Adjuvant Systemic Guidelines for Breast Cancer

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On behalf of Breast Clinical Network Group, Merseyside and Cheshire Cancer Network

Introduction

Adjuvant systemic therapy (endocrine therapy, chemotherapy and trastuzumab, alone or in sequence) is now offered to almost all patients following surgery for early breast cancer. Such treatments have an established role in decreasing relapse and prolonging survival. Decisions on which treatment(s) to offer a patient are based on estimates of both the risk of recurrence and the likelihood of response to the treatments offered. All patients should be considered for entry into appropriate clinical trials.

The degree of axillary lymph node involvement at diagnosis is the single best prognostic factor¹. However, discrimination of risk within node negative patients remains difficult. Histological grade, tumour size and lymphovascular invasion appear the most important prognostic factors². Over-expression of HER-2 seems to be a significant prognostic factor as well as being predictive of response to trastuzumab and is associated with an increase of 1.5-2 fold in the relative risk of mortality³. Young age (< 35 years) also seems to be an independent prognostic factor with a similar impact on survival as HER-2 over-expression⁴. However, recurrence risk is a continuous variable and while a number of decision aids exist - consensus guidelines⁵, molecular profiles⁶ and mathematical⁷/computer⁸ models - none of these have been validated in a prospective randomised trial.

Oestrogen (ER) and HER-2 receptor status provides useful predictive information on which cancers are likely to respond to endocrine therapy and trastuzumab³,⁹. Prediction of the likelihood of response to chemotherapy is more problematic. Several studies have suggested that ER positive tumours respond less well to chemotherapy than ER negative tumours. However, this has not been a consistent finding and there is still sufficient chance of benefit to justify its use in patients with high risk ER positive cancers. Older patients (> 70 years) are another group where considerable uncertainty exists about the magnitude of benefit from chemotherapy. The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analyses have suggested that older women may benefit less from chemotherapy than younger women⁹. However, older women are grossly under-represented in trials of adjuvant chemotherapy (where the median age is usually around 50) which makes interpretation of available data difficult.

The decision aid ADJUVANT! (www.adjuvantonline.com) can be helpful to estimate the risk/benefit of treatment options⁸. However, the ultimate decision should involve a multidisciplinary discussion encompassing absolute risks of recurrence and breast cancer mortality, potential benefits and side-effects of treatment (with attention to the fitness of the patient) and patient preferences.
Adjuvant Endocrine Therapy
Adjuvant endocrine therapy is recommended for all patients with ER positive early breast cancer. Treatment options depend on the menopausal status of the patient.

Premenopausal women
Among women with ER positive disease, the EBCTCG meta-analysis confirmed that five years of tamoxifen almost halved the annual recurrence rate and reduced the annual breast cancer mortality rate by a third\(^9\). The proportional risk reductions seen with tamoxifen are little affected by age and result in an absolute improvement in 15 year recurrence and breast cancer mortality. Five years of adjuvant tamoxifen has therefore become standard adjuvant endocrine treatment for premenopausal women with ER positive breast cancer. The benefit of continuing tamoxifen beyond five years is still uncertain.

Ovarian ablation or suppression has also been shown to reduce recurrence and improve survival, with a benefit equal in magnitude to CMF\(^10\). The value of ovarian ablation/suppression over and above chemotherapy and/or tamoxifen in premenopausal women with ER positive disease is unclear and the subject of ongoing clinical trials.

It has become increasingly common, given the evidence of benefit from adjuvant aromatase inhibitors (AI) in postmenopausal women (see below), to consider treating women who develop amenorrhea after chemotherapy with AIs either immediately or after a short period on tamoxifen. Great care must be exercised however, as ovarian function can recover beyond one year post chemotherapy\(^11\). Biochemical monitoring of ovarian function requires highly sensitive immunoassays not usually available in most hospitals and it may be preferable to continue on tamoxifen or to use a combination of ovarian suppressions and an AI if desired.

Postmenopausal women
Five years of tamoxifen can no longer be considered to be unequivocally the best adjuvant endocrine treatment for postmenopausal women with ER positive breast cancer. Several large randomised trials, as well as the results of the 2005/6 EBCTCG overview, show a benefit from either substituting AI for tamoxifen or using a sequential tamoxifen-AI regimen\(^12\)\(^-\)\(^15\). Thus, with the possible exception of patients with very low risk disease (e.g. low grade T1N0 tumours), postmenopausal patients should receive an aromatase inhibitor at some point during treatment.

The optimal strategy for the use of adjuvant AIs remains unclear. The strategy of using a sequential tamoxifen-AI strategy has some theoretical advantages. The use of two treatments with different mechanisms of action might be superior in overcoming treatment resistance while limiting the risk of osteoporosis associated with prolonged use of an AI. However, a sequential treatment strategy might disadvantage patients at higher risk for relapse in the first 2-3 years after surgery. A third strategy - extended adjuvant treatment
after 4-5 years of tamoxifen - has also been shown to be beneficial although it is unclear how long to continue the AI.

