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Review Article

Adjuvant and neoadjuvant therapy for breast cancer

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Abstract

Systemic therapies for operable breast cancer patients have improved outcomes and have thus become standard treatments. Recently, new molecular target drugs and regimens are being developed based on the predicted sensitivity for specific breast cancer histological types. Systemic therapy is selected according to recurrence risk, with the treatment for low-risk patients being de-escalated, while high-risk patients receive aggressive systemic treatment with an adequate dose and duration. Neoadjuvant systemic therapy has a different aim. The efficacy of systemic therapies, based on the sensitivities to drugs, is supported by improvements in the rate of breast-conserving therapy. The response to neoadjuvant systemic therapy is the most important factor for predicting outcomes and selecting the optimal adjuvant therapy. Novel biological markers unique to individual patients allow appropriate targeted therapy, which can achieve optimal efficacy.

Key words: breast cancer, adjuvant, neoadjuvant

Introduction

The multidisciplinary treatments for patients with operable breast cancer (BC) combine local, i.e. surgical and radiation therapies, with systemic treatments including a wide range of drugs. Systemic therapy especially is very important for improving disease-free survival (DFS) based on the control of micro-metastases with the potential to spread throughout the body. Predicting responses and determining the sensitivity of tumors to drugs are necessary for selecting the optimal treatment regimen. The systemic therapy is decided according to shared decision-making between patients and investigators based on benefits and risk such as adverse events. Costs must also be factored into these decisions.

The timing of systemic therapies for operable BC includes adjuvant therapy after surgery and neoadjuvant therapy before surgery. The efficacies of these therapies for improving DFS are essentially the same, if similar drugs and regimens are used based on previous studies (1). The drugs given as systemic therapy are classified into hormone therapy, chemotherapy and molecular target therapy. These drugs can be given alone, as a single agent, or used in multiple-drug regimens.

BC is divided into subtypes according to the expression of biological markers, mainly the estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) and Ki67. The definitions of luminal A like, luminal B like, HER2 enrich and triple negative type are ER-positive and Ki67 low, ER-positive and Ki67 high, HER2 positive and all negative (ER, PgR, HER2), respectively. This subtype classification is very useful for selecting the most appropriate systemic therapy. Endocrine therapies and anti-HER2 therapies are effective for BC with ER-positive and HER2-positive, respectively.

Adjuvant systemic therapy

The aim of adjuvant systemic therapy is to prolong survival by treating latent micro-metastases. Endocrine therapy, chemotherapy and anti-HER2 therapy based on different anti-cancer mechanisms can improve both DFS and overall survival (OS). The selection of these drugs is determined according to shared decision-making between patients and investigators based on baseline risk, which estimated by a number of lymph node metastases, invasive tumor

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Table 1. Adjuvant systemic therapy for early breast cancer

Therapy	Biology	Regimen
Hormone therapy	ER- and/or PgR-positive premenopause	TAM 10 (5) years, TAM + LH–RH agonist 5 years, EXE + LH–RH agonist 5 years
	ER- and/or PgR-positive postmenopause	AI 5 (10) years.
Anti-HER2 therapy	HER2-positive	Chemotherapy + Trastuzumab 1 year, Chemotherapy + Trastuzumab + Pertuzumab 1 year
Chemotherapy	Any	Anthracycline and/or taxane (+/−) capecitabine

TAM; tamoxifen, AI; aromatase inhibitor.

size, histological grade and molecular subtypes. Recently, the Ki-67 (1–3) expression score and multi-gene assay results (4–6) for cancer cells have been used to predict a benefit of chemotherapy for ER-positive BC patients (Table 1).

Adjuvant hormone therapy for ER-positive BC patients

Premenopausal patients with ER-positive BC are given tamoxifen (selective estrogen modulator, SERM) as hormone therapy (7). Tamoxifen reduces the risk of recurrence and death, regardless of age, menopausal status, lymph node metastasis and the use of chemotherapy.

Tamoxifen administration should be continued for 10 years (8). Tamoxifen, administered for a decade, can reduce BC-related deaths by 2.8% as compared to treatment for 5 years according to the ATLAS trial[ix]. Adding a luteinizing hormone-releasing hormone (LH–RH) agonist, which induces amenorrhea, to tamoxifen or exemestane [aromatase inhibitor (AI)] is recommended as adjuvant therapy for young patients and those at high risk for recurrence receiving adjuvant chemotherapy (9–11).

