EORTC NEWS AND REPORTS

These reports will appear on a monthly schedule whenever available. They are based on information provided by individuals or clinical and research groups pertinent to cancer research. More detailed information if needed may be obtained by writing to

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Guidelines for the preparation for publication of reports from EORTC Cooperative Groups

1. The chairman, convener or secretary of the Group is requested to mail the report to the office of the European Journal of Cancer & Clinical Oncology. The reports will be edited and published in the Journal within 6 to 8 weeks after reception in the office.
   Address : Institut Jules Bordet
   Rue Héger-Bordet, 1
   1000 Brussels (Belgium)

2. Please send the report typewritten on one side of page, triple spaced with a 5 cm left margin. Brevity is essential. Tables and figures are difficult to print and should be replaced by an appropriate text.

3. Please consult the reports published in the March 1989 issue of the Journal and consider them as models to be adopted for all reports with possible exceptional adaptations.

4. We request omission of list of names of attendants to the group meetings. Reports should be signed by either the chairman, convener, secretary of the group, or by all three ad libitum.

5. Please add as a conclusion to your report : "Additional information may be obtained by writing to the secretary of the group".

6. Protocols will be published at the request of the groups.

This office will be glad to receive your comments, criticism and suggestions on the edition and publication of your reports.

The Editor.

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WORKSHOP ON NEW APPROACHES TO PROBLEMS IN RADIATION ONCOLOGY: APPLICATIONS OF MOLECULAR BIOLOGY

Tucson, Arizona, U.S.A. November 12-15,1989

Information:
Mary Humphrey
Conference Coordinator
Arizona Cancer Center
(02)626-2276

THE EUROPEAN SOCIETY FOR UROLOGICAL ONCOLOGY AND ENDOCRINOLOGY

Düsseldorf,West Germany, Oct. 26 to 29, 1989

Information:
Ms. C. Seiler
Urologische Universitätsklinik
Moorenstr. 5
4000 Düsseldorf
West Germany
(211) 311 8110

INTERNATIONAL SYMPOSIUM ON "THE BIOLOGY OF HUMAN MALIGNANT LYMPHOMAS"

Bordeaux (France), March 5-6, 1990

Information:
Mrs. F. Capuron
Secretary of the International Symposium on "The Biology of Malignant Human Lymphomas"
INSERM
229 cours de l'Argonne
33076 Bordeaux Cédex, France

12th ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM

San Antonio, Texas, U.S.A., December 8-9, 1989

Information:
Terri Coltman, R.N.
Symposium Coordinator
4450 Medical Drive
San Antonio, Texas 78229
(512) 691-6700

BOOK RECEIVED

"ATLAS OF CANCER INCIDENCE IN THE NORDIC COUNTRIES" A collaborative study of the five Nordic Cancer Registries.

Eds: O. Moller Jensen, B. Carstensen, E. Glattre, B. Malker, E. Pukkala, H. Tulinius. 1988, 205 pages, $ 79 ISBN 952-90010-8-8

A excellently produced color atlas representing cancer incidence in the Nordic countries of Europe: Denmark, Finland, Iceland, Norway and Sweden. These countries are known for the high quality of their health services and the reliability of their registration. Patients registered here amount to 750,000 cases over the period 1970-1979 from a total population of approximately 22 millions.

The didactic as well as the esthetic qualities of this 205 pages atlas, with beautifully colored maps add to the scientific and epidemiological interest. This is a "must" for all libraries. Certainly all oncologists will want to consult and own a copy of this exceptional book. The text is in English.

H. Tagnon

REPORT EORTC QUALITY OF LIFE COOPERATIVE GROUP

Leiden, October 20-21, 1988

Chairman: S. Ahmedzai
Secretary: G. Bos-Branolte

1- Minutes of the Paris meeting, April 1988 are accepted
2- Chairman's report
The Breuer Committee will review our Study Group in March 1989 on the quality of protocols, publications and expenditure of finances.
S. Ahmedzai will contact Dr Staquet about the Belgium awards and also about the number of copies of the monograph sold.
Salvador (Barcelona) temporarily resigned.
3- Secretary's report
It was again stressed to send any relevant in formation and summaries of Project Group meetings to the secretary.
4- Treasurer's report
On October 14, 1988 the total account amounted to f.29.108,48 (about 15,000 dollars).
Members who participated in Protocol 15861 were kindly requested to send specific and relevant banking information, addresses of institutions and total amount in dollars to the treasurer so that she can arrange the transfers.

