Locally Advanced Breast Cancer

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Key Words. Breast cancer · Locally advanced · Inflammatory · Chemotherapy · Surgery · Radiotherapy · Breast conservation

ABSTRACT

Locally advanced breast cancer encompasses a heterogeneous collection of breast neoplasms and constitutes approximately 10%-20% of the newly diagnosed breast cancers. These cancers may have widely different clinical and biological characteristics. Patients with these tumors may be classified as stage IIb, III or IV breast cancer according to the American Joint Committee for Cancer Staging and End Results Reporting (TNM classification). Multidisciplinary therapy has become the treatment of choice for these patients. Primary or neoadjuvant chemotherapy followed by locoregional therapy, either surgery and/or radiotherapy, and postoperative systemic chemotherapy is now an accepted strategy. More than 70% of patients achieve an objective response (including pathological complete remission in 10%-25% of cases), and many patients experience downstaging through primary chemotherapy. Breast conservation is possible in 10%-40% of patients with locally advanced breast cancer; almost all patients initially are rendered disease-free, and long-term local control is achieved in over 70% of these patients. Primary chemotherapy is the initial choice of treatment for patients with locally advanced tumors, but it is unclear what the optimal sequence of subsequent therapies should be, whether one or two local treatment modalities are necessary, and whether any or different postoperative chemotherapy is needed. The efficacy of primary chemotherapy was demonstrated in several large prospective studies in patients with locally advanced breast cancer. The natural history of this disease was changed dramatically by the introduction of these combined modality therapies. Five-year disease-free survival rates of 35%-70% are commonly reported, and about 25%-40% of patients will survive beyond 10 years without recurrence. In summary, multidisciplinary therapy that includes primary chemotherapy provides appropriate local control and the possibility of breast conservation therapy; it increases surgical resectability and survival rates in patients with locally advanced breast cancer. The role of new innovative therapeutic strategies such as high-dose chemotherapy, with hematopoietic stem cell rescue, new cytotoxic agents and higher dose-intensity therapy is currently under evaluation in patients with locally advanced breast cancer. The Oncologist 1996;1:8-17.

INTRODUCTION

Locally advanced breast cancer (LABC) is a very common clinical presentation of mammary carcinoma in developing countries (30% to 60%). In spite of systematic screening, mammography programs and extensive public education campaigns for early detection of breast cancer in the USA, the incidence of LABC is still approximately 10%-20%. LABC is a heterogeneous group of tumors of varying clinical presentations and biological behavior whose only common bonds are the presence of a large primary tumor, or extensive regional lymph node involvement, and the absence of any evidence of distant metastases. Some patients have a rapid neoplastic evolution, whereas others present with a long history of tumor growth.

Historically, patients with LABC were treated with radical surgery and/or radiation therapy (RT). However the management of LABC was dramatically transformed over the past two decades [1-5]. Primary chemotherapy (CT) became an integral part of the multidisciplinary management of LABC, probably prolonging the disease-free survival (DFS) and overall survival (OS), and making breast conserving surgery a possibility for these patients. Because LABC is less common in industrialized countries and the heterogeneity of this disease makes the performance of controlled trials more complex, changes in the management of this area of breast cancer have received less public and media attention than those occurring in early cases of breast cancer.

In this article we will review the classification, natural history, clinical concepts and current multidisciplinary management of LABC.

CLASSIFICATION

Patients with stage IIb, III and IV of the TNM classification are included in LABC [6]. In this classification system,
patients are included if they have T1 or T2 tumors with any N stage, or any T category with N2 or N3 or regional M1 involvement. A T1 tumor is greater than 5 cm in its greatest dimension. A T2 tumor may be of any size but with direct extension to the chest wall or skin. Inflammatory breast carcinoma (IBC) is also included in this category.

For the classification of regional nodal involvement, N1 is defined as palpable, ipsilateral axillary nodes fixed to one another or to other structures. N2 denotes the presence of ipsilateral internal mammary nodes; and we define regional M1 as palpable, ipsilateral supraclavicular or infraclavicular nodes (previously classified as N3). All T and N permutations included in stage IIB, III or IV comprised many distinct substage possibilities. The presence of T1 or N1 or regional M1 lesions would result in inclusion in the stage IIB/IV unresectable subcategory. Most of the patients with either T1 or N1, but without T1, N1 or regional M1 lesions, are included in the stage II/IIIA or operable subcategory. LABC also includes T2 tumors that are too large in proportion to the size of the breast. IBC is a unique clinical-pathological entity that has recently been reviewed by Jaiyesimi et al. [7]. It is important to distinguish primary IBC from LABC with secondary, inflammatory changes. In many patients with LABC characterized by slow, gradual growth, some inflammatory changes may appear many months or years after the breast mass was first detected. Inflammatory changes in this context do not have the ominous prognostic connotation of primary IBC.