An increased risk of endometrial cancer is an adverse event specific to tamoxifen when taken by postmenopausal patients aged 54 years and older (12).

Taking an AI for 5 years is recommended as adjuvant hormone therapy for postmenopausal BC patients (13,14). Postmenopausal patients with high-risk BC especially need to take an AI for 10 years. The EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis reported that AI can reduce recurrence by 30% and death by 15% as compared with tamoxifen (15). The MA-17 trial revealed DFS to be significantly longer with 10 years than with 5 years of AI (16). However, there were significantly more bone-related adverse events (fracture, pain and osteoporosis) with longer AI administration. Tamoxifen is an alternative for patients suffering serious adverse events associated with AI.

Prospective randomized trials to confirm the efficacy of CDK 4/6 inhibitors, which can overcome hormone resistance, are currently ongoing.

Adjuvant hormone therapy can not only improve DFS but also prevent the occurrence of ipsilateral breast tumor. Adverse events related to endocrine therapies are also factors, which should consider due to determine treatment regimens.

Adjuvant chemotherapy for high-risk BC patients

BC patients with axillary lymph node metastases or high risk for recurrence should receive chemotherapy such as anthracycline (A) containing regimen or TC regimen (docetaxel and cyclophosphamide) or AC followed by taxane (docetaxel or paclitaxel) regimen as adjuvant chemotherapy (17). The efficacy of the TC regimen was confirmed in a prospective randomized trial (18,19). Chronic heart failure is one of the important adverse events associated with A administration. Dose-dense therapy, which shortens the treatment duration, can significantly improve both DFS and OS as compared with standard A containing regimens followed by a taxane. G-CSF support has been needed and severe anemia has been needed attention (20,21). Capecitabine is recommended a usage for TN BC with residual disease after neoadjuvant systemic therapy based on previous clinical trial (22). To optimize the administration of adjuvant chemotherapy, the recurrence score based on a multi-gene panel examination of cancer tissue (Oncotype DX, Mammaprint, PAM 50, Curebest) (Table 2) is useful (23–25). Chemotherapy is not recommended for early BC patients with low RS by Oncotype DX based on clinical trial (26). Trials to confirm the prognostic performance of PARP (poly ADP ribose polymerase) inhibitors, which exert a synthetic lethality in the setting of BRCA mutations, are currently ongoing (Table 3).

Adjuvant anti-HER2 therapy for HER2-positive BC patients

Trastuzumab, which is an anti-HER2 molecular target therapy, in combination with adjuvant chemotherapy is recommended for patients with HER2-positive cancer and those with breast tumors larger than 1 cm (27). Trastuzumab should not be used simultaneously with AC because heart failure is an adverse event associated with both drugs. Trastuzumab monotherapy without chemotherapy is not recommended, due to a lack of evidence supporting the efficacy of this drug given alone. For patients with small tumors, i.e. from 0.5 to 1 cm in largest diameter, the decision to administer trastuzumab is made in consideration of both risks and benefits. There is prospective data indicating the efficacy of adjuvant weekly paclitaxel with trastuzumab for low-risk HER2-positive BC (28). For high-risk patients with node positive cancer, pertuzumab, which is another anti-HER2 molecular target therapy, is added to trastuzumab (29). Pertuzumab has been found to improve DFS in patients with invasive disease without increasing the incidence of adverse events. The optimal duration of anti-HER2 drug administration is one year (30,31). One dataset showed 1-year treatment with neratinib after trastuzumab to improve DFS. Whether to administer neratinib should be decided taking recurrence risk, adverse events and high costs into consideration. T-DM1 (trastuzumab emtansine) is recommended a usage for HER2-positive BC with residual disease after neoadjuvant systemic therapy based on previous clinical trial (32).

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Table 2. The new drug being confirmed the efficacy by ongoing adjuvant trial for breast cancer

subtype	Drug (study name)			
ER-positive	Pembrolizumab (Keynote)	Abemaciclib (MONARCHE)	Palbociclib (PENELOPE, PALLAS)	Olaparib (Olympi A)
ER-negative HER2-positive	T-DM1 (Kaitlin)			
Triple negative	Atezolizumab (Impassion)	Olaparib (Olympi A)		

Table 3. Multigene assay for breast cancer

	Company	Gene	Method	Prospective trial
Oncotype DX	Genomic Health	21	RT-PCR	TAILORx
MammaPrint	Agendia	70	Microarray	MINDACT
PAM 50	Nanostring Tech.	50	RT-PCR	
Curebest	Sysmex	95	Microarray	

RT-PCR, real-time polymerase chain reaction.