5. Next Meeting The Spring meeting will take place in Paris, Library Hôtel Dieu, April 28 and 29, 1989. The annual meeting will be hosted by Monika Bullinger, Munich, Nov. 3-4, 1989.

General Discussion Leiden meeting, 21-22 October 1988.
Razavi asked for rules about fundraising activities with the pharmaceutical industries.
Ahmedzai reacted to some negative reactions on fundraising for his project(s) by stating that it is ethical and acceptable to accept money.
Crabeels mentioned that every EORTC Group has its own rules for fundraising.
Ahmedzai remarked that specific guidelines have to be discussed whenever relevant. He also decided that instruments and questionnaires developed as an activity of our Study Group have to stay property of our QL-Group.

PROTOCOLS
The following (preliminary) protocols have been discussed:
1. Core Questionnaire for Cancer Clinical Trials (EORTC Protocol 15861 Aaronson).
2. Survey of Psychosocial Oncology Professionals in Europe (van Geffen, Bolund).
3. Quality of Life of Bone Marrow Transplant Patients (Zittoun).
4. A Short Training Programme in Psychosocial skills for Oncology Staff (Delvaux).
5. High Dose Megestrol Acetate for Cachexia (Ahmedzai).
6. Stress among Nurses in Palliative Care Units (Ahmedzai).

Up to now a summary for the Newsletter was received by Delvaux. Dr. Hürny sent two references.

REPORT EORTC BREAST CANCER COOPERATIVE GROUP

(London)November 10-11, 1988

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

Participants:
J. Andersen (Odense), A. Baildam (Manchester), P. Bakker (Amsterdam), H. Barteling (Amsterdam), D. Becquart (Antwerpen), L. Beex (Nijmegen), J. Berner (Lodz), M. Blichert-Toft (Odense), S. Bretti (Torino), P. Bruning (Amsterdam), M.A. Chaudary (London), M. Coibion (Brussel) R. Coleman (London), M. Daniels (Barcelona), R. Da Luz (London), G. De Keizer (Tilburg), J.E. De Vries (Zwolle), Z. Doran (London), M. Dünser (Innsbruck), E. Engelsman (Amsterdam), I. Fentiman (London), H. Franklin (Amsterdam) R. Freitas (London), J. Jassem (Gdansk), J.P. Julien (Rouen), I. Karydas (Athens), J.G.M. Klijn (Rotterdam), S.J. Leinster (Liverpool), T. Lerut (Leuven), W. Mattheiem (Brussels), F. Mignolet (Data Center), M. Nooy (Leiden), G. Olthuis (Rotterdam), R. Paridaens (Brussels), O.J. Repelaer van Driel (Leiden), E. van der Schueren (Leuven), J.A. van Dongen (Amsterdam), A.N. van Geel (Rotterdam), E. van Limbergen (Leuven), K. Vantongelen (Leuven), J.A. van Zijl (Stellenbosch), J. Wildiers (Leuven), F. Zoetmulder (Amsterdam).

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. The group unanimously elected E. van der Schueren as chairman, J.P. Julien as secretary, and J. Wildiers as treasurer. Their functioning will officially 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, for the use in future advanced disease trials, clear 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 decisions of the Working Party are included.
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. After short presentation of the procedure, K. Vantongelen presented the results observed in 10 centers participating in trials 10854 or 10854.
The overall quality of data is 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 incorrect transfer from medical chart onto the study forms.
The site visits revealed important side information concerning the influence of protocol and form quality; the local data collection systems and the use of the referred WHO systems.
The procedure and the findings will be used for the elaboration of recommendations towards the different cooperative groups regarding quality control of the study data and a publication is prepared.

