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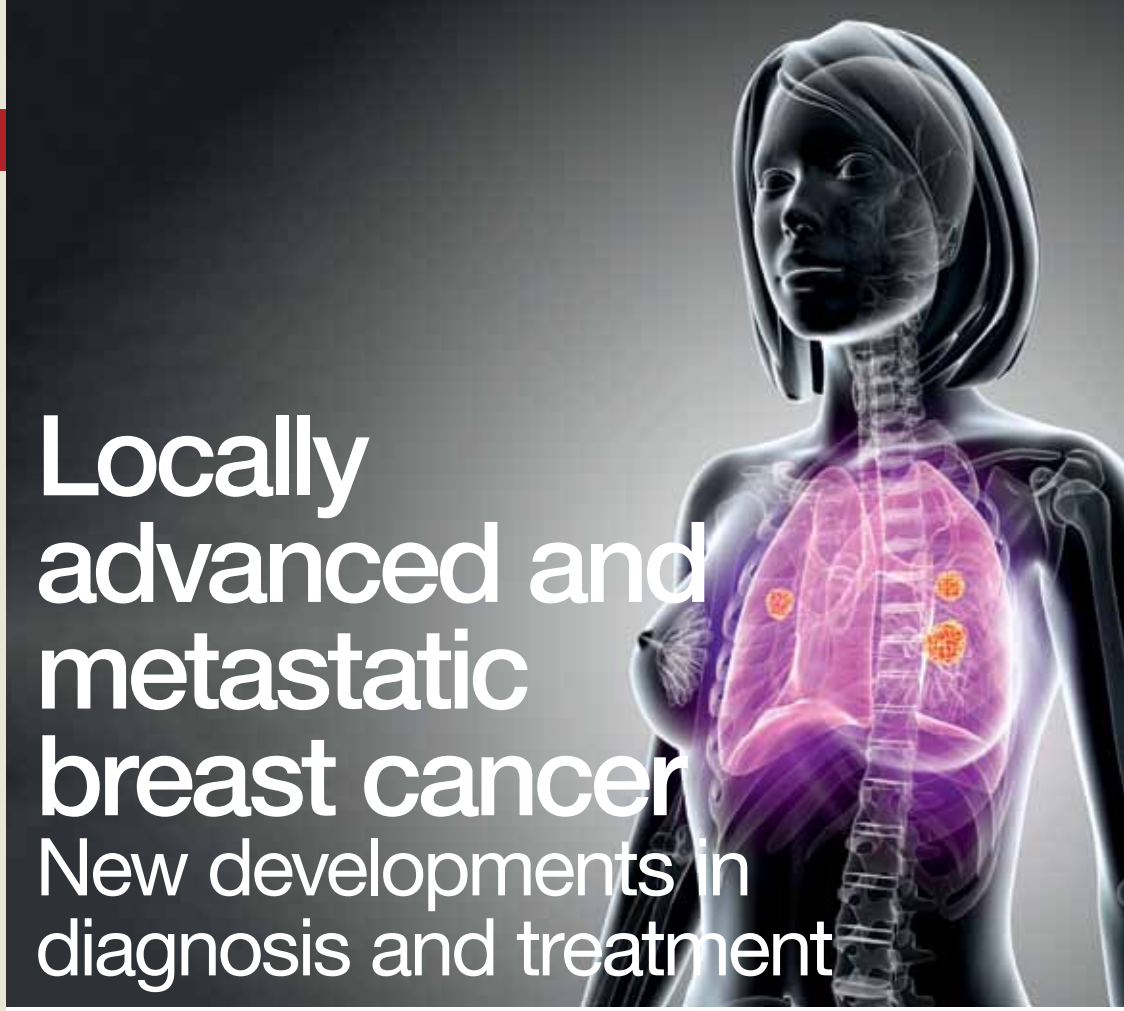

Locally advanced and metastatic breast cancer

New developments in diagnosis and treatment

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New systemic agents and integrated multidisciplinary management of patients have increased the length of survival in patients with locally advanced or metastatic breast cancer. The management of these patients is discussed in this second article of a three-part series on advances in the diagnosis and treatment of breast cancer.

