Pergamon

European Journal of Cancer Vol. 31A, No. 11, pp. 1754–1759, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00479-3

Meeting Highlight

Fifth International Conference on Adjuvant Therapy of Breast Cancer St Gallen, March 1995

The old city nucleus of St Gallen/Eastern Switzerland, with the courtyard of the old Carolingian Abbey, the baroque Gallus Cathedral to the left and the Gothic St Laurenzen Church to the right.

International Consensus Panel on the Treatment of Primary Breast Cancer*

A. Goldhirsch, W.C. Wood, H.-J. Senn, J.H. Glick and R.D. Gelber

INTRODUCTION

BREAST CANCER is a heterogeneous disease. The choice of primary treatments available today is based on features of the patient, the tumour, and the response to treatment. We have learned that the medical and social environment within which patients are being treated contribute to this heterogeneity with respect to the interpretation of available data on prognosis and cost–benefit of treatments. All of our knowledge about the selection of therapies is derived from results of case series and randomised clinical trials. Randomised clinical trials provide unbiased evidence of relative treatment efficacy on a *selected* patient population. A meta-analysis of randomised clinical trials is extremely effective in reducing statistical uncertainty.

In March 1992, the Consensus Panel of experts at the 4th

International Conference on Adjuvant Therapy of Primary Breast Cancer in St Gallen, Switzerland, developed a series of guidelines and recommendations for the selection of treatments in several patient populations [1, 2]. These guidelines and recommendations were mainly based upon the synthesis of results from individual clinical trials, and the findings from the Worldwide Overview [3] that had been made public a few months before the conference. Since then, there has been a shift in the proportion of women who are considered candidates for adjuvant therapy as a result of the statistically significant effects of chemotherapy, tamoxifen, and ovarian ablation identified in the overview.

During the past 3 years, several new concepts and treatment strategies have been studied. Some of these can be considered to assist in the treatment of patients today, while others are still undergoing clinical investigation for a better definition of their usefulness. Table 1 describes some examples of these findings and their implications or status relative to patient care. These subjects were presented and discussed at the 5th International Conference on Adjuvant Therapy of Primary Breast Cancer held in St Gallen, Switzerland, in March 1995. At the last session a panel of experts discussed prognostic and predictive factors, treatments for ductal carcinoma *in situ* (DCIS) and small screening-detected tumours, and controversial issues related to the adjuvant treatment of node-negative and node-positive breast cancer. In this commentary, we describe some areas of ongoing research and update the treatment recommendations presented 3 years ago.

PROGNOSIS AND PREDICTION OF RESPONSE

Several factors have been identified attempting to define the prognosis of patients who should not receive any form of adjuvant systemic therapy. The panel agreed that a population of patients having less than 10% mortality at 10 years would not be candidates for receiving routine adjuvant systemic therapy. All other patients could benefit from additional postoperative therapy. Consequently, evaluating the prognosis of patient subgroups today is relevant only within the context of the adjuvant treatments received.

Factors predicting treatment response are those which identify patient subpopulations having a larger or smaller response to a given systemic treatment. Estimating the magnitude of the treatment effect is important for determining the usefulness of a given treatment approach. The *P*-value only indicates the strength of evidence against a null hypothesis and is not a measure of the magnitude of treatment effect. Consequently, a factor which appears to distinguish responders from non-responders based on the calculated *P*-values may, in fact, predict a quantitative difference in response which is positive for all subpopulations. Evidence of an interaction between treatment group assignment and a potential treatment response prediction factor is required to justify selective withholding of therapy, when an overall result is positive. Randomised clinical trials, which include a large number of study patients, are required to adequately define these factors for clinical use.

The distribution of initial presentations of breast cancer diagnosed in recent years has changed. The incidence of non-invasive tumours and small, screen-detected invasive cancers is increasing. Table 2 includes these two types of presentation as distinct categories in addition to the node-negative and node-positive subpopulations. In addition, Table 2 shows the prognostic factors used to define candidates for some form of adjuvant therapy and the predictive factors used to "fine tune" the treatment selection based on considerations of relative effectiveness of available therapeutic regimens.

