

ARTICLE

Side-effects of systemic therapy for the management of breast cancer

A Gudgeon, MB ChB

Oncology Unit, Life Vincent Pallotti Hospital, Cape Town, South Africa

Corresponding author: A Gudgeon (anneg@iafrica.com)

Systemic treatment for breast cancer is given as neoadjuvant therapy to reduce tumour bulk before surgery, and as adjuvant therapy after surgery to control micrometastatic disease, reduce tumour bulk and improve quality of life in metastatic disease. Systemic therapy is divided into endocrine therapy, chemotherapy and biological response modifier therapy. All therapies will cause a higher rate of anxiety and depression, and loss of libido, which for many is a major problem. In pre-menopausal patients fertility issues should be discussed as the agents used can cause a decrease in or, in some cases, loss of fertility.

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The decision to administer systemic therapy should be made by a multidisciplinary team consisting of oncologists, radiotherapists, surgeons, nurses and social workers.

For breast cancer it is given for three reasons:

- neoadjuvant therapy to reduce tumour bulk before definitive surgery
- adjuvant therapy after surgery to control micrometastatic disease, and
- to reduce tumour bulk and improve quality of life in metastatic disease.

Any adjuvant agent can be given in metastatic therapy, but the aim of treatment here is to reduce tumour-related side-effects. As it is not the objective to replace the latter by treatment-related side-effects, metastatic disease is treated with single-agent sequential drugs, while adjuvant therapy employs drug combinations aimed at eliminating micrometastatic disease and reducing drug resistance.

The downside of combination therapy is an increase in side-effects. There are many new drugs being used for cancer management and the alleviation of side-effects. One of the major advances in the management of nausea associated with chemotherapy is the improvement in anti-emetic medication.

Systemic therapy is divided into:

- endocrine therapy
- chemotherapy, and
- biological response modifier therapy.

Before embarking on any systemic therapy, patients should be counselled, as all therapies will cause a higher rate of anxiety and depression, and loss of libido, which for many is a major problem.

In pre-menopausal patients fertility issues should be discussed, as systemic therapies can cause a decrease in or, in some cases, loss of fertility.

Endocrine therapy

Endocrine therapy is designed to reduce oestrogen availability to oestrogen receptor (ER)-positive tumour cells and to reduce tumour growth. In the pre-menopausal patient this is done by blocking the

cellular surface oestrogen receptor by using a hormone receptor antagonist, e.g. tamoxifen, or by eliminating oestrogen production by blocking functioning ovaries with a luteinising hormone-releasing hormone (LHRH) analogue (effectively a chemical oophorectomy). In post-menopausal patients endocrine therapy blocks the production of oestrogen from androgens under the influence of the aromatase enzyme complex by using aromatase inhibitors.

The generalised effects of these drugs are to reduce oestrogen availability; therefore side-effects such as hot flushes, genito-urinary system dysfunction, e.g. vaginal dryness, bladder irritability, and loss of libido are common in both pre-menopausal and post-menopausal patients.

Pre-menopausal women

Tamoxifen is the most common endocrine chemotherapeutic agent used. Its major side-effects are hot flushes, weight gain, loss of libido and sexual dysfunction, mood swings, some vaginal dryness and bladder irritability, altered menstrual cycles and ovarian cysts. Patients should be warned not to become pregnant while on tamoxifen as it is teratogenic. An increased incidence of deep vein thrombosis and pulmonary embolus has been reported, along with ocular toxicity, mainly retinopathy, macular oedema and cataracts.

LHRH analogues are used in patients who cannot tolerate tamoxifen. This places the patient into menopause, with hot flushes, amenorrhoea, and associated menopausal side-effects. Bone mineral density (BMD) is also reduced and should be monitored.

Post-menopausal women

Aromatase inhibitors

As aromatase inhibitors deprive post-menopausal women of oestrogen, menopausal effects are exaggerated. The main side-effects are hot flushes, arthralgias and myalgias, reduced libido, a dry vagina and skin, and thinning of hair. As BMD is reduced, it should be carefully monitored (the main reduction is in the first two years of therapy). If necessary, a bisphosphonate can be given in combination with the aromatase inhibitor.

Tamoxifen

This drug is also administered to post-menopausal patients, with the same side-effects as in pre-menopausal women, except for the

menstrual changes. However, tamoxifen has a weak oestrogenic effect on the endometrium without the protection of endogenous progesterone production in pre-menopausal patients. Consequently, there have been reported cases of endometrial carcinoma because of the unopposed oestrogen stimulation with this agent. The incidence is small and the tumours are mainly low grade, but regular follow-up by a gynaecologist is recommended.

Selective oestrogen receptor modulators (SERMs)

SERMs modify the ER and prevent downstream signalling. As these agents are given by intramuscular injection, one of the side-effects is pain at the injection site. Other side-effects are hot flushes and weight gain.