Key points

- **Patients with locally advanced breast cancer are typically managed with curative intent to optimise treatment outcomes.**
- **Patients with metastatic breast cancer almost always have incurable disease and the primary aims of treatment are to improve symptom control, quality of life and survival.**
- **New systemic agents and integrated multidisciplinary management have increased the length of survival in patients with these breast cancers.**
- **Early palliative care referral should be offered to patients with metastatic breast cancer so that they may benefit from symptom management, nursing support and potentially improved survival.**
- **Oncological emergencies such as neutropenic sepsis and spinal cord compression require urgent referral for treatment.**

Significant improvements have occurred in the outcomes of a diagnosis of breast cancer, through progressive small advances in diagnosis and management. This second article of a three-part series considers locally advanced breast cancer, including the rare and aggressive form inflammatory breast cancer, and metastatic breast cancer. The first part, published in the June 2013 issue of *Medicine Today*, reviewed early breast cancer and the third article, to be published in a subsequent issue, will cover current diagnostic tools, psychosocial care and risk factor modification in the increasing number of breast cancer survivors.[1]

Patients with locally advanced breast cancer are typically managed with curative intent to optimise treatment outcomes. In patients with metastatic breast cancer, the primary aims of treatment are to improve symptom control, quality of life and survival, as these patients almost always have incurable disease.

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ADVANCES IN MANAGEMENT OF LOCALLY ADVANCED AND METASTATIC BREAST CANCER

- Integrated multidisciplinary management of patients
- Neoadjuvant systemic therapy for locally advanced breast cancer aims to improve surgical outcomes
- Use of anti-HER2 agents (trastuzumab and lapatinib); second-generation anti-HER2 agents now entering clinical practice
- Sequential single-agent chemotherapy as effective as doublet and triplet treatment; 'all drugs over time' minimises toxicity and maximises quantity and quality of life
- Early rather than late referral to palliative care services is likely to improve survival
- RANK ligand inhibitors (e.g. denosumab, given subcutaneously) taking place of intravenous bisphosphonates as antiresorptive agents in treatment of bone metastases
- Resection of the primary tumour in patients with bone-only metastatic disease may have a survival benefit (being tested in clinical trials) now that more effective systemic therapy is being used and giving longer survival after diagnosis
- Tailored exercise programs now recognised as having a role in improving treatment tolerance and psychosocial wellbeing

ABBREVIATIONS: HER2= human epidermal growth factor receptor 2; RANK = receptor activator of nuclear factor kappa-B.

Considerable advances in the length of survival have been made with the advent of effective new systemic agents and integrated multidisciplinary management of patients (see the box on this page).

LOCALLY ADVANCED BREAST CANCER

Locally advanced breast cancer is defined according to the features in the box on page 35, and encompasses a range of conditions from a large cancer that may not be very different except for size from smaller cancers, to a grossly locally advanced cancer that has invaded the overlying skin and/or the underlying chest wall (Figure 1). This type of cancer accounts for about 10% of newly diagnosed breast cancers, and there is some evidence that incidence is decreasing, particularly in mammographically screened populations.[2]

Factors that influence the prognosis of patients with locally advanced breast cancer are similar to those for early breast cancer – for example, the extent of lymph node involvement and the grade, size and receptor status of the primary tumour.[3] Despite the gross nature of some presentations, the underlying tumour biology is not always aggressive, particularly when the tumour may have been present for some years (then often associated with patient neglect).

In contrast to patients with early breast cancer, patients with locally advanced disease should routinely undergo staging investigations including CT scan of the chest and abdomen and bone scan, as there is a higher pretest probability of finding clinically occult metastatic disease.

The presence of metastases would change the intent of treatment from potentially curative to palliative, and may impact on local and systemic treatment choices. However, local therapy remains important in this group of patients to prevent or control ulcerating disease, which may be painful and/or bleed and can be chronically infected, with an odorous discharge.

Treatment options

Patients who present with locally advanced disease and are sufficiently fit are usually treated with multimodality therapy (systemic therapy, surgery and radiotherapy) to maximise long-term disease control. Such therapy results in long-term survival (i.e. cure) in approximately 50% of patients.[2] The optimal sequencing of the treatment modalities remains controversial and should be individualised.