DUCTAL CARCINOMA *IN SITU* (DCIS)

The primary treatment of non-invasive DCIS requires clarification. Patients with DCIS should have breast surgery similar to that of invasive cancer—total removal of the primary tumour with clear resection margins. If it is not possible to achieve this goal, mastectomy is necessary. If there is no invasive component, no additional prognostic information is obtained by removal of the axillary lymph nodes. Therefore, axillary dissection is not indicated. Radiation therapy to the conserved breast after a complete surgical removal of a DCIS lesion showed a significant relative reduction (4-fold) of subsequent invasive tumour growth in the breast, although the number of such events occurring without radiation therapy was small (less than 10% within the first 5 years in the NSABP Trial B-17) [4]. Thus, cost–benefit considerations should be used for deciding whether radiation is indicated to reduce the risk of a relatively rare event. Randomised clinical trials are currently underway to better define patient, tumour, and surgical treatment characteristics that could influence the selection of radiation therapy in this setting. There is no indication for systemic adjuvant therapy for patients presenting with DCIS alone at the present time. Ongoing trials will clarify the role of therapy with tamoxifen to reduce the risk of invasion and relapse in this patient population.

SMALL, SCREENING-DETECTED INVASIVE TUMOURS

The surgical treatment of these tumours (detected by screening mammography only and usually smaller than 1 cm) should follow the general guidelines for treating breast cancer—total removal of the malignant lesion with clear margins. The issue of whether axillary clearance may be avoided is still controversial since some of the patients will have lymph node involvement. In fact, the prognostic information derived from the histopathological examination of the lymph nodes is important for defining prognosis and treatment selection. Radiation therapy to the conserved breast is indicated, since data are not available to select a subpopulation of patients who will not significantly benefit from the application of this modality. Systemic treatment should be considered for all patients with factors indicating dire prognosis (e.g. node-positive presentation). For all other patients, the use of systemic therapy such as tamoxifen is still a matter of clinical research.

LYMPH NODE-NEGATIVE BREAST CANCER

During the past 3 years, a larger proportion of patients with node-negative breast cancer have been considered candidates for

Correspondence to A. Goldhirsch.
A. Goldhirsch is a member of the International Breast Cancer Study Group, Ospedale Civico, 6900 Lugano, Switzerland; W.C. Wood is at the Department of Surgery, Emory University School of Medicine, 1364 Clifton Road, N.E. Atlanta, Georgia 30322, U.S.A.; H.-J. Senn is at Medizinische Klinik C, Kantonsspital, 9007 St Gallen, Switzerland; J.H. Glick is at the University of Pennsylvania Cancer Center, 6 Penn Towers, 3400 Spruce Str., Philadelphia, Pennsylvania 19104-4283, U.S.A.; and R.D. Gelber is at the Dana-Farber Cancer Institute, 44 Binney Str, Boston, Massachusetts 02115, U.S.A. Other Consensus Panel participants: K. Antman, M. Baum, B. Fisher, J. Forbes, M. Kaufmann, J. Kurtz, H. Mouridsen, K. Pritchard and C.-M. Rudenstam.
*First published in the *Journal of the National Cancer Institute*, 4 October 1995, Vol. 87, No. 19.

Table 1. Recent research findings presented at the 5th International Conference on Adjuvant Therapy of Primary Breast Cancer and their implications for patient care

