A Promising Selective Cure

by Dr Lynette Ngo

Molecular targeted therapies for breast cancer

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Targeted therapies have significantly changed the treatment of breast cancer over the past 10 years. For decades, intravenous cytotoxic chemotherapy has been the hallmark of cancer treatment. It acts by inhibiting rapidly dividing cells, including cancer cells and certain normal tissues. Efforts to improve survival in breast cancer have increasingly been focused on novel drug therapies that interfere with specific molecules and pathways involved in tumour growth and progression. Targeted cancer therapies hold the promise of being more selective for cancer cells than normal cells, thus harming fewer normal cells, reducing side effects, and improving quality of life.

A greater understanding of the underlying biology of breast cancer has led to the recognition that breast cancer is not a single entity, but a heterogeneous disease. Three major clinical subtypes of breast cancer are recognised; (i) hormone receptor-positive breast cancer (tumours expressing estrogen receptors and/or progesterone receptors) (ER- and/or PR-positive), (ii) human epidermal growth factor receptor 2-amplified breast cancer (HER-2 positive) and (iii) triple negative breast cancer (tumours lacking ER, PR and HER-2 overexpression).

The targeted drugs currently available or in development for breast cancer will be discussed in 3 sections; (i) hormone receptor antagonists, (ii) HER2-directed therapy, and (iii) other targeted therapies.

New targeted drug therapies are constantly being explored in clinical trials for patients with hormone receptor-positive breast cancer.

Hormone Receptor Antagonists

Hormone receptor-positive breast cancers comprise the most common type of breast cancer, accounting for up to 65% of all breast cancers. The first molecular target in the development of targeted drugs was estrogen receptor (ER), which hormone receptor-positive breast cancers require for growth. When estrogen binds to ER, the resulting hormone-receptor complex activates the expression of genes involved in cell growth and proliferation. Since estrogen deprivation is the goal in the treatment of hormone-sensitive breast cancer, drug therapies were developed to reduce estrogen production, block signalling through the ER, or degrade the receptor.

Tamoxifen is a selective estrogen receptor modulator (SERM) that specifically competes with estrogen for the binding sites in ER in the breast to exert a cytostatic effect. In early stage hormone-receptor positive breast cancer, Tamoxifen prolongs survival and reduces breast cancer recurrence in both premenopausal and postmenopausal women.[1] Tamoxifen has also been proven to improve survival in patients with hormone receptor-positive metastatic breast cancer.[2-5]

Aromatase inhibitors (AIs) decrease circulating levels of estrogen by blocking the action of the enzyme aromatase, which converts androgens into estrogens in the peripheral tissue. Because the ovaries of premenopausal women can produce enough aromatase to override the inhibition, AIs are contraindicated in premenopausal women. Three AIs are currently commercially available — Anastrozole (Arimidex), Exemestane (Aromasin), and Letrozole (Femara). In postmenopausal women with early stage hormone receptor-positive breast cancer, treatment with an AI results in an increased reduction in the risk of recurrence compared to treatment with Tamoxifen.[6] Women who are treated with Tamoxifen for two or three years and then switched to treatment using an AI, also have reduced recurrence rates as well as an increased survival.[6] In the first-line treatment of postmenopausal patients with hormone receptor-positive metastatic breast cancer, AIs also have superior overall survival when compared to Tamoxifen.[7]

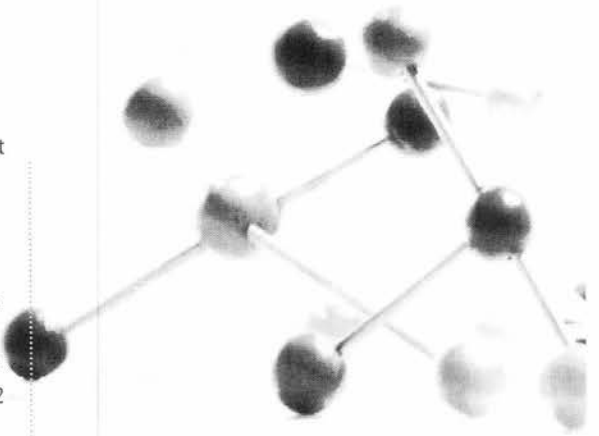
Fulvestrant is an estrogen receptor (ER) antagonist. It binds to the ER and promotes its destruction, thereby reducing ER levels inside cells. Studies have shown Fulvestrant to be as effective as AIs and as well tolerated for the treatment of hormone receptor-positive metastatic breast cancer.[8,9]