Neoadjuvant therapy

The term 'neoadjuvant' is used to describe primary or preoperative systemic therapy in the locally advanced setting of breast cancer. It aims to improve surgical outcomes and is associated with high rates of clinical response.

Women with locally advanced breast cancer benefit from systemic chemotherapy to a similar extent as do those with early breast cancer. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed an improved overall survival with the use of chemotherapy, regardless of tumour size and nodal status.[4]

Trastuzumab should be added to chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)-positive cancer, which has a relatively high response rate. Primary hormone therapy is a reasonable option, particularly for older patients with strongly oestrogen receptor (ER)-positive disease or patients who refuse treatment that may cause significant side effects, which is often the reason behind cases associated with neglect.

Surgery and radiotherapy

Surgery has a role at some stage for most patients with locally advanced breast cancer, and is conventionally in the form of total mastectomy. Many patients are not suitable for breast-conserving treatment (wide local excision plus radiotherapy) at presentation because of the large tumour size. However, preoperative systemic therapy may reduce the tumour bulk and

Figure 1. Locally advanced breast cancer infiltrating the skin.

increase the likelihood of successful breast-conserving therapy. Depending on the subtype of breast cancer, there is a 5 to 40% chance of a pathological complete response, with no viable cancer found in the surgical specimens.

The timing of radiotherapy and surgery depends on the response to systemic therapy. If there has been a good response and the tumour is resectable, usually surgery is performed followed by radiotherapy, primarily to improve local and regional disease control. However, radiotherapy may be given before surgery in patients with tumours that have become resectable, particularly patients who will have immediate reconstruction.

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer is a rare and aggressive form of locally advanced breast cancer, accounting for approximately 2% of all breast cancer cases. It is characterised by diffuse erythema and oedema, described as peau d'orange, due to tumour emboli within the dermal lymphatics (Figures 2 and 3).

This distinct subgroup of locally advanced breast cancer may present without an underlying mass, leading to diagnostic delay and confusion with mastitis. Inflammatory breast cancer that presents early with skin involvement needs to be distinguished from a locally advanced breast cancer infiltrating the skin late in the disease because the prognoses differ.

Although inflammatory breast cancer is highly aggressive, cure is achieved in about one-third of patients with the use of optimal multimodality therapy.

Treatment options

Multidisciplinary treatment is essential in patients with inflammatory breast cancer, and the sequencing of treatment modalities is important. In contrast to most cases of early breast cancer and many cases of locally advanced breast cancer, surgery is not usually the initial treatment. Preoperative chemotherapy is typically given initially, followed by surgery and radiotherapy to optimise local and regional control. Radiotherapy may also be given before surgery, especially if immediate breast reconstruction is planned.

METASTATIC BREAST CANCER

Metastatic breast cancer, also known as advanced or secondary breast cancer, refers to invasive cancer that has spread beyond the breast and regional lymph nodes to distant sites, typically bones, lungs, liver and brain. It may be present at the initial diagnosis of breast cancer in approximately 6% of cases but usually develops after the diagnosis of an early breast cancer. About 20% of patients with lymph node-positive early breast cancer will develop metastatic disease.

The median survival of patients with metastatic breast cancer is 18 to 24 months, but the range is wide, extending from a few months to many years. The pattern of metastatic disease is an important prognostic factor – for example, patients with bone-only disease frequently live more than three to five years (see the box on page 36).

The site of metastases relates to the underlying tumour biology:

- HER2-positive breast cancer has a predilection for brain metastases
- ER-negative, progesterone receptor (PR)-negative and HER2-negative disease (triple-negative phenotype) has a tendency for visceral metastases, especially of the liver and lungs
- ER-positive disease has a predilection for the initial metastatic site to be bones.

FEATURES OF LOCALLY ADVANCED BREAST CANCER

The presence of one or more of:

- primary breast cancer larger than 5 cm
- invasion of the overlying skin and/or underlying chest wall
- clinically enlarged and abnormal ipsilateral axillary, supraclavicular and/or internal mammary lymph nodes
- inflammatory breast cancer (a distinct subgroup)

Treatment options

There is a wide range of treatment options available for patients with metastatic breast cancer, and important considerations need to be made when selecting treatment. These considerations include the following:

- tumour factors – hormone receptor status, HER2 status, extent and sites of metastases and time elapsed since any previous adjuvant treatment
- patient factors – age, performance status, comorbidities, patient preference and availability of resources
- previous treatments administered.

