Systemic adjuvant therapy of breast cancer

Breast cancer treatment is one of the success stories of our time.

IRENE BOEDDINGHAUS, ***MB ChB, MD, MRCP***
UCT Private Academic Hospital, Cape Town

Irene Boeddinghaus qualified at the University of Cape Town. She did her specialist training in Medical Oncology in London, and obtained an MD from the University of London in Biochemical Endocrinology (looking at aspects of hormonal treatment of postmenopausal breast cancer). She works in private practice in a two-woman partnership where her interest is breast diseases including breast cancer.

Disease-free breast cancer patients and overall survival have increased markedly over the last 30 years owing to a greater understanding of the pathophysiology of the disease and the consequent improved use of available standard agents, as well as the development of new targeted treatments. However, half a million people worldwide die annually of breast cancer, and many challenges remain.

What is adjuvant treatment?

- It is treatment given after definitive surgical management.
- It is intended to eradicate *micro*metastases (Figs 1a and b).

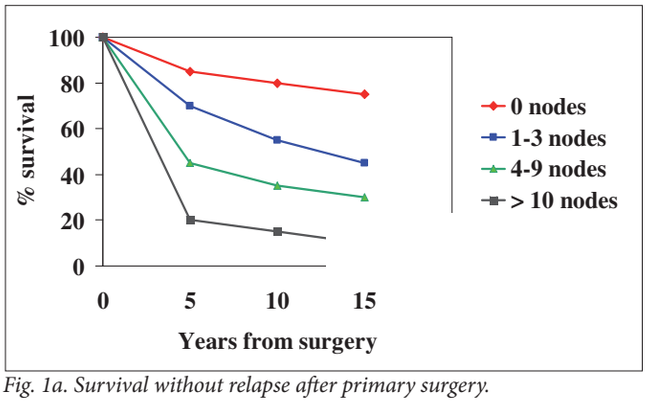

Fig. 1a. Survival without relapse after primary surgery.

- In breast cancer adjuvant treatment may consist of cytotoxic chemotherapy, radiotherapy, and targeted therapy, e.g. trastuzumab (Herceptin) and hormonal therapy, alone or in combination. The role of radiation treatment to the breast and surrounding area (and the systemic effect of this local treatment) is covered elsewhere in this edition of *CME*.

Who gets what?

- Breast cancer is not a uniform disease.
- Our understanding of the various types of breast cancer and how these cancers react to treatment is at best incomplete.
- This, then, is the oncologist's dilemma, and among treating oncologists there will probably be as many opinions and treatment plans as there are doctors.

Decision-making guides

Decision-making guides include:

- The biannually published St Gallen Update,[1] which stratifies patients into high-, medium- or low-risk categories, with consequent treatment recommendations (Fig. 2). However, this is based on risk, and not on likelihood of response, and therefore has little meaning for the individual patient.
- The website Adjuvant!Online (www.adjuvantonline.com/index.jsp), which allows more personal risk stratification, but it too is statistically derived.

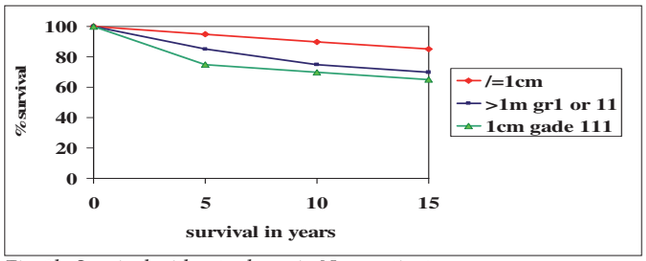

Fig. 1b. Survival without relpase in N-ve patients.

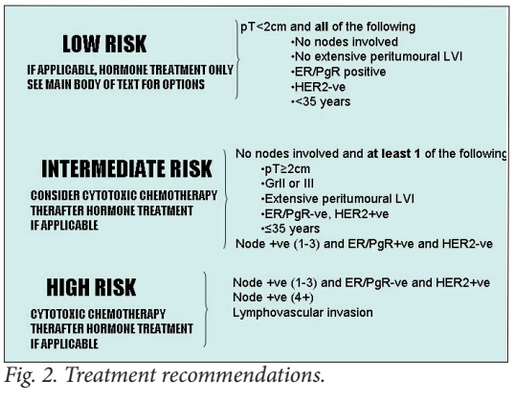

Fig. 2. Treatment recommendations.

