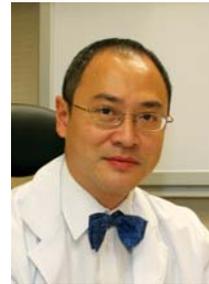




Systemic Adjuvant Therapy for Invasive Breast Cancer

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 August 2007.

Introduction

Adjuvant treatment for breast cancer saves lives. Both chemotherapy and endocrine therapy, and independent of each other, are effective in reducing relapse risk and increasing survival.

A working principle is that adjuvant therapy should be considered if the estimated risk of relapse is greater than 10%. The benefits of adjuvant treatment should be balanced against toxicity.

A decade or more ago, postoperative systemic adjuvant therapy of breast cancer was very simple, mainly consisting of 5 years of tamoxifen and /or chemotherapy. Chemotherapy then was CMF - Cyclophosphamide, Methotrexate and Fluorouracil.

Nevertheless, the survival advantage (hazard ratio of 0.79) of the CMF regimen was sustained up to 30 years when the series was updated in 2005¹. Furthermore the same regimen yielded a hazard ratio of 0.65 at 20 years when used in node-negative oestrogen-receptor negative breast cancer.

This fact was demonstrated time and again by the meta-analysis by the Early Breast Cancer Trialists' Collaborative Group² (EBCTCG). Both chemotherapy and endocrine therapy effectively reduced the risk of relapse and improved survival in invasive breast cancer. At 15th year, the relapse rates were 41.1% vs 53.5% in favour of chemotherapy. The corresponding overall mortality rates were 32.4% vs 42.4%. With adjuvant Tamoxifen, which was administered for 5 years in endocrine receptor (ER) positive breast cancer patients, the corresponding relapse risk at 15 years were 33.2% vs 45%, in favour of endocrine therapy. The corresponding mortality rates were 25.6% vs 34.8%.

Research in the last 10 years had made big steps in reducing disease relapse and increasing survival with new pharmaceutical agents. At present, patients after surgery can be categorised according to prognostic factors (Table 1) and major international guidelines are available for a risk-adapted treatment approach³.

Important pathological parameters include: number of metastatic axillary nodes, grading, endocrine receptor status, tumour size, HER2 over-expression, presence of peri-tumoral vascular invasion and age. Patients are then categorised to low, intermediate and high-risk groups.

What's new in Endocrine Therapy

Aromatase inhibitors are new in adjuvant endocrine therapy for endocrine-receptor positive breast cancer.

The old standard hormonal therapy (5 years of Tamoxifen) for oestrogen receptor (ER) positive disease has the drawback of a slight increase in endometrial cancer (around 1 additional case per 1,000 patient-years of drug use) and side effects like increased thromboembolic events. Furthermore, the risk of relapse of hormonal-dependent tumours is known to extend beyond 10 years after surgery, which is not helped by extending treatment with Tamoxifen beyond 5 years.

Aromatase inhibitors, in postmenopausal patients, are better than Tamoxifen. Several large randomised studies such as ATAC⁴, BIG-98⁵, IES⁶ and MA-17⁷ trials have all shown significant survival benefit and better tolerance of aromatase inhibitors (AI) than 5 years of Tamoxifen. In these trials, AIs were either used upfront (Anastrozole or Letrozole), after 2-3 years of Tamoxifen (Exemestane), or as extended adjuvant therapy (Letrozole) after 5 years of Tamoxifen.

Actually, the present guideline from American Society of Clinical Oncology (ASCO) on hormonal therapy recommends the use of an AI at 'some point in time' in the adjuvant hormonal therapy of postmenopausal ER-positive patients.

In premenopausal patients, the use of a luteinising hormone releasing hormone (LHRH) agonist (eg Goserilin) for 2 years has been proven to give equivalent results to CMF chemotherapy⁸ - the old standard. This effect was the same in both node-positive and node-negative patients. This reversible medical castration therefore, is an alternative to chemotherapy in low-risk (eg node-negative disease) patients who want to avoid the side-effects of chemotherapy.



What's new in chemotherapy

Since the turn of the century, the anthracycline-containing (adriamycin, epirubicin) regimens have replaced CMF as standard adjuvant chemotherapy. From the EBCTCG meta-analysis anthracyclines provided an extra advantage in survival than CMF, especially in women younger than 50.

One of the latest regimen of anthracycline is FEC100 (epirubicin 100 mg / sq m).It has been shown to be superior to FEC 50 (epirubicin 50 mg / sq m) in a recent 10-year update¹¹. The difference in relapse and survival rates were about 5%.

The addition of taxanes (paclitaxel or docetaxel) to anthracycline-containing regimens was shown to give additional survival benefit with an absolute gain of 2% to 7% in different randomised trials.

For paclitaxel, the drug is given for four cycles after four cycles adriamycin and cyclophosphamide (AC) (CALGB protocol 9344⁹) every 3 weeks or given in a 'dose-dense' fashion (every 2 weeks instead of 3) with growth factor (G-CSF) support in between cycles (CALGB protocol 9741¹⁰), which was shown to give superior survival effects to the same drugs given every 3 weeks.