Treatments should be tailored to the needs of individual patients, and a multidisciplinary team in the hospital and community should support these patients. This team would include general practitioners and palliative care medical, nursing and allied health professionals.

Radiotherapy and sometimes surgery may be indicated for the control of locally symptomatic disease, such as pathological

Figure 2. Inflammatory breast cancer, showing the characteristic diffuse erythema.

Figure 3. Peau d'orange, the oedema due to tumour emboli within the dermal lymphatics characteristic of inflammatory breast cancer.

fracture of bone metastasis. However, the mainstay of treatment for metastatic breast cancer is systemic therapy, including the following:

- hormone therapy, for patients with hormone receptor positive cancer
- chemotherapy, irrespective of hormone receptor status
- biological (targeted) therapy with anti-HER2 agents (i.e. trastuzumab and lapatinib), for HER2-positive disease, in combination with either hormone therapy or chemotherapy.

METASTATIC BREAST CANCER: FACTORS PREDICTIVE OF IMPROVED SURVIVAL

- Hormone receptor-positive tumour (i.e. ER- or PR-positive disease)
- HER2-negative tumour (with the exception of the triple-negative subgroup, which is usually associated with a poorer prognosis)
- Metastases in bone or chest wall or lymph nodes only (compared with visceral metastases involving the liver, lungs, bone marrow, brain, meninges and others)
- Low volume of tumour
- Complete clinical response to treatment
- Long disease-free interval from initial therapy to presentation with metastatic disease

Hormone (endocrine) therapy

Hormone therapy is the preferred first-line treatment for patients with hormone receptor-positive metastatic disease unless there is rapidly progressing disease or large volume visceral metastases. It is a common misconception that chemotherapy works better than hormone therapy. However, chemotherapy generally provides a more rapid response and hence is often chosen in the presence of symptomatic or rapidly progressive visceral disease.

In premenopausal women, tamoxifen with or without ovarian suppression (with a luteinising-hormone releasing hormone agonist such as goserelin) is used.