Not all patients with hormone-receptor positive breast cancer respond to Tamoxifen or AIs. One of the mechanisms of endocrine resistance is aberrant signalling through the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway. There is growing evidence of close interaction between the mTOR pathway and ER signalling. Everolimus is a targeted drug which inhibits mTOR. In a phase III study (BOLERO-2), patients with hormone receptor-positive metastatic breast cancer who had progressed on AIs and were treated with a combination of Exemestane and Everolimus had higher overall response rates and improved progression-free survival compared to women who were treated with Exemestane alone. The combination of Everolimus plus Tamoxifen is also an option for patients previously treated with an AI.[10]

New targeted drug therapies are constantly being explored in clinical trials for patients with hormone receptor-positive breast cancer. Entinostat is a small molecule inhibitor of class I histone deacetylases, which are proteins required for the control of gene expression. It exerts an anti-proliferative effect and promotes apoptosis in breast cancer cell lines. Preliminary results of a clinical trial evaluating Entinostat in women with metastatic hormone receptor-positive breast cancers who had progressed on AIs showed that patients receiving combination therapy with Exemestane and Entinostat had improved progression-free survival compared with patients receiving Exemestane alone.[11] Results from confirmatory clinical trials are still pending.

HER-2 Directed Therapy

Signalling through the epidermal growth factor receptor (EGFR) family stimulates growth in breast cancer cells. The most important member of the EGFR family in breast cancer is the



transmembrane glycoprotein receptor, HER-2. Approximately 20% of breast cancers overexpress HER-2. Amplification of HER-2 is associated with a worse clinical outcome.

Trastuzumab (Herceptin), a monoclonal antibody that interferes with the HER-2 receptor has been exceptionally successful in both the adjuvant and palliative setting. In HER-2 positive metastatic breast cancer, treatment with Trastuzumab prolongs overall survival.[12-14] Adjuvant Trastuzumab after chemotherapy reduces relapse risk, improves disease-free survival as well as overall survival.[15] Even upon disease progression, continued HER-2 blockade with Trastuzumab is associated with a longer time to progression of disease.[16]

Unfortunately, over 50% of HER-2 over-expressing breast cancers are primarily resistant to Trastuzumab. Tumours expressing a truncated form of HER-2 may also not respond to Trastuzumab. A second drug that targets HER-2, as well as other members of the EGFR family, is now available for women with advanced HER-2 positive breast cancer. Lapatinib, in combination with chemotherapy, has demonstrated significant improvement in overall survival when patients with HER-2 positive metastatic breast cancer whose disease have progressed after previous treatment with Trastuzumab.[17-19] Lapatinib can also be used in combination with AIs for the first-line treatment of postmenopausal women with HER-2 positive, hormone receptor-positive metastatic breast cancer[20] or in combination with Trastuzumab, in patients whose disease has progressed on Trastuzumab.[21]

Pertuzumab is a new class of targeted drugs which inhibit protein-protein interactions, circumventing Trastuzumab resistance. It is a monoclonal antibody which binds to HER-2 at a region distinct from Trastuzumab, blocking its activation. Binding and activation of this specific region results in interaction with other HER-family receptors and sends growth-promoting signals to the tumour cells.[22,23] In a phase III study (CLEOPATRA), first-line treatment of patients with metastatic HER-2 positive metastatic breast cancer who received Pertuzumab, in addition to the combination of Trastuzumab and Docetaxel, revealed an increased progression free survival and overall response rate compared with those who did not.[24] An adjuvant trial with dual inhibition of the EGFR signalling pathway using Trastuzumab and Pertuzumab is currently underway.

