*Eur J Cancer Clin Oncol*, Vol. 24, No. 1, pp. 3–8, 1988.
Printed in Great Britain

0277–5379/88$3.00+0.00
Pergamon Journals Ltd.

# Activities of the EORTC Breast Cancer Co-operative Group: an Overview

J. WILDIERS,* K. VANTONGELEN,* J.A. VAN DONGEN,† N. ROTMENSZ,‡ R. SYLVESTER‡ and the members of the Group§

**U.Z. St. Rafael, Kapucijnenvoer 35, 3000 Leuven, Belgium, †The Netherlands Cancer Institute, Amsterdam, The Netherlands and ‡EORTC Data Center, 125 Bd de Waterloo, 1000 Brussels, Belgium*

## INTRODUCTION

THE EORTC Breast Cancer Co-operative Group was created in 1962 by oncologists from various European countries, with the aim of performing clinical research in breast cancer. The history and activities of the group between 1962 and 1982 were described in 1983 [1]. This paper will present a summary of the present activities of the group and of the recently closed studies.

Fourteen active and 17 probational member institutions from 11 countries currently participate in 10 active protocols, dealing with every stage of the disease. Recent activities of the group have also resulted in collaboration with different disciplines, involved in the field of breast cancer, namely diagnostic radiology, epidemiology and pathology.

Intensive collaboration has been realized with other EORTC cooperative groups, especially the Radiotherapy Group and the Quality of Life Study Group.

## ORGANIZATION

Formal statutes describe the aims and organization of the Breast Cancer Co-operative Group (BCCG).

The BCCG is fundamentally a multidisciplinary organization, performing prospective studies on the treatment of breast cancer. The group works in close collaboration with the EORTC Data Center, where the administrative and statistical aspects of the studies are performed and centralized.

Members of the group are institutions, who can be probational or active members. New probational members are elected for 2 years, and they are expected to contribute at least 10 evaluable patients per year to acquire full membership. Rules for publications and authorship are laid down in the statutes.

## STUDIES IN STAGE I AND II OPERABLE DISEASE

*Trial* 10801*; phase III randomized clinical trial to assess the value of breast conserving therapy in Stage I and II breast cancer. Study Coordinators: J.A. van Dongen, H. Bartelink, The Netherlands Cancer Institute, Amsterdam* [2]

This study was activated in December 1980 and closed in June 1986. 902 patients have been entered in the study, 157 Stage I and 745 Stage II patients.

Patients are randomized to undergo either a modified radical mastectomy, or a local excision with axillary dissection and intensive radiotherapy, consisting of external irradiation 50 Gy in 5 weeks in 25 fractions, followed by a boost of 25 Gy with iridium or external irradiation.

The review of pathology and radiology material is ongoing. Preliminary results were presented at this meeting. So far no differences are seen in local recurrence rate and survival. Quality of life studies are an important part of the trial. The study remains open to follow-up.

*Trial* 10850–10851; *two separate phase III trials on operable breast cancer in the elderly. Study Coordinator: I.S. Fentiman, Guy's Hospital, London, U.K.* [3]

This double study was activated in parallel in September 1985 and is still open. Thirty-eight patients have been entered in study 10850 and 30 in study 10851.

In study 10850, patients are randomized to modified radical mastectomy (MRM) or tumorectomy with tamoxifen.

In study 10851 modified radical mastectomy is compared to tamoxifen alone. Operable breast

§Active and probationary members are listed in Tables 1 and 2.

cancer patients are eligble if they are 75 years or older and fit enough to undergo general anesthesia. Patients entered in the tamoxifen arm who develop local progression or recurrence in the breast are treated by MRM. Thirteen institutes are participating. They can enter patients in 10850 or in 10851, but not in both.

