

Breast Cancer – What do we know?

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HOW COMMON IS BREAST CANCER?

Breast cancer is the commonest cancer in women worldwide and in Singapore. Locally, there are on average 1300 new cases annually. This accounts for nearly one-third of all new cancers diagnosed in Singaporean women. In addition, what is disturbing is the continued upward trend of breast cancer incidence locally.

With increased public awareness and availability of mammographic screening, more patients with breast cancers are diagnosed at an earlier stage. Earlier diagnosis generally means these patients would have higher cure rates and hence a better cancer-free future. However, despite adequate therapy, there are some patients who relapse while others are less able to tolerate the prescribed treatment given to them. This has created a need for increasing ongoing research efforts focusing on “personalized” or tailored

therapy where each individual patient with breast cancer is treated based on their potential risks of relapse, benefits from and tolerability of the prescribed treatment.



HOW DO WE TREAT BREAST CANCER?

In general, the management of breast cancer can be broadly divided into two categories – local and systemic therapies. Local therapy involves surgery and radiation. Surgery may be in the form of either a complete removal of the breast (mastectomy), a quadrant of the breast where the tumour lies (quadrantectomy) or just the lump (lumpectomy or wide excision) with a clear negative margin around it. The indication for radiation to the chest wall or breast after surgery depends on the size, extent of the tumour and involvement of axillary lymph nodes.

The various modalities of systemic treatment include chemotherapy, endocrine or hormonal and targeted therapies. The decision for treatment not only depends on the stage of the cancer such as the size of the tumour and the number of lymph nodes involved but also the type of breast cancer. The latter means whether the cancer is hormone receptor positive or negative which would imply if the tumour would respond to hormonal therapy and if there is Human Epidermal Growth Factor Receptor 2 (HER2) over-expression. HER2 is a member of the family of receptor tyrosine kinases responsible for cell growth and survival. The over-expression of the HER2 gene

used to portend a poor prognosis until recently when anti-HER2 targeted therapy became available. Another subgroup of breast cancers, which is known as triple negative (hormone receptors and HER2 negative) is probably associated with the worst prognosis and is the focus of many ongoing trials now. An update of the various modalities of systemic treatment is elaborated below.

HOW DO DOCTORS DECIDE WHO NEEDS WHAT TREATMENT?

No two breast cancer patients are the same. In addition, cancer treatment is associated with at least mild to moderate toxicities though majority are generally reversible within a short period of time. Hence there is a need to individualize therapy for our patients and prescribe treatment only to those who need and benefit from it. In order to tailor appropriate anti-cancer treatment for the patients, we need to first risk stratify their tumours. Conventionally, prognostic factors (ie. factors which help to predict the relapse risks) of breast cancers include the patients' age and medical comorbidities, grade and stage of cancer by TNM (Tumour, Node and Metastases) as well as the characteristics of the breast cancer i.e. hormone receptor and HER2 positivity.

Gene Assays: Oncotype Dx™

Recently, there are various assays available which look beyond the morphology of the cancer cell at the molecular level to try to characterize them better. One such commercially available assay is the Oncotype Dx™. This is an assay which examines 21 genes of the surgically removed breast tumour (16 cancer genes and 5 reference genes). The 16 cancer genes are involved in various pathways associated with cell proliferation, HER2, oestrogen and invasion. The Recurrence Score (RS) is then computed from a formula, which would define the risk of breast cancer relapse in 10 years for that particular patient. This would also enable us to estimate the potential benefit from addition of chemotherapy to tamoxifen in patients with hormone receptor positive breast cancers which makes up more than 60% of all breast cancers. Specifically, the RS stratifies patients to low, intermediate and high risks categories. Patients in the low risk category generally have a very good prognosis or outcome. They will do very well with only hormonal therapy and benefit little from the addition of cytotoxic chemotherapy. However, those who have a high risk of relapse should be offered systemic chemotherapy in addition to hormonal therapy. The conundrum lies in the management of patients of intermediate risk based on the RS. This subgroup is currently being evaluated in multi-centre clinical studies to define the additional benefits of chemotherapy.