Field or treatment	Status of research/implications for patient care
Genetics	Isolation of *BRCA1*, description of *BRCA2*, evidence for the presence of *BRCA3* and *BRCA4*. Not ready for screening to define individual risk. Will present new challenges to manage severe personal, ethical, and therapeutic dilemmas, when widely available. Ongoing and future chemoprevention trials will have an important impact upon dealing with genetic information.
Timing of surgery for premenopausal women	Some data from retrospective series suggest that surgery on or during the luteal phase of the menstrual cycle is associated with a better prognosis compared with the follicular phase. This issue is controversial due to several studies which do not confirm these findings. Prospective investigations might clarify whether the endocrine environment which characterises the luteal phase is beneficial for reducing micrometastatic enhancement during and immediately after surgery.
Biological therapies, immunotoxins, antibodies and gene therapy	In preclinical and phase I/II clinical investigations, mainly in patients with advanced disease. Involving particularly growth factors and angiogenesis. Still to enter clinical trials in the adjuvant setting.
New factors for prediction of treatment responsiveness	*c-erbB2* expression for prediction of response to anthracycline-containing chemotherapy, and resistance to treatment with tamoxifen or CMF: results require confirmation in prospective randomised clinical trials. *Ki67* expression as marker for proliferation (substitute for tumour grading): results require confirmation and definition of cost and benefit.
Tamoxifen: definition of long-term effects	Increased risk of endometrial cancer by 2–4-fold. Overwhelmed by proven benefit with respect to breast cancer risk and overall survival advantage.
"Full dose" chemotherapy	Reduction of full dose chemotherapy, except according to objective toxicity guidelines, might be detrimental in terms of treatment results. This should influence patient care outside clinical trials. The use of haematopoietic growth factors is still experimental.
"High dose" chemotherapy	The administration of a 4–10-fold increase in chemotherapy dose with autologous bone marrow or peripheral blood progenitor cell support (with the aid of haematopoietic growth factors) is a promising approach for patients at high risk of relapse. The use of this modality outside the context of clinical trials is not justified pending results of randomised, controlled ongoing studies.
Taxanes	Found to be very effective in metastatic and locally advanced disease. The use of taxanes in the adjuvant setting outside the context of clinical trials is not justified pending results of ongoing studies.

Table 2. Presentation of breast cancer: categories with treatment implications

Disease presentation	Prognostic factors used in the definition of risk	Predictive factors used for the selection of adjuvant treatment
Non-invasive tumours: DCIS	Clear margins	None
Small invasive tumours: screening-detected	Nodal status	None
Node-negative (optimally at least 10 nodes examined)		
Minimal/low risk	Tumour size	Oestrogen receptors
"Good" risk	Grade	Age
"High" risk	Oestrogen receptors	Menopausal status
Node-positive	Number of nodes involved	Age Oestrogen receptors Menopausal status

Table 3. Definition of risk categories for patients with node-negative breast cancer

Factors	Minimal/low risk (all of the listed factors)	"Good" risk	"High" risk (at least one of the listed factors)
T-size*	<1 cm	1–2 cm	>2 cm
ER status†	Positive	Positive	Negative
Grade†	Grade 1 (uncertain relevance for tumours <1 cm)	Grade 1–2	Grade 2–3
Age‡	>35 years		

* It was generally agreed that pathological tumour size (of invasive component) was the most important prognostic factor for defining additional risk of relapse; † ER status and grade are expressions of the malignant transformation of the tumour cell, and it is difficult to precisely dichotomise these features to indicate a good versus bad prognosis; ‡ Patients who develop breast cancer at a young age are considered to be at high risk of relapse, although an exact age threshold for this increased risk has not been defined. While acknowledging this fact, the panel did not accept age as a factor to influence the choice of type of treatment (chemotherapy or endocrine therapy).

adjuvant systemic therapy. The accurate definition of a node-negative status requires that a sufficient number of axillary nodes be examined. Investigations focused on this staging subject indicated at least 10 lymph nodes as appropriate for obtaining the proper prognostic information [5]. Other methods for defining prognosis have not yet been able to provide sufficient information to substitute for axillary lymph node examination. Many of these methods investigate proliferation features of the primary tumour and its metastatic potential (e.g. micrometastases detected in the bone marrow). Neither ploidy nor S-phase was recommended for routine use.

The baseline prognosis of patients with node-negative disease can vary substantially, depending upon several features. Table 3 displays the factors contributing to the allocation of patients to risk categories.