CLINICAL FEATURES AND DIAGNOSIS

Because LABC is so heterogeneous and includes a wide range of subgroups and because of modifications in staging classification, it is difficult to precisely estimate the frequency of LABC. While in developing countries LABC represents up to 50% of the newly diagnosed breast cancers, in the USA it constitutes between 10% and 20% of all new breast cancers. The clinical diagnosis of LABC is usually not difficult. Patients uniformly present with a large breast mass. Other symptoms often reported are edema, redness, nipple retraction, pain, skin dimpling, an axillary mass and breast ulceration. Most physical findings are obvious upon inspection or palpation. However, in younger women, some tumors infiltrate the breast diffusely and a discrete mass is difficult to palpate. More than 75% of patients have clinically palpable axillary and/or supraclavicular adenopathy, and 65%-90% of patients have pathologically confirmed lymph node metastasis; >50% have more than four nodes involved [4, 8-10]. Most of the LABCs are operable; only 25%-30% are diagnosed at an inoperable stage. Therefore, we can extrapolate that only 5% of all newly diagnosed breast cancers in the USA are found in stage IIIB/IV (inoperable).

A physical examination, bilateral mammogram and ultrasound of the breast and its draining lymphatics determine the extent of involvement within the breast and the nodal chains, the presence of additional tumor foci within the same breast or the contralateral breast, and the extension of the tumor to deeper structures.

A core needle biopsy is quite effective in establishing the diagnosis and also allowing tumor samples to be obtained for hormone receptors, DNA studies and other biomarkers. The sensitivity and specificity of fine-needle aspiration are quite high in LABC [11]. The only disadvantages of cytological diagnosis are the inability to differentiate between in situ and invasive carcinoma, and scant material on which to perform additional studies. Excisional biopsies are not indicated in patients with LABC.

STAGING

Appropriate staging procedures should be performed in patients with LABC since the probability of distant metastases is high. Approximately 20% of these patients, appropriately staged, have detectable distant metastases at the time of diagnosis. We recommend that after a complete history, a physical examination be performed with great attention to the evaluation of both breasts and all surrounding lymph node-bearing areas. All tumors should be described by the longest perpendicular diameters in cm, and the presence of palpable axillary, supraclavicular and subclavicular nodes, with exact measurements of their longest perpendicular diameters, should be included. A close-up photograph is useful in the staging of patients with T1 tumors. Ideally, the initial evaluation should be done simultaneously by the medical oncologist, surgical oncologist and radiotherapist.

After the physical examination and bilateral mammogram, the following additional tests are recommended: a biochemical profile, including tests of liver and renal function, and calcium level; chest x-ray; bone scans; radiographs of areas that appear to be abnormal on the bone scan; computed tomography of the liver and an ultrasonography of the breast and regional lymph nodes to precisely assess the tumor extent. The importance of an accurate initial assessment of the extent of primary tumor burden cannot be overemphasized since the efficacy of subsequent local treatment will depend mostly on this initial assessment.

NATURAL HISTORY

There is no recorded information about the natural history of untreated LABC. Many of the published series of patients treated with radical surgery, RT or combinations of both were published 20 or 30 years ago. From the surgical point of view, we can subdivide LABC into operable, stage IIB (T1, N1; previously classified as stage IIIA) and IIIA, and inoperable, stage IIB and regional IV (previously classified as stage IIIB) breast cancer. Patient selection influenced outcome substantially.
more than treatment did. Some authors have tried to compare the results of surgery alone to RT alone, or combinations of both [4]. However, the groups were hardly comparable because many of the tumors treated with RT alone were not suitable for surgical resection in the first place. For instance, although most surgical series that included stage IIIB breast cancer included patients with pectoral muscle fixation or skin involvement, most excluded cases with supraclavicular node involvement, arm edema or chest wall fixation. Since these patients are known to have the worst prognosis after local therapy alone, this exclusion probably substantially improved the outcome of the surgical series. On the other hand, the older RT series had fewer selective inclusion criteria, accepting all patients. Therefore, the outcomes in RT series were usually inferior to those reported in surgical series.

