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Local-Regional Treatment of the Patient With Inflammatory Breast Cancer

Michael C. Stauder · Wendy A. Woodward

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Abstract Inflammatory breast cancer (IBC) is a diagnosis based on a constellation of clinical features including a rapid onset of breast erythema and edema (peau d'orange) of a third or more of the skin of the breast and with a palpable border to the edema. Incidence has increased although it makes up only 1–4 % of all breast cancer diagnoses. In spite of some encouraging recent clinical outcome data, published local-regional control rates are consistently lower than expected in non-IBC and are of particular concern in this disease that readily progresses locally to carcinoma en cuirasse. With a focus on radiotherapy, this review provides a critical evaluation of the recent literature evaluating local-regional treatment of IBC, highlights new findings in the local-regional management of IBC, and offers an introduction to future directions regarding the optimal treatment and management of IBC.

Keywords Inflammatory breast cancer · Post-mastectomy · Radiation therapy · Metastatic disease · Modified radical mastectomy · Radiosensitizer · DNA repair · Immunotherapy · PARP inhibitor · Stem cells · Mevalonic acid · Statin · Recurrence · Breast cancer

Introduction

The diagnosis of inflammatory breast cancer (IBC) comprises only a small subset of all breast cancers in the USA yet accounts for up to 10 % of breast cancer mortality. The incidence of IBC is increasing and, based on Surveillance, Epidemiology and End Results Program (SEER) and North American Association of Central Cancer Registries database figures, has more than doubled over the last 30 years [1, 2]. This increase is higher than that for the incidence of non-IBC. In addition, overall survival (OS) is significantly worse for IBC compared to non-IBC, but despite the increased incidence, the OS has changed only slightly over that same period of time. This has been primarily attributable to advances in systemic chemotherapy since local-regional control (LRC) rates have remained relatively constant [3].

When looking at historical data, the treatment outcomes for patients with non-metastatic IBC treated with trimodality therapy show a less than optimal rate of LRC. The 5-year range for LRC according to a recent review is 73–92 % [4]. Compared to a 97 % 5-year rate of LRC in non-IBC patients treated with a contemporary regimen of neoadjuvant chemotherapy, modified radical mastectomy, and adjuvant RT, the rate of LRC in IBC is remarkably low [5]. As a result, aggressive local therapy, which includes RT acceleration, bolus (tissue equivalent used to increase RT skin dose), and/or total dose escalation is likely needed to help improve LRC rates in this population [6–8].

Recent Literature in the Local-Regional Management of IBC

Choice of Surgical Procedure

In the trimodality management of IBC, chemotherapy is generally delivered as the initial treatment. In non-IBC patients, previous studies have shown that frequently, neoadjuvant chemotherapy can allow for an increased rate of

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M. C. Stauder (✉) · W. A. Woodward
Division of Radiation Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1202, Houston, TX, USA
e-mail: mstauder@mdanderson.org

M. C. Stauder
e-mail: wwoodward@mdanderson.org

breast preservation surgery in patients that otherwise were previously ineligible. In one large cooperative group study, the frequency of lumpectomy in patients with tumor size ≥5.1 cm was increased from 8 to 22 % with the use of neoadjuvant chemotherapy. On long-term follow-up, no effect on OS was seen in these patients [9].

In patients with positive lymph nodes at presentation or on sentinel lymph node biopsy, the possibility of omitting axillary lymph node dissection (ALND) has emerged as a new area of controversy among the non-IBC population [10, 11]. Neither of these approaches has been evaluated in an IBC patient population and at present, and consistent with National Comprehensive Cancer Network guidelines, nothing other than mastectomy with full ALND, or modified radical mastectomy can be recommended for the surgical management of IBC [12].

Aggressive Radiotherapy Regimens

A large retrospective study from the University of Texas MD Anderson Cancer Center showed an increased rate of LRC compared to historical standards using a hyperfractionated, dose-escalated radiotherapy technique [13]. This relationship is especially true in patients with involved margins, age≤45, and a poor response to chemotherapy. The radiotherapy techniques described therein have become the standard of care at our institution.

Other published single-institution studies also show an improvement in LRC rates when RT acceleration, bolus, or dose escalation is used. Investigators from Cleveland Clinic report a 100 % 5-year LRC rate in patients receiving more than 60.4 Gy of RT compared to 83 % in those receiving 60.4 Gy or less [8]. A more recent study from Mayo Clinic which details their institutional experience with once-daily RT has comparable results, reporting a 5-year LRC rate of 81 %. In this experience, an aggressive use of daily skin bolus substitutes for an increased total radiation dose, but also resulted in a 46 % rate of grade 3 radiation dermatitis [14].

In another study of 107 patients treated with a moderate dose (median 50.4 Gy) and daily skin bolus, the LRC rate at 5 years was equal to 87 %. Of note, however, in patients receiving>60 Gy, a LRC rate of 100 % was observed [7]. Among these recent studies, it appears clear that acceleration, bolus, and/or total dose plays an important role in local control and one of these strategies is warranted in all IBC cases [15].