Currently many people undergo burdensome cytotoxic chemotherapy of no benefit to them, either because they are already cured, or because they will relapse despite treatment. Conversely, some who would benefit are denied treatment because they are perceived to be low-risk patients. It is hoped that this will change in the near future with the validation of tumour genetic testing. At least one such test is commercially available in South Africa, but the results of confirmatory trials are still outstanding and full-scale implementation is premature.

Cytotoxic chemotherapy

- The days of 'one size fits all' approach have passed. The choice of agent and method of administration depend on tumour and patient characteristics.
- Furthermore, since patients are expected to live 30 - 40 years after treatment, the sequelae of blunderbuss treatment must be taken into account.

Table I. Commonly used drugs and their combinations

Anthracyclines	Alkylating agents	Anti-metabolites	Taxanes	Common combinations
Epirubicin (E)	Cyclophosphamide (C)	5-fluorouracil (F)	Docetaxel (T)	CMF
Adriamycin (A)			Paclitaxel (P)	AC followed by T
				FEC
				FEC followed by T
				CAF
				TAC
				FEC followed by P

- Adjuvant treatment is generally given as 4 - 6 cycles (sometimes more) at 3-weekly intervals. This allows for recovery of normal tissue, but not of mutated, less resilient cancer cells (Fig. 3).

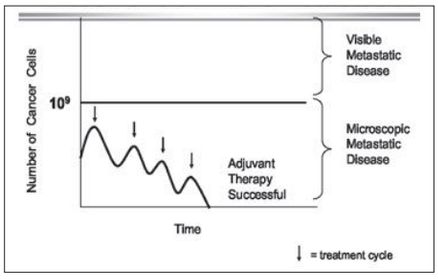

Fig. 3. Treatment of micrometastases.

- Current, commonly used drugs and their combinations are shown in Table I.
- At least part of the benefit derived from chemotherapy in older premenopausal patients comes from the effect on the ovaries.
- Anthracyclines should be used with caution in patients with cardiac compromise, and patients should have their cardiac reserve checked by multiple-gated arteriography (MUGA) or echocardiography scan before commencing chemotherapy.
- More recently it has been shown that the benefit associated with anthracyclines is probably limited to a small minority of patients and it is possible that in future many patients will probably not need treatment with these drugs.

The side-effects of commonly used cytotoxic drugs in breast cancer are listed in Table II.

Modern anti-emetics have largely brought under control intractable nausea and vomiting, but myelosuppression still has an associated mortality rate, and most medical aid plans will not contribute towards prophylactic granulocyte-stimulating colony factors with standard regimens. Febrile neutropenia requires prompt evaluation, and usually admission for broad-spectrum intravenous antibiotics.

Targeted treatment

This is discussed in the article on trastuzumab (Herceptin) and novel therapies elsewhere in this edition of *CME*.

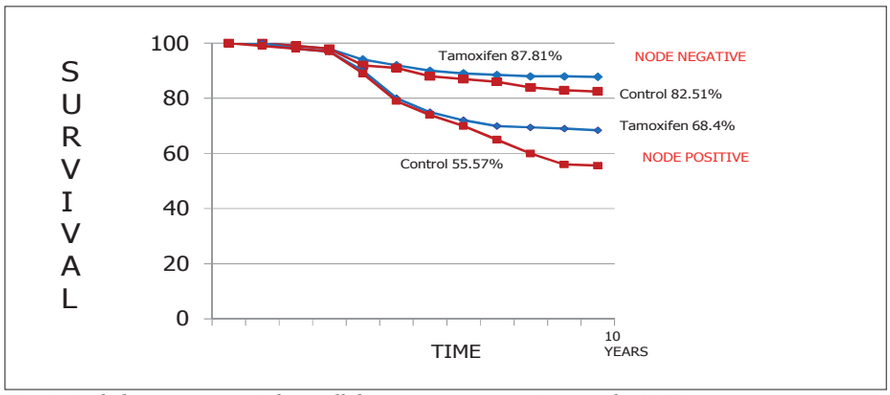

Fig. 4. Early breast cancer trialists collaborative group overview results 2005.

