Metastatic breast cancer

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This fourteenth article in our series on breast disease gives an overview of what to look for in the patient with a past history of early breast cancer and how to assess and support the patient with metastatic breast cancer in the general practice setting. Information about the latest medical oncology treatments, including new chemotherapies and targeted 'biological' therapies is provided.

Steady improvements in the treatment of early breast cancer have resulted in fewer women developing distant recurrence. However, about 20% of women with a history of early breast cancer will ultimately develop metastases. Metastatic disease, while not curable, is treatable. The aims of treatment are to maximise quantity and quality of life, while accepting that there is no realistic prospect of cure. The general practitioner is crucial in managing the woman with metastatic breast cancer, providing a link between the oncology treatment team and the patient and her family.

Survival of patients with metastatic breast cancer has been improving significantly over the past 2 decades with a median survival now of about 2 years. However, many patients who develop 'late' metastases after a disease free interval of at least 3 years without visceral disease (eg. bone only) can survive up to 10 years. The number of treatment options has increased substantially during this time. For each patient, there are likely to be several therapies that may control the disease, often for months, sometimes years. Most patients remain well until late in their disease.

While the main focus of treatment is the use of systemic drugs to control disease progression, a number of other approaches may also be helpful including draining of effusions in the outpatient setting, radiotherapy and the judicious use of medications to improve pain, nausea and constipation. The palliative care service has therefore evolved as an integral part of the multidisciplinary breast cancer treatment team.

What to worry about

The patient with previous early breast cancer

Helping patients find balance between being anxious about every ache on the one hand, and reluctant to seek medical advice on the other, is a challenge for both GPs and oncologists. Clinical trials have not demonstrated a benefit for intensive surveillance.[1] A good rule of thumb is that if a symptom is clearly new (eg. hip pain) and persists for 2–3 weeks, it is sensible to consider investigation.

Most such symptoms will not be due to cancer recurrence, and it is rare that a first presentation of metastatic disease represents an urgent or life threatening problem. Clinical commonsense can be applied such as plain X-rays and a trial of simple analgesics. However, if the problem persists or the patient is particularly anxious about cancer recurrence, a bone scan is likely to clarify the matter.

Most other potential modes of presentation of metastatic disease can be handled in this way, with persistent symptoms generally best investigated with imaging (*Table 1*).

The patient with known metastatic disease

Metastatic breast cancer is a heterogeneous disease. When assessing new symptoms, it is helpful to be aware of the extent of documented disease, as this will suggest the likely cause of symptoms. For example, a women with disease confined to bone who develops abdominal symptoms may have constipation secondary to opiates rather than new liver metastases.

Developments that signal the need for urgent or semi-urgent assessment include significant changes in bone pain and increasing breathlessness (*Table 2*). Severe bone pain may be a warning of an impending fracture. Plain X-rays are often more helpful than bone scans in establishing whether the patient is in need of surgical stabilisation before more definitive radiotherapy.

In the setting of vertebral disease, a worsening of pain should raise the question of possible spinal cord compression or involvement of the cauda equina. A

Table 1. Metastatic disease – symptoms, management and investigations

Symptom	Initial management	More definitive investigation
Musculoskeletal	Clinical assessment, plain X-rays, simple analgesia	Bone scan
Dyspnoea	Clinical assessment, chest X-ray to exclude obvious effusion or cardiomegaly	CT chest, cardiac echo, CTPA scan depending on clinical picture
Abdominal symptoms	Abdominal exam looking for masses or RUQ pain. Liver function tests looking for gross abnormalities (adjuvant chemotherapy or endocrine therapy can cause mild fatty change)	CT abdomen
Persistent headache	Usual headache management	A first metastatic presentation with cerebral metastases is unusual, but new headaches that persist or worsen would justify a CT of the brain

band-like sensation felt across the trunk, stiffness or weakness of the legs and difficulty walking (spinal cord), or sphincter disturbance and 'saddle anaesthesia' (cauda equina) signal the need for immediate referral to an oncology centre that provides magnetic resonance imaging (MRI), radiation oncology and neurosurgery.

Hypercalcaemia is becoming less common now that bisphosphonates are routinely given to women with known bone metastases. However, it is still a diagnosis to consider in patients who develop unexplained nausea, constipation, generalised aches, and polydypsia and polyuria. Hypercalcaemia typically occurs in the presence of skeletal metastases, but this is not always the case.

Women presenting with dyspnoea require careful evaluation and investigation as there are many possible causes, some requiring urgent attention (*Table 3*). Pulmonary embolism may present in a 'silent' fashion, with gradually deteriorating exertional dyspnoea. Computerised tomography pulmonary angiography (CTPA) is the investigation of choice, especially in the presence of lung metastases as a false positive V/Q scan can occur. It can also assess the presence of a significant pericardial or pleural effusion, although it is not the investigation of choice if this is suspected. Other pathologies to consider in the dyspnoeic patient include anaemia, radiation pneumonitis, and lymphangitis.