For all types of LABC, whether or not operable, distant metastases were the most frequent type of treatment failure, and appeared in the majority of patients within 24 months after diagnosis. In addition, a very high percentage of patients developed locoregional failure, whether the initial treatment consisted of surgery alone or RT alone. The radical mastectomy was developed especially for LABC, but the local failure rate after surgery alone may be as high as 60%. The five- and 10-year survival rates for patients with LABC after radical mastectomy vary between 10%-40% and 0%-30%, respectively [4].

The outcomes in RT series were usually inferior to those reported in surgical series. The five-year survival figures varied from 10% to 30%, and very few reports provided 10-year survival figures, in part because few patients survived 10 years. Local recurrence rates ranged from 25% to 72%, suggesting that even local control was often inadequate. Several investigators have shown a clear dose-response correlation for RT. Therefore, the local control rate may vary, depending on the administered dose. Mastectomy combined with preoperative or postoperative RT seemed to produce improved local and regional control rates but did not modify survival rates since distant metastases were the ultimate determinants of outcome [4]. When only local therapies were used, the median DFS and OS durations for patients with LABC ranged from 8-12 months and 24 months, respectively. The 10-year survival in 3,575 patients with LABC after locoregional therapy was 22% (Table 1) [4]. In conclusion, the outcome for patients with LABC treated with local therapies only was, in general, consistently very poor.

**MULTIDISCIPLINARY THERAPY**

**Theoretical and Clinical Considerations**

In the early 1970s, recognizing the high propensity of early breast cancer to generate distant micrometastases, several groups pioneered the use of adjuvant systemic therapy as a curative strategy against breast cancer [12-14]. Based on these theoretical considerations and the poor prognosis of patients with LABC, systemic combination CT was introduced as the primary treatment in these patients [1, 2-4, 15-29]. In this strategy, systemic therapy is known as neoadjuvant or primary CT. This treatment was preferred because the major problem in LABC is distant metastases, rather than the local disease. After CT is administered for three to four cycles and its efficacy is assessed, regional therapy is administered in the form of surgery, RT, or both, and is followed, in turn, by additional postoperative CT, followed by RT and hormonotherapy (>50 years, estrogen receptor positive [ER+]). The advantages and disadvantages of this strategy are detailed in Table 2. The advantages include the earlier initiation of systemic therapy, before the vasculature of the tumor is altered by surgery or RT, and before many resistant clones have the chance to arise. Furthermore, the medical oncologist has the opportunity to assess the efficacy of systemic therapy in vivo. If systemic treatment is not effective, the oncologist can discontinue the ineffective therapy, avoid unnecessary toxicity and institute an alternative form of systemic therapy. Moreover, downstaging of a tumor may allow for breast-conserving surgery and render inoperable tumors resectable. On the other hand, the disadvantages of this strategy include the lack of accurate initial pathological staging and the potential for emerging drug resistance due to the large tumor burden. In addition, if CT is ineffective, local treatment is delayed for several weeks.

**PRIMARY CHEMOTHERAPY RESULTS**

**Objective Response**

Our group pioneered multidisciplinary therapy, including primary CT with anthracycline-containing regimens.
We enrolled 598 patients in three studies [1, 3-5, 15, 16]. In the first two studies, after three cycles of CT, local treatment in the form of a total mastectomy with level one and two axillary dissection, RT, or both were completed. After local therapy, additional CT was administered. In the second study, the role of a noncross-resistant postoperative CT regimen (vinblastine, methotrexate, fluorouracil and folinic acid) was randomly investigated. In the third study, all patients received four cycles of primary CT with an anthracycline-containing regimen. Doxorubicin was given as a 72-h continuous infusion. In all, 367 patients with noninflammatory LABC were evaluated in the first two studies (174/193); 148 of them had stage IIB/IIIA, and 219 had stage IIIB/regional IV disease. After primary CT, 63 (17%) and 250 (68%) patients achieved clinical complete remissions (CR) and partial remissions (PR), respectively. All but nine patients were rendered disease-free after primary CT and initial local therapy.