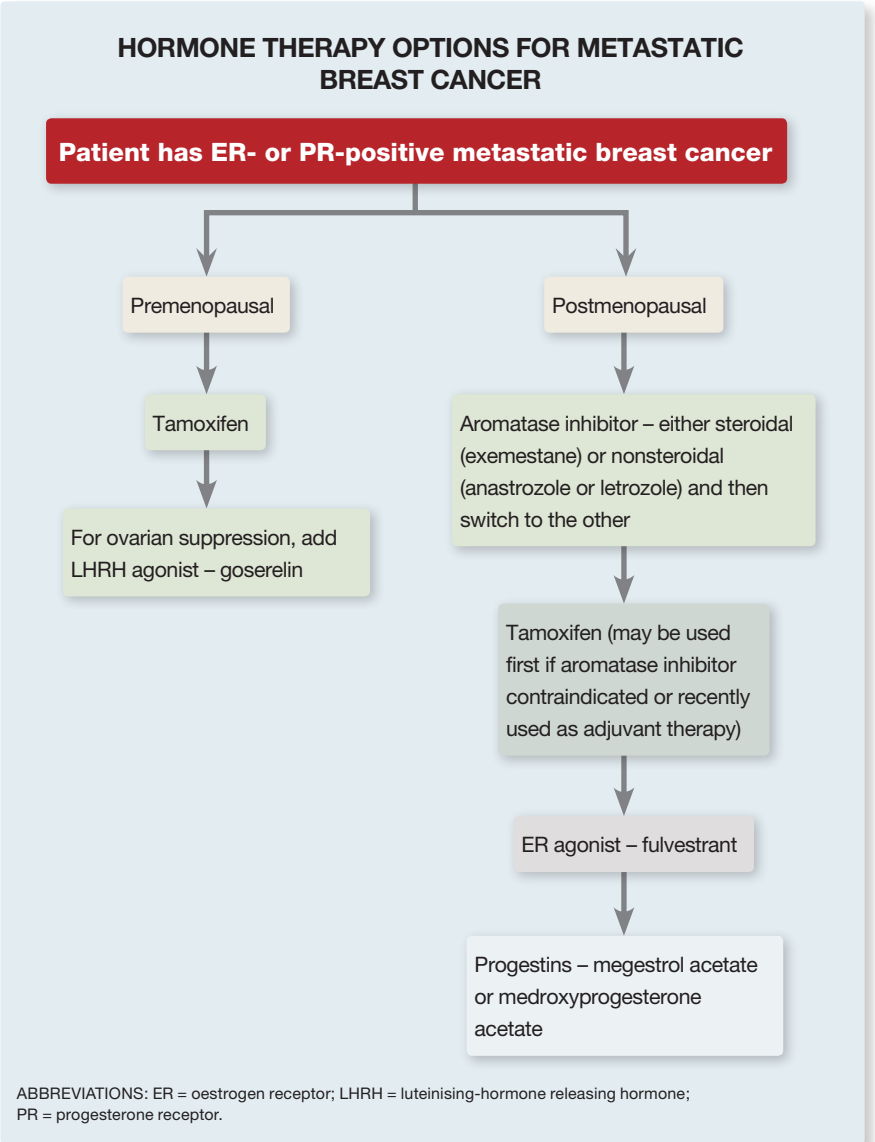
For postmenopausal women, an aromatase inhibitor is usually given. Tamoxifen may be used in postmenopausal women if an aromatase inhibitor is contraindicated or has recently been used as adjuvant therapy. Other hormonal manipulations may also be considered in second- or-third-line setting, such as fulvestrant (an ER antagonist administered monthly intramuscularly) and progestins (megestrol acetate or medroxyprogesterone acetate, which are PR agonists and have antioestrogenic effects). Recent data suggest that drugs such as everolimus reverse resistance to aromatase inhibitors but these are not yet funded in Australia and add toxicity. Generally, hormone therapy is discontinued when the decision is made to switch to chemotherapy. It may be reinstated after chemotherapy is completed, particularly if a good response is obtained.

The options for hormone therapy in patients with metastatic breast cancer are summarised in the flowchart on page 38.

Chemotherapy

Palliative chemotherapy should be considered for patients with symptomatic disease (particularly rapidly progressive visceral metastases) or hormone-resistant disease. Recent data suggest that sequential single-agent chemotherapy is as effective as doublet and triplet treatment, except when a more rapid response is needed. There is no consensus on the sequence and combination of drugs, but consideration should be given to the previous treatment responses, cumulative toxicity, ease of administration and patient preference.

The general concept is that 'all drugs over time' is the best strategy to minimise toxicity and maximise quantity and quality of life, and this is responsible for the extended survival beyond five years for many patients. Patients are counselled that they are likely to go on and off



chemotherapy, interspersed with hormone therapy if they have hormone receptor-positive tumours, for the duration of the disease. However, it is important to discontinue chemotherapy when there is minimal or no response, unacceptable toxicity or the patient is no longer fit for active therapy.

Biological (targeted) therapies

The only current targeted therapies in common use for metastatic breast cancer are the anti-HER2 drugs for patients with HER2-positive disease.

Trastuzumab is administered intravenously either alone or in combination with chemotherapy or hormone therapy. Although treatment with trastuzumab is associated with a possible increased risk of congestive cardiac failure, this risk is low when routine cardiac monitoring is used, and usually reversible on stopping the drug.

The oral drug lapatinib is a small-molecule tyrosine kinase inhibitor directed against the epidermal growth factor receptor (EGFR) and patients with HER2. It is PBS listed for use in combination with the oral chemotherapy agent capecitabine for patients with HER2-positive metastatic breast cancer that has progressed on trastuzumab. Although this oral combination is convenient, it generally has greater toxicity, in particular diarrhoea and nausea, than trastuzumab combinations.

Many second-generation anti-HER2 agents have shown benefit in clinical trials and will enter practice in Australia once funding arrangements are approved. Current data support their use in combination with other anti-HER2 drugs.

