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Review

Post-operative radiotherapy in the management of metastatic inflammatory breast cancer

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ABSTRACT

With this review, we aimed to describe the role of adjuvant radiotherapy in the therapeutic management of metastatic inflammatory breast cancer, a rare and aggressive disease historically characterized by high rates of recurrence and poor prognosis. In the context of a multimodality approach, Post-Mastectomy Radiotherapy (PMRT) affirms its role as an appriopriate treatment strategy to improve loco-regional tumor control in selected patients. Further validation in prospective trials is required to better define a standardized therapeutic management of this disease.

1. Introduction

Inflammatory breast cancer (IBC), firstly described by Lee and Tennenbaum in 1924[1], is a form of breast cancer characterized by high aggressiveness. It corresponds to approximately 1–5% of all breast tumors and it is classified as T4d according to the TNM.[2,3]

Almost 30% of IBC patients are already metastatic at the time of diagnosis. Metastatic inflammatory breast cancer (mIBC) typically shows high rates of loco-regional recurrence (LRR) and poor prognosis,[4] constituting a challenge for the clinician to find the best therapeutic approach. A multidisciplinary treatment strategy is highly recommended for women with mIBC. Multimodality treatment including preoperative chemotherapy, modified radical mastectomy, post-operative radiotherapy of the chest wall and regional lymph nodes, together with adjuvant systemic therapy (if needed) have contributed to improve prognosis and to limit local disease progression.[5,6]

Loco-regional radiotherapy can reduce the risk of LRR, an occurrence that could have a detrimental effect on patients' quality of life and lead to death in some critical cases.[7]

The objective of this study is to briefly analyze the role of post-operative radiotherapy (RT) in mIBC in terms of loco-regional control (LRC) and distant disease progression, and to discuss the technical aspects of loco-regional irradiation.

2. Metastatic IBC characteristics

Inflammatory breast cancer (IBC) is an uncommon and highly aggressive type of locally advanced breast cancer (LABC).[5] A multidisciplinary approach is recommended, nevertheless IBC typically shows poor prognosis, with almost 35% overall survival rate at 5 years.[5] IBC mainly affects young women and its diagnosis is specifically based on clinical criteria. There is typically a skin involvement. Main clinical features are quick development of erythema in less than half of the breast, edema, peau d'orange, nipple retraction, rapid swelling, warmth and redness. An underlying palpable mass is not always detectable.[4,5] A great problem about IBC is the delayed diagnosis related to its clinical presentation that can mimic an infection (mastitis or cellulitis) or abscess, although typical signs of infections such as fever or leukocytosis are usually absent.[5,8] One of the most important pathological characteristics of IBC is the finding of tumor emboli in the dermis tumor parenchyma and dermal lymphovascular spaces, which lead to draining lymph vessels obstruction.[9] All this contributes towards producing clinical skin changes. Tumor emboli origin could be related to over-expression of E-cadherin, a transmembrane glycoprotein implicated in cell adhesion.[10] To demonstrate dermal lymphatic involvement, it is necessary to carry out a skin punch biopsy.[4]

IBC is a high-grade ductal carcinoma, often not expressing hormone (estrogen and progesterone) receptors. This feature is

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associated with a more aggressive clinical behavior and a worse prognosis, with a median survival of 2 years.[11] In many cases of IBC, HER2 (human epidermal growth factor receptor) overexpression has been detected, but its clinical significance in this setting is not clear.[11] However, Zell et al. have shown that HER2 positive status should not be considered as prognostic of decreased survival in IBC, whereas it is useful to identify patients that benefit to receive targeted therapy with Trastuzumab.[12] Other molecular markers have been evaluated, such as the expression of p53, whose mutations are associated with an aggressive form of IBC, early metastasis and lower response to chemotherapy.[4,13] Growth factors such as VEGF (vascular endothelial growth factor) are overexpressed in IBC, resulting in increased angiogenesis. This could explain the high incidence of lymphatic and blood metastasis and the angioinvasive potential of the tumor.[4,11] An overexpression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and X-linked inhibitor of apoptosis (XIAP), two key regulators of cellular pro-survival pathways, has also been identified and their inhibition could potentially lead to a reduced tumor emboli formation.[9,11]

3. Role of radiotherapy in the clinical management

Post-mastectomy radiotherapy (PMRT) plays a pivotal role in the loco-regional treatment of mIBC.[4–6,14–17] With the development of more effective systemic treatments, complete or partial pathologic response has increased, allowing the use of RT for a greater number of patients. Nevertheless, due to the rarity of this disease, limited data are available in this setting (Table 1).