Adjuvant treatment for patients with node-negative disease (Table 4) varies substantially according to the baseline prognosis. For patients considered at "high" risk, the treatment choice follows an algorithm similar to node-positive disease, considering that their prognoses are similar, if the node-negative population is untreated. For these patients the chemotherapy used in clinical trials, especially those included in the overview [3], was mainly a cyclophosphamide, methotrexate and 5-fluorouracil (CMF)-based regimen. The use of anthracyclines for these patients is currently undergoing investigation. For patients with minimal/low risk disease, the question of whether to treat with tamoxifen or not depends on a cost–benefit analysis which should take into account the low relapse rate within the first 10 years, and the potential reduction in the incidence of contralateral breast cancer which has been shown to occur. Patients classified as "good" risk may be assigned to receive an endocrine treatment with tamoxifen. For premenopausal women in this category, other forms of hormonal manipulations, including ovarian ablation and chemotherapy, remain investigational.

LYMPH NODE-POSITIVE BREAST CANCER

Treatment selection for patients with node-positive disease was extensively studied in previous years. During the past

Table 4. Adjuvant treatment for patients with node-negative breast cancer

Patient group	Minimal/low risk	"Good" risk	"High" risk
Premenopausal			
ER-positive	Nil versus Tamoxifen*	**Tamoxifen** Ovarian ablation* Chemotherapy* GnRH analogue*	**Chemotherapy** ± Tamoxifen* Ovarian ablation* GnRH analogue*
ER-negative	NA	NA	**Chemotherapy**
Postmenopausal			
ER-positive	Nil versus Tamoxifen*	**Tamoxifen**	**Tamoxifen** ± Chemotherapy*
ER-negative	NA	NA	**Chemotherapy** ± Tamoxifen*
Elderly	Nil versus Tamoxifen*	**Tamoxifen**	**Tamoxifen**; if ER-negative: **Chemotherapy** ± Tamoxifen*

NA, not applicable; GnRH, gonadotrophin releasing hormone; ER, oestrogen receptor; Nil, no adjuvant treatment. Treatments in "bold" accepted for routine use or baseline in clinical trials.

* Treatments still being tested in randomised clinical trials.

3 years, very little has changed with respect to treatment recommendations for this patient population. Table 5 shows the treatments available for patients with node-positive disease.

SPECIFIC ASPECTS OF TREATMENT

Ovarian ablation

The worldwide overview results [3] on ovarian ablation were obtained mainly from trials comparing this modality (surgical- or radiation-induced) to surgery alone. The 15 year follow-up presented in the overview was sufficiently convincing to include ovarian ablation as a clinically relevant treatment option. It had also emerged from data of trials with hormone receptor information that, as expected, ovarian ablation is likely to benefit exclusively patients with oestrogen-receptor (ER) positive primaries [6]. The trials of chemotherapy with or without ovarian ablation had a shorter follow-up, and therefore contributed less information to the overview. They seemed to indicate that oophorectomy added to chemotherapy may have an effect greater than chemotherapy alone. The combination, however, remains experimental, since trials comparing it with oophorectomy (or gonadotrophin releasing hormone [GnRH] analogues) alone are ongoing. The relatively small number of patients included into trials investigating oophorectomy (only 1817 patients younger than 50 years were included in the overview), the patient's psychological desire to avoid castration, and the concern about its late sequelae are the main reasons that this modality has not been very widely accepted.

Tamoxifen

The benefit from treatment with tamoxifen in terms of reduced incidence of relapse and mortality is clearly overwhelming. The risk related to uterine cancer is increased and varies among countries. It is, however, clear that a 3-fold increase in the incidence of endometrial cancer, which is below 1%, should be taken into account for postmenopausal women. The duration of treatment with tamoxifen should be between 2 and 5 years, and current trials compare durations of 5 and 10 years, or lifetime. New data will be available in the near future to establish the most beneficial duration of treatment with this drug.