*Trial* 10853*: a phase III randomized trial of treatment options for ductal carcinoma* in situ *of the breast (DCIS). Study Coordinator: I.S. Fentiman* [4]

Activated in January 1986, this trial is still open and 30 patients have been entered until now. The aim of this study is to determine the value of external irradiation to the breast after wide excision of DCIS. Patients are randomized to observation or to external radiotherapy 50 Gy. The EORTC Breast Group Pathology Panel will review the biopsy specimens and radicality of the excision.

This protocol is conducted in co-operation with the EORTC Radiotherapy Group.

*These four studies explore a number of important issues in the primary treatment of breast cancer. The breast conserving therapy was the subject of a large trial, and this methodology will be further explored in the future. Different treatment schedules will be compared.*

*In the treatment of elderly patients and in ductal* in situ *carcinoma the trials explore the possibilities of reducing the intensity and the toxicity of treatment. Co-operative studies are especially useful in rare forms of the disease; the group is in the process of organizing trials on lobular carcinoma* in situ *and in Paget's disease.*

## ADJUVANT THERAPY

*Trial* 10854*: a phase III trial of perioperative adjuvant chemotherapy in operable breast cancer. Study Coordinator: C.J.H. van de Velde, AZ Leiden, The Netherlands* [5]

Activated in June 1986, 300 patients have entered this study which is still open. Patients with operable breast cancer are randomized to receive either no chemotherapy or chemotherapy (FAC) on the first postoperative day.

Rules for additional chemotherapy in node positive patients are standardized in the protocol.

## LOCALLY ADVANCED DISEASE

*Trial* 10792*: controlled trial to assess the contribution of cytotoxic chemotherapy and/or endocrine therapy to the primary treatment of locally advanced breast cancer by radiotherapy. Study Coordinators: R.D. Rubens, J.L. Hayward, Guy's Hospital, London, U.K.* [6]

From December 1979 to November 1985, 410 patients entered this study. Patients with locally advanced breast cancer were randomized to treatment by either (1) radiotherapy alone; (2) radiotherapy with endocrine therapy (ovarian ablation + prednisolone in premenopausal, tamoxifen in postmenopausal); (3) radiotherapy with 12 cycles of a combination of cyclophosphamide, methotrexate and fluoro· racil; (4) radiotherapy + endocrine therapy + chemotherapy.

Endocrine treatment and chemotherapy each significantly delay time to local recurrence. For time to distant metastases and survival the effects are much less marked, and at present only significant for the effect of endocrine treatment on survival. The definitive analysis awaits further follow-up.

*In the field of adjuvant systemic therapy, the group chose to study new treatment modalities in early disease. In locally advanced disease effect of adjuvant endocrine and cytotoxic therapy is prospectively studied.*

## STUDIES IN ADVANCED DISEASE

*Trial* 10811: *adriamycin vs. 4-epi-adriamycin. A randomized phase III study in advanced breast cancer. Study Coordinator: A.T. van Oosterom, U.Z. Antwerpen, Belgium* [7,8]

From June 1982 to June 1986, 259 patients were entered in this study by 10 institutions.

An extensive extra-mural review was performed. Recent analysis revealed no significant differences in response rate, duration of remission or in duration of survival between the two drugs. The cardiac toxicity analysis will be performed in association with the EORTC Soft Tissue and Bone Sarcoma Group.

*Trial* 10808*: 'classical' CMF vs. 3-weekly intravenous CMF in postmenopausal patients with advanced breast cancer. Study Coordinator: E. Engelsman, The Netherlands Cancer Institute, Amsterdam, The Netherlands* [9]

Between June 1981 and May 1984, 333 postmenopausal patients with advanced breast cancer were randomized to receive CMF (cyclophosphamide, methotrexate, fluorouracil) as their first chemotherapy, either as classical CMF or as CMF intravenously. This study is closed and completed.

The results of this study clearly indicated higher response rates for the classical scheme. The expected advantages of the intravenous schedule were not confirmed.