Table 2. Symptoms requiring urgent assessment

Symptom	Initial management
Increasing bone pain	X-ray involved limb • Long bones • Back Assess for any neurological signs in the legs
Worsening dyspnoea	Assess for pleural effusion Consider pulmonary embolus Consider pericardial effusion
Unexplained vomiting	Consider hypercalcaemia Consider brain metastases Consider liver metastases

Treatment

Treatment of metastatic breast cancer needs to be flexible given the heterogeneity of the disease. Different approaches will be appropriate at different stages of the disease. Systemic anticancer therapies consist of endocrine treatments, cytotoxic chemotherapy, and newer targeted biological agents. Surgery and radiotherapy may also be useful in particular circumstances and supportive therapies are an important component of management either with or after systemic treatments.

Endocrine therapy

Endocrine therapy is highly effective in women who have oestrogen or progesterone receptor positive disease, and it may delay the need for chemotherapy for months or years. Using endocrine therapy as first line treatment gives results equivalent to using chemotherapy first line in the metastatic setting, unless there is rapidly progressive visceral disease.[2] Initial choice of agent will depend on the patient's menopausal status and what endocrine treatment has been used before as adjuvant therapy.

For premenopausal women, tamoxifen is effective, as is ovarian suppression. Ovarian suppression can be achieved with oophorectomy or monthly injections of a luteinising hormone releasing hormone (LHRH) analogue such as goserelin. For postmenopausal women, the aromatase inhibitors (anastrozole, letrozole, or exemestane) are well tolerated and slightly more effective than tamoxifen.[3]

Chemotherapy

Where the tumour is hormone receptor negative, or hormone receptor positive but resistant to endocrine therapy, chemotherapy currently offers the best chance of controlling the disease. The aim of chemotherapy is to improve cancer symptoms enough to make the

side effects and inconvenience of treatment worthwhile, and this requires careful judgment and discussion with the patient. In general, longer courses of chemotherapy result in better quality of life than short (less than 3 months) courses of treatment.[4] Chemotherapies are available in both intravenous and oral forms, and are often well tolerated (*Table 4*).

Targeted 'biological' therapies

Decades of molecular research are finally paying off, and a number of new agents are being tested in the management of cancers. In general, these new drugs block proliferative pathways other than the hormone receptor pathways. The monoclonal antibodies (with names ending in 'mab') are generally given intravenously and tend not to have chemotherapy-type side effects such as vomiting, hair loss and low blood counts.

Trastuzumab (Herceptin) has made a dramatic impact on the management of women who have HER2 positive breast cancer. Approximately 20% of women will show amplification of the HER2 gene, leading to an increased amount of receptor on cancer cells and a susceptibility to the blocking action of Herceptin. The test for positivity is an immunohistochemical stain that can be done on the original primary tumour; treatment is given intravenously every 3 weeks. Herceptin in combination with taxane chemotherapy leads to longer overall survival than taxane chemotherapy alone.[5] *Figure 1a, b* shows the response of liver metastases to chemotherapy combined with Herceptin. There is a risk of cardiotoxicity resulting in cardiac failure, especially where Herceptin is used in combination with anthracyclines. Monitoring for development of cardiomyopathy with regular gated heart pool scans (GHPS), looking for a reduction in left ventricular ejection fraction, is recommended.

There are a number of other related agents that have shown initial promising results and are expected to become part of routine practice over the next 5 years. Standard practice may evolve into short 'debulking' courses of cytotoxic chemotherapy, followed by longer term 'maintenance' treatment with some of these agents, many of which are given orally.

Table 3. Presentation of dyspnoea

Causes of dyspnoea	Diagnostic approach
Pleural effusion	Chest exam and chest X-ray will detect obvious effusions – if these are clear, the dyspnoea is not due to pleural effusion
Pulmonary embolus	Always needs to be considered, especially if the chest is clear
Pericardial effusion	Often difficult to detect clinically and needs to be considered when dyspnoea is unexplained. Cardiac echo is the usual investigation, but if CT of the chest is contemplated anyway, this will exclude significant pericardial fluid
Lymphangitis	Often not seen on chest X-ray and needs chest CT for diagnosis

Locally directed treatments

Surgery is indicated for some symptomatic or isolated metastases. This may be in the form of resection of lesions, for example cerebral deposits or stabilisation in the form of plating an involved bone to prevent impending fracture.

Radiotherapy is highly effective in the management of acute pain related to cancer. Pain from bony metastases generally responds to a short course of palliative radiotherapy, giving relatively fast symptom control. Radiation is also very useful in the treatment of local (breast or chest wall) recurrence, as well as the control of lesions in the central nervous system such as spinal cord compression or brain metastases.

Palliation and support services

Palliative care and symptom control services are best incorporated early into the management team, especially for difficult to manage symptoms. Palliative care physicians frequently manage patients receiving anticancer treatments. They provide valuable help in the control of all symptoms both physical and psychological. In addition, involvement of a psychologist or psychiatrist is frequently utilised to support both the patient and her family.

