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REVIEW ARTICLE

Hyperthermia for locally advanced breast cancer

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Abstract

Hyperthermia (HT) has a proven benefit for treating superficial malignancies, particularly chest wall recurrences of breast cancer. There has been less research utilising HT in patients with locally advanced breast cancer (LABC), but available data are promising. HT has been combined with chemotherapy and/or radiotherapy in the neoadjuvant, definitive and adjuvant setting, albeit in series with small numbers of patients. There is only one phase III trial that examines hyperthermia in LABC, also with relatively small numbers of patients. The goal of this review is to highlight important research utilising HT in patients with LABC as well as to suggest future directions for its use.

Keywords: *hyperthermia, locally advanced breast cancer, radiation*

Introduction

Patients with locally advanced breast cancer (LABC) constitute a heterogeneous population. While they were initially classified as having 'inoperable' disease [1], more recently, the term LABC has been applied to patients having stage IIB-IIIC disease [2]. Treatment of these patients has evolved over the years and now often consists of neoadjuvant chemotherapy followed by surgical resection when feasible, with adjuvant radiotherapy (RT) [3–8] and hormonal therapy where appropriate. Prior to the use of combined modality therapy, five-year survival rates of 25% to 45% were reported [9–11]. With more modern therapies, this rate has been reported as high as 80% for patients with IIIA disease and 45% for IIIB, which is still less than satisfactory [6, 12].

Within the subset of LABC, patients may range from resectable T3N0 disease to unresectable T4N2 disease. For the latter, there is no standard of care and treatment may include a variety of chemotherapeutic/hormonal agents with or without radiotherapy, in the hopes of improving resectability [13–19]. For patients able to undergo surgical resection, the rate of pathologic complete response (pCR) has been shown to be significantly correlated with improved overall survival [7]. Hyperthermia (HT) has the potential to increase the pCR rate.

Concurrent chemoradiotherapy

The rationale for the use of concurrent chemoradiotherapy is strong, and has been utilised in numerous other sites including head and neck, lung and gynaecological cancers [20–22]. Paclitaxel, docetaxel and 5-fluorouracil have been shown to act as radiation sensitisers in breast cancer [13, 14, 23–29]. Thirty patients with surgically unresectable LABC were treated with 5-fluorouracil and concurrent radiotherapy to a dose of 50 Gy at the University

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of Southern California [13]. All patients went on to have mastectomy with primary skin closure. They achieved a pCR (defined as no residual tumour cells) rate of 17% and no ≥ grade 3 acute or late toxicities were reported. With a median follow up of 22 months, the crude disease-free survival was 83%; no patient who achieved a pCR had recurred at the time of their analysis.

Two prospective phase I/II trials were carried out at the University of Chicago, utilising concurrent chemoradiotherapy (paclitaxel ± vinorelbine) for unresectable locally advanced including inflammatory breast cancer [14]. The radiotherapy dose was 60–70 Gy to the breast and 60 Gy to the draining lymphatics; it was administered in a week-on, week-off schedule. Of the 33 patients studied, a subset of 16 had non-metastatic LABC and they were analysed separately. Of these 16 patients, 13 (81%) underwent subsequent mastectomy at the completion of concurrent chemoradiotherapy, and seven had a pCR (44%) [14]. With a median follow-up of 44 months, four-year actuarial locoregional control, disease-free survival and overall survival were 83%, 33% and 56%, respectively. There were two acute grade 4 toxicities (neutropenia and skin), and four late grade 3 complications (joint, lymphoedema, and skin/subcutaneous in two).

Several additional series have treated patients with neoadjuvant paclitaxel or docetaxel concurrent with radiotherapy, with the goal of surgical resection [27–29]. Pathological CR was defined as having no residual invasive cancer in the specimen, although carcinoma in situ could still be present [27, 28]. Reported pCR rates ranged from 16% to 34%; acute toxicities were common – more so with docetaxel than paclitaxel – but ≥ grade 3 toxicities were rare. The authors concluded that this combination therapy was safe, and warranted further comparative study with neoadjuvant chemotherapy alone [27–29].

Hyperthermia for LABC

Hyperthermia has also been combined with radiotherapy in an effort to improve local control, which is especially important in the unresectable subgroup of LABC. Hyperthermia's ability to affect cells in S phase, inhibit sub-lethal damage repair and improve oxygenation make it an attractive therapy to combine with radiation and/or chemotherapy in the hopes of synergy [30–33]. The ultimate goal with the addition of hyperthermia to treatment for LABC is improved tumour kill, which most often is assessed with the rate of clinical complete response/partial response (cCR/pPR), and if the patient undergoes surgery, pCR. In addition to the inherent biology of an individual tumour, achieving a CR with thermoradiotherapy depends on the size of the tumour, the dose of radiotherapy used, and the ability to adequately heat the tumour, which can be especially challenging with large burdens of unresectable disease [34–38].

Hyperthermia has been quite effective in the treatment of chest wall recurrences of breast cancer (see Review in this issue of the *International Journal of Hyperthermia*), and has led some to use HT in the setting of LABC (Table I). Most reported series are single institution series [39–52] or anecdotal case reports [53–56]. The goal of utilising HT is to improve the rate of pCR, which hopefully translates into prolonged disease-free and overall survival.