*Trial* 10852*: short vs. long-term CMF in postmenopausal patients with advanced breast cancer. A phase III study. Study Coordinator: M.A. Nooij, AZ Leiden, The Netherlands* [10]

Since December 1985, 100 patients have been entered in this study which is still open for accrual. After induction treatment of 6 cycles of CMF, all patients who are not showing progressive disease are randomized to continuous treatment until relapse, or discontinuation of the treatment until

relapse. The aim of the study is to examine if intermittent therapy influences the duration of response and/or survival. The ultimate aim is to decrease the toxicity of the treatment.

*Trial* 10871: *a randomized phase II trial of doxorubicin in different dosages and schedules for advanced breast cancer, used as second line in CMF refractory patients. Study Coordinator: M.A. Nooy, AZ Leiden, The Netherlands*

Patients with progressive disease are randomly allocated to receive classical adriamycin in a 3-weekly scheme or low dose adriamycin weekly. Antitumor activity and the toxic effect of doxorubicin in a low dose and standard dose are studied. The trial was activated in June 1987 and is conducted according to the phase II study-master protocol for the screening of anthracycline dosages and analogues.

*In these four chemotherapy trials, the group studied one new agent and different schedules of therapy aiming essentially to reduce treatment toxicity.*

*Trial* 10832: *comparison between alternating and sequential administration of three non-cross-resistant chemotherapy regimens in combination with tamoxifen in advanced breast cancer. A phase III trial. Study Coordinator: R. Paridaens, Inst. Bordet, Brussels, Belgium* [11]

Open since January 1984, 131 patients have been included in this study, which remains open for accrual. Patients with advanced breast cancer are randomized to sequential or alternating administration of three non-cross-resistant chemotherapy regimens: (1) CMF regime: cyclophosphamide, methotrexate, fluorouracil; (2) ADM–DBD regime: doxorubicin, dibromodulcitol; (3) DDP–VDS regime: cisplatin, vindesine.

*Trial* 10835: *assessment of cyclic combination chemotherapy with estrogenic recruitment in advanced breast cancer. Phase III and double blind trial. Study Coordinator: R. Paridaens, Inst. Bordet, Brussels, Belgium* [12]

Activated in August 1983, 166 patients have been entered in this study, which remains open for accrual. To be eligible, patients must have hormone-dependent (steroid receptor +) advanced disease. The endocrine part of the regimen consists of deep and prolonged estrogen suppression by castration in premenopausal patients, and aminoglutethimide and hydrocortisone. Chemotherapy with FAC is given as a bolus injection every 3 weeks: fluorouracil, adriamycin, cyclophosphamide. Exactly 24 h before the chemotherapy either a placebo or ethinyloestradiol is administered. This trial studies the effect of estrogenic recruitment.

*The two preceding studies introduce new concepts in the treatment of advanced disease, aiming at improvement of the therapeutic results.*

*Trial* 10802: *oral medroxyprogesterone acetate (MPA) treatment of postmenopausal patients with advanced breast cancer. An evaluation of the dose–response relationship at two dose levels. A phase III trial. Study Coordinator: C. Rose, Finsen Institutet Copenhagen, Denmark* [13]

From September 1980 to October 1983, 316 patients with advanced disease, resistant to prior cytotoxic and endocrine therapy, entered this study. The patients were randomized to two dose levels of oral MPA: 300 and 900 mg daily. No significant difference was demonstrated between the two dose levels.

*Trial* 10834: *a randomized phase II study assessing the value of aminoglutethimide (AG) vs. Trilostane vs. medroxyprogesterone acetate (MPA) vs. hydrocortisone (HC) in patients with advanced breast cancer. Study Coordinator: C. Rose, Finsen Institutet Copenhagen, Denmark* [14,15]

Between October 1983 and November 1985, 192 postmenopausal patients with advanced breast cancer were randomly allocated to receive either AG +HC or MPA or trilostane+HC or HC alone. Time to progression was comparable in the four groups. Side-effects were more pronounced in the trilostane + HC group.