Chemotherapy

Neoadjuvant and adjuvant chemotherapy are given using multiple drug regimens to achieve maximum efficacy, but this leads to an increase in side-effects. All side-effects are increased in patients >60 years and in those with comorbid medical conditions, e.g. diabetes, hypertension, infections, or recent surgery.

Common combinations used in breast cancer are those containing an anthracycline such as adriamycin (A) or 4-epi-adriamycin (E) with cyclophosphamide (C), 5-fluorouracil (5-FU) (F) and a taxane (T) such as docetaxel or paclitaxel. Commonly used regimens are FEC plus T, AC plus T, CAF and CEF. Less commonly, the older regimen of CMF (cyclophosphamide, methotrexate and 5-FU) is used.

Common side-effects

Myelosuppression is often a dose-limiting toxicity, with leucopenia being more common than thrombocytopenia or anaemia. Scheduling of the regimen is based on the nadir of myelosuppression.

Nausea and vomiting, once severe with many regimens, is now well controlled with new intravenous and oral anti-emetics, and is rarely problematic. Complete alopecia often occurs with many regimens, but is nearly always reversible within 3 - 6 months after completion of chemotherapy. Tiredness is common and not fully understood, as it is often unrelated to anaemia or anorexia.

Neurotoxicity can occur with the class of drugs known as spindle blockers and is a dose-dependent effect. The most commonly used agents in breast cancer are paclitaxel and docetaxel. Peripheral neuropathy is the most common side-effect with numbness and paraesthesia of the fingers and toes. Neurotoxicity is less commonly seen with vinorelbine.

Many of the chemotherapies used can lead to hypersensitivity reactions – from mild skin rashes to hypotension, dyspnoea, and bronchospasm.

Mucositis, oral ulcers, dry itchy eyes and bladder sensitivity with chemical cystitis may occur with varying frequency. Most of the drugs used have some or all of these side-effects, which are very rarely problematic.

Plantar palmar erythema is more commonly seen with drugs used in metastatic disease, such as oral 5-FU combinations, e.g. capecitabine or liposomal doxorubicin, when the palms and soles become red and very sensitive, sometimes blistering.

Because many of the drugs given intravenously are potent vesicants, one must ensure that there is absolutely no extravasation of any drug. Even so, anthracyclines in particular can cause pain and phlebitis at a site of venous drainage away from the needle insertion.

Cardiotoxicity

The main drugs responsible for cardiotoxicity are the anthracyclines. The changes may be acute and transitory, but may occur late and

cause severe cardiac damage. Myocytes of the cardiac muscle are damaged permanently and the long-term effects are dependent on the extent of the damage. As patients survive longer after adjuvant therapy, they present with late cardiac problems. These changes are less when the doses are based on body surface area (m²) calculations, but can occur idiosyncratically with small doses. Cardiologists stress the need for careful cardiac monitoring. Even in the case of a normal echocardiogram, if the ejection fraction has decreased by as little as 10%, the patient should be referred to a cardiologist. Other drugs such as cyclophosphamide, 5-FU and paclitaxel can also cause cardiotoxicity, but less commonly in the doses used.

All side-effects, except for alopecia, are manageable and reduced or eliminated by premedication and dose scheduling according to body surface area. It is important to discuss all side-effects with the patient before treatment so that they are fully informed.

Biological response modifiers

Monoclonal antibodies

Trastuzumab

Trastuzumab is the best-known example of this class of drug, which blocks HER2 receptors, down-regulating the HER2 expression and interrupting cell signalling pathways. The main toxicities are infusion-related with chills, headache, generalised pains and occasionally hypersensitivity. Care must be taken when treating patients with pre-existing cardiac dysfunction, as a decrease in left ventricular ejection fraction (LVEF) and congestive cardiac failure can occur.

Bevacizumab

This drug inhibits malignant angiogenesis. Toxicities include bleeding complications and thromboembolic events, including myocardial infarction, stroke and angina. Hypertension, proteinuria and nephrotic syndrome can occur. Hypersensitivity may manifest as fever and chills. Common central nervous system symptoms include dizziness and depression.

Small molecules

Lapatinib

This is a tyrosine kinase inhibitor that blocks intracellular downstream signalling. Side-effects include skin rash, myelosuppression, neurotoxicity, fatigue, nausea, vomiting, diarrhoea and myalgia and arthralgia.

Everolimus

This is an m-TOR inhibitor that blocks intracellular signalling pathways. Side-effects may include fatigue, oral ulcers, nausea, vomiting, opportunistic infections and pulmonary toxicity. Hyperlipidaemia and hyperglycaemia may also occur.

Conclusion

The management of breast cancer has become more personalised and a multidisciplinary team should decide on the systemic regimens used. In future, more targeted therapies will be used. Most side-effects resulting from chemotherapy can be managed. The newer drugs are not less toxic than the older ones, but their side-effects must be managed differently.

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