Chemotherapy regimen

CMF combination chemotherapy given on days 1 and 8 every 4 weeks (with cyclophosphamide given either intravenously (i.v.) on the same days as M and F, or orally on days 1–14), or a similar combination chemotherapy is the treatment of choice for patients with node-negative disease. The CMF regimen or an anthracycline-based combination such as doxorubicin and cyclophosphamide (AC), or cyclophosphamide, doxorubicin, and fluorouracil (CAF), is considered to have similar treatment effects for patients with node-positive disease [7]. Data indicate that CMF should be given for the duration of six courses, while four courses of an anthracycline combination chemotherapy yield similar results [8].

Chemotherapy dose

Reducing the chemotherapy dose is detrimental in terms of treatment results. These are the convincing results of a randomised comparison between the full doses of a CAF regimen chemotherapy and a 50% dose reduction [9]. On the other hand, doubling the dose intensity of the alkylating agents in the AC regimen did not increase therapeutic yield [10]. Furthermore, the routine use of marrow growth factors to obtain an enhancement of dose intensity is still experimental.

Chemoendocrine therapies

The combination of cytotoxic agents, like doxorubicin and cyclophosphamide, and tamoxifen was associated with a better therapeutic outcome when compared with tamoxifen alone, especially in patients with tumours classified as ER-positive [11]. The best way to combine chemotherapy and tamoxifen is unknown, especially if the cytotoxic regimen does not include anthracyclines. In fact, laboratory studies demonstrated that chemotherapy cell kill was inhibited in the presence of tamoxifen [12]. Clinical data also suggest a negative interaction between cytotoxics (alkylating agents and 5-fluorouracil) and tamoxifen [13]. This issue, however, is still under study.

Table 5. Adjuvant treatment for patients with node-positive breast cancer

Patient group	Treatments
Premenopausal	
ER-positive	**Chemotherapy** ± Tamoxifen*
	Ovarian ablation ± Tamoxifen*
	GnRH analogue*
	Chemotherapy ± Ovarian ablation (GnRH analogue) ± Tamoxifen*
ER-negative	**Chemotherapy**
Postmenopausal	
ER-positive	**Tamoxifen** ± Chemotherapy*
ER-negative	**Chemotherapy** ± Tamoxifen*
Elderly	**Tamoxifen**; if ER-negative: **Chemotherapy** ± Tamoxifen*

GnRH, gonadotrophin releasing hormone; ER, oestrogen receptor.
Treatments in "bold" accepted for routine use or baseline in clinical trials.
* Treatments still being tested in randomised clinical trials.

High dose chemotherapy with peripheral blood progenitor cell or bone marrow support

There are several randomised trials currently being conducted to investigate this issue. Indirect evidence exists from two single institution phase II studies (Duke University, U.S.A. and the Milan National Cancer Institute, Italy) that this approach might be advantageous in terms of treatment results. Although these approaches are promising, they are very costly, and should, therefore, be used only in the context of randomised clinical trials. The validation of high dose chemotherapy is essential for best defining its indications and yield.

Taxanes

Taxanes have been tested in metastatic and locally advanced disease and their efficacy at least partially defined [14]*. There are, in fact, several open questions about the proper schedule of administration for these agents and about their association with other active cytotoxics, especially anthracyclines. The testing of taxanes in the adjuvant setting will be carried out in the near future. In the meantime, their use in adjuvant regimens outside of clinical trials is not indicated.

The elderly

Older patients with a long-term survival expectancy should be considered for adjuvant systemic therapies in the same way as younger postmenopausal patients. Extrapolating from data available from younger cohorts, it is stressed that, if chemotherapy is indicated, no lower dose of cytotoxics should be given. Lowering the dose intensity may slightly reduce the side-effects of the drugs, but unfortunately will compromise the treatment efficacy. Thus, adjuvant cytotoxics should be completely avoided rather than be given at a low dose, unless the low dose is given within the framework of a controlled clinical trial.

Hormone replacement therapy (HRT)

No data are available about the long-term safety of oestrogens given for menopausal symptoms to patients with a past diagnosis of breast cancer. Some information on the efficacy of progestins to relieve hot flashes has been generated, but the data are relatively short-term and do not relate to the safety of these compounds [15]. The use of HRT in this context remains an important matter for future investigation.

