



Recent Medical Advances in Breast Cancer

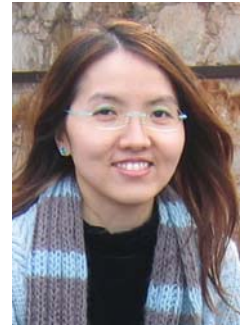
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Introduction

Breast cancer is the most common female cancer in the world.¹ It is also the most common female cancer in Hong Kong with 1 in 22 cumulative life-time risk.²

Over the last two decades, there have been remarkable advances in the screening, diagnosis and treatment of breast cancer. Surgical resection of the primary tumour remains the basis for cure of early breast cancer. Adjuvant radiotherapy is given according to the tumour risk to help prevent local recurrence. Adjuvant chemotherapy and/or endocrine therapy help to prevent disease relapse by targeting occult micrometastasis. Through understanding new pathways, pharmacogenomics and predictors of response, the outcome of breast cancer has improved dramatically in recent years with the advent of targeted therapy while the choice of therapy depends not only on risk assessment incorporating both patient and tumour-related prognostic factors, but also biomarkers and drug toxicity profile.

Adjuvant therapy has proven to be effective in preventing both local and distant relapses.³ Traditionally, the selection of adjuvant systemic therapy has relied on both patient and tumour-related factors. Patient factors include age at presentation, menopausal status and comorbidities. Tumour-related factors include tumour size, tumour grade, lymph node involvement, the presence or absence of oestrogen receptors (ER), progesterone receptors (PgR) and the HER-2 receptor status.

Evolution of Chemotherapy for Breast Cancer

Indications for Adjuvant Chemotherapy

Randomised trials have shown improved survival with the use of adjuvant chemotherapy after breast cancer surgery.³ Young age at presentation, pathological tumour size of more than 2 cm, high grade of tumour, presence of peritumoural vascular invasion, positive axillary lymph nodes, hormone-negative tumours and over-expression or amplification of the HER2/neu gene are indications for adjuvant chemotherapy.⁴ However, adjuvant treatment should be tailored to individuals, taking into account patients' comorbidities and preferences.

Adjuvant Chemotherapy - Past and Present

In the 1970s, CMF (Cyclophosphamide, Methotrexate and 5-FU) was the backbone of adjuvant chemotherapy for breast cancer.^{3,5} The Milan research group decided in the early 1980s to challenge CMF by introducing anthracycline-based regimens in the adjuvant setting. Compared with standard CMF, anthracycline-containing regimens reduced the annual risk of recurrence by 12% and the annual risk of death by 11%.³ This difference was seen with regimens such as FAC (5-FU, Adriamycin, Cyclophosphamide) and FEC (5-FU, Epirubicin, Cyclophosphamide), whereas 4 cycles of AC (Adriamycin, Cyclophosphamide) appears to be equivalent to 6 cycles of CMF and has become a standard adjuvant regimen.^{6,7} The taxanes were introduced into clinical practice in the 1990s, and have emerged as powerful compounds in breast cancer in several adjuvant clinical trials. The addition of four cycles of paclitaxel (Taxol®) after a standard course of AC was shown to improve the disease-free survival (DFS) and overall survival (OS) of patients with node-positive primary breast cancer.⁸ The Breast Cancer International Research Group (BCIRG) 001 study showed similar enhancement of DFS and OS with the use of adjuvant docetaxel (Taxotere®). Significant improvement of DFS was seen in 6 cycles of TAC (Docetaxel, Adriamycin, Cyclophosphamide) compared to 6 cycles of FAC (82% vs 74%).⁹ In a recent randomised phase III study, 4 cycles of TC (Docetaxel, Cyclophosphamide) were shown to be superior to AC, in terms of improved DFS. TC is associated with more peripheral neuropathy, myalgia and arthralgia and febrile neutropenia while AC is associated with more nausea and vomiting and cardiotoxicity. Currently, TC is considered as an alternative to AC especially in patients with background of significant heart disease.¹⁰

Discovering the Optimal Dose and Schedule

Duration and the most optimal schedule of adjuvant chemotherapy are also being critically reappraised. Recent study has shown that treatment with AC followed by weekly paclitaxel is associated with improved DFS and OS in comparison with treatment with AC followed by 3-weekly paclitaxel regardless of hormone receptor expression.¹¹ On the other hand, dose-dense regimens, i.e. giving the same type of chemotherapy with same dosage every 2 weeks instead of every 3 weeks with continuous recombinant granulocyte colony-stimulating factor (G-CSF) support, have been shown to improve both the DFS and