In the first study, at a median follow up of 11 years, the median DFS for patients with stage IIB/IIIA disease had not been reached; for the patients with stage IIIB/regional IV disease it was 30 months. The median OS for stage IIB/IIIA disease had not been reached and for stage IIIB it was 48 months. The five- and 10-year DFS rates for patients with stage IIB/IIIA disease were 71% and 40%, respectively. The five- and 10-year DFS rates for patients with stage IIIB/regional IV disease were 33% and 30%, respectively. The five-year OS rates for stage IIB/IIIA and stage IIIB/regional IV were 84% and 44%; the 10-year OS figures were 56% and 26%, respectively [4, 15]. The five-year DFS and OS rates in the second study were similar to those of the first study [15]. Treatment with a noncross-resistant postoperative CT regimen did not significantly affect DFS and OS. The high objective response rate was also confirmed in our third study. The objective response rate to primary CT was 73% in 160 evaluable patients with LABC [16]. Compared to our historical institutional experience, the local control rate, and five- and 10-year DFS and OS rates for LABC were substantially improved by this multidisciplinary program.

A number of other centers have developed similar strategies (Table 3). The common theme is the use of primary or induction CT, followed by local treatment, which is “sandwiched” between primary and adjuvant systemic treatments. There are major variations in CT programs, type and aggressiveness of local treatment, duration of treatment and eligibility criteria [17-31]. Several CT combinations have been used for the treatment of LABC, although in most published trials an anthracycline-based regimen was preferred. The overall response and CR rates following primary CT are depicted in Table 3. As the table shows, 50%-95% of patients with LABC achieved an objective response, including 5%-50% clinical CR rates. This latter range is somewhat deceiving since only two of the many trials have shown CR rates in excess of 25% [22, 26]. The trial conducted by Lippman et al. [22] reported a 52% clinical CR rate, but it is likely that this CR rate was artificially high due to the methods used to evaluate and define a CR. The trial conducted by Powles and associates [26], included mostly patients with stage I and stage II breast cancer, and the higher CR rate reported might be due to patient selection rather than increased efficacy of primary chemotherapy. As a consequence of this high frequency of objective responses, approximately 70% of patients with LABC undergo downstaging (the primary tumor or regional lymph nodes decrease by at least one stage category).

In most of these trials, a fixed number of primary CT cycles was employed [2-4]. However, in a few trials primary CT was continued until reaching maximal response. These trials have shown that there is immense variability in the time required to achieve maximum response. Some patients reached maximal response after one month, whereas others needed up to eight months to reach such a response.

A clinical CR does not necessarily represent a pathologically proven CR. In fact, the pathological CR rate varied from 3%-33% in different trials and approximately only two-thirds of the patients with a pathologically proven CR were artificially high due to the methods used to evaluate and define a CR. The trial conducted by Lippman et al. [22] reported a 52% clinical CR rate, but it is likely that this CR rate was artificially high due to the methods used to evaluate and define a CR. The trial conducted by Powles and associates [26], included mostly patients with stage I and stage II breast cancer, and the higher CR rate reported might be due to patient selection rather than increased efficacy of primary chemotherapy. As a consequence of this high frequency of objective responses, approximately 70% of patients with LABC undergo downstaging (the primary tumor or regional lymph nodes decrease by at least one stage category).

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<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment Program</th>
<th># Patients Treated</th>
<th># Patients with &gt;50% Response (%)</th>
<th>Complete Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hortobagyi</td>
<td>FAC × 3</td>
<td>174</td>
<td>152 (87)</td>
<td>17</td>
</tr>
<tr>
<td>Hortobagyi</td>
<td>VACP × 3</td>
<td>193</td>
<td>161 (83)</td>
<td>18</td>
</tr>
<tr>
<td>Booser</td>
<td>FAC × 4</td>
<td>160</td>
<td>116 (73)</td>
<td>8</td>
</tr>
<tr>
<td>DeLena</td>
<td>AV × 4</td>
<td>74</td>
<td>132 (65)</td>
<td>15</td>
</tr>
<tr>
<td>Rabens</td>
<td>AV × 4</td>
<td>12</td>
<td>6 (50)</td>
<td>17</td>
</tr>
<tr>
<td>Hobar</td>
<td>FAC × 3</td>
<td>36</td>
<td>26 (72)</td>
<td>8</td>
</tr>
<tr>
<td>Conte</td>
<td>DES-FAC × 3</td>
<td>39</td>
<td>28 (72)</td>
<td>15</td>
</tr>
<tr>
<td>Lippman</td>
<td>CATPFL × 3(3-11)</td>
<td>51</td>
<td>45 (88)</td>
<td>52</td>
</tr>
<tr>
<td>Cocconi</td>
<td>CMF(T) × 4</td>
<td>49</td>
<td>23 (47)</td>
<td>8</td>
</tr>
<tr>
<td>Perloff</td>
<td>CAFPr × 3</td>
<td>113</td>
<td>78 (69)</td>
<td>18</td>
</tr>
<tr>
<td>Jacquillat</td>
<td>VBTFMAFPr × 2(4)</td>
<td>98</td>
<td>89 (91)</td>
<td>23</td>
</tr>
<tr>
<td>Powles</td>
<td>MMiMe × 4</td>
<td>34</td>
<td>32 (94)</td>
<td>44</td>
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<td>Rosso</td>
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<td>113</td>
<td>73 (65)</td>
<td>10</td>
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<tr>
<td>Poddubnaya</td>
<td>AMCCMF</td>
<td>503</td>
<td>317 (63)</td>
<td>2</td>
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<tr>
<td>Calais</td>
<td>MViCF</td>
<td>80</td>
<td>41 (51)</td>
<td>18</td>
</tr>
<tr>
<td>Touboul</td>
<td>FACV × 4</td>
<td>82</td>
<td>45 (55)</td>
<td>10</td>
</tr>
</tbody>
</table>

