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Anti-Tumour Treatment

Management of inflammatory breast cancer: Focus on radiotherapy with an evidence-based approach

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SUMMARY

Inflammatory breast cancer represents a rare and extremely aggressive subtype of breast cancer. Due to its rarity, prospective studies are a difficult goal to obtain in this field.

Nowadays a multimodal approach seems to be the standard approach. Role and timing of surgery, radiotherapy and chemotherapy are still debated issues. In this scenario interest is rising in molecular and target therapies.

We performed a review analyzing the management of this unfavorable disease focusing on the role of radiotherapy, with particular emphasis on levels of evidence.

Introduction

Inflammatory breast cancer (IBC) is a rare clinicopathologic entity characterized by rapid progression and aggressive behavior from the onset of disease. It accounts for approximately 1–6% of total breast malignancies. Lee and Tannenbaum first introduced the term "inflammatory" in 1924, when they described a series of patients presenting peculiar breast clinical features (peau d'orange, skin erythema) associated with a poor prognosis.[1] The mean age of women diagnosed with IBC is significantly younger than all the other histological types, and even nowadays women affected by this subtype of breast cancer show a poorer prognosis when compared with other more common breast cancer (BC) subtypes.[2–4] While for a certain amount of time IBC was described as a subtype of locally advanced BC (LBC) more and more evidences have clearly demonstrated that IBC and LBC are two distinct entities both from a clinical and a histological point of view.[5] From a clinical perspective, it is crucial to distinguish two clinical varieties of IBC that are commonly described in the literature and observed during the clinical practice: the primary IBC and the secondary IBC. The term "primary IBC" is used to describe the de novo development of IBC in a previously normal breast. On the other hand, "secondary IBC" refers to the development of inflammatory skin changes that resemble primary IBC either in a breast that already had cancer or on the chest wall after a mastectomy for non-IBC.[6] In this review we will focus exclusively on the primary IBC. Adopting the TNM system, IBC is designated as primary tumor stage T4d.[7]

Analyzing the molecular aspects, the majority of IBC can be categorized as Human Epidermal Growth Factor Receptor 2 (HER2) amplified, basal like, breast cluster often with a low expression of claudin. The absence of estrogen receptors (ER) and progesterone receptors (PgR) has been correlated with a shorter disease-free survival (DFS) and poor clinical outcome, and this correlates with the clinical history of women affected by this disease.[6] Despite the rapid progressive nature of IBC, 70% of patients present a loco-regional disease at the time of diagnosis, accounting for the aggressive multimodality therapeutic approaches that must be taken when treating this rare form of breast cancer.[8]

Treatment approaches

The therapeutic approach to IBC should be multimodal, involving systemic therapy, surgery and radiotherapy. Due to the ER and PgR negativity, systemic therapy is mainly chemotherapy (CT).

The goal of primary systemic treatment is to downstage tumor to allow surgery; incorporation of taxanes and trastuzumab plus anthracyclines in HER2 positive patients is associated with higher pathologic complete response (pCR). Major prognostic factors are

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complete tumor regression after neoadjuvant CT, complete and partial regression of inflammation after three months of CT, limited erythema at presentation and complete regression of inflammatory symptoms after 8 months. In particular the pCR to CT is associated with a loco-regional control (LC) of 95% at 5 years.[9–11]

A recent consensus panel[12] agreed that the only method of definitive surgery to be offered to women with IBC following preoperative systemic treatment is a modified radical mastectomy (MX). A skin sparing MX approach is contraindicated and breast-conserving approaches may only be attempted within the context of a clinical trial. Breast reconstruction surgery could be an option for patients undergoing radical modified MX, although the timing of surgery still remains a debated problem. Another controversy is represented by the decision to perform a sentinel-node biopsy or an axillary lymph node dissection (ALND), even if ALND in most series of patients seems to be the most appropriate approach.[13] The role of radiotherapy (RT) in IBC treatment still represents a debated issue in the management of this complex pathologic entity.[6]

We reviewed the evidences of IBC management, with particular emphasis on RT timing, schedules and fractionation.

Evidence based medicine, evidence levels in IBC treatment

Levels of evidence is a ranking system, ranging from I to IV, introduced in the evidence-based medicine era in order to assess the strength measured in clinical trials and research studies (Table 1).

