ABC of breast diseases

Medical treatment of early breast cancer. III: chemotherapy

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Adjuvant chemotherapy is of significant survival benefit in women aged <70 years with moderate to high risk breast cancer. The benefits seem to be greater in younger women. This is mainly because of biological factors, including a higher incidence of grade III and hormone receptor negative cancers. Ovarian failure induced by chemotherapy is also likely to be a factor in women with oestrogen receptor positive tumours. Chemotherapy benefit is also seen in high risk women aged >50 years, but for many of these women endocrine therapy alone may be just as effective, except when the tumour is grade III, tests positive for human epidermal growth factor receptor 2 (HER2), or there is multiple node involvement. Risk benefit considerations are always important here because of toxicity, and consensus criteria have been defined to aid in selecting patients for treatment.

Which chemotherapy regimen?

Evidence shows that anthracycline regimens with doxorubicin or epirubicin achieve a significant further survival improvement (around 4-5%) over treatment with cyclophosphamide, methotrexate, and fluorouracil (CMF), and these are increasingly used as standard. In the United Kingdom, a sequential combination of anthracyclines followed by CMF is widely used after the national epirubicin adjuvant trial (NEAT) found it to be more effective than CMF alone. This regimen, however, uses eight courses of treatment over seven months; regimens of a shorter duration may be as effective. Indeed, finding the minimum duration for effective treatment is an important challenge in adjuvant chemotherapy.

In patients with node positive cancer, two trials showed a small but significant benefit in disease free survival for sequential paclitaxel after anthracycline chemotherapy, but only one of the trials showed survival benefit. Another taxane, docetaxel, given in combination with anthracyclines rather than sequentially, showed a 6% five year survival advantage over anthracyclines alone. Results of other adjuvant taxotere trials are awaited, including the British taxotere as adjuvant chemotherapy trial (TACT), which is one of the largest in the world. Taxane has not been shown to benefit women with node negative cancer.

The CALGB 9741 (cancer and leukemia group B 9741) trial of accelerated (sometimes called dose dense) chemotherapy gave treatment at two week rather than three week intervals, with support from granulocyte colony stimulating factor (G-CSF) to overcome the risk of neutropenic sepsis. It showed that accelerated two-weekly doxorubicin and cyclophosphamide for four cycles followed by paclitaxel for four cycles improved disease free survival and overall survival over the same eight courses given conventionally at three week intervals in women with node positive breast cancer, with four year disease free survival of 82% and 75% respectively. In addition, the accelerated arm of the trial was associated with less neutropenic sepsis. The shortened duration of adjuvant treatment associated with accelerated chemotherapy will probably be attractive to patients, and the reduced risk of neutropenic sepsis may save resources. Further trials in this area are needed.

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Disease free (top) and overall (bottom) survival in a randomised study of adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) compared with fluorouracil, doxorubicin, and cyclophosphamide (FAC). Adapted from Martin M. *N Engl J Med* 2005;352:2302-13

Data from CALGB 9741 study of dose density disease free survival by dose density (top), and overall survival by dose density (bottom). Adapted from Citron M, et al. *J Clin Oncol* 2003;21:1431-9

Chemotherapy with hormonal therapy

Data indicate that using chemotherapy and tamoxifen sequentially is more effective than using either alone for women with high risk oestrogen receptor positive cancer. Results indicate that efficacy is greater when tamoxifen is given after chemotherapy rather than concurrently. No data exist on whether the same is true for ovarian ablation or aromatase inhibitors, but it would seem prudent to assume so.

A retrospective analysis indicated that premenopausal women (< 40 years) who undergo amenorrhoea induced by chemotherapy have a better outlook than those who continue to menstruate. This raises the possibility that ovarian suppression may be beneficial after chemotherapy if menses persist, but this must be balanced against the side effects of the menopause. Several ongoing trials have been established to clarify the role of ovarian function suppression with chemotherapy, tamoxifen, and an aromatase inhibitor in premenopausal women with endocrine responsive disease.

High dose chemotherapy with haemopoietic stem cell rescue

Trials show high morbidity and no benefit from this approach, in contrast to progress with new drugs and accelerated techniques using haemopoietic support with GCSF.

Trastuzumab

Around 20% of breast cancers overexpress HER2, and this is associated with an adverse prognosis. Trastuzumab is a humanised monoclonal antibody directed against the external domain of the receptor with clinical activity as a single agent in patients whose cancers overexpress HER2. More importantly, trastuzumab improves survival when given in combination with paclitaxel and docetaxel in patients with metastatic disease, and it achieves high rates of tumour regression with other drugs including vinorelbine. Trials have explored its use as adjuvant treatment in HER2 positive early breast cancer, and found a substantial improvement in disease free survival and overall survival. Trastuzumab is becoming a common component of adjuvant treatment programmes for most women whose tumours overexpress HER2.

Bisphosphonates

Bisphosphonates are drugs that inhibit osteoclast mediated bone resorption induced by tumours. Some adjuvant trials indicate that two years of oral clodronate reduces the incidence of bone metastases. One trial showed a small, but significant, improvement in overall survival. Further trials are underway with clodronate and the newer, more potent bisphosphonate zoledronate to define their long term effectiveness. Bisphosphonates seem to reduce the bone loss associated with use of aromatase inhibitors. Patients who receive an immediate aromatase inhibitor should have a baseline dual energy x ray absorptiometry scan to check bone density and a follow-up scan after two years. They should also be considered for bisphosphonate treatment if there is osteoporosis at diagnosis or major bone loss during treatment.

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Disease free survival from the HERA (herceptin adjuvant) trial that randomised 5100 women to standard adjuvant therapy (with or without three weekly trastuzumab for one or two years). Data shown to relate to patients that received one year of treatment. (DFS=disease free survival). Presented at the American Society Clinical Oncology, 2005

St Gallen consensus recommendations of adjuvant treatment for patients with operable breast cancer*

Risk group	Endocrine responsive	Endocrine response uncertain	Endocrine non-responsive
Low risk	Endocrine treatment or none	Endocrine treatment or none	Not applicable
Intermediate risk	Endocrine treatment alone or chemotherapy followed by endocrine treatment†	Chemotherapy followed by endocrine treatment†	Chemotherapy
High risk	Chemotherapy followed by endocrine treatment†	Chemotherapy followed by endocrine treatment†	Chemotherapy

*Adapted from Goldhirsch A. et al. *Ann Oncol* 2005;16:1569-83.

†Some types of endocrine treatments apart from tamoxifen (which should be given sequentially) may be given concurrently with chemotherapy—for example, ovarian suppression.

Further reading

- Citron ML, Berry DA, Cirincione C, Hudis C, Winder EP, Gradisher WS, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukaemia Group B Trial 9741. *J Clin Oncol* 2003;21:1431-9
- Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-72
- Martin M, Pienkowski T, Mackey J, Pavlik M, Guastalla JP, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005;352:2302-13
- Henderson IC, Berry DA, Demetri GD, Cirincione C, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003; 21:976-83

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