REPORT EORTC BREAST CANCER COOPERATIVE GROUP MEETING
London, November 10-11, 1988

Chairman : J.A. Van Dongen (Amsterdam)
Secretary-Treasurer : J. Wildiers (Leuven)

Business Meeting Report

1. The minutes of the previous meeting in Brussels on May 5-6, 1988 were approved.
2. Finances. The treasury report presented by J. Wildiers was approved. The greatest part of the available money is used to refund member institutions according to their activities in studies during 1986. The Group is further partly financing the coming Consensus Meeting on Ductal Carcinoma in Situ (November 1988) and financially supporting the start of the organization of the 5th Breast Cancer Working Conference (September 1991).
3. Election of new officers. E. van der Schueren, chairman, J.P. Julien, secretary and J. Wildiers treasurer. Their functioning will offically begin from next meeting, May 1989. A permanent administrative structure is created and headed by K. Vantongelen.
4. Nicole Rotmensz is leaving the Data Center and will be replaced by Françoise Mignolet. On behalf of the Group, J.A. van Dongen expressed his gratitude towards Nicole, who has accomplished her function as data manager of the Group with great competence for so many years.
5. An amendment to the Group's statutes regarding the relation with pharmaceutical industries (PI) was presented and accepted. The major change concerns the access of the PI to administrative data and data on toxicity during the run of the trial. Data will be communicated through the study coordinator. The adapted version is included with the minutes. A copy of the complete version of the statutes is available on request.

Open meeting 10-11 November 1988

I. General Topics

1. Membership status : N. Rotmensz presented an overview of the activities from 1986 up to 1988. During 1986, 387 cases were registered by the Data Center. In 1987, 1000 patients were entered in the trials and for 1988, 973 patients have been registered up to October. This represents an important increase in number of patients and number of institutes participating in the group's trials mainly influenced by the ongoing POP adjuvant trial. Five new institutes become active members : Centre René Huguenin, St. Cloud - Centre F. Baclesse, Caen - Centre Oscar Lambret, Lille - Universita Cattolica, Roma - St. Savvas Hospital, Athens. The group is working now with 19 active centers and 18 probationary centers.

2. Dominant site of disease

E. Engelsman presented the proposals worked out by the Working Party on "Dominant Site of Disease". The Working Party has prepared explicit notes on the definition and the use of "dominant site of disease" and a method to document the total distribution of disease for future advanced disease trials. The Working Party will further elaborate general guidelines guaranteeing the uniformity in data collection and reporting results within the different group's trials. This will a.o. include standard definitions on menopausal status, treatment response, toxicity, tumor load, ER, disease-free interval.

3. Data Quality Control Results for two on-going breast cancer trials

The program is initiated by the EORTC Study Group on Data Management and started in January 1988.

K. Vantongelen presented the results observed in 10 centers participating in trials 10852 or 10854. The overall quality of data was found good, ranging from 78% up to 98% correct data, 7 centers having more than 90% correct data. The main cause for incorrect data was the wrong transfer from medical chart onto the study forms. Site visits revealed significant information concerning the importance of protocol and form quality ; the different data management structures available in the hospitals ; the local data collection systems and the use of the referred WHO systems. Procedure and findings will be used for recommendations to the different cooperative groups regarding quality control of data and publication.

4. EORTC Quality Control

E. van der Schueren reported on the recently accelerated quality control activities in the EORTC. One of the major objectives is the elaboration of comprehensive guidelines for the different steps of quality control to be used by the Cooperative Groups in their studies. Common criteria with respect to patient eligibility, evaluability, assessment of tumor response, toxicity and compliance to treatment are being developed. Quality control in surgery is still a very complex enterprise. The money available is limited. The deadline for the submission of projects for the period 1989-1990 is July 1, 1989. They will be evaluated. A group of surgeons (J.A. van Dongen, C. v.d. Velde, F. Zoetmulder and W. Mattheim) are investigating a program for quality control in surgery.

5. Structure and organization for future phase II studies

On behalf of M. Piccart, R. Paridaens proposed a possible structure for a phase II working group, as organized by the ECTG. The group was asked for his interest in this matter. For the next meeting a program will be prepared.

6. Monitoring accrual of patients in clinical trials

H. Franklin presented the results of a retrospective study of the Netherlands Cancer Institute for the period 1986 to July 1987.
The number of patients actually entered into the trials were, in most cases, a fraction of the initially selected group. The results highlighted aspects which should be taken into consideration when planning future trials or rectified during the trial's progress. They mainly confirm the opinion that entry criteria should be simple and should represent the general population who will receive the resulting treatment.

Studies on operable disease

Ongoing studies and new proposals

1. Protocol 10854 : phase III trial of perioperative adjuvant chemotherapy.
- The Leiden group investigated the quality of life in 30 patients entered in the study (equally balanced in both arms). The results revealed that patients receiving the CAF experienced a better quality of life, probably because of the attention they got from their environment.
- First results with the Theracool system were presented by O.J. Repelaer van Driel :
- it prevents hairloss in approximately 50% of the patients
- optimal duration of treatment is not yet defined
- the system is well tolerated by the patients.

The results will be combined with the French centers' findings and a report prepared for next year.

2. Protocol 10801 (radical versus conservative surgery) : the follow-up time will enable a first formal publication end of 1989. Agreement was reached that neu oncogen studies will be performed in part of the pathology material.

3. Protocol 10853 : phase III trial : wide excision followed by radiation therapy versus no additional radiotherapy, for patients with in situ ductal carcinoma of the breast. This trial accrued 100 patients by 20 centers. Participants are reminded to provide information on the ineligible cases. The group insists on having better forms for this trial.

4. Protocol 10873 : phase II trial : breast conservative therapy in Paget's disease of the nipple. Only 2 patients have been registered in this trial which was initiated recently. Ineligible cases have to be registered on diagnoses as well.

5. Protocol 10872 : a prevention trial of tamoxifen in women with lobular carcinoma in situ of the breast. The presently low accrual necessitates the reconsideration of the feasibility of this study.

6. Protocols 10850 and 10851 : phase III trials on operable breast cancer in the elderly.
10850 : tumour excision plus tamoxifen compared with modified radical mastectomy. So far, 94 patients entered.
10851 : tamoxifen alone compared with modified radical mastectomy. 87 patients randomized. A revision of the entry criteria is considered enlarging the eligible group. The study coordinator has sent a letter to the PRC with the request to include all patients from 70 years on. After agreement by the PRC this change in criteria may be officially adopted.

7. Protocol 10761 : assessment of immunotherapy in node positive patients. All patients were N+M0 and underwent radical modified mastectomy followed by RT and CMFx12. It was a double blind randomized trial (Levamisole 2,5 mg/kg daily 2 days/wk for 2 years vs placebo) and accrued by 316 patients during the period May 1976 to October 1980. Both arms are equally balanced regarding : node status, dose of CT completed, prognostic factors and premature withdrawals which were mainly due to early progression, excessive toxicity and refusal. This study with a follow-up of 9 years revealed no significant differences for both arms : toxicity identical in both arms, no significant difference for survival, progression, local recurrence or distant metastases. So far, the overall results could not demonstrate a statistically significant difference, although the trend is in slight favour of Levamisole. The known prognostic factors acted as expected.
R. Paridaens stressed the importance of microscopic automated computer analysis of grading PA data in adjuvant breast cancer trials. Institutes who could collect slides for analysis are urged to do so. The Pathology Group of the EORTC Breast Group has reviewed the pathology slides of the Levamisole trial.

8. Proposal for a study in conservative treatment of breast cancer (in cooperation with the Radiotherapy Cooperative Group). The comments of the PRC were presented and discussed. The major changes accepted by the Group include : the exclusion of T3 tumours ; standard treatment of the axilla by surgery ; the adjuvant treatment policy will be defined by center prior to participation and the centers should stick to one policy during the run of the trial.

APD in the management of bone metastases from breast cancer
R. Coleman presented an overview of the significance and prevalence of bone metastases in breast cancer. A phase II trial including 28 patients with bone metastases treated with APD i.v. 30 mg over 2 hours every two weeks, was presented. Results : 4 PR, 11 SD, 9 PD and 4 not evaluable. Subjective improvement was obtained in 9 cases. Toxicity was moderate and acceptable.

Locally advanced disease
The Bordet pilot study is restricted to inflammatory disease patients, receiving high dose chemotherapy (epirubicine/cyclophosphamide). The preliminary results are indicating high but acceptable hematological toxicity (recovering within scheduled time) and a good clinical response enabling surgery in half of the patients. The group is asked to continue the feasibility studies on intensive treatment schedules and come together, on a later date, with all the centers active in this field.

Advanced disease
1. **Diphosphonates** : two trial options are presented :
- APD for the prevention of bone lesions in patients with metastatic breast cancer, a double blind phase III trial ; proposal by P. Bruning : patients with M+ without bone lesions (negative bone scan and no lesions demonstrated on X-rays) are randomized to receive either APD 150 mg Bid orally or placebo, until death ; concomitant treatment i.e. all other cytostatic, hormonal, radiation therapy allowed. Most important end points are : time to bone metastases, time to hypercalcemia, incidence of RT in bone lesions, survival from the start of APD.
- A randomized phase III trial for secondary prevention and/or delay of bone metastases in locally advanced breast cancer using enteric coated "Leiden" tablets. L. Beex presented the so-called Leiden study. Patients are randomized to receive APD 2x150 mg orally/day vs no APD. Endpoints are skeletal disease free survival and disease free survival. Almost all centers represented at the meeting were actively interested in one of these studies. Negotiations with the different parties involved should lead to a definitive study proposal to be presented at the next group's meeting. The group is also aware of a potential bias arising from uncontrolled diphosphonates administration to EORTC trial results. However, from the presentation of H. Franklin (monitoring accrual of patients in clinical trials) it was clear that more than 80% of patients are not put into trials. This large group could be considered for future APD studies.

2. **Chemotherapy in elderly patients**
A proposal was shortly presented and discussed by M. Nooy. Patients >70 years, who had no prior chemotherapy, are randomized to receive either mitoxantrone (12 mg/m^2) or CMFx6 (low dose scheme). The protocol will be sent around to study the proposal more in detail.

3. **Data Center report and discussion of ongoing studies**
Protocol 10832 : comparison between alternating and sequential administration of three non-cross-resistant chemotherapy regimens. 169 patients have been randomized. Due to the rather high percentage of ineligible cases, the study will continue accrual for another 6 months.

Protocol 10852 : "short" versus long term chemotherapy with CMF in postmenopausal patients with advanced breast cancer.

Up to October, 1988, 245 patients are registered. External review is started. 350 patients are required in this trial to reach 200 randomized cases.

Protocol 10861 : randomized phase II study : second line endocrine treatment of postmenopausal patients with advanced breast cancer. A total of 148 patients entered the study so far. 215 evaluable cases are required to complete this study. Half of the cases entered were reviewed in the Data Center. The decision on closing 1 arm of the trial will be done by the study coordinators together with the statistician.

Protocol 10881 : randomized phase III trial for premenopausal advanced breast cancer patients randomized to receive either LHRH-agonist, or LHRH-agonist + tamoxifen or tamoxifen alone. For practical reasons, the trial was activated very recently and so far 9 patients have been randomized. A large number of new centers are interested in this study.

Protocol 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. The study accrued to 32 patients. Although the accrual is far under the expected number, the study coordinator prefers to continue for another 6 months and meanwhile to investigate the possibilities for continuing the study.

Prevalence of endometrial cancer in Nolvadex treated patients (W. Mattheiem)
The organization of a prospective randomized study is discussed. The Peto group will be asked to include the problem in their overview analysis of adjuvant therapy studies.

Next meetings
Barcelona, May 11-12, 1989
Leiden, November 9-10, 1989

List of commitments - London Meeting 11/88

Ongoing protocols :

I. Fentiman : 10853 DCIS : form discussion 10850-10851 : Elderly : modify inclusion criteria -> PRC -> approval sent to members

F. Zoetmulder : 10873 Paget : forms to be finalized

M. Nooij : 10871 Adria : investigate feasibility

P. Bruning, C. Rose, H. Mouridsen, R. Sylvester : decision on closing 1 arm of the study

New projects :

P. Bruning and L. Beex : final proposal(s) diphosphonate study

A.N. Van Geel : treatment policy local recurrence

General proposals :

Quality control in surgery : J.A. van Dongen, C. van de Velde, W. Mattheiem, F. Zoetmulder

Phase II Working Group : structure : M. Piccart, P. Bruning, M. Nooy, E. van der Schueren

Dominant Site of Disease Working Party : elaboration of standard guidelines : K. Vantongelen, H. Stewart, E. Engelsman, L. Beex, J. Wildiers

Letter to Peto Group -> prevalence of endometrial cancer in tamoxifen treated patients. J.A. van Dongen

Publications :

H. Mouridsen : 10811, cardiotoxicity data

C. Rose : 10802 MPA trial data

E. Engelsman : 10808 CMF classical vs IV

R. Paridaens : 10761 Levamisole

H. Mouridsen, C. Rose : 10834 : second line endocrine

J.A. van Dongen : 10801 breast conservative treatment

REPORT EORTC LUNG COOPERATIVE GROUP MEETING
Interlaken, August 31, 1988

Business meeting
As an introduction, new Chairman Dr. N. VAN ZANDWIJK presented future responsibilities in the Group :
Secretary : T.A.W. SPLINTER
Vice-Chairman : G. GIACCONE
Chairman of Surgery Subcommittee : P. ROCMANS
Chairman of Chemotherapy Subcommittee : J.G. McVIE
Chairman of the Radiotherapy Subcommittee : A. GREGOR
Members of the new Publication Committee : O. DALESIO - A. GREGOR - G. GIACCONE - N. VAN ZANDWIJK

Data Center Report
Small Cell Lung Carcinomas
Protocol 08845, conducted in collaboration with Lung Cancer Study Group (NCI) and ECOG, U.S.A : Adjuvant surgery in very limited disease.
Present accrual : 34 patients entered from EORTC, 39 from ECOG and 131 from NCI Lung Study Group. 46% experienced severe (grade III and IV) hematological toxicity.

Protocol 08877 : Alternating versus sequential radio-chemotherapy in limited disease.
Eleven patients randomized ; minimum needed : 30 patients in each treatment arm.

Protocol 08862 : Standard CDE chemotherapy followed by VIMP (carboplatin containing scheme) in extensive disease.
The study is still open and we want to know whether those 2 combinations are really not cross-resistant, please send second-line therapy forms by returning post.

Protocol 08854 : 4'epidoxorubicin in extensive disease patients older than 70 or considered unsuitable for conventional combination therapy (WHO Performance Status of 3).
Thirty-one patients registered ; minimum needed : 40.

Protocol 08873 : teniposide (VM26) in patients with brain metastases.
Thirty-six patients registered, the study now closed to entry ; next draft for a trial comparing teniposide versus teniposide + radiotherapy to be distributed soon.

Non-small cell lung carcinomas
Protocol 08861 : adjuvant therapy in completely resected disease.