Data from ongoing trials will hopefully make clear which strategy achieve the best outcome. In the interim, either approach is reasonable, with patients at high risk of early relapse (e.g. high grade, HER-2 over-expression, low ER or heavily node positive) being particularly suitable for upfront AI while these results are awaited. As yet, here are no randomised comparisons between the the adjuvant use of different drugs in this class (anastrozole, letrozole and exemestane) to guide the choice of AI. While awaiting the results of such trials, any of the AIs can be used in their licensed indications.

The use of aromatase inhibitors is associated with an increased risk of osteoporosis. All patients should be advised of lifestyle choices which can minimise this risk and should be assessed according to recently published guidelines\(^{16}\).

### Adjuvant Chemotherapy

Adjuvant combination chemotherapy can reduce recurrence and improve survival. Anthracycline based adjuvant chemotherapy regimens of 4-6 months duration significantly reduce the annual breast cancer death rate - by about 38% for women aged under 50 years and 20% for women aged 50-69 years\(^9\). Recent trials, largely in patients with node positive breast cancer, comparing taxane-anthracycine combinations or sequences with anthracycline-based treatment have shown further improvements in survival of a magnitude similar to the difference between anthracycline-based treatments and CMF\(^{17}\).

Several effective adjuvant chemotherapy regimens are available. Risk of recurrence, patient age, menopausal status and co-morbidity are important considerations when choosing appropriate treatment. The recommendations outlined below allow a range of options and should follow a discussion between doctor and patient of risks, benefits, side-effects and preferences.

#### Risk categories

<table>
<thead>
<tr>
<th>Risk categories</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Pathological or Clinical N2 or N3 or N1 with other high risk features</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>N1 without other high risk features or N0 with high risk features</td>
</tr>
<tr>
<td>Low risk</td>
<td>T1N0 without high risk features</td>
</tr>
</tbody>
</table>

#### < 60 years old, no serious co-morbidity

<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER negative</td>
<td>FEC-D</td>
<td>Node positive: FEC-D or E-CMF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Node negative: E-CMF</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>E-CMF or no treatment</td>
<td></td>
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</tbody>
</table>
High risk | Intermediate risk | Low risk
---|---|---
ER positive | FEC-D* or E-CMF* | Node positive: FEC-D* or E-CMF*
*followed by endocrine therapy | Node negative: E-CMF* | Adjuvant endocrine therapy

> 60 years old, no serious co-morbidity

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER negative</td>
<td>FEC-D or E-CMF</td>
<td>Node positive: FEC-D or E-CMF or EC or AC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Node negative: E-CMF or EC or AC</td>
</tr>
<tr>
<td>ER positive</td>
<td>FEC-D or E-CMF followed by endocrine therapy</td>
<td>Endocrine therapy +/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Node positive: FEC-D or E-CMF or EC or AC</td>
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<tr>
<td></td>
<td></td>
<td>Node negative: E-CMF or EC or AC</td>
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<td></td>
<td></td>
<td>E-CMF or EC or AC or no chemotherapy</td>
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<td></td>
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<td>Adjuvant endocrine therapy</td>
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</table>

> 70 years
Adjuvant endocrine treatment is standard for patients with ER positive disease. Patients with ER negative disease or high risk ER positive disease may be candidates for chemotherapy depending on general health and co-morbidity.

Patients with a contra-indication to or who choose not to have anthracyclines are candidates for CMF or Docetaxel-Cyclophosphamide.

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Adjuvant Trastuzumab

Four large randomised trials using adjuvant trastuzumab as treatment for patients with HER-2 over-expressing tumours either together with or after adjuvant chemotherapy have reported considerable therapeutic benefit with a reduction in the annual odds of recurrence of around 50% and the annual odds of death of around 30%\textsuperscript{17-20}. Adjuvant trastuzumab is therefore recommended for all patients with HER-2 over-expressing $T_{any}N_{1-3}$ or $> T_{1b}N_{0}$ tumours who receive adjuvant chemotherapy. There are no data on the efficacy of adjuvant trastuzumab in patients with node negative cancers $< 1$ cm. Currently, trastuzumab is administered every 3 weeks for one year - the results of trials of longer and shorter durations of treatment are awaited. Trastuzumab can be administered following anthracycline-based or taxane-based chemotherapy or together with adjuvant taxane monotherapy.

Initial trials of adjuvant trastuzumab confirmed the potential cardiotoxicity of this treatment already known from studies in metastatic disease\textsuperscript{21}. It is recommended that patients with a history of documented congestive heart failure, myocardial infarction (unless good long term prognosis confirmed by cardiologist), uncontrolled hypertension or unstable arrhythmias should not receive adjuvant trastuzumab. Patients should have a normal baseline left ventricular ejection fraction (LVEF) measured by ECHO or MUGA. Particular care should be taken in the decision to treat patients older than 50 with a low normal LVEF ($<55\%$) as 20% of this group experienced cardiotoxicity.

Patients should have LVEF measured at 4-monthly intervals during trastuzumab therapy. The NCRI has suggested guidelines for adjusting or stopping treatment if cardiac function deteriorates\textsuperscript{22}.

References