OS with lower incidence of febrile neutropenia in the dose-dense group.¹²

HER-2 Targeted Therapy

Targeting HER-2 with Trastuzumab

Up to 25% of women with breast cancer have human-epidermal growth factor receptor 2 (erbB-2 / HER-2) positive disease, which is associated with aggressive disease, a higher risk of relapse and a poorer prognosis.^{13,14} Trastuzumab (Herceptin®), a monoclonal antibody directed against the extracellular domain of HER-2, improves survival and quality of life when given in combination with taxanes as first-line therapy in women with metastatic breast cancer.^{15, 16} It could be either given as monotherapy or as a chemosensitiser in combination with cytotoxics such as taxanes or vinorelbine, and has demonstrated activity in heavily pretreated patients¹⁷. Four major international adjuvant trials - Herceptin® Adjuvant (HERA), National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831, and Breast Cancer International Research Group (BCIRG) 006 - including >13, 000 women with HER-2 positive breast cancer, have shown that one-year treatment of trastuzumab after adjuvant chemotherapy significantly improves DFS and OS among women with HER-2 positive breast cancer.¹⁸ A small Finnish trial, FinHer, investigating another regimen of trastuzumab, has also shown similarly positive results.¹⁹ Meta-analysis of these five randomised trials further supported the above benefits in terms of disease-free and overall survival.^{18, 20}

Trastuzumab is not associated with the adverse events that occur typically with chemotherapy such as alopecia, myelosuppression or vomiting. It is generally well tolerated, but occasionally associated with hypersensitivity or acute reaction which is seen mainly with the first infusion. Cardiotoxicity such as congestive heart failure remained at an acceptable level with reported overall incidence of about 0.6-4.1%.¹⁹ This is usually reversible when the drug is suspended. Therefore, close monitoring of the cardiac function with baseline and 3-monthly echocardiogram or MUGA scan is recommended.

Lapatinib - A Dual Tyrosine Kinase Inhibitor

Another novel targeted therapy, Lapatinib, is an oral dual small molecule tyrosine kinase inhibitor targeting both ErbB-2 (HER-2 / neu) and ErbB-1 (EGFR) receptors. It is active in combination with capecitabine (Xeloda®) in women with HER2-positive metastatic breast cancer that has progressed after anthracycline, taxanes and trastuzumab-based therapy, leading to significantly longer median time to progression and progression-free survival.²¹ Lapatinib is active in refractory metastatic breast cancer with potential benefit in patients with brain metastases. It has very low incidence of cardiotoxicity and is well tolerated.²² Results from the phase III randomised, double-blind, multicentre, placebo-controlled trials of lapatinib in the adjuvant setting such as the TEACH (Tykerb® Evaluation After Chemotherapy) trial are eagerly awaited to determine the role of lapatinib in the adjuvant setting.

Adjuvant Hormonal Therapy with Aromatase Inhibitors

The Advent of Aromatase Inhibitors

About two-thirds of women with breast cancer have positive oestrogen receptors and/or progesterone receptors and are candidates for adjuvant endocrine therapy. Five years of Tamoxifen, the selective oestrogen receptor modulator, has been the standard adjuvant hormonal therapy for women with hormone-positive disease since the 1970s.²³ Aromatase inhibitors are inhibitors of oestrogen biosynthesis, blocking aromatase, the enzyme responsible for converting androgens to oestrogens, thus suppressing oestrogen levels with no partial agonist activity. The third-generation aromatase inhibitors (AIs) which were introduced in the late 1990s, have expanded the adjuvant endocrine treatment options for postmenopausal women with hormone-receptor positive breast cancer and were shown to be superior to tamoxifen in improving the disease-free survival in several large, randomised controlled clinical trials.²³ The currently available AIs include the nonsteroidal compounds anastrozole (Arimidex®) and letrozole (Femara®), and the steroidal AI exemestane (Aromasin®).

Tamoxifen Remains the Gold-standard for Pre-menopausal Women

To date, tamoxifen remains the gold-standard for hormone-receptor positive disease in pre-menopausal women. Other options of ovarian function suppression include ovarian ablation by surgery or radiation, and the use of gonadotropin-releasing hormone (GnRH) agonists in the case of persistent ovarian activity after chemotherapy. Aromatase inhibitors are inactive in pre-menopausal patients and should not be used because in these women, AIs induce an increase in gonadotropin secretion secondary to the reduced negative feedback of oestrogen to the pituitary, leading to ovarian stimulation and a potential increase in ovarian size and function.¹

Different Adjuvant Strategies with Aromatase Inhibitors

Recent large, randomised controlled clinical trials have shown consistently the superiority of AIs over tamoxifen in postmenopausal women with early breast cancer and AIs are recommended to form part of the adjuvant endocrine therapy.¹ Three different strategies for integrating the use of AIs with tamoxifen as adjuvant therapy for hormone-responsive breast cancer include: (1) upfront 5-year use of an AI as an alternative to tamoxifen in the initial adjuvant setting ("primary upfront approach")^{24,25}; (2) "switching approach" whereby giving the patient 2-3 years of AI instead of tamoxifen after the patient survives disease free for 2-3 years of tamoxifen ("unplanned switching strategy") or planned from the time of surgery ("planned sequence strategy")²⁵⁻²⁸; and (3) as an extended adjuvant therapy, whereby the patient receives further 5-year AI therapy following completion of the recommended 5-year course of tamoxifen.^{29, 30}

However, it is unclear whether one of these AI strategies is superior to the other ones. The overall therapeutic index of AIs appears superior to that of



tamoxifen with proven improved efficacy and a better toxicity profile. AIs are less toxic than tamoxifen in terms of thromboembolic disease and endometrial carcinoma, while myalgia, arthralgia, increased tendency of osteoporosis and bone fracture are more frequently observed with AIs.