A = Adriamycin; V = Vincristine; F = 5-Fluorouracil; C = Cyclophosphamide; DES = Diethylstilbestrol; T = Tamoxifen; P = Premarin; L = Leucovorin; M = Mitomycin; Pr = Prednisone; Vb = Vinblastine; Mi = Mitoxantrone; Me = Methotrexate, Vi = Vindesin
patients treated with RT alone have no pathologically demonstrable remission.

**Randomized Studies**

Several randomized trials that included a substantial minority of patients with stage III breast cancer [32, 33], or that specifically targeted stage III breast cancer [34, 35], demonstrated that adjuvant CT, or adjuvant CT and RT, increased DFS and OS rates. What is not known at this time is whether the timing of systemic treatments (postoperative versus preoperative) alters the probability of benefit. One randomized clinical trial suggested that adjuvant CT after primary CT and RT resulted in longer time to progression and survival than the use of only primary CT and RT [17]. Several small randomized trials failed to show an additional survival benefit of primary CT over postoperative CT. However, these trials included small numbers of patients, and sizable differences in outcome could have easily been overlooked because of low statistical significance. More recently (Table 5) [36-43], several randomized trials were instituted comparing primary (neoadjuvant) and postoperative (adjuvant) CT. These trials included a mixture of stage II and stage III patients. One of these trials was recently updated and suggested a survival benefit in favor of primary CT [38]. However, there was no benefit in DFS, making interpretation of these data more complex. Four trials showed increased survival in patients who received primary CT; however, only one of these trials did reach statistical significance. Longer follow-up in additional, larger studies will be needed to determine the relative benefits of primary versus adjuvant therapies.

**Local/Regional Treatment and Local Control**

After primary CT, some programs have used surgical therapy alone, RT alone, or a combination of both treatments. Two prospective randomized trials have been reported in which surgery was compared with RT after primary CT. In both trials, surgery appeared to be equivalent to RT for local control and long-term survival [17, 18]. However, the local control rate in the studies was relatively low, in the 60%-70% range. In contrast, those phase II studies in which primary CT was followed by both surgery and RT have reported higher local control rates, in some cases reaching 85% (Table 6) [4, 20, 21, 23, 25, 44-46]. In our first two studies (367 patients), the locoregional failure rate for stage IIB/IIIA and IIIB/regional IV were 7% and 26%, respectively [15].

**Tolerance and Toxicity**

The same side effects and toxicity usually associated with adjuvant CT have been routinely reported with combined modality programs that included primary CT. In our initial trial, the acute and chronic major side effects included 19 febrile episodes, but no deaths related to infection. Nine patients developed clinical congestive heart failure and two died as a result. Two patients developed acute nonlymphocytic leukemia [4]. In general, surgical complications and short- and long-term complications of radiotherapy also appear to be similar to what had been previously reported in the literature. The use of primary CT does not appear to enhance surgical complications compared to complications that occur after primary surgical procedures. It is not clear at this time whether the sequential use of CT and RT results in additive or synergistic toxicity. In our own experience, in the early days