4. EORTC Quality Control.
E. van der Schueren reported on the recently accelerated quality control activities in the EORTC. One of the major objectives in the EORTC is the elaboration of comprehensive guidelines for the different steps of quality control, which could be used by the Cooperative Groups enabling them to implement a systematic quality control system for their different studies.
Common criteria with respect to patient eligibility, evaluability, assessment of tumor response, toxicity and compliance to treatment are being developed. Quality Control Projects for data management, radiotherapy and chemotherapy are activated, while quality control in surgery is still a very complex enterprise. The money available is limited and projects are critically evaluated. The deadline for the submission of projects for the period

1989-1990 is July 1st, 1989. A group of surgeons (J.A. van Dongen, C. v.d.Velde, F. Zoetmulder and W. Mattheiem) will start looking for a project on 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 next meeting a package will be compiled of matters needed to set up a solid structure. A more detailed view on the implications will enable the group to evaluate the willingness to invest in such a structure.

6. Monitoring accrual of patients in clinical trials. H. Franklin presented the results of a retrospective study done at the Netherlands Cancer Institute investigating, by identifying all new patients in the Hospital Tumor Registry, who would have been eligible for the cancer trials open during the period July 1986 to July 1987.
The numbers of patients actually entered into the trials were, in most cases, a mere fraction of the initially selected group. However, for each trial the reasons were different. 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 belief that entry criteria should be simple and should represent the general population who will receive the resulting treatment.

II. Studies for operable disease.

Ongoing studies and new proposals.

1. 10854: Phase III trial of perioperative adjuvant chemotherapy.
- An addendum to the forms including a coding guide, is added to the minutes.
- 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 CQF experienced a better quality of life, probably by the attention they got from their environment. Although total alopecia was important, the surgical procedure was more influencing their overall feeling.
- First results with the Theracool system were presented by O.J. Repelaer van Driel:
- it prevents hairloss in about 50% of the patients
-optimal duration of treatment is not yet defined
- the system is well tolerated by the patient.
The results will be combined with the French centers' findings and a report prepared for next year.

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

3. 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. 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. 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. The group prefered to await the coming Workshop Meeting on in situ carcinoma before deciding.

6. 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. 10761: Assessment of immunotherapy in N+ patients. All patients were N+Mo and underwent radical modified mastectomy followed by RT and CMFx12.
It was a double blind randomized trial (Levamisole 2,5mg/kg/d - 2 days/wk for 2 years vs Placebo) and accrued 316 patients during the period May 1976 to October 1980. Both arms are equally balanced regarding: N status; dose of CT completed; prognostic factors and premature withdrawals which were mainly due to early progression, excessive toxicity and refusals. 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 lines indicating survival are deverging after a long period in slight favour of levamisole. The known prognostic factors do behave as expected.
It was suggested to present the results of this study for publication in the New England Journal of Medecine.
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 tumors; 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.

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

IV. Locally avanced disease.

1. A.N. van Geel presented an overview of the literature while looking for clear cut criteria for stratification.

It is clear that the recent literature on locally advanced breast cancer is dealing with different groups.
From biological point of view two categories are recognized: the rapid growing tumors (mastitis carcinomatosis, "inflammatory" disease) and the slow growing tumors. Although it is very difficult to define "inflammatory" disease, in general it is clinically recognized.
Pilot studies are ongoing in Guy's Hospital and Bordet mainly based on high dose chemotherapy with or without ABMT.

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.

V. 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 rendomized to receive either APD 150mg Bid orally or placebo, until death, as 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 2x150mg 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 from diphosphonates 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 (12mg/m2) or CMFx6 (low dose scheme). The protocol will be sent around to study the proposal more in detail.

3. Data Center report and discussion ongoing studies.

10832: Comparison between alternating and sequential administration of three non-cross-resistant chemotherapy regimens.
169 patients have been randomized. Due to the rather high % of ineligible cases, the study will continue accrual for another 6 months.

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 achieve 200 randomized.

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.

10863: First line endocrine therapy for postmenopausal patients with advanced disease, studying continuous tomoxifen vs intermittent tamoxifen vs alternating tamoxifen and MPA. The study accrued 98 patients.

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

10871: A randomized Phase II trial of doxorubicin in different dosages and schedules for advanced breast cancer, used in second line in CMF refractory patients. The study accrued 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.

VI. Prevalence of endometrial cancer in Nolvadex treated patients. W. Mattheiem.

The organization of a prospective randomised study is discussed. The Peto group will be asked to include the problem in their overview analysis of adjuvant therapy studies.

J.A. van Dongen thanked the hosts for their kind hospitality and the members of the group for their active cooperation during the years of his chairmanship. He specially thanked his co-officers R. Paridaens and J. Wildiers and also K. Vantongelen for their dedicated support.