Bisphosphonates: Benefits Beyond Bones

Breast cancer patients with bony metastases experience fewer skeletal-related events³¹ and require less radiation therapy.³² The use of adjunct bisphosphonate therapy with adjuvant aromatase inhibitors has been proven to reduce treatment-related osteoporosis.³³ In the recent American Society of Clinical Oncology (ASCO) 2008 annual meeting, it was reported that the addition of zoledronic acid every 6 months to adjuvant endocrine therapy with tamoxifen or aromatase inhibitors have led to significantly prolonged DFS and OS in breast cancer women compared endocrine treatment alone group. This large clinical trial has demonstrated that anti-tumour activity of adjuvant bisphosphonate improves outcome beyond the effect of endocrine therapy alone.³⁴

Tailoring Treatment for Individuals

With understanding of the biology of breast cancer in the era of targeted therapy and tailored management of cancer patients, the hormone receptors and the HER-2 receptor remain the two main targets in breast cancer management. The selection of the most optimal management plan depends not only on the patient and tumour-related factors, but also the stage of the disease, and the predicted responsiveness of the tumour by molecular profiling while respecting patient's wish.

Neoadjuvant Systemic Therapy

Neoadjuvant, or pre-operative systemic therapy is increasingly used for patients with clinical stages II and III breast cancer to improve surgical outcomes. This application is not confined to inoperable or locally advanced breast cancer, but in the setting of operable disease with more aggressive curative intent and the aim of downstaging and downsizing the tumour, increasing the chance of breast-conserving surgery and assessing the drug sensitivity and treatment response. Patients who achieved a complete pathological response after neoadjuvant chemotherapy have demonstrated significantly superior DFS and OS compared to those who did not. Updated results also showed trends in favour of neoadjuvant chemotherapy for DFS and OS in women younger than 50 year-old.³⁵ Postmenopausal women with clinical stages II and III oestrogen receptor-positive breast cancer who are downstaged to pathological stage I disease with neoadjuvant endocrine therapy such as aromatase inhibitors have demonstrated favourable long-term outcome.

Improving Tolerability of Palliative Treatment and Directing at New Targets

Due to recent multiple advances in the treatment of breast cancer, more women with early breast cancer have become cancer survivors, while many women with aggressive disease or advanced disease at presentation live with their breast cancer for significant period of time.

Newer anti-cancer drugs have emerged with excellent potency but minimal toxicity. These include the better tolerated chemotherapy such as vinorelbine, gemcitabine and oral fluoropyrimidines (capecitabine) with minimal hair-thinning and vomiting. On top of targeted therapy such as trastuzumab and lapatinib, there is another new wave of monoclonal antibodies and tyrosine kinase inhibitors emerging. The combination of bevacizumab, monoclonal antibody against the vascular endothelial growth factor receptor (VEGF) and taxanes has shown activity in patients with metastatic breast cancer with increased progression-free survival.³⁶ Again, selection of palliative therapy should be based upon both the patient and tumour characteristics. Elderly patients with multiple comorbidities who have hormone-positive disease with bony metastasis only but no visceral disease may do well with hormonal therapy with AI but not necessarily chemotherapy, and all these new combinations of treatment have further improve the quality of life of breast cancer patients. Another new class of hormonal agent, Fulvestrant, an oestrogen receptor antagonist has shown clinical efficacy in postmenopausal breast cancer women with hormone-positive tumour who progress after second-line aromatase inhibitors.

Potential Molecular Markers

It is observed that clinical activity of a given drug may vary between different patients. Different breast cancer sub-types are now being identified with early preclinical data suggesting that in the future some molecular markers might have practical value in predicting treatment response. Topoisomerase II (TopoII) alpha gene aberrations are the most promising molecular predictors of anthracycline response.³⁷ HER-2/topoII co-amplified tumours are shown to be most sensitive to anthracyclines.

Triple Negative Breast Cancer

Although there are emerging potential targets for breast cancer, there is a distinct entity of breast cancer, which is associated with aggressive behaviour and poor prognosis, and typically do not express hormone receptors or HER-2 ("triple-negative" phenotype). Triple-negative breast cancer with a basal-like phenotype is characterised by high proliferation rate and BRCA1 gene dysfunction. Currently patients with this type of tumour cannot be managed with existing targeted treatments (trastuzumab and hormonal therapy) effectively but is associated with better response with platinum-based chemotherapy.³⁸ Further study on this particular subtype is recommended.

Conclusion

There is increasing hope for breast cancer patients. The hormone receptors and HER-2 receptor remain the two main targets for treatment. Through better understanding of breast cancer biology, identifying more new molecular markers and conducting quality randomised controlled clinical trials, we have achieved better outcome of breast cancer. At the same time, there remain many unexplored avenues for optimising the role of each target and new advances. The era of personalised medicine will become more complex in the future and the embracement of multidisciplinary and evidence-based medicine should continue be the standard of care for our breast cancer patients.



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