In 2008, Bristol et al. reported their experience at MD Anderson on the multimodality treatment of IBC. They retrospectively reviewed 192 patients treated with trimodality therapy (systemic chemotherapy, mastectomy and PMRT to chest wall, supraclavicular lymph node and axilla). In their analysis, they identified several factors influencing local recurrence: margin status, number of lymph nodes involved, response to systemic therapy, and the use of Taxanes. In this cohort of patients, the 5-year local control (LC) and overall survival (OS) were 84% and 51%, respectively.[14]

Le Scodan et al. retrospectively analyzed the impact of loco-regional RT on overall survival in 320 patients affected by mIBC (249 of the patients received radiotherapy alone, 41 received surgery plus radiotherapy, and 30 underwent surgery alone). The 3-year OS rate of the whole group was 43.3%, whereas it was only 26.7% in patients who were excluded from loco-regional RT.[15]

An international meeting held in Houston in 2010, including several experts on IBC, provided a consensus statement suggesting PMRT of the chest wall including supra-clavicular region and internal mammary lymph nodes for all women with IBC; this because of the high probability of regional node involvement, which is strongly correlated with loco-regional recurrence. A dose escalation to 66 Gy is recommended in young women (<45 years), those presenting with close or positive post-operative margins, poor response to pre-operative systemic treatments, and patients having four or more positive lymph nodes following chemotherapy.[4] In 2015, the DEGRO panel recommended PMRT of the chest wall and the supra and infra-clavicular nodes in all patients, independently of their response to chemotherapy. Pathologic complete response (pCR) after neo-adjuvant therapy seems to be correlated with improved survival and is considered an important prognostic factor.[17] In a recent retrospective study, Akay et al. analyzed 172 mIBC patients treated at their institution. They showed an increased 5-year OS and disease progression free survival (DPFS) compared with those who were treated with chemotherapy and surgery or radiotherapy alone. In this analysis, four different factors were identified as predictors for LRC: response to chemotherapy, pathologic complete response, surgery, and treatment with surgery and RT.[6]

In 2012, Yamauchi et al. published a review advising the use of PMRT in all mIBC patients. In patients with oligometastatic loco-regional disease, such as internal mammary and contralateral lymph node, they suggested irradiation of this site, if feasible.[5]

Takiar et al. reviewed a limited cohort of 36 patients with stage IV de novo IBC at presentation who completed PMRT $\geq$50 Gy to the chest wall, ipsilateral regional lymph node, and all M1 sites, when possible. The 2-year OS, PFS and LRC rates were 71%, 50%, and 86%, respectively. At 5 years, these values were 54%, 47%, and 86%. The authors reported that this multimodality treatment led to a durable NED status, suggesting that an aggressive approach could be adopted in highly selective cases.[16]

4. Radiotherapy treatment characteristics

Based on literature data, PMRT schedules adopted in locally advanced inflammatory breast cancer are suitable also for IBC metastatic patients.[7,17–20]

The radiotherapy clinical target volume (CTV) should encompass the entire chest wall and the draining regional lymphatics (ipsilateral axillary, infra-clavicular and supra-clavicular lymph nodes) (Fig. 1). The irradiation of the internal mammary lymph nodes is controversial, but it is recommended by some author because of the high probability of their involvement in this setting of patients, and correlating with local recurrence.[4]

Standard fractionation is the most frequently used, with prescription doses of 50–54 Gy (1.8–2 Gy per fraction) delivered to the chest wall and draining lymph nodes, plus 10 Gy boost to the chest wall scar.[7,14,16,18] Based on nodal involvement, an additional boost of 6–16 Gy can be delivered to the infra-clavicular or supra-clavicular region. The use of altered fractionation schemes relies on the opportunity to counteract tumor repopulation and therapy late effects,[21] but the superiority of these treatment schedules is matter of debate. Accelerated hyper-fractionated radiotherapy has been adopted, with a schedule of 45 Gy in 1.5 Gy per fraction, twice daily, and a boost of 15 Gy.[14,20] Liao et al.'s (20) study has shown

Table 1
Patients treatments characteristics.