To our knowledge there are no published metanalysis of randomized trials (level Ia) concerning IBC. The only published randomized trial (level Ib) about IBC is focused on CT of LBC and not specifically on IBC.[14]

The MD Anderson experience reported in 2007 by Gonzalez-Angulo[15] regards 398 patients with IBC treated between 1974 and 2005. All patients were treated under specific IBC-designed protocol and reviewed before a retrospective analysis by the institutional review board of MD Anderson. Women were divided into four groups depending on their decade of diagnosis; RT played a different role during the analyzed period with a trend towards post-operative treatment. However the authors concluded that survival was not influenced by the time of diagnosis. Almost all patients received anthracycline-based CT; before 1980 patients were treated with radical RT; after 1980 a multidisciplinary team evaluated the indication to surgery. RT was delivered at the completion of primary CT and after surgery in all patients. With the longest follow-up in primary IBC treated by a multidisciplinary team, this article confirmed the importance of pCR on LC; ultimately pCR and age were independent predictors of relapse-free-survival (RFS).

The MD Anderson series probably represents the biggest analysis about IBC focusing on radiotherapy (RT) development in terms of radical, neo-adjuvant and adjuvant intent with emphasis on the role of accelerated fractionations; the role of RT, in these different settings, will be further investigated in the following paragraphs of this review.

From the clinical evidence point of view, this publication can be regarded as a level IIa recommendation.

Among level III evidences three large series have been published, concerning at least 200 patients.[16–18]

Panades et al.[16] analyzed 308 IBC among 31763 BC treated between 1980 and 2000; 97.4% received RT to different volumes (97.7% tangent-pair technique to breast or chest wall; 98.8% to supraclavicular fossa; 20% to internal mammary chain; 7% with boost to primary site), doses (24 patients treated with 8 Gy in single fraction the day before starting CT; short-course RT, median 16 fractions, 36–50 Gy; long-course RT, 40–60.7 Gy) and timing (13.4% with early RT before CT or after 3 months; 86.6% with late RT). Despite IBC has a rapid growth potential, no difference in terms of local relapse free survival and BC survival was found associated with RT timing.

At Institut Curie[17] 232 IBC were treated between 1985 and 1999; all patients underwent neoadjuvant anthracycline-containing CT before RT plus eventual surgical approach. The Authors achieved better LC in patients treated with RT plus surgery when compared with patients treated with exclusive RT ($p = 0.04$); on the other hand, no difference emerged in terms of overall survival (OS).

The experience reported by Bristol at MD Anderson will be reported in details in the appropriate section of this review.

Concerning consensus conference evidence (level IV), an international expert panel on IBC recently concluded that primary systemic CT, surgery and RT should be included in the treatment plan of these patients.[12]

Radiotherapy in IBC management

Radical radiotherapy

RT represents the most effective non-surgical local treatment modality in oncology. Radical RT is a treatment delivered with intent to produce a high rate of LC. Most radical treatments are given over 4–6 weeks, in 1.8–2.75 Gray fractions to a total dose of 55–74 Gy in solid tumours. In this paragraph we will analyze the most important experiences of radical RT in IBC treatment.

In Table 2 we summarize the series of IBC patients treated with radical and/or preoperative RT.

Barker et al.[19] treated 111 patients from 1948 to 1976. All patients had histopathological diagnosis of primary IBC and no surgery other than biopsy was proposed to them. Sixty nine patients were treated with conventional RT (45 with 250 kV and 24 with ^{60}Co); 11 patients were treated with bi-fractionated (BID) RT; 31 patients underwent anthracycline-based CT for 3–4 cycles before and after BID RT until receiving a total dose of 450 mg/mq of doxorubicin. RT volumes were whole breast, axilla and internal mammary nodes in all patients; 31 patients were treated even to supraclavicular fossae. Patients underwent conventional once-daily fractionation until 1972; because of the poor LC (46% of loco-regional failure), from 1972 patients were treated with twice-daily irradiation. Total doses ranged from 51 to 54 Gy with a boost up to 70 Gy to the breast. First site of recurrence was skin of breast (46% recurrence rate in conventional fractionation versus

Table 1
Level of evidences.

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities