Metastatic disease of the breast and local recurrence

Mark Verrill

Abstract

Multimodality primary therapies for breast cancer combined with earlier detection have led to a sharp decline in the death rate from breast cancer in the UK over the last 40 years in the face of a rising incidence. The latest UK statistics from Cancer Research UK report 50,285 new cases of breast cancer in 2011 with 11,716 deaths from breast cancer recorded in 2012. Crudely, this equates to a cure rate in excess of 75% for all comers. Despite this good news, there are still significant numbers of women (and men) who suffer from either a local recurrence or metastatic disease following apparently successful treatment for early breast cancer (Stage I–III). Only a minority of individuals, 6.6% with the stage recorded at diagnosis, present with stage IV disease. This review considers the treatment options available to individuals with locally recurrent and advanced breast cancer (ABC).

Keywords Breast cancer; local recurrence; metastatic disease

Considerations when assessing a patient with ABC

There are four main considerations when assessing a patient with recurrent or metastatic breast cancer; the patient, tumour burden and distribution, tumour biology and previous treatments (Figure 1). These build a picture of the available treatment options which range from excision of locally recurrent disease with curative intent through systemic anticancer therapies (SACT) modifying the natural history of the disease to best supportive care.

Patient engagement in treatment choices at any stage of disease is paramount. The patient should be involved at all stages of decision making and the gold standard of care is for a secondary breast cancer nurse specialist to be present at each consultation and available for decision support. In the absence of a dedicated nurse, third sector organizations such as Maggie's provide invaluable support in their centres, which are situated adjacent to an increasing number of cancer centres and with more planned. In patients scheduled for SACT, there may be options to use drugs with different routes of administration and specific toxicities and patient preference in these situations should be considered.

Physical patient characteristics are also fundamentally important. There is a clear link between poor functional status and early mortality following drug treatment as well as an impact on longer term outcomes. Disturbance of organ function and residual toxicity from previous treatment can limit the ability to use particular drugs. Patients with visceral crisis, characterized by rapid and symptomatic progression of disease with disordered liver biochemistry may require treatment with a high likelihood of producing a brisk tumour response.[1] This may lead to selection of a cytotoxic chemotherapy in patients where endocrine therapy would otherwise be the treatment of choice. Assessment of menopausal status is required to select anti-endocrine therapies.

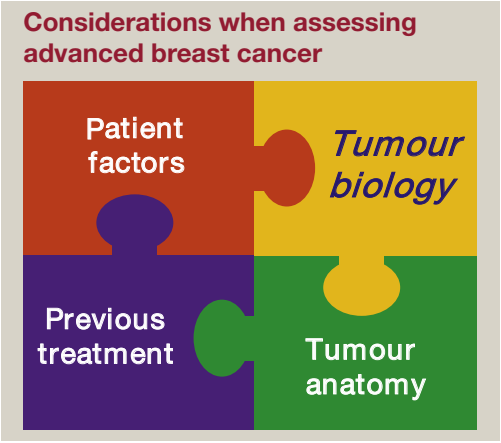

Figure 1

The distribution and burden of disease at recurrence defines the presenting symptoms and the goals in controlling them. While the systemic nature of metastatic breast cancer lends itself to 'whole body' treatment with systemic therapies, there are cases where local therapies or organ directed systemic treatments may be used. Local recurrences, brain metastases and spinal cord compression are most effectively treated with surgery and/or radiotherapy. Meningeal disease may require intrathecal chemotherapy. Bone metastases may need orthopaedic intervention to maintain function, radiotherapy for pain and specific bone directed therapies to prevent skeletal related events.

Locoregional recurrence

Following primary local therapy, there is an ongoing, albeit small, risk of recurrence in the conserved breast, the skin flaps following mastectomy or the axilla regardless of axillary treatment. In these sites, further surgery may allow macroscopic complete clearance of the recurrent disease and this should be considered in the multidisciplinary team (MDT) meeting. Local recurrence in a conserved breast is an indication for mastectomy and cannot usually be followed by radiotherapy due to the limitations to radiation dose resulting from previous treatment to the conserved breast. There is evidence that systemic therapy with endocrine therapy in oestrogen receptor (ER) positive patients and with chemotherapy in ER negative patients improves outcomes after excision and/or radiation for locoregional recurrence and, by extrapolation, anti-HER2 therapy should be considered in HER2-positive disease.[2] In cases where there is no option for locoregional therapy, the management options are the same as for overt metastatic disease. This includes many supraclavicular, infraclavicular and internal mammary nodal recurrences.

Mark Verrill *MA MB BChir FRCP is Head of the Department of Medical Oncology at the Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, UK. Conflicts of interest: none.*

Systemic anticancer therapies for advanced breast cancer

Knowledge of tumour biology is crucial to inform SACT strategies and it is vital to know hormone receptor (HR) and HER2 status. There are distinct strategies for management of each subgroup defined by HR and HER2, including for triple negative cancers (oestrogen, progesterone and HER2 negative).[1] There are also emerging therapies specifically directed at patients with *BRCA* gene mutation associated cancers. As a general principle, where there is a validated biological target with an appropriate associated therapeutic, use of a targeted therapy should be the first consideration in selecting anticancer drug therapy. Chemotherapy is increasingly regarded as an old fashioned and rather blunt tool, although it remains the standard of care in triple negative ABC and in combination with the majority of anti-HER2 therapies. Many patients with local or metastatic recurrence have previously been exposed to SACT in the adjuvant setting. This impacts on choice of therapies for ABC because of drug resistance, cumulative toxicities and, increasingly, funding restrictions based on tightly defined treatment pathways. Recently, standard definitions of primary and secondary (acquired) resistance to endocrine therapies have been agreed and published.[1] There is no corresponding consensus for cytotoxic treatments.

HR-positive HER2-negative disease

The majority of breast cancers are ER positive and so have the potential to benefit from anti-endocrine therapies (ET). Most patients with ER-positive cancers and regardless of recurrence risk based on other parameters will receive adjuvant anti-endocrine therapy as part of the treatment package for early breast cancer. In the advanced setting, patients with potentially endocrine sensitive disease should be considered for anti-endocrine treatment. Endocrine sensitivity in this context is defined as relapse more than 12 months after completing adjuvant endocrine therapy.[1]

Tamoxifen was the first licensed anti-oestrogen and remains the standard of care in premenopausal women. Gonadotrophin releasing hormone (GnRH) analogues can be used to render premenopausal women post menopausal and have the advantage over surgical or radiotherapy ovarian ablation of reversibility. The majority of recent clinical data in MBC are from trials in post-menopausal women so it is important to assess menopausal status in all women for whom anti-endocrine therapy is planned.

Trials of the non-steroidal aromatase inhibitors (AIs) anastrozole and letrozole in the late 1990s and their publication thereafter led to the establishment of this drug class as the standard of care as first-line treatment for post menopausal women with ER-positive (HER2 negative) advanced breast cancer.[3] Initially this choice was not affected by adjuvant treatment, which in the overwhelming majority of patients was tamoxifen. However, AIs are now part of the adjuvant therapy treatment standard and so in MBC their use as monotherapy is typically reserved for patients who are endocrine therapy naïve or with endocrine sensitive disease. The addition of the cyclin-dependent kinase (CDK) 4/6 inhibitor palbociclib to letrozole in the first-line treatment of ER-positive HER2-negative ABC extended progression free survival (PFS) from 10 to 20 months in a randomized phase II trial[4] and has led to accelerated approval by US Food and Drug Administration (FDA). A follow-up phase III trial has completed accrual and may give insights into the effect on overall survival (OS) as well as greater precision regarding the PFS effect.

Treatment of patients with endocrine resistant disease

Patients relapsing after prior endocrine therapy for breast cancer are regarded as having endocrine resistance. Primary resistance is defined by either relapse during the first 2 years of ET or progression within the first 6 months of first-line ET for MBC. Secondary or acquired resistance is defined as relapse during adjuvant ET but after the first 2 years or within 12 months of completing adjuvant ET or 6 or more months after the initiation of ET for MBC[1] (Table 1). Until recently there were surprisingly few data to inform optimal ET after a non-steroidal AI and the tendency was to cycle through the available anti-endocrine drugs or to use cytotoxic chemotherapy. The best evidence for anti-endocrine monotherapy in this setting is for Fulvestrant at a dose of 500 mg given 4-weekly with an additional loading dose 14 days after the first administration. In the CONFIRM trial comparing this schedule with a lower, 250 mg dose, time to progression was 6.5 months and overall survival 26 months.[5]

As our understanding of molecular biology increases, we have been able to target signalling pathways involved in endocrine resistance. Everolimus is a tyrosine kinase inhibitor directed at mTOR (mammalian target of rapamycin) and was tested in the Bolero-2 trial in which the combination of exemestane with everolimus was compared with exemestane alone. There was a statistically significant improvement in investigator assessed time to progression (6.9 months versus 2.8 months), although no significant survival advantage.[6] Everolimus adds a number of toxicities to endocrine therapy and its use requires close clinical supervision.

Palbociclib has also been tested in second-line in patients who had not previously received the drug and the combination of palbociclib with fulvestrant is clearly superior to fulvestrant alone although, to date, the licensing authorities have not considered this combination.[7]

Considerations in endocrine therapy[1]

- Visceral crisis
  - Severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease
  - Visceral crisis is not the mere presence of visceral metastases, but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible
- Endocrine resistance
- Primary endocrine resistance
  - relapse while on the first 2 years of adjuvant ET, or
  - PD within first 6 months of 1st line ET for MBC, while on ET
- Secondary (acquired) endocrine resistance
  - relapse while on adjuvant ET but after the first 2 years, or
  - relapse within 12 months of completing adjuvant ET, or
  - PD 6 months after initiating ET for MBC, while on ET

Table 1