Oncotype Dx™ has been validated in more than 600 lymph node-negative hormone receptor positive breast cancer patients given 5 years of tamoxifen therapy, which, for a long time, is standard treatment for this group of patients. The advantage of this assay is that archived tumour tissues (paraffin embedded formalin fixed tissues) can be used. However, as the test is only done in the United States for now, the cost of testing is substantial. A similar assay available called the Mammoprint® is a 70-gene signature from Amsterdam that requires frozen breast cancer tissues for analysis of the tumour gene profiles.

Chemotherapy

Chemotherapy comprises the administration of cytotoxic drugs which are usually given intravenously. Some of the commonly used intravenous chemotherapeutic agents for early breast cancer include anthracyclines such as doxorubicin (Adriamycin®), epirubicin (Ellence®); taxanes such as paclitaxel (Taxol®), docetaxel (Taxotere®) and alkylating agents such as cyclophosphamide (Cytosan®). Common chemotherapy side effects include loss of appetite, nausea and sometimes vomiting, fatigue, hair loss (alopecia), low blood counts and increased infection risks (myelosuppression). Nausea and vomiting are infrequently seen nowadays with most chemotherapy agents as there are very effective anti-nausea medications available in addition to the fact that many newer drugs do not actually cause much nausea or vomiting.

Certain drugs such as the anthracyclines, namely, doxorubicin (Adriamycin®) and epirubicin (Ellence®) may affect the function of the heart muscles though the risks are generally low. In view of the potential for cardiac risks, there is a recent change in paradigm to substituting anthracyclines with taxanes. A direct comparison of 4 cycles of doxorubicin and cyclophosphamide (AC) versus 4 cycles of docetaxel and cyclophosphamide (TC) in early stage breast cancers showed a significant survival benefit in favour of the latter (non-anthracycline arm) which is associated with much lower cardiac risks. Taxanes (such as paclitaxel and docetaxel) can cause numbness in the fingers and toes (peripheral neuropathy) as well as nail changes (onycholysis) in some patients. Once again, these effects are generally reversible upon cessation of treatment.

In the advanced disease setting, besides the drugs alluded to as above, other commonly used agents include gemcitabine (Gemzar®), vinorelbine (Navelbine®), capecitabine (Xeloda®), carboplatin and several others. A novel chemotherapy drug, ixabepilone (Ixempra®) is recently approved for breast cancers, which are refractory to anthracyclines and taxanes either alone or in combination with capecitabine, an oral chemotherapy drug. The efficacy of ixabepilone is currently being investigated in triple negative breast cancer.

There are a small number of oral chemotherapy drugs also available but are mainly restricted for use in advanced disease only. Examples include capecitabine and vinorelbine. A recent trial comparing a milder form of oral adjuvant chemotherapy with capecitabine versus conventional intravenous chemotherapy using CMF (cyclophosphamide, methotrexate and 5-fluorouracil) in elderly women with early stage breast cancer. The oral chemotherapy group did not do as well and had higher relapse rates. However, the criticism of the study was that the accrual was poor and the study closed before reaching the target enrollment of patients. Hence conventional chemotherapy should be discussed with elderly patients who have early breast cancer and are otherwise fit and in whom chemotherapy is indicated.

Endocrine Therapy

Endocrine therapy, also known as hormonal therapy, is generally indicated in patients whose breast tumours are hormone receptor positive i.e. either oestrogen or progesterone receptors or both are positive. These are generally oral tablets taken once daily to counteract the effects of the female hormone, oestrogen and hence create an internal milieu that is not conducive for the growth of breast cancer cells.

Tamoxifen was the standard endocrine treatment for all women regardless of age for the last 3 decades. A newer class of agents called aromatase inhibitors (AIs) has largely replaced tamoxifen as first line both for early and advanced breast cancers in postmenopausal women. Three such available drugs include anastrozole (Arimidex®), letrozole (Femara®) and exemestane (Aromasin®). The aromatase inhibitors have been compared head-to-head with tamoxifen in several large studies. Some of these studies evaluate AIs upfront versus tamoxifen after surgery and where indicated, after completion of chemotherapy while others compared switching to an AI after starting tamoxifen for 2 to 3 years or after completing 5 years of tamoxifen as extended adjuvant therapy. All these studies showed a consistent benefit in the use of AI compared to tamoxifen alone.