In addition to pain control, palliative care services can provide support for other common complaints of women with breast cancer including dyspnoea from recurrent effusions, discomfort from ascites, fatigue and nausea. Short stays in a palliative care/symptom control unit are sometimes required to gain control of symptoms. Palliative care services can also facilitate access to community physiotherapy and occupational therapy to promote mobility and independence in the home environment.

Community services are also integral to the care of patients with metastatic cancer. These services may involve community nursing, in combination with care by the GP. Referral to

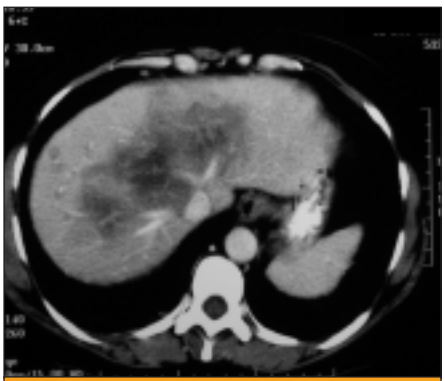

Figure 1a. Liver metastases in a woman with metastatic breast cancer before treatment

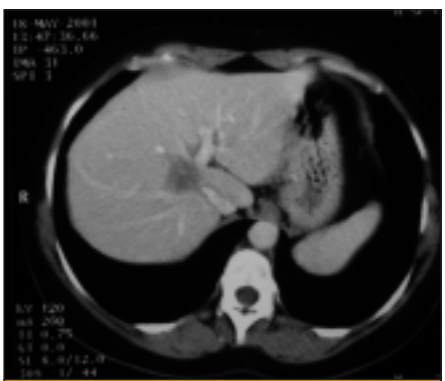

Figure 1b. After treatment with chemotherapy and Herceptin

Table 4. Newer chemotherapy options

Taxanes

Paclitaxel and docetaxel – can be given 3 weekly or weekly with minimal side effects (mainly paraesthesias of the hands and feet). Weekly administration does not usually cause complete alopecia

Capecitabine (Xeloda)

Oral chemotherapy – prodrug of 5FU. Minimal side effects with no alopecia. Associated with palmar plantar erythroderma (dose related)

Vinorelbine

Given intravenously weekly. No alopecia, and minimal side effects apart from constipation and a small amount of peripheral neuropathy

community services should be done early to allow a gradual increase in the delivery of care, as dictated by the woman's condition.

A dietician can also be of great support to provide nutritional information and advice to patients who are typically not tolerating a normal diet, particularly while on chemotherapy. Many patients will turn to various supplements or vitamins or special diets and will need to have some guidance in this area. While these approaches do give a sense of control back to the patient, they need to be balanced with the costs of potentially ineffective complementary treatments. Information from the USA National Cancer Institute in is a useful source of information about alternative therapies (http://nccam.nih.gov/health/bytreatment.htm).

Local breast cancer support groups are a major source of support for women with breast cancer. These groups often address issues not routinely dealt with in the doctor's office including appearance and sense of femininity, educational discussion groups, as well as support from other women who have either undergone or undergoing treatments for all stages of breast cancer.

Conclusion

Women with metastatic breast cancer are surviving longer, and are therefore providing increasing challenges to all practitioners involved in their care. Although the multidisciplinary team remains central to the delivery of care for these women, the GP plays an important role in providing support as well as the early provision of assessment and ongoing management. The GP also provides important connections with the families of these patients to assist in the psychological aspects of care.

Conflict of interest: none declared.

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2006 is an election year for the college, with the key positions of President, Censor-in-Chief and Registrar Representative on Council to be decided. All Fellows, Members and Registrar Associates are eligible to vote for the President. Only Registrar Associates can vote for the Registrar Representative on Council. Voting for the Censor-in-Chief is by the College Censors, all State Faculty Censors and the members of the Board of Examiners. The college will provide information on each Presidential and Registrar Representative candidate for members, as follows:

- A special 'election edition' of FridayFax after the close of nominations
- A 'meet the candidates' section on the college's website, giving the opportunity for a candidate to provide his/her reasons for nominating and their priorities for the role, together with a curriculum vitae and photograph.

Information on Censor-in-Chief candidates will be forwarded to those eligible to vote. Any member wishing to nominate for these positions can access the nomination information via the college's website after nominations open. Enquiries to Pam Garrard at pam.garrard@racgp.org.au or phone 03 8699 0577.

David Wright
Chief Executive Officer
RACGP

Position	Nominations open	Nominations close	Results announced	Voting material mailed	Ballot closes	Declaration of poll
President	8 May 2006	6 Jun 2006	9 Jun 2006	19 Jun 2006	18 Jul 2006	19 Jul 2006
Censor-in-Chief/ Registrar Representative	5 Jun 2006	4 Jul 2006	7 Jul 2006	7 Aug 2006	5 Sep 2006	6 Sep 2006

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