Extent of Radiation Treatment Volumes

Post-mastectomy radiation including the chest wall, level III, supraclavicular nodes, and internal mammary nodes is standard of care in this aggressive disease with a propensity to involve all nodal stations. PET/CT and upfront medical imaging are extremely helpful in setting PMRT field borders and ensuring adequate dose to initially involved nodes [16]. Standard radiation therapy fields for IBC include generous margins on the initially involved skin especially in the inferior and medial directions. If necessary, the fields should include the skin of the upper abdomen and encroach upon or include a portion of the contralateral breast (Fig. 1a). Given the skin involvement in IBC, it becomes an important target and care should be taken to ensure no gaps on the skin exist when matching fields. The overlapping of field borders by 2–3 mm is one approach to avoid this issue associated with minimal toxicity.

Tumor involvement of the dermal lymphatics, which is the pathologic hallmark of IBC, as well as post-operative changes, may promote aberrant lymphatic drainage making the failure pattern of IBC somewhat unpredictable. Patients with IBC can often have progression via skin and dermal lymphatics to the contralateral upper abdomen, breast, or lymph node areas (Fig. 1b, c). The prevalence of local progression to carcinoma en cuirasse also provides an impetus for the use of large radiation therapy fields. Involvement of the contralateral lymph node drainage basins, while not common in non-IBC, is sufficiently common to merit bilateral imaging in patients with IBC. PET/CT scan data for 177 patients with IBC demonstrates that 27 % of patients had involvement of the contralateral nodal basins, and 13 (7.3 %) had isolated contralateral disease without other distant metastases. Local control of the contralateral nodal basin(s) was achieved in all 13 patients with either definitive or post-surgical radiation [17•]. This suggests that definitive treatment of bilateral disease in patients with limited contralateral nodal metastases may have some benefit. As a result, further studies evaluating the extent of radiation therapy volumes are warranted.

Management of Metastatic IBC

Up to 30 % of patients with IBC present with metastatic disease [2]. Historically, patients with metastatic disease have been treated with systemic therapy alone given the very low survival. However, current hypotheses suggest that additional local therapy may be beneficial as a way to improve OS rates in patients with M1 IBC and it is certainly critical for local control in this at risk population. Recent SEER database analysis reports a 2-year OS of 39 % in patients with M1 IBC [1]. Primary tumor resection resulted in a 51 % decreased risk of death compared to those who did not undergo surgery [18]. In addition, a recent single-institution study reported that surgery plus radiotherapy was associated with a statistically significant OS benefit compared to either treatment alone. Additionally, local control was four times more likely (HR 0.25 for recurrence) in patients receiving surgery compared to patients who received chemotherapy alone [19•].

Further, a report from MD Anderson shows that in addition to systemic therapy, treatment of all metastatic sites that can be

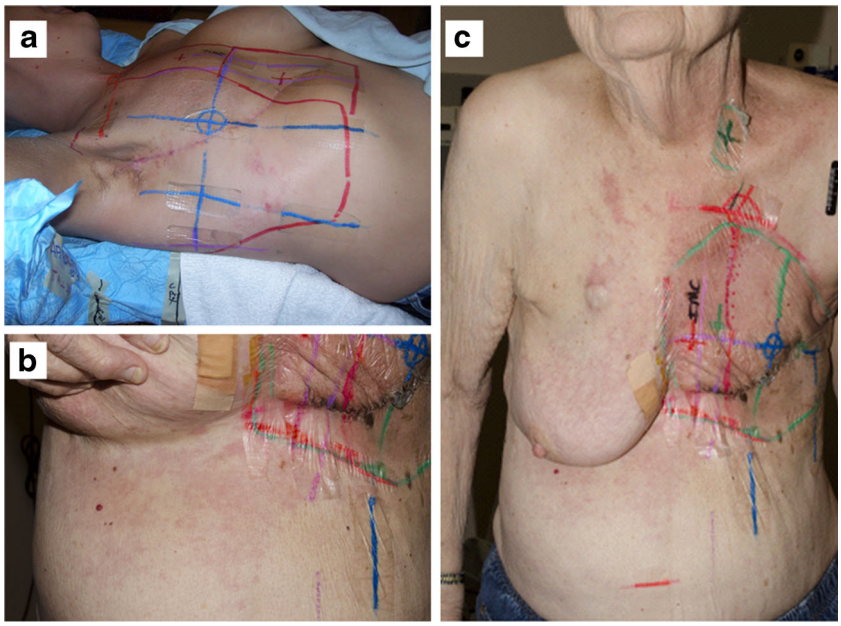

Fig. 1 **a** Standard radiation therapy fields for IBC include generous inferior and medial margin which should include the skin of the abdomen and encroach upon or include the contralateral breast. **b** Relationship of inappropriately small RT fields to observed tumor spread into the skin of the abdomen. **c** Evidence of progression within the skin of the contralateral abdomen, breast, and infraclavicular area

treated safely with radiotherapy is associated with durable NED status in the select cohort of patients offered this approach. This is especially true in patients with hormone receptor positive disease and patients who have a complete pathologic response to chemotherapy. These 177 patients with metastatic IBC treated with this aggressive PMRT approach had an actuarial local-regional recurrence rate (LRR) of 14 % at 31 months median follow-up [20•]. This rate is very similar to the 8–22 % historical 5-year LRR reported in several studies including only stage III IBC patients without metastatic disease [21, 22].

Future Directions in the Management of IBC

Radiosensitizers

Given the need for improved LRC rates, recent clinical trials have focused on adding radiosensitizing agents in order to maximize the therapeutic benefit of radiotherapy. A recently completed phase 2 trial in high-risk, triple-negative IBC and non-IBC patients with inoperable or marginally operable gross disease highlights the challenges of developing a good radiosensitizer for use in the clinical setting [23]. Patients in this trial had excessive grade 3 toxicity with twice daily 825 mg/m^2 capecitabine dosing and when changed to once daily given only on days RT was given, the trial needed to be stopped early at unplanned interim analysis due to futility.

Given the preponderance of triple-negative receptor subtype in IBC, the use of a poly (ADP-ribose) polymerase (PARP) inhibitor is potentially of interest in IBC. In early studies examining PARP inhibition, anti-tumor effect was demonstrated when given orally [24, 25]. When used with chemotherapeutic agents, PARP-inhibitors sensitize cells to agents such as topoisomerase I inhibitors, alkylating agents, and temozolamide [26, 27]. To prepare to evaluate its role as a radiosensitizer, a phase 1 study looking at the use of the PARP-inhibitor veliparib administered concurrently with chest wall and nodal RT in patients with inflammatory or locally recurrent breast cancer was undertaken by the TBCRC [28]. This clinical trial has recently completed accrual and we anticipate the results later this year.

The function of PARP inhibitors makes it a very intriguing candidate for use as a radiosensitizer. Mechanistically, DNA damage results in the recruitment of PARP 1/2 to the site of damage and acts as a catalyst for the formation of PAR which interacts with proteins involved in the cellular response to DNA damage [29]. This is especially true in patients with BRCA mutations [24, 25, 30]. Examples of the action of PAR include increasing access to breakage sites by interacting with histones, signaling the extent of DNA damage and mediate the recruitment of DNA repair factors such as XRCC1 to the site of DNA damage [31].

Immunotherapy

Although there is no overt, consistent pathologic infiltrate in IBC, careful examination of white cells in IBC tumors has not yet been undertaken. All of the reported triple-negative subtypes, including the immunomodulatory subtype are also evident in IBC cohorts, although this subtype is not disproportionately represented in IBC [32]. Bertucci et al. have also recently demonstrated that the response to chemotherapy in IBC is related to an immune response [33•]. Although further examination is required to determine if IBC is truly an immunogenic

disease, it is noteworthy that the downstream molecular effects of radiation on tumor cells also make it an ideal agent to combine with immunomodulatory agents.

Radiation exposure causes cells to provide a source of antigen for the immune system as tumor cells label themselves with death signals [34]. As a result, several potential pathways exist in order to provide a therapeutic gain when combined with RT. The programmed death-1 (PD-1) pathway which is active in T cells can be utilized to enhance killing of tumor. PD-1 is induced on the surface of T cells after activation and acts as a negative regulatory molecule by limiting T cell function, helping to maintain an immunosuppressive tumor microenvironment, decreasing production of proinflammatory cytokines, and preventing progression through the G1 phase of the cell cycle [35–37].

There is strong support in preclinical studies for enhanced radiation effect and an increase in LRC rates with the use of RT combined with anti-PD1 agents [38]. In addition, an abscopal effect or tumor regression distant to the site of radiation can often be observed in murine models when anti PD-1 agents are combined with RT [39]. As future clinical trials are developed for IBC, this approach will certainly be embraced if these preliminary results continue to provide a clinical benefit in other breast cancer subtypes.

Mechanisms of Radiation Resistance

Several authors have suggested that radiation resistance is a function of persistent stem-like cancer cells in aggressive cancers after radiation exposure [40–42]. Van Laere et al. have convincingly demonstrated an enrichment of virtually all mammary or breast cancer-related stem cell signatures in IBC [43]. Of many purported breast cancer stem cell survival pathways, mevalonate, which is activated in basal breast cancer stem cells, has also recently been demonstrated to play an important role in radiation resistance in IBC [44]. Specifically, Lacerda et al. recently demonstrated that simvastatin radiosensitizes mammosphere-initiating cells (MICs) of IBC cell lines but radioprotects MICs of non-IBC cell lines. In this retrospective clinical study of 519 IBC patients treated with post-mastectomy radiation, actuarial 3-year local recurrence-free survival (LRFS) was higher among statin users, and on multivariate analysis, statin use was shown to be independently associated with a higher LRFS [45•]. These data are certainly intriguing and warrant further investigation particularly in light of the findings by Martin and Van Golen demonstrating disparate cholesterol uptake and storage in IBC vs. non-IBC cells [46].

Conclusions

Overall rates of LRC in IBC have been low, especially compared to non-IBC. The continued improvement of systemic therapy options have made achieving LRC in IBC even more important. As we move forward, in order to help improve LRC outcomes, development of the various novel techniques described here will likely become a priority.

Compliance with Ethics Guidelines

Conflict of Interest

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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