*Trial* 10861: *a randomized phase II study in postmenopausal patients with advanced breast cancer assessing the value of different doses of aminoglutethimide (AG) with or without the addition of hydrocortisone (HC). Study Coordinator: C. Rose, Finsen Institutet Copenhagen, Denmark* [16]

Activated in September 1986, 47 patients have been entered in this study, which remains open. Patients are randomized to receive either a medium dose or a low dose of AG with or without HC or HC alone. The aim is to evaluate in a randomized study the endocrine effects, the tumor response and the side-effects of low dose AG with or without HC.

*Trial* 10863: *continuous tamoxifen (TAM) vs. intermittent TAM vs. alternating TAM and medroxyprogesterone acetate (MPA). First-line endocrine therapy for postmenopausal patients with advanced breast cancer, a phase III study. Study Coordinator: L. Beex, St. Radboud Ziekenhuis, Nijmegen, The Netherlands* [17]

This study was activated in May 1987. Patients with advanced disease are treated with TAM for 4 months. Responding and stable patients are randomized to continuous tamoxifen until progression, or intermittent tamoxifen or intermittent alternating TAM–MPA. Endpoint of the treatment is progressive disease during tamoxifen therapy.

*Endocrine treatment remains important in the palliative*

*therapy of advanced disease. Different dosage schemes and dose levels studies are carried out and some new agents have been put to trial. Decreasing treatment toxicity and prolongation of the response duration are the main aims of these studies.*

## CONCLUSIONS

The physician treating patients with breast cancer is still faced with a great number of questions and uncertainties. The EORTC Breast Cancer Co-operative Group is trying to provide an answer to some of these problems by organizing controlled prospective randomized trials. These trials have covered some aspects of primary treatment and early disease, of adjuvant therapy and of systemic treatment of advanced disease.

The group has known a considerable expansion in the last few years. Thirty-one treatment centers are now joining efforts to improve the survival and the quality of life of patients with breast cancer.

In operable breast cancer, a large trial on breast conserving therapy was closed to entry in June 1986 and is actively followed. Special emphasis will be directed to the analysis of the pathology specimens and mammograms. Two active trials study the treatment of operable breast cancer in elderly patients (10850–10851), and one compares different treatments in ductal carcinoma *in situ* (10853). Perioperative adjuvant therapy with cytotoxic agents in operable breast cancer is studied in trial 10854. New studies in operable breast cancer are in preparation: breast conserving therapy will be studied in collaboration with the EORTC Radiotherapy Group, and studies on lobular carcinoma and Paget's disease are being prepared. Locally advanced inoperable breast cancer is the subject of study 10792 which needs further follow-up. In advanced disease two chemotherapy trials examine different schedules of first-line therapy (10852) and of second-line therapy with adriamycin (10871). Two endocrine protocols examine new schedules of tamoxifen administration as first-line therapy in hormone-sensitive tumors (10863), and different dose levels of aminoglutethimide as second-line treatment of advanced disease in postmenopausal women. Therapy of premenopausal patients with LHRH analogs will be studied in a new trial which is in preparation. New therapeutic concepts are tested in trial 10832, where alternating non-cross-resistant chemotherapy schedules are used, and in trial 10835, where cyclic combination chemotherapy with estrogenic recruitment is studied.

Special attention is paid to the quality of the data generated by the group. External review of pathology specimens, X-rays, documents, and treatment evaluation is an important part of our work.

The EORTC Breast Cancer Co-operative Group cordially invites every institution interested in clinical research on breast cancer to contact the secretariat, from whom information about protocols and membership applications are available on request:

Johan Wildiers, M.D.
Secretary of the Breast Cancer Co-operative Group
Uz St.Rafael
Kapucijnenvoer 33
3000 Leuven, Belgium
tel. 016-21.22.10

## EORTC BREAST CANCER CO-OPERATIVE GROUP

*List of protocols now open for patient entry—June* 1987

### Stage I–II

10850–10851: Phase III trials of operable breast cancer in the elderly.
Study Coordinator: I.S. Fentiman