Though the optimum duration of use or the best AI is not yet conclusively known for now, the choice of AI versus tamoxifen should be individualized for every patient. Tamoxifen is associated with an increased risk of blood clots (thromboembolism) and rarely cancer of the lining of the womb (endometrium). AIs, however, have higher risks of bone and joint aches as well as osteoporosis especially in patients with pre-existing osteopenia (thin bones). In addition, AIs should only be prescribed for postmenopausal women as they do not work in either pre- or peri-menopausal women whose ovaries are still producing an abundance of oestrogen.

Currently, an assay, known as the Amplichip™ is available commercially to evaluate if tamoxifen is helpful for a particular patient with breast cancer depending on the patient's ability to metabolise tamoxifen to its active component, endoxifene, via liver enzymes cytochrome P450 (CYP2D6). Importantly, the same patient who benefits most from tamoxifen is also most likely to experience its side effects such as hot flushes. Those patients who are not able to metabolise the drug would perhaps derive more benefit from an aromatase inhibitor rather than tamoxifen.

Targeted Therapy

Targeted therapy has recently gained much attention amongst the medical community and patients alike. Most of the targeted therapies are either monoclonal antibodies (given by intravenous infusion) or small molecule tyrosine kinase inhibitors (usually oral tablets). The three drugs in this category currently approved for breast cancer are trastuzumab (Herceptin®), bevacizumab (Avastin®) and lapatinib (Tykerb®).

Trastuzumab and lapatinib are both approved in HER2 positive breast cancer in Singapore. Trastuzumab is indicated both for early and advanced breast cancers in combination with chemotherapy. The duration of treatment in early stage disease is one year whereas for metastatic breast cancer, the actual duration would depend on the patient's response to treatment and side effects if any. It is given as an intravenous infusion.

Lapatinib has been approved in patients whose tumours are resistant to trastuzumab. It has been approved in combination with the oral chemotherapy drug, capecitabine. These two drugs are generally well tolerated. Trastuzumab may cause fever and chills at the time of infusion which are self-limiting. Importantly, it may cause weakening of the heart muscles though it is largely reversible with cessation of the treatment and careful follow up of the heart function. Lapatinib is probably at least as effective as trastuzumab and likely has a lower risk of cardiac side effects. However, it is associated with risks of diarrhoea, rash, ulcers and hand-foot syndrome (a condition whereby the palms and soles become dry, may crack or blister in severe cases). It is currently being investigated in HER2 positive early stage breast cancers to assess if it is effective in reducing relapse risks especially in cases where the relapse occurs in the brain.

The other targeted agent approved in breast cancer is bevacizumab. It is a monoclonal antibody that targets the vascular endothelial growth factor receptor (VEGF) and inhibits the growth of a network of blood vessels supplying oxygen and nutrients to the tumour cells. It was approved for treatment of advanced breast cancer in combination with chemotherapy (taxanes) after a trial showed almost doubling of response rates and time to progression in treatment naïve patients with advanced breast cancer. Its use in previously treated advanced breast cancers is also being evaluated currently in clinical trials. For early stage disease, a large multi-centre trial is evaluating the role of bevacizumab in triple negative early stage breast cancers treated with chemotherapy (BEATRICE: Bevacizumab as adjuvant treatment of triple negative breast cancer).

CONCLUSION

With a deepening of our understanding of breast cancer and the availability of many novel compounds being investigated in advanced breast cancers as in many other areas in oncology, it is possible the cure of breast cancer is well within sight in the near future. In the foreseeable future, only patients who truly benefit from and are able to tolerate will need to undergo the various systemic treatments for breast cancer thus sparing many others who do not need additional treatment as they are cured after surgery.

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