FACULTY

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New treatment paradigms in HER2+ early breast cancer – how will this affect the role of the surgeon?

LEARNING OUTCOMES

On completion of this newsletter, participants will be better able to:

- **Describe** the role of neoadjuvant systemic therapy in the treatment of early breast cancer
- **Recognise** patients with breast cancer who would benefit from neoadjuvant targeted therapy
- **Outline** the importance of the multidisciplinary team in the management of early breast cancer
- **Identify** clinical tools and decision aids to assist in management of early breast cancer

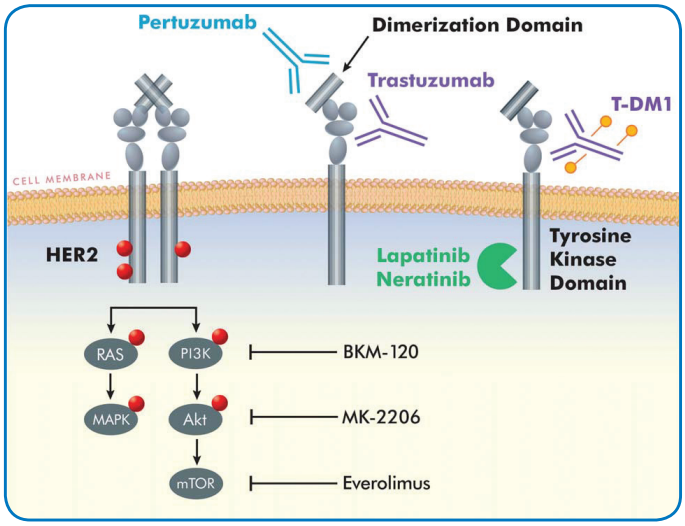
MANAGEMENT OF EARLY BREAST CANCER

Early stage breast cancer treatment is complex, involving a combination of local modalities, systemic therapies and supportive measures, each of which can be delivered in a variety of possible sequences.[1, 2] Decision-making therefore now involves not only the selection of specialty services, but a consideration of the sequence in which they are administered.[3] Neoadjuvant systemic therapy (NAT), including combinations of cytotoxic chemotherapy and targeted molecular agents, has significantly improved patient outcomes.[3, 4] It is therefore emerging as a preferred treatment approach for many patients bearing aggressive forms of breast cancer such as the human epidermal growth factor receptor 2 positive (HER2+) subtype and the triple negative subtype.[1, 5, 6]

Neoadjuvant therapy in HER2+ breast cancer

The approval of anti-HER2 targeted molecular therapies, has changed the outlook for patients with HER2+ breast cancer.[7] The combination of these drugs with chemotherapy in the neoadjuvant setting has been shown to significantly improve patient outcomes.[4]

Figure 1. Schematic for HER2+ directed agents.[8]



Adapted from Zelnak AB, Wisinski KB. Management of patients with HER2-positive metastatic breast cancer: is there an optimal sequence of HER2-directed approaches? Cancer. 2015;121(1):17-24.

Practice points

- Optimal treatment strategies for women with early breast cancer require a multidisciplinary team consisting of breast surgeons, medical oncologists, radiation oncologists, breast pathologists, breast radiologists and breast nurses.[1]
- Neoadjuvant systemic therapy can help facilitate breast-conserving surgery in women with early breast cancer by reducing tumour size.[3]
- Australian and international guidelines recommend that patients with HER2+ breast cancer be evaluated for anti-HER2 targeted neoadjuvant therapy.[1, 12, 24]
- Patient decision aids can support shared decision making in the management of early breast cancer.[22]

Benefits of neoadjuvant therapy

Breast-conserving surgery is considered the primary surgical choice for breast cancer.[1] Neoadjuvant therapy may help reduce tumour size and can thereby facilitate breast conservation.[3] Avoiding mastectomy and reducing the extent of surgery provides benefits of quicker recovery and fewer post-operative complications.[3] Another advantage of NAT is the ability to safely delay surgery in some circumstances to help obtain optimal post-operative results.[3] This may include patients for whom the results of genetic testing may influence their local therapy decisions.[3] The option of neoadjuvant therapy provides women with adequate time to have genetic counselling and testing, to more carefully consider local therapy options, consult with reconstructive surgeons and radiation oncologists and consider the most appropriate local therapy for themselves.[3]

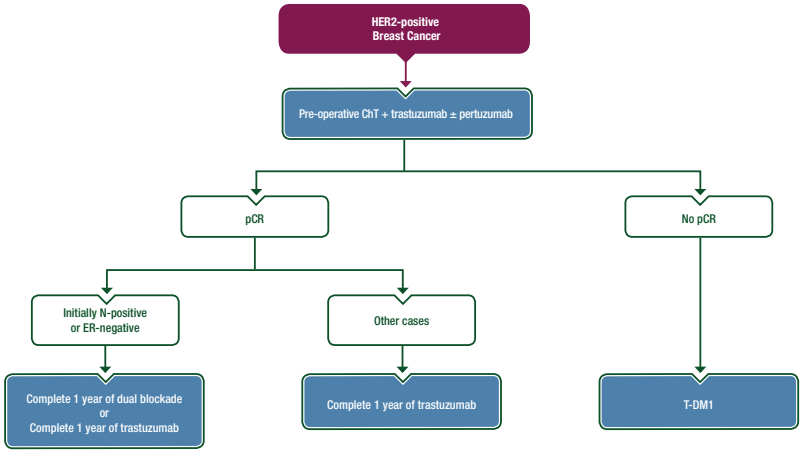
It has been suggested that NAT could also provide a way to assess the *in vivo* response of the tumour to treatment, with the tumour's response acting as a surrogate for that of invisible micrometastases.[9] The absence of residual invasive disease in the breast and axillary nodes, defined as pathologic complete response (pCR), correlates with fewer future relapses.[9, 10] A pooled analysis showed that patients who attain pCR have improved survival, with the prognostic value greatest in aggressive subtypes of breast cancer, although it could not validate pCR as a surrogate endpoint for improved overall survival or event-free survival in all breast cancer subtypes.[11]