CONCLUSION

The panel members attempted to answer many questions related to the best use of treatments investigated in randomised clinical trials. They were convinced, however, that much more progress could be achieved if participation in clinical trials became more acceptable to the public as well as to the medical community. Treatment advances, even those of modest magnitude, will have an important influence on breast cancer mortality and/or patients' quality of life because of the high incidence of the disease.

* This review paper was published after the Meeting, during the preparation period of the manuscript, and was added for clarity and completeness.

1. Glick JH, Gelber RD, Goldhirsch A, Senn H.-J. Meeting highlights: adjuvant therapy for primary breast cancer. *J Natl Cancer Inst* 1992, **84**, 1476–1485.
2. Glick JH, Gelber RD, Goldhirsch A, Senn H.-J. Adjuvant therapy of primary breast cancer. *Ann Oncol* 1992, **3**, 801–807.
3. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment for early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992, **339**, 1–5, 71–85.
4. Fisher B, Constantino J, Redmond C, *et al.* Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993, **328**, 1581–1586.
5. Axelsson CK, Mouridsen HT, Zedeler K for the Danish Breast Cancer Cooperative Group (DBCG). Axillary dissection of level I and II lymph nodes is important in breast cancer classification. *Eur J Cancer* 1992, **28A**, 1415–1418.
6. The International Breast Cancer Study Group. Late effects of adjuvant oophorectomy and chemotherapy upon pre-menopausal breast cancer patients. *Ann Oncol* 1990, **1**, 30–35.
7. Shapiro CL, Henderson IC. Late cardiac effects of adjuvant therapy: too soon to tell? *Ann Oncol* 1994, **5**, 196–198.
8. Fisher B, Brown AM, Dimitrov NV, *et al.* Two months of doxorubicin–cyclophosphamide with and without interval reinduction therapy compared with six months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol* 1990, **8**, 1483–1496.
9. Wood WC, Budman DR, Korzun AH, *et al.* Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *N Engl J Med* 1994, **330**, 1253–1259.
10. Dimitrov N, Anderson S, Fisher B, *et al.* Dose intensification and increased total dose of adjuvant chemotherapy for breast cancer (BC): findings from NSABP B-22. *Proc Am Soc Clin Oncol* 1994, **13**, 64 (abstr. 58).
11. Fisher B, Redmond C, Legault-Poisson S, *et al.* Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the National Surgical Adjuvant Breast & Bowel Project B-16. *J Clin Oncol* 1990, **8**, 1005–1018.
12. Osborne CK. Interactions of tamoxifen with cytotoxic chemotherapy for breast cancer. In Jordan VC, ed. *Long Term Tamoxifen For Breast Cancer*. Wisconsin, The University of Wisconsin Press, 1994, 181–198.
13. Fisher B, Redmond C, Brown A, *et al.* Adjuvant chemotherapy with and without tamoxifen: five-year results from the National Surgical Adjuvant Breast and Bowel Project Trial. *J Clin Oncol* 1986, **4**, 459–471.
14. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med* 1995, **332**, 1004–1014.
15. Loprinzi CL, Michalak JC, Quella SK, *et al.* Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994, **331**, 347–352.

Notes—Other consensus panel participants: Karen Antman (Columbia-Presbyterian Hospital, New York, NY). Michael Baum (Royal Marsden Hospital NHS Trust, London, U.K.), Bernard Fisher (University of Pittsburgh School of Medicine, PA), John Forbes (University of Newcastle, Hunter Oncology Center, Waratah, Australia), Manfred Kaufmann (University of Heidelburg, Federal Republic of Germany), John Kurtz (University of Geneva, Switzerland), Henning Mouridsen (Rigshospitalet, Copenhagen, Denmark), Kathleen Pritchard (Toronto-Bayview Regional Cancer Center, Ontario, Canada) and Carl-Magnus Rudenstam (Sahlgren's Hospital, Göteborg, Sweden).

A. Goldhirsch is chairman of the Scientific Committee of the International Breast Cancer Study Group, a foundation (Swiss by-laws) dedicated to clinical research in the field of adjuvant treatment of breast cancer.