NEXT MEETINGS: Barcelona 11-12 May 1989

Leiden 9-10 November 1989

REPORT EORTC SOFT TISSUE AND BONE SARCOMA GROUP

Lugano, Switzerland, October 29, 1988

Chairman: J. Rouëssé
Secretary: J. Verweij

In view of the plans to initiate studies on chemotherapy combined with hematopoietic colony stimulating factors (CSF's) reports were given on presently available data.

Dr. W. Steward (Christie Hospital, Manchester)
In Manchester a phase I study on granulocyte-macrophage (GL)-CSF was performed using a 40 minutes intravenous infusion daily. White blood cell (WBC) increments could be obtained at doses above 3 g/kg.

There was a biphasic rise in WBC at doses above 10 g/kg/day and a fall of WBC within 48 hours after discontinuation of GM-CSF. The maximum tolerated dose was 60 g/kg and was determined by sudden death, pericarditis and severe dyspnoea.

From this and other phase I studies it can be concluded that the optimal way of administration of GM-CSF is by continuous infusion, but subcutaneous administration appears to be almost as effective and is certainly more convenient for the patient. With respect to side effects, glycosylated and non-glycosylated GM-CSF's appear to have different profiles (Table I).

Severe long term toxicity in man has as yet not been observed, but potential risks of long term uses of all CSF's might be:
- diversion of stem cells into specific lineage;
- reduction in the production of other cells;
- stimulation of natural leucocytes to produce potentially toxic products;
- increased expression of cell surface antigens with enhancement of local inflammatory response;
- bone marrow aplasia after long term administration of chemotherapy in combination with CSF.

Dr. T. Tursz (Institute Gustave Roussy, Villejuif)
A phase I study using daily s.c. injections of non-glycosylated GM-CSF for 10 days is presently ongoing in the Institute Gustave Roussy. Only 6 patients are now evaluable, but a rise in WBC could already been observed at doses of 250 and 500 g/m2/day, while remarkably they also find a rebound effect on platelet counts.

Dr. J. Verweij (Rotterdam Cancer Institute)
In Rotterdam a study is ongoing where a standard dose of twice daily s.c. administered glycosylated GM-CSF is being used. However different numbers of days of administration (1,3,5,7 and 10) are investigated in cohorts of 6 patients. The patients are not receiving GM-CSF after the first course of chemotherapy and thus can serve as their own control with regard to the effect of the GM-CSF introduction. Although the study is not yet finalized, the impression is that 10 days of GM-CSF administration results in a better decrease in chemotherapy-induced WBC toxicity than fewer days of administration. At the Free University in Amsterdam similar data are available for continuous infusion.

Proposals for new studies in advanced soft tissue sarcomas
There was general agreement that in view of the response rates in soft tissue sarcomas using standard doses of cytotoxic drugs, our aim in using CSF's should be trying to increase the dose of the cytotoxic drugs rather than trying to reduce toxicity.
For several reasons it was decided to use the combination of doxorubicin and ifosfamide for future studies, drafting the following phase II-study protocols subsequently.

a. doxorubicin 75mg/m2 + ifosfamide 5gr/m2 on day 1, followed by GM-CSF s.c. once daily d 2-16, q 3 weeks.

b. doxorubicin 75mg/m2 + (if feasible) day 1 + ifosfamide (dose yet to be set) day 1-3, followed by GM-CSF s.c. once daily d 2-16, q 3 weeks.

c. doxorubicin + ifosfamide in the optimal ways of administration (to be derived from a and b) + GM-CSF s.c. twice daily.

Study a) is scheduled to start in March/April 1989 and to replace the ongoing study EORTC 62851 (at present randomly comparing doxorubicin and doxorubicin + ifosfamide).

Dates of next meetings:
March 17-18, 1989: Antwerp September 1-2, 1989: London April 18-20, 1990: Warsaw

TABLE I : SIDE EFFECTS OF GM-CSF

SIDE EFFECT	GLYCOSYLATED GM-CSF	NON-GLYCOSYLATED GM-CSF
CANULA EXIT BLOCKAGE	+	+
ABDOMINAL PAIN	+	-
ERUCTATION	+	-
FLUID RETENTION	+	-
PRURITUS	+	+
BONE PAIN	-	+
LOCAL ERYTHEMA	+	-