Best management of locally advanced inoperable breast cancer

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Locally advanced breast cancer (LABC) is a heterogeneous disease; it includes disease which is either extensive within the breast and/or in ipsilateral nodal areas. These cancers vary widely in biological characteristics and clinical behavior, ranging from locally aggressive but systemically "indolent", to *de novo* generalised disease. LABC includes: (1) large breast tumours (>5 cm in diameter); (2) cancers that involve the skin of the breast or the underlying muscles of the chest; (3) cancers that involve multiple local lymph nodes (those located in the arm pit or the soft tissues above and below the collar bone) and (4) inflammatory breast cancer (IBC). The clinical management of LABC is complex and should be tailored to the individual patient, according to the biological features of the disease. A multidisciplinary approach is recommended combining systemic therapy (chemotherapy and/or hormone therapy and biological agents) and in some cases radiotherapy. LABC is reported to occur in 10–15% of all new primary breast cancer diagnoses [1]. At least 20–30% of women with breast cancer wait more than 8 weeks from the initial symptom(s) until they seek clinical assessment [2,3]. Richards et al reported a 12–19% decrease in 5-year survival in those women with delays of 3 months or more versus those with a shorter time to diagnosis [4]. The following factors have been cited as causes of patient delay: poor access to health care, lack of preventive health-care habits, increasing age, having child-care/elder care obligations, notion that the symptoms are benign, poor education, misperception of risk, embarrassment, fear of chemotherapy and breast loss and concern about being a hypochondriac and pessimist about survival [3–5,6]. IBC is an aggressive disease that progresses rapidly and carries a very grim prognosis. It is characterised by erythema, rapid enlargement of the breast, skin ridging and a characteristic "peau d'orange" appearance of the skin secondary to dermal lymphatic tumour involvement. Although a palpable tumour may not be present, about 55–85% of patients will present with metastases to the axillary or supraclavicular lymph nodes. Accurate diagnosis is critically important, as multimodal therapy can significantly improve outcomes if instituted early enough. The treatment of LABC is complex, and to complicate matters further, when it appears as a recurrent disease it can be considered as a "moving target" since previous treatment delivered in the adjuvant setting may affect treatment choice at recurrence.

Patients with stage IIIB or IIIC disease – including those with IBC and those with isolated ipsilateral internal mammary or supraclavicular lymph-node involvement – are often inoperable. Patients with stage IIIB or IIIC disease who respond to primary chemotherapy should be treated until the response plateaus or to a maximum of six cycles (minimum four cycles), after which several case series have demonstrated that locoregional control is improved [7–12]. The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear and should be individualised. In the absence of evidence on this subgroup of patients, it is reasonable that they receive locoregional radiotherapy (including nodal irradiation). The role of completion mastectomy should be individualised and based on technical and disease factors. Following the completion of chemotherapy, pre- or postmenopausal patients with locally advanced (operable and inoperable) hormone-responsive tumours should receive endocrine therapy according to their menopausal status. Patients with HER2-positive breast cancer who received chemotherapy in combination with trastuzumab should receive trastuzumab maintenance therapy. In the case of inflammatory breast cancer the role of anti-angiogenic agents has been explored in either HER2-positive or -negative disease. Inflammatory breast cancer is characterised pathologically by high vascularity and increased microvessel density because of the high expression of angiogenic factors such as vascular endothelial growth factor (VEGF). Use of bevacizumab, a VEGF-targeting monoclonal antibody, resulted in substantially improved progression-free survival and response in patients with advanced breast cancer and showed neoadjuvant activity in patients with previously un-

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treated locally advanced breast cancer or IBC. In a recent study, neoadjuvant treatment with bevacizumab, trastuzumab and chemotherapy was efficacious and well tolerated in patients with previously untreated primary IBC [13–15]. Treatment of LABC and IBC requires a coordinated multidisciplinary approach that should be individualised depending on tumour characteristics and response to treatment. The treatment may include a combination of chemotherapy, endocrine therapy, biological therapy and radiotherapy. While the prognosis in these cases is poor compared with that for other presentations of breast cancer, a reasonable survival and quality of life can be obtained with a team approach to treatment. All patients with LABC and IBC should be considered candidates for clinical trials to evaluate the most appropriate fashion in which to administer the various components of multimodality regimens.

Conflict of interest statement

No conflict of interest to declare.

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