Eur J Cancer Clin Oncol, Vol. 19, No. 12, pp. 1665–1669, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00
Pergamon Press Ltd.

An Overview of the EORTC Breast Cancer Cooperative Group's Activities

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INTRODUCTION

THE BREAST Cancer Cooperative Group comprises oncologists from various Western European countries who conduct clinical research in breast cancer. Created in 1962, this group was first affiliated to the GECA (Groupe Européen de Chimiothérapie Anticancéreuse), which later became the EORTC. During the last few years the activities of the group have considerably expanded, so that many clinical trials are now activated, covering every stage of disease. During 1981, 419 cases and during 1982, 700 cases were registered by the Data Center, whereas the patient accrual never exceeded 200 cases per year previously. This increase, occurring in parallel to the rise of participating member-institutions, confirms the growing interest for cooperative anticancer research in Europe.

This paper will briefly describe the organization of the Group and will review its past activities. An overview of the ongoing clinical trials will also be presented with the hope that this information could trigger new centers to joint their efforts to ours.

ORGANIZATION OF THE GROUP

Working in close cooperation with the EORTC Coordinating and Data Center, the Group comprises a chairman, elected for 3 yr, a secretary–treasurer, a statistician, a data manager and member-institutions represented by one or several of their clinicians. Membership is open to every institution interested in participating in the clinical studies. New probationary members are elected for 2 yr. They then obtain the status of active member, and maintain this provided they include each year at least 10 evaluable cases into the group's trials. At present the Group comprises 12 active member-institutions, listed in Table 1.

Twice a year the Group holds a meeting, during which important scientific and administrative matters are discussed, i.e. protocols, publications, membership, elections, finances. For a new trial, a Protocol Committee, nominated by the Group, elaborates the protocol with the assistance of the statistician, the data manager and sometimes with clinical expert subcommittees, i.e. pathologists, radiotherapists, biochemists, etc.

PAST ACTIVITIES

During the 1962–1973 period the activities of the Group were almost exclusively restricted to endocrine therapy trials in advanced disease. The following drugs were tested: delta-1-testololactone (1962–1964), 6-aminochrysène (1967), estramustine phosphate (1969) and antiprolactin drugs [bromocryptin, CG603 and L-dopa (1972)] [1–8]. The Group was the first to demonstrate the antineoplastic activity of an antiestrogen, nafoxidine, which was found to be as effective as ethinylestradiol in postmenopausal women [9–11]. Nafoxidine, however, exhibited troublesome skin side-effects (ichtyosis and photosensitization), explaining why it was rapidly supplanted by tamoxifen, a less toxic analog [12].

Yet, in 1974, a combination of tamoxifen and two alternating regimens of chemotherapy, AV (adriamycin + vincristine) and CMF (cyclosphosphamide + methotrexate + fluorouracil), was tested by the Group [13]. The achievement of high response and complete remission rates stimulated the Group to pursue investigations in the field of hormonochemotherapy.

During the last few years many trials were initiated, covering all stages of disease and using all available therapeutic modalities, i.e. surgery,

||Active members are listed in Table 1.

Table 1. *Active members of the Breast Cancer Cooperative Group*

Institution	Country	Local physician(s)
Akademisch Ziekenhuis, Leiden	The Netherlands	M. Nooy, A. T. van Oosterom
Akademisch Ziekenhuis Sint Jan, Brugge	Belgium	A. Clarysse
Akademisch Ziekenhuis Sint Rafaël, Leuven	Belgium	E. Van der Schueren, K. Vantongelen, J. Wildiers
Antoni van Leeuwenhoek Ziekenhuis, Amsterdam	The Netherlands	H. Bartelink, E. Engelsman, E. Hamersma, F. Van Dam, J. A. van Dongen
Centre Henri Becquerel, Rouen	France	J. P. Julien
Finsen Institutet, Copenhagen	Denmark	H. T. Mouridsen, C. Rose
Guy's Hospital, London	Great Britain	J. L. Hayward, R. D. Rubens
Institut Jules Bordet, Brussels	Belgium	J. C. Heuson, J. Lustman, W. H. Mattheiem, R. Paridaens
Marika Eliadi Institute, Athens	Greece	S. Vassilaros
Ospedali Riuniti, Parma	Italy	G. Cocconi
Radiotherapeutisch Inst., Rotterdam	The Netherlands	J. Blonk-van der Wijst, J. Klijn, G. Olthuis, S. The
Sint Radboud Ziekenhuis, Nijmegen	The Netherlands	L. Beex, A. Koenders

radiotherapy, hormonotherapy, chemotherapy and immunotherapy. The design of recently completed and currently active protocols will be summarized in the next two sections. The scientific value of the trials and the expertise of all active members enabled the Group to organize three international meetings: the EORTC Breast Cancer Working Conferences, held in Brussels (1975), Copenhagen (1979) and Amsterdam (1983).

RECENTLY COMPLETED STUDIES

Five trials, recently completed, are briefly described here.

Trial 10761*; study coordinator: J. C. Heuson, Inst. J. Bordet, Belgium*

The potential contribution of immunotherapy to adjuvant chemotherapy in node-positive resectable breast cancer was assessed. After modified radical mastectomy, all patients with homolateral metastatic nodes were treated by internal mammary chain irradiation and 12 cycles of chemotherapy (CMF, q 4 weeks). They were randomized to receive for 2 yr either a placebo or levamisole. Three hundred and nine eligible patients were entered between July 1976 and October 1980. A recent interim analysis revealed no significant difference in the recurrence rates, disease-free interval or overall survival between the levamisole and the placebo groups [14]. The study remains open to follow-up.

Trial 10762*; study coordinator: H. T. Mouridsen, Finsen Institutet, Denmark*

The study investigated the utility of adding tamoxifen to a standard chemotherapy regimen as first-line treatment of postmenopausal women with advanced disease. Two hundred and sixty-three patients with measurable lesions were randomized to receive CMF or CMF + tamoxifen. The results clearly indicated that hormono-chemotherapy yielded higher response rates, more complete remissions and longer response durations than chemotherapy alone [15].

Trial 10805*; study coordinator: A. T. van Oosterom, AZ Leiden, The Netherlands*

Patients with advanced disease were randomly allocated to receive either carminomycin, a new anthracyclin derivative, or adriamycin. The analog was less cardiotoxic than the parent compound but unfortunately exhibited very low antineoplastic activity [16]. The randomized phase II design used in this trial represents a master protocol further used' by the Group for screening of new anthracyclins.

Trial 10791*; study coordinator: R. Paridaens, Inst. J. Bordet, Belgium*

In this phase II study the antineoplastic activity of PALA, a new inhibitor of pyrimidine synthesis, was investigated. Two partial remissions only were observed among 29 heavily pretreated patients. The drug was almost devoid of

hematologic toxicity, whereas mucocutaneous side-effects were dose-limiting [17].

Trial 10803; *study coordinator: R. Paridaens, Inst. J. Bordet, Belgium*

A potentially synergistic combination of *cis*platinum + vindesine was tested in heavily pretreated cases [18]. The final 20% response rate found under these unfavorable conditions indicates that the combination is active and that it is worth using earlier in the course of disease.

Trial 10802; *study coordinator: H. T. Mouridsen, Finsen Institutet, Denmark*

Although medroxyprogesterone acetate (MPA) has been used for a long time in advanced breast cancer, recent studies have suggested that very high dosages of this drug might achieve better results than conventional doses, even in heavily pretreated patients. In this phase III trial patients were randomly allocated to receive either 300 or 900 mg daily by the oral route. The study is closed to entry and final results will be available very soon after peer review of case records.

CURRENTLY ACTIVE PROTOCOLS

Six trials are running at present. The first two (10801 and 10821) deal with patients with operable disease; the third (10792) is conducted in patients with locally advanced primary breast cancer; and the last three (10807, 10808 and 10811) explore new therapeutic modalities in advanced (stage IV) disease.

Trial 10801; *study coordinator: J. A. van Dongen, A. van Leeuwenhoek Ziekenhuis, The Netherlands*

This study, activated in December 1980, was designed to assess the value of breast-conserving therapy in stage I–II operable breast cancer. Patients are randomized to undergo either the standard surgical procedure, i.e. modified radical mastectomy, or lumpectomy plus axillary node dissection and aggressive radiotherapy with iridium implants. All node-positive cases receive six courses of adjuvant CMF.

Trial 10821; *study coordinator: J. C. Heuson, Inst. J. Bordet, Belgium*

This pilot study initiated in April 1983 evaluates long-term preoperative chemotherapy in patients with operable breast cancer and palpable homolateral axillary nodes proven to be metastatic by fine-needle aspiration cytology or throughcut biopsy. Chemotherapy with CMF is started, up to a maximum of six cycles (according to response), before a modified radical mastectomy is performed.