<table>
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<tr>
<th>Author</th>
<th>Treatment</th>
<th># Patients</th>
<th>Median F/U</th>
<th>Local Control Rate (%)</th>
<th>IIB-III/IIIA/IIIB-IV</th>
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<td>Hortobagyi</td>
<td>CT ± S ± RT + CT</td>
<td>367</td>
<td>80 m</td>
<td>84</td>
<td>148/219</td>
</tr>
<tr>
<td>Touboul</td>
<td>CT + RT ± S + CT</td>
<td>82</td>
<td>70 m</td>
<td>82</td>
<td>42/40</td>
</tr>
<tr>
<td>Cardenas</td>
<td>CT + S/RT + CT</td>
<td>23</td>
<td>52 m</td>
<td>78</td>
<td>?</td>
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<tr>
<td>Hobar</td>
<td>CT + S ± RT + CT</td>
<td>36</td>
<td>34 m</td>
<td>81</td>
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<tr>
<td>Conte</td>
<td>CT + S + CT ± RT</td>
<td>39</td>
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<td>72</td>
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</tr>
<tr>
<td>Jacquillat</td>
<td>CT + RT + CT</td>
<td>98</td>
<td>40 m</td>
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<td>113</td>
<td>37 m</td>
<td>63</td>
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<tr>
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<td>CT + RT + CT</td>
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<td>36 m</td>
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<td>CT + S + CT</td>
<td>65</td>
<td>36 m</td>
<td>70</td>
<td>7/58</td>
</tr>
<tr>
<td>Aisner</td>
<td>CT + S + CT</td>
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<td>24 m</td>
<td>59</td>
<td>–27</td>
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<tr>
<td>Calais</td>
<td>CT + S + RT + CT</td>
<td>80</td>
<td>38 m</td>
<td>94</td>
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<td>Boyages</td>
<td>CT + RT + CT</td>
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<td>DeLena</td>
<td>CT + RT ± CT</td>
<td>110</td>
<td>18 m</td>
<td>54</td>
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of combined modality therapy, RT with photons to the internal mammary chain in combination with anthracycline-containing CT was associated with an increased risk of cardiac damage if the lesion originated in the left breast [4]. However, over the past decade, the use of electron beam therapy to cover the internal mammary chain, and the administration of anthracyclines by a 72- to 96-h continuous infusion has eliminated this overlapping toxicity [47].

In patients whose tumors are not amenable to breast conservation, delayed chest wall reconstruction is an alternative option.

Prognostic Factors

Initial tumor size, the presence of skin edema, tumor S-phase fraction, thymidine labeling index, number of axillary nodes involved, ER, PR, histological and nuclear grade, extent of residual disease, and objective response after primary CT are all important prognostic factors for this group of patients [4, 48, 49]. In our first study, patients with ER+ or unknown tumors had better DFS and OS rates than did those with ER−. Response to primary CT correlated closely with prognosis. Patients who achieved CR had DFS and OS rates considerably superior to those with a PR or no change after the primary CT regimen. Compliance with the treatment regimen was also an important prognostic factor for survival. It is of interest that pathologic lymph node involvement after primary CT retains prognostic importance, and, in fact, in our evaluation by multivariate analysis, is the most important prognostic indicator [48]. Predictors of tumor response to primary CT have also been reported. Initial tumor size and nuclear grade are independent predictors of response [50]. Other predictors of tumor response to primary CT include S-phase fraction, ER, and ploidy. A recent report suggested that patients with tumors with high S-phase fractions responded more often than those with low S-phase fractions [51]. The results of new prognostic factors such as p53 and c-erbB-2 oncogene expression were recently reviewed [52]. Whether these prognostic indicators can select individual patients who might benefit more than others from multidisciplinary strategies remains to be established. Therefore, their clinical usefulness outside of a clinical trial remains in question.

<table>
<thead>
<tr>
<th>Author</th>
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<th># Patients</th>
<th>Clinical (%)</th>
<th>Pathological (%)</th>
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<tbody>
<tr>
<td>Hortobagyi</td>
<td>CT ± S + RT – CT</td>
<td>174</td>
<td>17</td>
<td>8</td>
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<td>Booser</td>
<td>CT + S + CT + RT</td>
<td>160</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Hobar</td>
<td>CT + S + RT + CT</td>
<td>51</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Conter</td>
<td>CT + S + CT</td>
<td>51</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Schwartz</td>
<td>CT + S + CT ± RT</td>
<td>90</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>Cocconi</td>
<td>CT + S + CT + RT</td>
<td>49</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

32 patients did not receive CT
5 calculated from survival curve
DOSE INTENSIFICATION