Authors	N. of pts	Chemotherapy	Surgery	Radiotherapy	Total dose	Volume	LC	OS	Follow-up (median)
Le Scodan (2009)	249	no	no	definitive	48.67 Gy (mean dose)	B, SN, AN		3-y 43.4%	39 months
	41	no	yes	adjuvant	48.67 Gy (mean dose)	CH, SN, AN		3-y 43.4%	39 months
	30	no	yes	no				3-y 43.4%	39 months
	261	definitive	no	no				3-y 26.7%	39 months
Akay (2014)	93	neoadjuvant	no	adjuvant (18)	51 Gy	B, SN, AN, IM	18% at last fu	5-y 10%	33 months
	79	neoadjuvant	yes	adjuvant (68)	51 Gy	CH, SN, AN, IM	81% at last fu	5-y 47%	33 months
Takyar (2014)	36	neoadjuvant	yes	adjuvant	50–54 Gy	CH, SN, AN, IM	2-y 86%, 5-y 86%	2-y 71%, 5-y 54%	31 months

CH = chest wall; SN = supraclavicular nodes; AN = axillary nodes; IM = internal mammary nodes; B = breast.

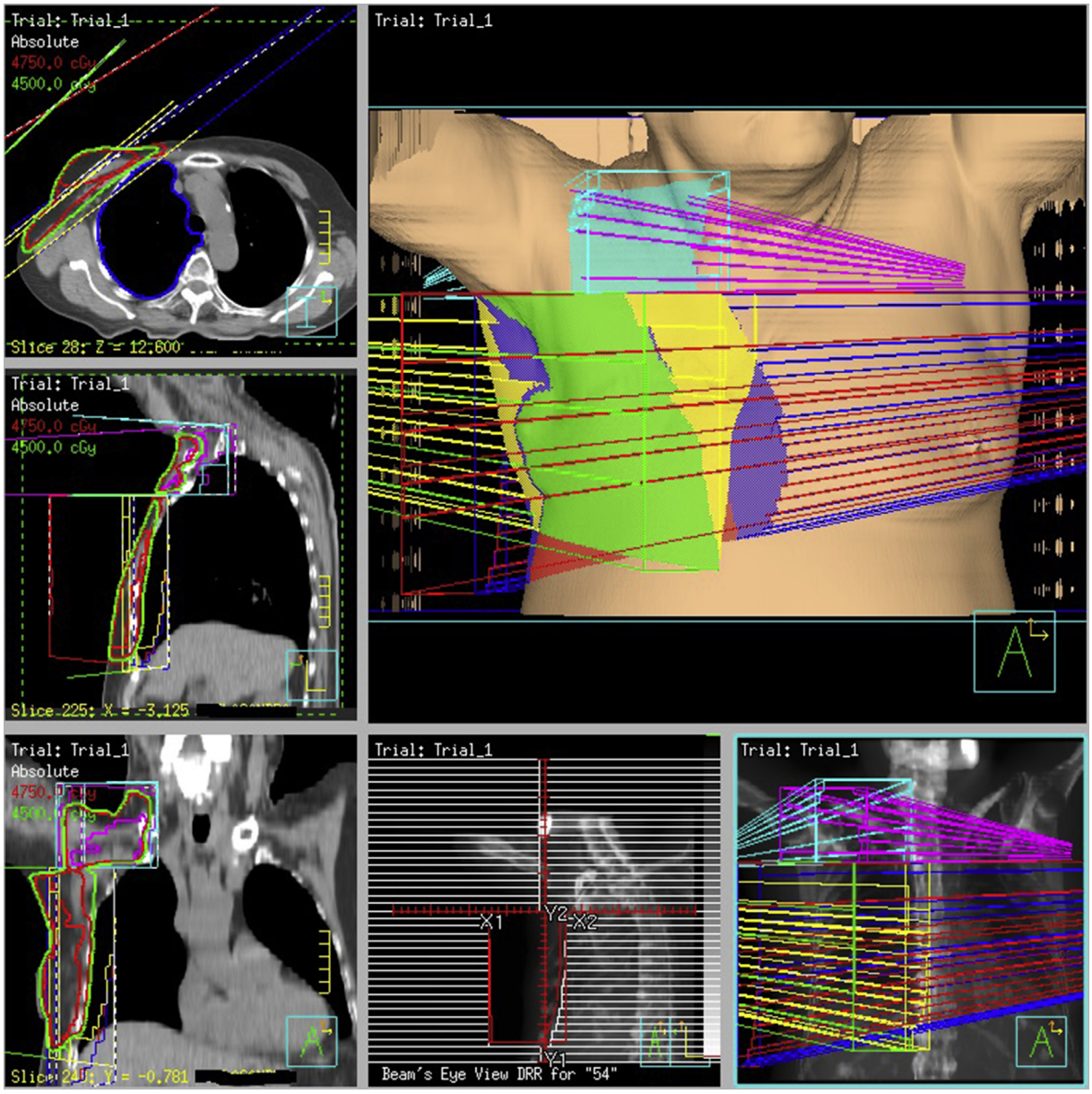

Fig. 1. Treatment Plan of a patient undergoing PMRT (Post Mastectomy Radiotherapy) for a mIBC (metastatic Inflammatory Breast Cancer).

statistically significant differences in terms of LRC and OS comparing two groups with different radiotherapy dose escalation: the first one received (from 1977 to 1985) 60 Gy to the chest wall and 45–50 Gy to the regional lymphatics while the other group 51 Gy to the chest wall and the regional lymph nodes, plus 15 Gy boost to the chest wall scar. LRC and OS were better in the last group. Bristol et al. (14) have used standard fractionation (50 Gy with 2 Gy per fraction, plus 10 Gy boost) from 1977 to 1981, while they adopeted hyper-fractionated radiotherapy (45 Gy with 1.5 Gy twice-daily per fraction, plus 15 Gy boost) from 1982 to 1985, and 51 Gy with 1.5 Gy twice daily, plus 15 Gy boost after 1985. They demonstrated better 5-y LRC rate in the accelerated fractionation group (84% vs 81%) and in the higher dose group, receiving 66 Gy (88% vs 78%). In the univariate analysis, they had better response rates in a subset of women who met at least one of these negative prognostic factors: age <45 years, close or positive or unknown margins after surgery, poor response to neoadjuvant systemic treatment.