Hormonal treatment

For patients whose cancers are hormone-receptor positive, adjuvant treatment with one of the drugs available offers a potentially huge benefit with relatively few side-effects. The magnitude of this benefit is often under-appreciated by patients, with 5 years of adjuvant tamoxifen giving a 50% decrease in relapse rate over 10 years, and a decreased chance of death of 30% (Fig. 4).

Fig. 4 holds true (with minor adjustments) for pre-menopausal and post-menopausal women, and for node-negative and node-positive disease.[2] Hormonal treatment for 5 years has been shown to decrease contralateral breast cancer by up to 50%. Treatment can differ for pre- and post-menopausal women.

Premenopausal women

- Five years of adjuvant tamoxifen is still the gold standard. This should be commenced

Table II. Side-effects of commonly used cytotoxic drugs and treatment

Side-effect	Treatment
Neutropenia	Granulocyte-stimulating colony factors. Urgent full and differential blood count if associated fever or systemically unwell. Admit for investigations and broad-spectrum anti-biotics if febrile neutropenia
Alopecia (temporary)	Wig (do *not* use a cold cap, as constricted arterioles protect hair follicles at the expense of scalp relapse)
Nausea and vomiting	Potent anti-emetics prescribed in conjunction with chemotherapy. If still a problem, consider adding meto-clopramide, prochlorperazine pr (e.g. Stemetil) or oral steroids (e.g. Betanoid 4 - 8 mg tds)
Oral mucositis	Prevented by granulocyte-stimulating colony factors. Antiseptic mouthwashes and topical analgesics are useful. Rarely severe enough to require oral opioids
Diarrhoea	Loperamide HCl. Push fluids. Rarely (but occasionally) life-threatening. If in doubt, admit for IV rehydration. Can alternate with constipation. Be careful not to over-treat
Constipation	GIT motility agents. Can alternate with diarrhoea. Be careful not to over-treat
Thrombophlebitis and pain	Analgesics
Fatigue and lethargy	Rest
Headache, body pain	Analgesics

Table III. Side-effects of tamoxifen and treatment

Side-effect	Treatment
Hot flushes	Commonest side-effect, often partly caused by the effect of chemotherapy on the ovaries. Often abates spontaneously within the first year of treatment. Treat in the first instance with venlafaxine 75 mg od
Weight gain	Can be very distressing. Encourage healthy eating and exercise. Often partly caused by the onset of menopause together with chemotherapy
Fluid retention	Usually minor. Encourage exercise. Occasional judicious use of diuretics
Vaginal discharge	Common. Usually clear, colourless, odourless. Reassure only. If bloody, PV ultrasound in women with a uterus to check endometrial thickness
Endometrial thickening	Extremely rare. PV ultrasound in women with a uterus to check endometrial thickness. Requires hysterectomy
Nausea	Usually mild. If taking tamoxifen at night, consider taking it in the morning, and vice versa
Skin rash	Rare, but can be very itchy when it occurs. Antihistamines often unhelpful. Requires drug termination
Eye disturbances	A decrease in visual acuity and new cataracts require ophthalmic assessment
Venous thrombo-embolism	Use an aromatase inhibitor (see below) rather than tamoxifen if patient is at risk. Advise DVT stockings and aspirin/low-molecular-weight heparin on long-haul flights

after completion of chemotherapy (on the basis that cytotoxics kill dividing cells, and tamoxifen stops cells dividing).

The side-effects of tamoxifen are well described (Table III).

- Tamoxifen is classed as a SERM (selective oestrogen-receptor modulator), acting either as an agonist or antagonist, depending on cell-specific recruitment of helper molecules. Therefore tamoxifen is a partial agonist in bone (which expresses the oestrogen receptor), and endometrium. The latter is responsible for the increased incidence of endometrial cancer seen with long-term tamoxifen use. It is important that patients are made aware that the incidence of breast cancer recurrence far exceeds that of endometrial cancer.
- For those unable to tolerate tamoxifen, 2 - 5 years of a gonadotrophin-releasing hormone (GnRH) agonist depot subcutaneously, monthly or 3-monthly, is an alternative. This has been less well studied. Ovarian suppression together with tamoxifen is currently being researched in the Suppression of Ovarian Function Trial (SOFT). GnRH agonists have largely superseded permanent ovarian ablation by surgery or radiotherapy.

Postmenopausal women

The introduction of third-generation aromatase inhibitors (AIs), anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin) into the adjuvant setting has extended the treatment options for postmenopausal patients.