A prospective, phase I/II single institutional trial from Duke University treated 18 patients with LABC (including inflammatory breast cancer) with paclitaxel-based concurrent thermochemoradiotherapy [40]. Radiotherapy was administered in 2 Gy fractions to a dose of 50 Gy to the breast and draining lymphatics, with HT given twice weekly. Patients who did not undergo surgical resection received an additional 10 to Gy boost. Of the 18 patients, 15 had an objective clinical response, of whom six (33%) were considered cCR. Thirteen of these patients underwent mastectomy and three of the six cCR patients had a documented pCR (23%). This rate of pCR is similar to other reported series of LABC patients treated with concurrent chemoradiotherapy (range 16–44%) [13, 14, 27–29]. Whether the patients were strictly comparable is uncertain. The Duke patients may well have been more advanced.

In addition to treatment efficacy and toxicity, tumour oxygenation was measured before and 24 hours after the first HT session to analyse how it contributed to treatment outcome. Those patients who had hypoxic tumours prior to treatment had a statistically significant improvement in oxygenation after HT to levels that were no longer hypoxic. Those patients with well-oxygenated tumours initially and those that had documented improved oxygenation all achieved either a cCR or cPR. Toxicity during therapy included moist desquamation in 16/18 patients and third degree burns in two patients. Of the 13 patients who underwent mastectomy, nine experienced problems with wound healing, but ultimately all healed.

A recently published phase I/II trial from Duke investigated the use of neoadjuvant liposomal doxorubicin, paclitaxel and HT in 47 patients with LABC, 14 (33%) of whom had inflammatory breast cancer [57]. After surgical resection, all patients received adjuvant radiotherapy, and all those that did not achieve a pCR received additional chemotherapy. The clinical combined (CR and PR) response rate was 72%; four (9%) patients achieved a pCR. Those patients who achieved a pCR had higher

Table I. Summary of selected hyperthermia trials in the setting of LABC.

Study	Number of patients	Treatment schema	Results	Toxicity
Jones et al. [40] (prospective)	18; all unresectable	Neoadjuvant paclitaxel/HT/RT→ surgery if feasible	13 patients had MRM 15 had cR (18%); 6 (33%) had cCR pCR in 3 (23%)	Moist desquamation in 16 (89%) 3rd degree thermal injury in 2 (11%) 9/13 (69%) had self-limited wound healing after surgery
Vujaskovic et al. [57] (prospective)	47; 19 were unresectable and 5 were candidates for BCT at presentation	Neoadjuvant liposomal doxorubicin/paclitaxel/HT→surgery→ RT +/- adjuvant chemotherapy (43 completed neoadjuvant treatment)	16 pts eligible for BCT; 8 had it, all others had MRM pCR in 4 (9%), pPR in 22 (51%)	27 (66%) grade 4 neutropenia 4 (9%) with any thermal injury; 1 (2%) with 3rd degree burn
Hofman et al. [51] (retrospective)	40; 33 were unresectable	HT/RT (No mention of surgical intervention if any)	cCR 42% (for T2, T3, T4 disease) 25% for inflammatory disease	Moist desquamation 'slight' in 10 (25%) and 'severe' in 3 (8%) 5 (13%) developed thermal injury
Hand et al. [61] (Prospective, randomised)	29; all unresectable	(1) Definitive RT in 12 versus (2) HT/RT in 17	(1) 8 (67%) had cCR (2) 10 (59%) had cCR	Not reported
Welz et al. [63] (retrospective)	13	10 received neo- or adjuvant chemotherapy; HT/RT was administered adjuvantly	3-year local control 75%	Self limited skin toxicities; specifics not provided

HT, hyperthermia; RT, radiotherapy; MRM, modified radical mastectomy; cR, clinical response (either partial or complete); cCR, clinical complete response; pCR, pathologic complete response; BCT, breast conservation therapy; pPR, pathologic partial response.

cumulative equivalent minutes (CEM 43) at T90 (tenth percentile of temperature distribution) (mean 28.6 minutes versus 10.3 minutes, $p = 0.038$) than those who did not.

The authors postulated that their pCR rate was lower than seen with neoadjuvant taxane monotherapy (~26%, range 11–31%), due to the difference in patients studied; NSABP B27 enrolled patients with T1–3 tumours, while this trial had primarily T3/T4 lesions, with nearly a third having inflammatory breast cancer [58]. Despite having more aggressive disease, four-year disease-free and overall survival rates were quite reasonable at 63% and 75%, respectively. As one might expect with this intensive chemotherapy regimen, haematological toxicity was significant, with 27 (66%) patients developing grade 4 neutropenia. Only four (9%) patients experienced thermal injury.

In addition to the clinicopathological endpoints reported in the trial, the authors also prospectively analysed several potential predictors of treatment response [57]. Tissue from these patients was collected prior to their receiving neoadjuvant chemotherapy, and gene expression profiling was performed [59]. The authors were able to identify genetic patterns to help characterise inflammatory breast cancer, the presence of hypoxia, as well as signatures that predict the persistence of malignant cells in lymph nodes after neoadjuvant chemotherapy [59].