Current recommendations for neoadjuvant therapy in HER2+ breast cancer

European Society for Medical Oncology (ESMO) guidelines recommend that neoadjuvant targeted therapy be given to all HER2+ early breast cancer patients who do not have contraindications to its use, with the possible exception of selected cases with low risk (eg. T1N0 tumours).[1] The addition of a second agent for the duration of 1 year may also be considered in high-risk patients, as shown in Figure 1.[1] The eviQ guidelines endorse patients with HER2+ breast cancer being evaluated for anti-HER2 targeted therapy using combination chemotherapy and targeted therapy.[12]

Recent studies suggest that using the results of NAT to determine further adjuvant therapy offers the possibility of improved outcomes.[13, 14] The CREATE-X study of patients with HER2- showed that giving adjuvant chemotherapy with capecitabine after neoadjuvant therapy with standard chemotherapy improved disease-free survival and overall survival.[13] The KRISTINE study of HER2 positive patients showed that traditional neoadjuvant chemotherapy plus dual HER2-targeted blockade resulted in significantly more patients achieving a pathological complete response compared to T-DM1 and pertuzumab.[14]

Figure 2. HER2+ breast cancer treatment.[1]
ChT = chemotherapy, HER2 = human epidermal growth factor receptor-2, N-positive = node positive, pCR = pathologic complete response, T-DM1 = trastuzumab emtansine.



Adapted from Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019

Take home message

"Neoadjuvant systemic therapy is emerging as a preferred treatment approach for many patients bearing aggressive forms of breast cancer, including the HER2+ subtype. A combination of anti-HER2 targeted therapies and chemotherapy has been shown to significantly improve patient outcomes. Not all these agents are reimbursed on the Pharmaceutical Benefits Scheme. Nevertheless, Australian guidelines currently endorse the consideration of combination chemotherapy and dual targeted therapy in patients with HER2+ breast cancer."

Table 1. PBS funding of neoadjuvant agents used in the treatment of HER2+ breast cancer[15, 16, 17]

Agent	TGA indicated for neoadjuvant treatment	PBS funding available for neoadjuvant treatment	Criteria
Trastuzumab	Yes – for locally advanced disease in combination with neoadjuvant chemotherapy and followed by adjuvant trastuzumab	Yes	LVEF must be ≥ 45% and have no symptomatic heart failure
Pertuzumab	Yes – for inflammatory, locally advanced or early stage (either > 2cm in diameter or node positive) breast cancer as part of a complete treatment regimen for early breast cancer	No	

Adapted from Australian Government. Trastuzumab 2019 [cited 2019 October 31st]. Available from: http://www.pbs.gov.au/medicine/item/10383L-10391X-10401K-10402L-10581X-10588G-10589H-10597R-4632T-4639E-4650R-4703M-7264H-7265J-7266K-7267L.
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Australian Government. Pertuzumab 2019 [cited 2019 October 31st]. Available from: http://www.pbs.gov.au/medicine/item/10267J-10268K-10308M-10309N-10333W-10334X.

ROLE OF THE MULTIDISCIPLINARY TEAM

The treatment algorithm for breast cancer has become increasingly complex and therefore requires both the expertise of a wide range of specialists and communication between them to formulate an optimal treatment strategy.[18] Australian guidelines now recommend that treatment for early breast cancer be provided by a multidisciplinary team consisting of at least medical oncologists, breast surgeons, radiation oncologists, breast radiologists, breast pathologists and breast nurses. Other specialties that may be required include medical genetics, oncoplastic reconstructive surgery and allied health.[3]

DECISION AIDS IN MANAGEMENT

Women with early stage breast cancer can often choose between treatment options that have different outcomes in regard to life expectancy, cosmetic results, long-term side effects or treatment burden.[22] Shared decision-making is therefore an important aspect of care and this can be supported by the use of a patient decision aid.[22]

Decision aids are non-directive, unbiased tools that provide patients with evidence-based information about their treatment options and expected outcomes using clear verbal and visual formats.[23] Systematic reviews have shown that they can help enable more realistic expectations among patients, reduce decisional conflict and increase active participation in management decisions.[23]

For an example of a patient decision aid for early breast cancer, please visit https://www.uofmhealth.org

Course resource centre

Guidelines

- Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019.
- American Society of Breast Surgeons. Performance and practice guidelines for the use of neoadjuvant systemic therapy in the management of breast cancer. 2017.

Review articles

- Chatterjee A, Erban JK. Neoadjuvant therapy for treatment of breast cancer: the way forward, or simply a convenient option for patients? Gland Surg. 2017;6(1):119-24.

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