Symptom management and palliative care

Palliative care referral (emphasised as 'supportive care' and not purely as 'terminal care') should be offered early to patients with metastatic breast cancer so they may benefit from the available services and are not confronted by referral at a late stage. Recent data in studies of patients with lung cancer, almost certainly also applicable to those with breast cancer, demonstrate significant improvement in survival with early rather than late referral to palliative care services.[5]

Management of symptoms such as pain, constipation and dyspnoea often require multimodal therapies addressing physical, pharmacological and psychological ramifications. Underdosing of analgesics such as opiates is common and practitioners treating these patients should be aware that adequate pain control is essential and that concerns of opiate addiction are often overemphasised in this clinical context. Additional nursing support at home and terminal care are best managed through a multidisciplinary palliative care team.

Palliative radiotherapy

Brain metastases

Optimal management of patients with brain metastases requires a multidisciplinary approach. Palliative treatment should be tailored to the performance status of the patient and informed by the

number, size and location of the brain metastases, status of the extracranial disease and prior therapy.

Surgical resection is generally recommended for patients with a solitary or limited number of brain metastases, stable systemic disease and good performance status. Postoperative whole brain irradiation further decreases the risk of intracranial recurrence. Stereotactic radiosurgery may be an option for selected patients with a limited number of brain metastases, and allows sparing of normal brain tissue.

Whole brain irradiation alone is used for patients with multiple brain metastases, progressive extracranial disease or poor performance status. Corticosteroids are usually used during radiotherapy and then tapered off after radiotherapy to manage symptomatic intracranial oedema associated with brain metastases and this treatment.

Bone metastases

Analgesics, antiresorptive bone agents (previously bisphosphonates but increasingly receptor activator of nuclear factor kappa-B [RANK] ligand inhibitors) and systemic therapy are typically recommended in combination with palliative radiotherapy for painful bone metastases.

Palliative surgery is appropriate for treatment of pathological fracture and prophylactic treatment of impending fracture, and in selected patients with spinal cord compression at one or two adjacent vertebral levels.

Osteoclast inhibitors

Bisphosphonates were standard of care for women with bone metastases to reduce the risk of 'skeletal-related events' including pain, fractures and need for radiotherapy. Both oral and intravenous formulations are available. Gastrointestinal side effects from oral forms and monitoring of renal function need to be considered.

Denosumab (a RANK ligand inhibitor) has been shown to be more efficacious than zoledronic acid and is now available, with the advantage that it is given as a subcutaneous injection.

Bisphosphonates and denosumab are associated with the rare but serious complication of osteonecrosis of the jaw, most commonly in patients with periodontal disease, the risk of which is reduced by preventive dental assessment and management. Denosumab is potent in reducing calcium levels, and supplementation is regularly required except when it is used to treat malignant hypercalcaemia.

Hypercalcaemia of malignancy in breast cancer patients is almost always due to large volume bone metastases and should be managed aggressively, including with large volume rehydration.

Palliative surgery for the breast primary

Resection of the primary breast cancer in the setting of metastatic disease at diagnosis is controversial. Until recently it was thought that there was no survival benefit in removing the primary tumour. However, with improvements in the efficacy of systemic therapy and survival after the diagnosis of metastatic breast cancer, recent case series suggest that there may be a survival benefit from resecting the primary tumour, almost exclusively in patients with bone-only metastatic disease.[6] This fits with yet to be proven biological theories of metastases involving constant reseeding of tumour cells into the circulation from the primary tumour. A randomised clinical trial to address this question is being undertaken.

Other palliative procedures

Metastatic disease may result in the development of malignant ascites or pleural effusions for which drainage often provides symptomatic relief. This is significantly less frequently required in recent years because of improvements in systemic therapy.

Oncological emergencies

Neutropenic sepsis

Neutropenic sepsis should be considered in all patients who develop a fever when undergoing chemotherapy. Fever is defined as one temperature reading above 38.3°C or two readings above 38°C taken an hour apart, in the context of the expected nadir (lowest point) of white cell count according to the chemotherapy schedule.

These patients require immediate assessment and antibiotics to prevent worsening sepsis and death. A full examination should be performed to identify any focus of infection and urgent blood samples taken to document the full blood count and renal function. Blood cultures should be taken peripherally and from any venous access devices.