Analysing the same group of patients, Craciunescu et al. studied dynamic contrast-MRI (DCE-MRI) prospectively [60]. They developed a morpho-physiological tumour score (MPTS), that, when measured pre-treatment, showed excellent promise to be able to predict response to neoadjuvant chemotherapy and HT.

A Dutch retrospective analysis of 40 patients with LABC treated with thermoradiotherapy reported a 42% cCR rate for non-inflammatory patients and 25% rate for patients with inflammatory breast cancer [51]. Only 7 (18%) patients had technically 'operable' disease. HT was given once weekly, and RT was given in 2 Gy fractions to the breast and regional nodes to a total dose of 50 Gy, with a 6 Gy boost to grossly enlarged lymph nodes. The three-year local control was 46%; the authors suggested that dose escalation above the 50–56 Gy utilised might improve this control rate. No mention was made as to whether any patients underwent mastectomy, or if any of the 33 patients who were deemed unresectable prior to therapy were downstaged to allow surgical resection.

The only phase III randomised trial that evaluated HT for intact LABC patients was conducted by the Medical Research Council (MRC) [61]. Its results were pooled by the International Collaborative Hyperthermia Group, after accrual of four other competing trials was less than expected; the vast majority of patients in this combined analysis had chest wall recurrences of breast cancer [62]. The MRC trial had two different patient sub-groups; one with recurrent disease, and one with locally advanced carcinomas of the intact breast, the latter of which contained only 29 patients [61]. All 29 patients had T3/4 lesions, and were considered inoperable; whether patients went on to have surgical resection was not reported. Seventeen patients were randomised to 'definitive' thermoradiotherapy, while the other 12 received radiation alone. Radiation was prescribed in 2 Gy fractions to a total dose of 50 Gy, followed by a 15 Gy boost to gross tumour; whether regional lymphatics were treated was not reported. Hyperthermia was administered once weekly, with a goal of maintaining a minimum temperature of 43°C for 60 min, for a total of 6 HT sessions. Thermometry probes were placed both into, and on the surface of tumours for temperature monitoring.

Of the 17 patients who received thermoradiotherapy (details of the 12 who received RT alone were not reported), nearly 50% (8/17) presented with distant metastatic disease. They were irradiated to a median dose of 64 Gy (range 36-70 Gy), and all 17 received at least three HT sessions; 11 of them received all six planned treatments. Ten out of 17 (59%) of patients who received thermoradiotherapy achieved a cCR, versus eight out of 12 (67%) in those treated with radiotherapy alone; these differences were not statistically significant.

When thermal parameters in these LABC patients were compared to the patients with recurrent disease in the same trial, several statistically significant differences were found. Most thermal indices were similar among the two groups (including T_{90} and T_{50}), but time averaged T_{max}, T_{max} (peak) and %sensors > 43°C were all lower in the patients with intact breasts [61]. The authors postulated that these discrepancies could be explained by the fact that while patients with recurrent disease had larger areas of disease (median 93 versus 44 cm^2, $p = 0.04$), patients with intact breasts had greater tumour depths. In addition, the response rates may have been higher in the patients with locally advanced disease if the HT was able to be administered and have a higher percentage of sensors > 43°C, as the goal of HT in the trial was to maintain all thermometry probes at > 43°C for 60 min, suggesting the patients with intact breasts were not heated adequately with the technique utilised.

Some patients with LABC still undergo surgical therapy upfront and adding HT to RT in the adjuvant setting after mastectomy has been performed. Welz et al. reported a retrospective single

institution subset analysis of 13 patients who were treated with thermoradiotherapy in the adjuvant setting; 10 of these patients received either neo- or adjuvant chemotherapy (none received concurrent chemotherapy) [63]. HT was added to radiotherapy in this 'high-risk' population for margins <1 cm/R1 resection, T3/4 disease, >3 positive axillary lymph nodes or grade 2/3 tumours. There was only one local recurrence observed, at 31 months after treatment (median follow up 28 months), for a three-year actuarial local control rate of 75%.

Conclusions

The goal of adding hyperthermia to radiotherapy and/or chemotherapy is to increase response rates, and hopefully local control and disease-free survival. It has a strong theoretical basis, and has been shown to have benefit in the setting of chest wall recurrences of breast cancer. As preoperative chemotherapy has been shown to improve outcomes in the setting of LABC, it seems intuitive to intensify preoperative therapy so as to further improve these outcomes. The addition of HT to preoperative chemoradiotherapy has been shown to increase cCR and pCR rates more so than chemotherapy alone in small series and is similar to some reports of concurrent chemoradiation. Cooperative randomised trials need to be performed that look at HT + chemotherapy versus HT + chemoradiotherapy or chemoradiotherapy alone, in the neoadjuvant setting to see if HT adds an advantage. The lack of widespread access to institutions with the experience to perform HT is a critical barrier to such trials and needs to be addressed. Measures of tumour physiology, in particular tumour oxygenation, either invasively or non-invasively, may help better select patients who could benefit from these approaches.

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