10853: Phase III trial of treatment options for ductal cancer *in situ* of the breast (DCIS).
Study Coordinator: I.S. Fentiman

### Adjuvant study

10854: Phase III trial of perioperative adjuvant chemotherapy in operable breast cancer.
Study Coordinator: C.J.H.V.D. Velde

### Advanced disease

10832: Phase III trial: comparison between alternating the sequential administration of three non-cross-resistant chemotherapy regimens in combination with tamoxifen.
Study Coordinator: R. Paridaens

10835: Phase III and double blind trial assessing the cyclic combination chemotherapy with estrogenic recruitment.
Study Coordinator: R. Paridaens

10852: Phase III trial: short vs. long-term CMF in postmenopausal patients.
Study Coordinator: M.A. Nooij

10861: Randomized Phase II study in postmenopausal patients comparing different doses of aminoglutethimide with or without the addition of hydrocortisone.
Study Coordinator: C. Rose

10863: Phase III trial: first-line endocrine therapy for postmenopausal patients comparing

continuous tamoxifen vs. intermittent tamoxifen vs. alternating tamoxifen and medroxyprogesterone acetate.

Study Coordinator: L. Beex

10871: A randomized Phase II trial of doxorubicin in diffent dosages and schedules, used in second line in CMF refractory patients.

Study Coordinator: M.A. Nooij

*Table* 1. *Active members of the Breast Cancer Co-operative Group*

| | |
|---|---|
| Guy's Hospital, London | United Kingdom |
| UZ St. Rafael, Leuven | Belgium |
| Univ. Stellenbosch, Tygerberg | R.S.A. |
| Finsen Insitutet, Copenhagen | Denmark |
| Inst. Jules Bordet, Brussels | Belgium |
| The Netherlands Cancer Inst., Amsterdam | The Netherlands |
| Radiotherapeutisch Inst. Rotterdam | The Netherlands |
| Centre Henri Becquerel, Rouen | France |
| Medical Academy, Gdansk | Poland |
| Cancer Institute, Lodz | Poland |
| Ospedali Riuniti, Parma | Italy |
| University Hospital, Innsbruck | Austria |
| Akademisch Ziekenhuis, Leiden | The Nethelands |
| Sint Radboud Ziekenhuis, Nijmegen | The Netherlands |

*Table* 2. *Probational members of the Breast Cancer Cooperative Group*

| | |
|---|---|
| Centre Hospitalier de Tivoli, La Louvière | Belgium |
| Hospital Clinic, Barcelona | Spain |
| A.Z. Middelheim, Antwerpen | Belgium |
| William Harvey Hospital, Ashford | United Kingdom |
| Marika Eliadi Institute, Athens | Greece |
| Maria Ziekenhuis, Tilburg | The Netherlands |
| St. Lucas Ziekenhuis, Amsterdam | The Netherland |
| A.Z. St. Jan, Brugge | Belgium |
| Erasmus Ziekenhuis, Rotterdam | The Netherlands |
| AMC, Amsterdam | The Netherlands |
| Univ. Hospital, Utrecht | The Netherlands |
| Int. Nat. Dei Tumori, Milano | Italy |
| St. Elisabeth Ziekenhuis, Turnhout | Belgium |
| OLV. Ziekenhuis, Amsterdam | The Netherlands |
| Centre R. Huguenin, St. Cloud | France |
| Policl. A. Gemelli, Roma | Italy |
| Centre F. Baclesse, Caen | France |