- These are extremely potent inhibitors of the enzyme responsible for the post-menopausal production of oestrogen in fat, muscle, the adrenal glands, and normal and cancerous breast tissue, resulting in the decrease of post-menopausal oestrogen to undetectable limits.
- This 20-fold decrease is enough to result in almost universal cell-cycle arrest in breast cancer cell lines *in vitro*. When these drugs are administered for 5 years to hormone-positive postmenopausal women, relapse rates are at least as good as, and in some cases better than, 5 years of tamoxifen.
- None has yet shown a survival benefit over tamoxifen in an intention-to-treat population.
- It is vital to establish incontrovertibly the patient's postmenopausal status, as women with residual ovarian function will be stimulated by these agents. This is particularly true for women rendered postmenopausal by cytotoxics, where recovery of ovarian function can occur 3 - 5 years later.

Recently, data have been published showing a statistically significant survival benefit for swapping from tamoxifen to exemestane at 2 - 3 years in centrally confirmed oestrogen receptor-positive, disease-free patients.[3] In the absence of contraindications, this approach is now recognised as the standard of care in South Africa. However, proponents of the 'AI upfront' approach argue that patients at high risk of early relapse are disadvantaged by this approach as they are likely to have relapsed before it is time to switch. Much has been published about which patient to treat with which AI, and when, but the differences between them are likely to be minor. Until trials mature, treatment should be guided by contraindications and cost profile.

Table IV. Side-effects of third-generation AIs and treatment

Side-effect	Treatment
Osteoporosis	All patients require a bone densitometry test before commencing AIs. Do not commence AIs in patients with t-scores <-1.5 or with significant other risks for osteoporotic fractures. All patients to be given calcium supplements. Bisphosphonates work well, but new-generation drugs (more potent, fewer side-effects) are not licensed for this indication. Almost all bone loss occurs in first 2 years
Joint and muscle pain	Can be quite debilitating. Occasionally swapping from one drug to another will resolve the problem. NSAIDs help. Some fish oils may help
Vaginal dryness, loss of libido, bladder symptoms	Seek these symptoms actively, as many patients are reluctant to mention them. Can be very distressing.[4] Non-hormonal lubricants (e.g. Replens) may help. Do not use topical oestrogen replacement without seeking expert oncological opinion. Testosterone not effective for low libido unless there is an associated low testosterone level
Venous thrombo-embolism	Less than with tamoxifen. Use preferentially when risk is increased
Hot flushes	See Table III
Weight gain	Less than with tamoxifen
Hypercholestrolaemia	Use with caution in patients with abnormal lipid profile. Monitor and treat accordingly. Tamoxifen probably preferable in these patients

The side-effects of all the third-generation AIs are roughly the same (Table IV).

- Node-positive postmenopausal patients who have completed 5 years of adjuvant tamoxifen should be offered extended adjuvant treatment with 2 years of letrozole, unless contraindicated. This approach offers substantial benefit,[5] and has been shown to be effective in women up to 24 months after completion of adjuvant tamoxifen.

References

1. Goldhirsch A, Wood W, Gelber R, *et al.* Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 2007; 18(7): 1133-1144.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365: 1687-1717.
3. Coombes RC, Hall E, Gibson LJ, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; 350: 1081-1092.
4. Fallowfield L, Cella D, Cuzick J, *et al.* Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol* 2004; 22: 4261-4271.
5. Goss PE, Ingle JN, Martino S, *et al.* Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; 97: 1262-1271.

In a nutshell

- Breast cancer is not a uniform disease.
- Patients are therefore prescribed one of a multitude of differing adjuvant regimens.
- Treatment decisions may not be ideal and are currently based on risk, not likelihood, of response.
- Different cytotoxics have markedly different side-effect profiles.
- Febrile neutropenia requires prompt evaluation and usually admission for intravenous antibiotics.
- Trastuzumab (Herceptin) is only effective in those who over-express the HER2 receptor – approximately 25% of early breast cancer cases. It has few side-effects.
- Adjuvant hormone treatment differs in pre- and postmenopausal women.
- Five years of tamoxifen is still the gold standard for oestrogen receptor/progesterone receptor-positive premenopausal patients.
- Postmenopausal women require either tamoxifen or an aromatase inhibitor or both in sequence.