Docetaxel has also been tested against standard anthracycline-containing regimens and shown to confer survival benefit. It can be given as the TAC¹² regimen (Taxotere, Adriamycin, Cyclophosphamide) every 3 weeks, but growth factor support to prevent severe neutropenia should be given. Alternatively, it can be given in three 3-weekly cycles following three cycles of FEC 100 as in the French PACS-01¹³ study. Five-year DFS rates were 73.2% with FEC and 78.4% with FEC-D. Five-year overall survival rates were 86.7% with FEC and 90.7% with FEC-D, demonstrating a 27% reduction in the relative risk of death. At present these regimens, together with the dose-dense regimen giving four cycles of paclitaxel as mentioned above, are the most common 'third generation' chemotherapy administered in high-risk node-positive disease.

Targeted therapy with trastuzumab against the HER2/neu receptor.

Following trials showing dramatic improvement of response rates when trastuzumab was combined with chemotherapy in HER2/neu oncogene amplified metastatic breast cancer, large-scale randomised studies have been conducted in the use of trastuzumab in the adjuvant setting. Preliminary results of these trials¹⁴⁻¹⁷ have been published with more than 13,000 patients accrued. Even though median follow-up time of some of these trials has been just over 1 year, a significant relapse-free survival gain (absolute gain of up to 18%) was reported for all of these trials. Although the optimal duration of trastuzumab treatment and the optimal sequence of its use with

respect to chemotherapy is not known, it is generally recommended that one year of adjuvant trastuzumab should be considered for high-risk HER2/neu amplified or over-expressed breast cancer after acknowledging the potential cardiac risk of the drug, especially when it is used concurrently with chemotherapy.

Risk-adapted systemic adjuvant therapy for invasive breast cancer

In summary, the most appropriate systemic adjuvant treatment depends on the estimated risk of relapse of the breast cancer. At present this is done by evaluating the clinical prognostic factors, including the number of metastatic axillary nodes, the ER status, the grading of tumour and age, and placing patients into risk categories such as the St Gallen 2005 risk categories. In international guidelines of adjuvant treatment, the aggressiveness of recommended therapy depend on the estimated risk, and the exact treatment needed would depend on predictive factors: ER and Her2/neu oncogene status.

Finally the patient's general condition, co-morbidities and wishes are the most important modifying factors. Aggressive chemotherapy might not be tolerated in elderly patients with significant medical conditions and might not be appropriate even if the prognostic factors suggest a very aggressive cancer. Medical castration, which is likely to have reversible effects on ovarian function, might be the preferred treatment in those with few involved axillary nodes and who do not want the side-effects of chemotherapy (eg alopecia and potential infertility). However, even good guidelines cannot replace detailed personalised discussion with the patient, and the optimal therapy should be a highly individualised decision for each patient.

Table 1. Risk categories of invasive breast cancer (adapted from International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005)

RISK CATEGORY	NODAL STATUS	FACTORS	OTHER PROGNOSTIC
LOW	Negative	AND	Tumour ≤2 cm AND grade 1 AND No vascular invasion AND HER2/neu not amplified nor over-expressed AND age ≥ 35
INTERMEDIATE	Negative	AND	Tumour >2 cm OR grade 2-3 OR Presence of vascular invasion OR HER2/neu amplified or over-expressed OR age >35
		AND	HER2/neu not amplified nor over-expressed
HIGH	1-3 positive	AND	HER2/neu amplified or over-expressed
	OR > 4 positive		



Table 2. Guidelines of systemic adjuvant therapy according to the risk

RISK CATEGORY	HORMONE SENSITIVE CANCER	HORMONE-RESISTANT CANCER
LOW	Hormonal therapy or none*	Not applicable
INTERMEDIATE	Hormonal therapy alone, OR Chemotherapy then hormonal therapy (trastuzumab therapy considered in HER2/neu amplified or over-expressed)	Chemotherapy alone (trastuzumab therapy considered in HER2/neu amplified or over-expressed)
HIGH	Chemotherapy then hormonal therapy OR Hormonal therapy alone*, (trastuzumab therapy considered in HER2/neu amplified or over-expressed)	HER2/neu amplified or over-expressed

* Indicates alternative treatment option in the case of preference of physician or patient, or medical contraindications.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Systemic Adjuvant Therapy for Invasive Breast Cancer" by Dr. Michael MC Cheung, and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 August 2007. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Adjuvant therapy for breast cancer improves relapse-free survival only.
2. The effect of adjuvant treatment lasts for only 5 years.
3. Only the number of positive axillary nodes matters in prognosis.
4. Aromatase inhibitors are effective only in post-menopausal breast cancer patients.
5. In pre-menopausal patients, LHRH agonists are superior to chemotherapy in reducing relapse risk.
6. Anthracycline-containing chemotherapy has replaced the CMF regimen in adjuvant therapy.
7. Taxane-containing regimens have a higher efficacy than anthracycline-containing regimens.
8. Adjuvant trastuzumab should be given for at least one year.
9. The critical toxicity for adjuvant trastuzumab is cardiac toxicity.
10. Adjuvant therapy should be given to all breast cancer patients.



ANSWER SHEET FOR AUGUST 2007

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2007 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Name (block letters): _____ HKMA No.: _____

HKID No.: _____ - _____ X X (x) Other Membership No. (please indicate): _____

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Answers to July 2007 issue

Head & Neck Surgery

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