For clinically unwell patients with abnormal vital signs, broad-spectrum intravenous antibiotics should be given within 60 minutes of presentation, without waiting for full blood count or culture results. No source of infection is found in more than 70% of patients, and sepsis is commonly due to endogenous flora from the gastrointestinal tract. Patients with expected short duration of neutropenia, no comorbidities, no evidence of hepatic or renal dysfunction and who are clinically not unwell and considered to be at low risk of complications may be treated as outpatients with oral antibiotic therapy. However, only the treating oncology team should make this decision.

Spinal cord compression

Early diagnosis and multidisciplinary treatment of spinal cord compression are critical for maximising recovery of neurological functions. It should be suspected in patients who present with neck or back pain, motor or sensory loss, and autonomic dysfunction. An urgent MRI of the spine should be undertaken if the clinical presentation is suspicious for spinal cord compression.

FINANCES AND CANCER: ADVICE FOR PATIENTS

The diagnosis of cancer has been documented to be associated with a high out-of-pocket cost in Australia, despite most services being provided in a hospital- or community-funded setting.

Work

- Discuss with employer the types of leave available.

Superannuation/Sickness insurance

- Check if funds can be accessed.
- Pensions and subsidies may be available for carers.

Banking

- Discuss restructuring mortgage repayments.

The Cancer Council

- The Cancer Council Australia (http//:www.cancer.org.au) may be able to provide one-off free financial assistance and offers referral service for legal advice, financial counselling and planning, and accessing superannuation.

Government assistance

- Patients and carers may be eligible for payments from Centrelink or help from the Government's Mortgage Assistance Scheme.

Travel and accommodation

- State and territory governments often partially reimburse the costs incurred by patients who need to travel more than a certain distance (e.g. 100 km) for treatment and consultations.
- Community or volunteer transport services are available for travel to and from treatment centres.
- Disability parking permits are easily obtainable for all patients with impaired functionality or their carers.

Can Assist

- Can Assist (http//:www.cancerpatients.com.au) is a not-for-profit organisation that provides specialised accommodation, care and financial assistance for country patients affected by cancer.

Corticosteroids should be administered and treatment commenced as soon as possible. Surgical decompression is appropriate for patients with a single level metastasis. For patients who are not surgical candidates, palliative radiotherapy should be administered urgently.

Supportive care

Patients, families and friends benefit from the support and counselling provided by their multidisciplinary treating team, including doctors, care coordinators, social workers, psychologists and other allied health and nursing professionals. Interventions to assist with finances, counselling of children, end of life planning (including advanced care directives) and the many other impacts of the disease are essential. Information on finances and cancer is given in the box on page 41.

Resources

'Look Good Feel Better' (http://lgfb.org.au) is a free community program that offers workshops on beauty techniques for women having chemotherapy or radiotherapy to help maintain self-image during cancer treatment. Advice is given on how to wear make-up, scarves and wigs.

Can Teen (https://www.canteen.org.au) provides support for young people aged between 12 and 24 years who either have cancer or are the siblings or children of someone who has cancer.

'My kite will fly' (http://www.mykitewillfly.com.au) is an Australian website designed for families to help them cope with the diagnosis, treatment and loss of a loved one from cancer.

'Hopes & Hurdles' is a comprehensive resource (print and CD) published by Breast Cancer Network Australia (http://www.bcna.org.au/hope-hurdles-pack). It was developed in consultation with women living with secondary breast cancer.

Exercise programs

The role of tailored exercise programs, even in patients with widespread metastases, in maintaining fitness, improving treatment tolerance and psychosocial wellbeing, is being increasingly recognised. The presence of metastatic disease should lead not to advice for inactivity but rather to encouragement for active participation in strength and endurance building programs – but only after assessment by a trained exercise physiologist, physiotherapist or similarly qualified professional.

SUMMARY

Patients with locally advanced breast cancer are generally treated with curative intent. Treatment requires a multimodality approach of systemic therapy, surgery and radiotherapy. In metastatic breast cancer, the aim of treatment is palliation of symptoms and maximising quality and quantity of life, while limiting toxicity from therapy. New systemic agents and integrated multidisciplinary management of patients have increased the length of survival in patients with these breast cancers and patients are now requiring care plans similar to patients with other chronic conditions. MT

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