grade 3 skin toxicity:
	17	80	Weekly		8 of the 33
Burstein *et al.,* 2006[49]	16	60	Weekly	MAST: 4500 plus 400–1000	Pneumonitis in 3 of 16
	24	135–175	Every 3 weeks	BCT: 4500 plus 1000–1600	
Chakravarthy *et al.,* 2006[50]	38	30	Twice weekly	4500 plus 1400	Skin toxicity: 1
Chen *et al.,* 2010[51]	44	175	Every 3 weeks	3960 plus 1400	Grade 3 skin toxicity: 2

Pts = patients; BCS = breast-conserving surgery; MAST = mastectomy; BCT = breast-conserving therapy.

TABLE II Concurrent chemoradiotherapy with demonstrated survival benefits in solid malignancies

Tumour type	*Indication*	*Chemotherapy agent or agents*	*Benefit*
Head and neck	Locally advanced disease	Cisplatin, 5FU, cetuximab	Improved organ preservation and survival
NSCLC	Stage IIIB, nonmetastatic inoperable disease	Cisplatin, carboplatin, etoposide, paclitaxel	Curative in poor surgical candidates
SCLC	Limited stage disease	Cisplatin, etoposide	Curative in approximately 20%
Esophageal	Locally advanced	Cisplatin, 5FU	Increase cure rate, survival, and organ preservation
Glioblastoma	Adjuvant	Temozolomide	Survival benefit

5FU = 5-fluorouracil; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer.

TABLE III Concurrent chemoradiotherapy in locally advanced (LABC) or inflammatory breast cancer

Reference	*Disease stage*	*Chemotherapy*	*Pts (n)*	*RT dose (Gy)*	*Toxicity*	*Outcome*
Kosma *et al.,* 1997[53]	ULABC failed first-line chemotherapy	5FU 500 mg/m^2 twice weekly	17	75–90 (4–5 twice weekly)	Grade 2 RT pneumonitis: 1 Grade 2 skin toxicity: 2	CR in 5; 3 underwent mastectomy, with all 3 experiencing a pCR
Skinner *et al.,* 2000[55]	IIB–III	Paclitaxel (30 mg/m^2) twice weekly for 8 weeks	29	45	Surgical complications: 41%	Response rate: 89%
Formenti *et al.,* 2003[47]	IIB–III	Paclitaxel 30 mg/m^2 twice weekly	44	45 plus 18	Grade 3 skin toxicity: 7%	CR: 16%
Kao *et al.,* 2005[48]	ULABC (IIIB–C)	Bolus infusion vinorelbine (20 mg/m^2 day 1) plus continuous infusion (20–30 mg/m^2 daily×4 days)	16	60	Moist desquamation: 8	pCR in 7 of 15
Bollet *et al.,* 2006[52]	II–III	5FU 500 mg/m^2 daily days 1–5, and vinorelbine 25 mg/m^2 days 1 and 6	60	50	Grade 4 hematologic: 22%	pCR in 27%
Gaui *et al.,* 2007[54]	ULABC failed first-line chemotherapy	Capecitabine 850 mg/m^2 for 14 days	28	50	Grades 3–4: none	pCR in 1; 82% became operable
Chakravarthy *et al.,* 2006[50]	II–III	Paclitaxel 30 mg/m^2 twice weekly	38	45 plus 14	Skin toxicity: 1	pCR in 13 (34%)
Adams *et al.,* 2010[14]	IIB–III	Paclitaxel 30 mg/m^2 twice weekly	105	45 plus 14	NA	Pathologic response in 34%

Pts = patients; RT = radiotherapy; ULABC = unresectable LABC; 5FU = 5-fluorouracil; CR = complete response; pCR = pathologic complete response; NA = not available.

Two phase I/II Canadian studies of concurrent neoadjuvant radiation with weekly docetaxel in patients with locally advanced noninflammatory breast cancer (OTC 1159 and OTC 1202) are underway, but have yet to report results. In one study using preoperative weekly dose-escalated docetaxel with 6 weeks of daily radiation, followed by postoperative doxorubicin and cyclophosphamide, early indications are that weekly doses of 30 mg/m^2 docetaxel for 8 weeks given with standard radiation treatment are well tolerated (Spayne J. Personal communication). In the second study, administration of every-three-weeks 5-fluorouracil, epirubicin, and cyclophosphamide in standard adjuvant dosing, followed by weekly docetaxel at 35 mg/m^2 with 6 weeks of concurrent daily radiation administered preoperatively is also reasonably well tolerated and appears to be associated with an increased pCR rate (Brackstone M. Personal communication). Both single-arm studies aim to evaluate whether the addition of concurrent radiation to a taxane in the neoadjuvant setting for LABC is associated with an increase in the rate of pCR. Longer-term objectives include evaluating whether patients who achieve a pCR experience a higher 5-year DFS rate than do their non-pCR counterparts. Ultimately, a randomized controlled trial will be designed to evaluate whether the pCR rate is significantly higher with concurrent neoadjuvant chemotherapy and RT than with sequential therapy and to determine definitively whether the relationship between pCR and survival persists with the addition of regional therapy modalities such as RT. It will be important to determine the reliability of pCR as a surrogate measure of DFS or OS in patients treated with combined modalities in breast and other cancer sites.

A possible disadvantage of CCRT is that it might preclude concurrent reconstructive surgery if skin toxicity is more pronounced (no data are yet available to clarify this concern). In contrast, simultaneous administration of chemotherapy and RT limits the duration of treatment and the required hospital visits, without compromising quality of life[56]. The cost-effectiveness of the approach also makes it an attractive alternative in developing countries, where a reduction in hospital visits improves compliance and access to care and reduces the financial burden of cancer care to the country.

5. CONCLUSIONS

When used in LABC, neoadjuvant therapy does not yield the high response rates seen and frequently cited in patients with operable tumours. Although pCR rates can be impressive in patients with triple-negative and HER2-positive disease, poor outcomes are likely for patients who achieve less than a pCR. Furthermore, for most patients whose tumours are not among those high-proliferative subtypes (that is, the estrogen receptor–positive group), pCR might not be an appropriate surrogate for outcome. In inoperable LABC, CCRT can offer a valuable opportunity to improve outcomes. The optimal chemotherapy agent, and its dose and administration schedule, is not known. Promising results with concurrent twice-weekly paclitaxel and RT emphasize the need for larger prospective studies.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to disclose.

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