Trastuzumab emtansine (T-DM1) is a combination of Trastuzumab, conjugated to an antimitotic agent, maytansine (DM1).[25] In the phase III EMILIA trial, patients with HER-2 positive metastatic breast cancer who have progressed on Trastuzumab had a longer overall survival, improved response rate and decreased risk of disease progression when treated with T-DM1, compared to treatment with Lapatinib and Capecitabine.[26] Moreover, patients treated with T-DM1 had reduced toxicities.

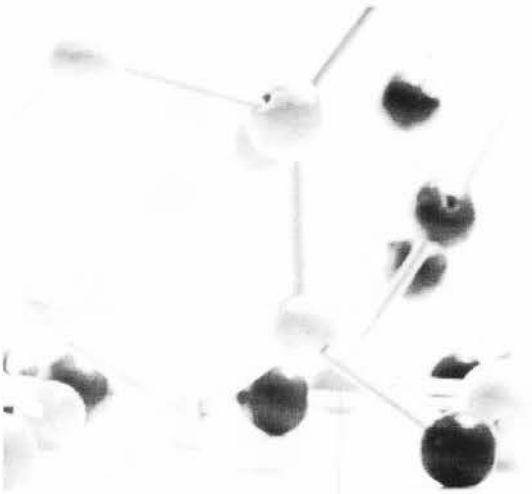
Although Pertuzumab and T-DM1 are not currently commercially available in Singapore, market release of these targeted drugs is in the pipeline in the coming years and holds promise for prolonging survival and improving Trastuzumab efficacy for HER-2 positive advanced breast cancer.

Other Targeted Therapies

Angiogenesis is an important mechanism by which tumours promote their own continued growth and metastasis. Because of the central role that angiogenesis plays, drugs inhibiting the angiogenic cascade have been developed.

Bevacizumab is the first monoclonal antibody developed against vascular endothelial growth factor (VEGF). The landmark E2100 study demonstrated increased response rates and significantly prolonged progression free survival in patients with metastatic breast cancer who had Bevacizumab added to chemotherapy.[27] However, Bevacizumab was associated with an increased number of serious side effects, including gastrointestinal bleeding, stroke and wound healing complications. Moreover, subsequent studies did not show an improved overall survival advantage.[28-31] Hence, Bevacizumab has now been relegated to the role of a drug which should only be used in a carefully selected population of patients.

Women with hereditary breast cancers have germline BRCA-1 and/or BRCA-2 gene mutation, rendering the cancer cells defective in DNA repair. Poly (ADP-ribose) Polymerase-1 (PARP-1) is a DNA-binding protein involved in detection and repair of DNA strand breaks. Inhibiting PARP in BRCA-mutated cancer cells results in the inhibition of the remaining DNA repair mechanism, resulting in tumour cell death. BRCA-1 and BRCA-2 associated breast cancers are thus particularly sensitive to PARP-1 inhibitors. Triple negative breast cancers are tumours lacking in therapeutic targets such as ER or HER-2. This disease is aggressive and if untreated, has a poor prognosis. Up to 20% of patients with triple-negative breast cancer have BRCA mutations, particularly



in BRCA-1 mutations. In a study where women with metastatic breast cancer and BRCA-1 or BRCA-2 mutations were treated with the PARP inhibitor, Olaparib, overall response rates were an impressive 41% without significant toxicityv.[32,33] When patients with metastatic triple negative breast cancer were treated with a combination of chemotherapy and another PARP inhibitor, Iniparib, in a phase II study, response rates, progression free survival and overall survival were significantly improved.[34] Unfortunately, this benefit could be confirmed in a subsequent phase III trial.[35]

Conclusion

The era of targeted therapies has contributed to the rapid advancement of breast cancer treatment. Targeted drugs have increased cure rates in localised breast cancer and improved survival in metastatic breast cancer. It is the hope that breast cancer treatment will one day be individualised based on the unique set of molecular targets produced by the tumour. The challenge at present is the need to identify more clinically relevant biomarkers that can predict drug sensitivity and clinical benefit so that medical oncologists can better select appropriate patients for specific targeted drugs and balance relative benefit with risk. The promise of true personalised cancer therapy can only become a reality with more systematically designed biomarker-driven clinical trials. MG

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