The most frequent approach to cover the entire chest wall is to use paired opposed tangential photon fields. Bristol et al. (14), in order to decrease lymphatics and margins recurrences, use both electron and photon tangent fields. The most frequent approach is composed by paired photon fields, delivered to the lateral chest wall, in association with an appositional electron field to the medial one and the upper internal mammary lymph nodes.

Patients generally lie in the supine position, with both arms raised above the head, hanging a wing-board.

In some studies skin bolus (0.5–1 cm) was used for better skin dose coverage, which might correlate with local-control.[7,14] The application of skin bolus on the chest wall has been described in both Damast and Bristol's study (7, 14). It was applied every day in the first study, while in the latter it was applied only during the first 20 days of treatment, and then according to skin reactions.

Conformal radiotherapy (3DCRT) with high-energy photons (6–10 MV) is generally used, but electron based technique showed same results in terms of loco-regional outcomes.[7] 3DCRT and

intensity modulated radiation therapy (IMRT) planning can be used, but the latter should be preferred if the CTV includes internal mammary lymph nodes for better conformity and organs at risk sparing.

5. Conclusions

Despite therapy improvements, metastatic IBC is an extremely aggressive disease with high rates of both distant and loco-regional recurrence and poor prognosis.[16] Based on few data in literature, PMRT has shown good results in term of loco-regional tumor control, as part of multimodal treatment.[14] In the oligometastatic setting, patients with better prognosis (those responding to chemotherapy) might benefit of PMRT together with metastasis directed therapy, such as ablative radiotherapy, which gives local control rates ranging from 80% to 100% and might have an impact on disease progression.[22,23] However, due to the rarity of the disease and the heterogeneity of this patients' setting (different site of metastases at diagnosis, different molecular characteristics and pathologic response to neo-adjuvant therapy) it is very difficult to stratify them in different risk classes. A multidisciplinary approach is required and prospective trials are needed to develop a more uniform and standardized management of these patients.

Declaration of interests

None.

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