Adjuvant therapy with bone modifying agents

Bisphosphonate as adjuvant systemic therapy is reportedly effective in postmenopausal and premenopausal patients receiving LH–RH agonist therapy. The EBCTCG meta-analysis indicated that bisphosphonate reduces the incidence of bone metastasis, suppresses distant metastasis and improves OS (33). However, the risk of bone fracture is lessened only for postmenopausal patients. As yet, we have no data for bisphosphonate monotherapy, i.e. administration without another systemic therapy.

The efficacy of RANKL inhibitors, which are bone-modifying agents, is currently being examined in a prospective trial. The results from ABCSG-18 indicated the significantly prognostic efficacy (34) and prevention of bone fracture of adjuvant RANKL inhibitors (35). Guidelines for the most appropriate duration and adjuvant bisphosphonate agents are eagerly awaited.

Neoadjuvant systemic therapy

Neoadjuvant chemotherapy (NAC) was mainly recommended for locally advanced BC without distant metastasis. Currently, the aims of NAC are dramatically changed according to current data of clinical trials (27,39). The purpose of NAC is not only increasing the breast-conserving surgery rate but also precision medicine (adjuvant capecitabine or T-DM1 for early BC with residual disease) according to efficacy of NAC.

Regimen selection aims to obtain the maximal anti-cancer effect according to cancer biology. Anti-HER2 drugs are used for HER2-positive BC patients (36). The response to NAC, especially a complete response (pCR), is a prognostic factor in patients who are ER-negative and/or HER2-positive. ER-positive postmenopausal BC patients are candidates for neoadjuvant hormone therapy. Prospective trials designed to evaluate the safety of foregoing surgery in patients with pCR in response to NAC are currently ongoing.

Neoadjuvant chemotherapy

A meta-analysis confirmed that if patients use the same drugs, there is no difference in outcomes between adjuvant and neoadjuvant systemic therapies (37).

The breast-conserving rate in patients receiving NAC is better than that of those given adjuvant therapy. However, there is a report describing a higher local recurrence rate in patients treated with NAC (38). The standard NAC regimen is AC followed by a taxane. Anti-HER2 drugs increase the pCR rate for HER2-positive patients (39). Notably, the combination of pertuzumab and trastuzumab exerts greater efficacy without severe adverse events (40). Carboplatin added to the standard regimen may be effective for triple negative BC patients, especially with BRCA1/2 mutation. It is anticipated that novel regimens, which use molecular target agents, chosen based on drug sensitivity predictions, will be developed in near future.

Future studies should focus on other molecular target drugs to determine their effects, when given as escalation therapy, in non-pCR patients.

Neoadjuvant hormone therapy

Neoadjuvant hormone therapy increases the breast-conserving therapy rate for ER-positive postmenopausal BC patients (41). AI is used as neoadjuvant hormone therapy. The anti-cancer effects of neoadjuvant hormone therapy are similar to those of NAC (42). However, there is no evidence for the optimal duration of treatment or the long-term outcomes. Trials comparing NAC and hormone therapy showed breast-conserving rates to be similar, but there were fewer adverse events with hormone therapy than with NAC. AI is more effective than tamoxifen as neoadjuvant hormone therapy.

Neoadjuvant hormone therapy is not recommended to premenopausal patients because data supporting this option are lacking. Tamoxifen as neoadjuvant hormone therapy did not show efficacy similar to that of NAC. Tamoxifen with LH–RH agonist administration increases the breast-conserving rate. Neoadjuvant hormone therapy is increasingly being selected based on sensitivity to hormone therapy and facilitates deciding whether to administer adjuvant chemotherapy (43). The NEOS trial based their strategies for treating ER-positive postmenopausal patients on the response to 6-month neoadjuvant hormone therapy. There are other trials utilizing the Ki67 score after 2 weeks of neoadjuvant hormone therapy to determine whether adjuvant chemotherapy is warranted.

Conclusion

The duration and regimens of adjuvant therapy have been changed according to evidences of clinical trials. The purpose of neoadjuvant

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therapy has also changed for early BC. The shared decision-making is very important to determine the systemic therapy (on or off, adjuvant or neoadjuvant) for early BC with each subtype.

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