One of the research directions to improve the survival of patients with LABC is dose intensification of primary or postoperative CT. A recent study in patients with early breast cancer treated with anthracycline-containing regimens demonstrated that doses lower than the standard dose produce an inferior DFS and OS [53]. On the other hand, a recent report from a randomized study with higher doses of cyclophosphamide plus granulocyte colony-stimulating factor failed to show any additional benefit from higher doses [54]. It is unclear if doses higher than the standard dose would impact the outcome of these patients. Several reports of open phase II trials in patients with LABC have suggested a higher response rate [55, 56]. No definite survival benefits have been reported; however, comparative trials are necessary to assess the relative value of dose intensification in this group of patients. A randomized phase III study is under way at The University of Texas MD Anderson Cancer Center. The preliminary results of this trial showed a higher objective response rate in the higher dose arm (98% versus 76%), but the pathological CR rates were similar [57]. The role of very high-dose CT with peripheral hematopoietic stem cell rescue is being studied in patients with a higher risk of relapse after primary CT, such as patients with four or more positive axillary nodes after primary CT. The role of this strategy is also being investigated after primary CT as a consolidation CT.

BREAST CONSERVATION

Historically, patients with LABC were not considered candidates for breast-conserving surgery. The inclusion of primary CT in the multidisciplinary treatment of patients with LABC resulted in 10%-40% of patients achieving such a remarkable reduction in tumor size that treatment with a segmental mastectomy followed by RT resulted in a realistic option for patients with LABC. The goal of this strategy is to obtain optimal local-regional control with minimal disfigurement [58]. Breast-conserving surgery for LABC was developed by several institutions following the same criteria used for breast conservation in stage I or small stage II breast cancer [4, 17, 22, 25, 58]. However, there is great variability in the methods and patients’ selection criteria utilized for breast conservation. Whether the same criteria used for patients with early breast cancer are appropriate for breast conservation in LABC is unknown. Other centers employed different multidisciplinary breast-sparing strategy, primary CT, followed by RT, followed by postoperative CT [22, 25].

After primary CT, the primary tumor may disappear completely or may partially decrease in size. The tumor may lose all its infiltrating components so that only residual noninvasive carcinoma is left. It is unknown at this point which is the most frequent manner in which primary tumors decrease in size after primary CT. However, documentation of downstaging is absolutely necessary in order to define the optimal terms of surgical removal and to maximize local control. Only prospective collection of data will determine what is the optimal limit of surgical excision, whether positive margins have the same implications after primary CT as they do in untreated patients, and whether a persistent tumor with marked CT-related changes compromises local control.

Our current practice includes primary CT with a doxorubicin-containing regimen for four cycles. Multidisciplinary evaluation is performed at baseline and after primary CT. If patients fulfill the rigorous criteria (including absence of extensive intramammary lymphatic invasion, negative resection margin, resolution of skin edema, small residual tumor size, no evidence of multicentric lesions or diffuse calcifications, and appropriate tumor:breast size ratios) for breast conserving surgery, then this option is offered to our patients with LABC, followed by postoperative CT. RT is given at the completion of all CT. In summary, to augment the probability of breast conservation for LABC, several strategies can be pursued. Primary CT could be followed by wide excision and RT for patients with excellent tumor reduction. Primary CT can be followed by RT in patients with less marked tumor reduction to maximize downstaging and permit a limited surgical resection. Chemotherapy can also be combined simultaneously with RT, expecting additive effects on the primary tumor volume. Finally, primary CT can be followed by RT alone in those patients who had significant tumor downstaging, after maximal response to CT.

At this time it is unknown which of these strategies is optimal in terms of tumor reduction, cosmetic outcome, and local control. Therefore, well-designed, multicentric randomized clinical trials are needed to determine the optimal strategy.

INFLAMMATORY BREAST CARCINOMA

IBC is a very rare oncological entity. It constitutes only 1%-4% of breast cancer cases in the USA. IBC is a clinical-pathological entity that has been defined in many different ways [7]. We define IBC as a clinical entity characterized by rapid onset and an evolution shorter than three months, with diffuse involvement of the breast, usually without an underlying palpable mass. The physical exam is characterized by erythema, skin edema, and the presence of ridging. Histopathological demonstration of dermal lymphatic invasion is considered confirmatory evidence but is neither necessary nor pathognomonic for the diagnosis. Like LABC, distant metastases were and are the most frequent type of treatment failure, and a very high percentage of
patients develop locoregional failure. Few if any patients survive beyond two years. The results after treatment consisting of surgery alone were totally inadequate. RT used as the only therapeutic strategy produced local control in a substantial fraction of patients but was unable to modify the natural history of this entity [7]. Anthracycline-containing primary CT produces objective responses in 60%-80% of patients, and the majority of them are rendered disease-free with the multidisciplinary therapy (primary CT and RT, or CT, surgery and RT). In contrast with historical experience, five-year survival rates in the 30%-50% range have been reported consistently, and at 10 years, 30% of patients remain alive, most of them free of metastatic breast cancer. In general, the DFS and OS data after multidisciplinary therapy are similar to those achieved with stage IIIIB/IV, noninflammatory LABC.