## REFERENCES


1. Paridaens R, Mattheiem WH, van Dongen JA *et al.* An overview of the EORTC Breast Cancer Cooperative Group's activities. *Eur J Cancer Clin Oncol* 1983, **19**, 1665–1669.
2. van Dongen JA, Bartelink H *et al.* Randomized clinical trial to assess the value of breast conserving therapy in stage I and stage II breast cancer. Fourth EORTC Breast Cancer Working Conference 1987. Abstract 1.2.
3. Fentiman IS. Phase III trials on operable breast cancer in the elderly. Fourth EORTC Breast Cancer Working Conference 1987. Abstract 1.4.
4. Fentiman IS. A phase III randomized trial of treatment options for ductal carcinoma *in situ* of the breast. Fourth EORTC Breast Cancer Working Conference. Abstract 1.5.
5. van de Velde CJH. Perioperative (POP) adjuvant chemotherapy in operable breast cancer. Fourth EORTC Breast Cancer Working Conference. Abstract 1.3.
6. Rubens RD, Hayward JL, Fentiman IS *et al.* Controlled trial to assess the contribution of cytotoxic chemotherapy and/or endocrine therapy to the primary treatment of locally advanced breast cancer by radiotherapy. Fourth EORTC Breast Cancer Working Conference. Abstract 1.6.
7. van Oosterom AT, Mouridsen HT, Wildiers J *et al.* Doxorubicin versus epirubicin, a preliminary report of an on-going randomized Phase II–III study in pretreated breast cancer patients. In: Bonadonna (ed.), *Advances in Anthracycline Chemotherapy: Epirubicin.* Masson, 1985.
8. van Oosterom AT, Anderson M, Wildiers J *et al.* Adriamycin versus 4-epi-adriamycin, report of a second line randomized phase III study in advanced breast cancer. Fourth

EORTC Breast Cancer Working Conference. Abstract 1.7.
9. Engelsman E, Rubens RD, Klijn JEM *et al.* 'Classical' CMF versus three-weekly intravenous CMF in postmenopausal patients with advanced breast cancer. Fourth EORTC Breast Cancer Working Conference. Abstract 1.8.
10. Nooij MA, Beex LVAM. Short versus long-term CMF in postmenopausal patients with advanced breast cancer. A phase III study. Fourth EORTC Breast Cancer Working Conference. Abstract 1.9.
11. Paridaens R, van Zijl J, Julien JP *et al.* Comparison between alternating and sequential administration of three non-cross-resistant chemotherapy regimens in combination with tamoxifen in advanced breast cancer. A phase III trial. Fourth EORTC Breast Cancer Working Conference. Abstract 1.10.
12. Paridaens R, Julien JP, Klijn J *et al.* Assessment of cyclic combination chemotherapy with estrogenic recruitment in advanced breast cancer. Phase III and double blind trial. Fourth EORTC Breast Cancer Working Conference. Abstract 1.11.
13. Rose C, Mouridsen HT, Engelsman E *et al.* Oral medroxyprogesterone acetate treatment of postmenopausal patients with advanced breast cancer. An evaluation of the dose–response relationship at two dose levels. A phase III trial. Fourth EORTC Breast Cancer Working Conference. Abstract 1.12.
14. Rose C, Mouridsen HT, Wildiers J, Paridaens R, Rotmensz N, Sylvester R. A randomized phase II study comparing aminoglutethimide vs. trilostane vs. MPA vs. hydrocortisone. Abstract 'International Symposium on Hormonal Manipulation of Cancer', Rotterdam, June 1986.
15. Rose C, Mouridsen HT, Wildiers J *et al.* A randomized phase II study comparing aminoglutethimide vs. trilostane vs. MPA vs. hydrocortisone in patients with advanced breast cancer. Fourth EORTC Breast Cancer Working Conference. Abstract 1.13.
16. Rose C, Mouridsen HT, Bruning PF. A randomized phase II study in postmenopausal patients with advanced breast cancer comparing different doses of aminoglutethimide with or without the addition of hydrocortisone. Fourth EORTC Breast Cancer Working Conference. Abstract 1.14.
17. Beex LVAM, Rose C. Continuous tamoxifen vs. intermittent tamoxifen vs. alternating tamoxifen and MPA. First line endocrine therapy for postmenopausal patients with advanced breast cancer, a phase III study. Fourth EORTC Breast Cancer Working Conference. Abstract 1.15.