Trial 10792; *study coordinator: R. D. Rubens, Guy's Hospital, U.K.*

The object of this trial, activated since December 1979, is to test the utility of adding a systemic treatment either with chemotherapy (12 cycles CMF), endocrine therapy (ovarian irradiation + prednisolone for 5 yr in premenopausal women; tamoxifen 10 mg b.d. for 5 yr in postmenopausal women) or both to radiotherapy, considered as the standard reference treatment in locally advanced breast cancer. Patients are randomized to receive, after completion of radiotherapy, either no further treatment (controls), endocrine therapy (HT), chemotherapy (CT) or both (HT + CT).

Trial 10807; *study coordinator: R. Paridaens, Inst. J. Bordet, Belgium*

The trial, initiated in June 1981, explores a potentially synergistic hormonochemotherapeutic combination used as first-line treatment in advanced disease. A deep and prolonged suppression of endogenously produced estrogens is achieved by continuous treatment with aminoglutethimide and hydrocortisone. Cyclic chemotherapy with FAC is given every 3 weeks, exactly 24 hr after one tablet of ethinylestradiol (EE_2) has been administered. The latter intends to recruit neoplastic cells into the mitotic cycle, thereby amplifying the killing effect of cycle-active cytotoxic drugs. Preliminary results are very favorable, with a high proportion of partial and complete remissions. A randomized phase III trial aiming to test the utility of estrogenic recruitment (EE_2 vs placebo before FAC), restricted to presumably hormone-dependent (ER+) cases, will be initiated during 1983.

Trial 10808; *study coordinator: E. Engelsman. A. van Leeuwenhoek Ziekenhuis, The Netherlands*

In this randomized phase III trial, initiated in June 1981, two schedules of CMF are evaluated as first-line treatment in advanced disease. The 'classical' schedule consists of oral cyclophosphamide on days 1–14 and i.v. methotrexate and fluorouracil, given on days 1 and 8 every 4 weeks. In the 'new' CMF all drugs are given i.v. on day 1 every 3 weeks. If the 'new' CMF were as active as the 'classical' one, it might then be preferred because its schedule is more simple. It would also allow us to control exactly the dosage of cyclophosphamide received by every patient, solving problems related with bad compliance or digestive absorption.

Trial 10811; *study coordinator: A. T. van Oosterom, A.Z. Leiden, The Netherlands*

Patients with advanced disease are randomly allocated to receive 4-epiadriamycin or adriamycin. Both drugs are compared with regard to their antineoplastic activity and their side-effects. As explained earlier, this trial is conducted according to a randomized phase II study-master protocol established for the screening of new anthracyclin analogs. After completion of this protocol, the next drug to be tested will be mitoxantrone.

CONCLUSIONS AND PERSPECTIVES

The studies conducted by the Group pursue the important aims of improving the survival and quality of life of patients at every stage of disease. The first-line treatment, initiated for adjuvant or palliative purposes, is based on a multimodal strategy, likely to achieve the best immediate results. In operable breast cancer attempts are made to save the breast by using aggressive but selective radiotherapy (trial 10801) or by exploring the value of long-term preoperative chemotherapy (trial 10821). In locally advanced, inoperable disease the contribution of systemic therapy with hormones and/or chemotherapy is assessed (trial 10792). In advanced disease new therapeutic schedules (trial 10808) or new concepts are tested, i.e. amplification of chemotherapeutic action by adequate hormonal manipulation in hormone-dependent cases (trial 10807) or by the use of alternating non-cross-resistant combinations (trial 10741 already completed, to be replaced by another that is in preparation). New combinations, new compounds or presumably less toxic analogs of existing drugs (trial 10811 and two trials in preparation) are then tested in second or third line, at a later stage of disease.

During its last meeting, in May 1983, the Group emphasized the need for a better definition of prognosis in individual patients and created a subcommittee of pathologists. Efforts had already been made since 1973 for standardizing the technique of steroid receptor assays [19, 20]. Most of the active member-institutions are now participating in interlaboratory quality controls so that the results of standardized estrogen receptor assays might be used as selection or stratification criteria in trials to be activated in the near future. Thus new hormonal or anti-hormonal compounds might be tested in a selected group of presumably hormone-dependent cases (ER-rich tumors); vain hormonal manipulations should be avoided in receptor-poor cases, who will be included sooner in phase II trials of new cytotoxic compounds or combinations.

The EORTC Breast Cancer Cooperative Group welcomes every institution interested in participating to the above-listed clinical trials. Protocols, information and membership application forms can be obtained upon request by writing to the following address:

Dr. R. Paridaens
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Institut J. Bordet
rue Héger-Bordet, 1
B 1000 Brussels, Belgium.

Tel.: 02/537.02.38.

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