The results from our institute were recently reviewed by Buzdar et al. [15]; we treated 178 patients in four trials. Of these patients, 72% achieved a major objective response, including 12% who achieved CR. Only one patient developed progressive disease during primary CT. After primary CT and RT, 92% of patients were rendered disease-free. The median DFS and OS for this group were 21 months and 40 months, respectively. The overall locoregional control rate was 82%. At 10 years after diagnosis, 30% of patients remained disease-free and alive. Objective response (CR + PR) to primary induction CT was the main prognostic factor. Fifty percent of patients with CR remained disease-free after 10 years. In summary, the introduction of primary CT to the multidisciplinary management of IBC has changed the uniformly lethal natural history of this unique entity. It is in this group of patients that the most dramatic demonstration of the efficacy of multidisciplinary therapy that includes primary CT was observed.

**DISCUSSION**

After decades of high rates of therapeutic failure in patients with LABC, we have come to realize that local treatments, either surgery alone, RT alone or a combination of both, are inadequate therapies for these patients. We have learned that multidisciplinary treatment should be used, and additional studies of the biology are mandatory to reach a better understanding and treatment of this disease. We need to develop better staging and imaging techniques to define the extent of primary and regional tumor involvement at baseline and following primary CT. Systematic prospective assessment of ultrasonography, computerized tomography, magnetic resonance imaging, and axillary and internal mammary lymphoscintigraphy is needed for this purpose. We also need to develop better biological markers to assess the aggressiveness of the disease. A detailed histopathological assessment of biopsy specimens is necessary to identify cell type, degree of differentiation, vascular and lymphatic invasion, hormonal receptors status, etc. We need to assess in more detail the contribution of other new prognostic factors.

Although the optimal chemotherapeutic regimen has not yet been defined, information to date suggests that the best results are obtained with doxorubicin-containing regimens. The role of hormonotherapy has not been defined; therefore, clinical trials designed to establish the value of adding hormonal therapy to the multidisciplinary therapy are necessary.

After primary CT, it is unclear what the optimal sequence of subsequent therapies is, whether one or two local treatment modalities are necessary, and whether any or different postoperative CT is needed. The optimal local therapy (or therapies) and the best sequencing with combination systemic therapies need to be defined. Are there subsets of patients who can be treated with systemic therapy and surgery alone, or with systemic therapy and RT alone? What fraction of patients with LABC can be treated with conservation of the breast? Or should all patients be treated with both surgery and RT in addition to systemic therapy for optimal local and systemic control? Additional refinements of these strategies, including the selection of postoperative CT based on the response to primary CT, may further improve the outcome in patients with LABC.

The treatment of patients with LABC provides an optimal scenario to assess the role of this multidisciplinary strategy in patients with early breast cancer.

The role of high-dose CT is being evaluated as a treatment to consolidate the effects of primary CT, and in patients with high risk of relapse after primary CT (patients with >4 metastatic axillary lymph nodes). Clinical trials with several new and effective cytotoxic agents such as docetaxel, paclitaxel and vinorelbine are just beginning. Monoclonal antibodies to specific tumor antigens, oncogenes, growth factors or their receptors have opened the possibility of innovative and potentially more selective treatments. Clinical investigation during the next decade will establish the role of these new modalities in the overall management of patients with LABC.

In summary, LABC encompasses a heterogeneous collection of breast neoplasia with widely different clinical and biological characteristics. Multidisciplinary therapy has become the treatment of choice for patients with LABC. It provides appropriate local control, the possibility of breast conservation therapy and increased survival rate in patients with LABC. The natural history of this disease changed dramatically with the introduction of multidisciplinary therapy. Five-year DFS rates of 35%-70% are commonly reported, and about 30%-40% of patients survive beyond 10 years without recurrence. Whereas progress has been made in the treatment of these patients, still more than 50% of these patients die of metastatic disease. New directions...
REFERENCES


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