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
EORTC Data Center
125 Boulevard de Waterloo
1000 Brussels
Tel : (2)539.28.05 - Fax : (2)539.03.74

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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.

INFORMATION ON THE DATA CENTER OF EORTC

Telefax : (2)539.03.74

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BOOKS

Multimodal Treatment of Ovarian Cancer
Editors : P.F. CONTE, R. ROSSO, N. RAGNI, J.B. VERMORKEN
Monograph Series of the EORTC (Volume 20)
Raven Press, New York, 1989
329 pages
ISBN 0-88167-476-1 (Order Code 1942)

Progress and Controversies in Oncological Urology II
Progress in Clinical and Biological Research Volume 269
Editors : F.H. SCHRÖDER, J.G.M. KLIJN, K.H. KURTH, H.M. PINEDO, T.A.W. SPLINTER, H.J. de VOOGT
EORTC Genitourinary Group Monograph 5
628 pages
ISBN 0-8451-5119-3

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REPORT EORTC G.I. TRACT CANCER COOPERATIVE GROUP MEETING PARIS, OCTOBER 7-8, 1988

Chairman : U. METZGER

H. Bleiberg was elected as new Chairman of the Group ; J.C. Pector remains Secretary for one year.

1.0 Recently closed to patients' entry

1.1Rectum

40761 : **Preoperative radiotherapy as adjuvant treatment in operable rectal cancer** (Study coordinator : A. Gerard, Brussels)
Methods : Patients randomized to no adjuvant treatment or preoperative irradiation therapy administered in a dosage of 34.5 Gy divided into 15 daily doses of 2.3 Gy.
Results : Four hundred sixty six patients accrued between June 1976 and September 1981. Tolerance and side effects of preoperative irradiation found acceptable. Overall 5 year survivals similar in both groups. Local recurrence rates at 5 years were 30% and 15% in control group and the adjuvant radiotherapy group respectively (p = 0.003). Results to be published in "Annals of Surgery".

40811 : **Controlled trial of resectable (stage C1, C2, C3) rectal cancer to evaluate postoperative radiotherapy**
Methods : Patients randomised between no radiotherapy and radiotherapy after surgery (46 groups in 23 fractions given in 30 to 38 days).
Results : One hundred and seventy one patients registered until protocol closed in December 1986. Follow up excellent for all institutions, with the exception of 2 which have been excluded from the study. Patients and tumor characteristics similar in both groups. Radiotherapy given after a 34 day median duration after surgery but in 28/76 patients, radiotherapy began after 50 days or more. Four irradiated patients developed an intestinal occlusion. Follow up is continuing.

1.2 Colon

40812 (Study coordinator : U. Metzger, Zürich).
To determine if the use of 5FU through the portal vein improves survival of patients who received curative surgery for colorectal cancer.
Treatment schedule : patients who had curative resectable colon cancer (Dukes A-C) distributed in 3 groups : 1) no adjuvant therapy ; 2) portal vein perfusion with 5000 IU heparin/day for 7 days ; 3) portal vein perfusion with 500 mg/m$^2$ 5FU + 5000 IU heparin for 7 days.
Results : Up to June 1987, 245 patients have been randomized. Due to a low accrual rate patient entry has been stopped. The treatment was well tolerated and toxicity was low. Data on disease free survival and survival not yet available.

40781 : **Double blind phase III clinical trial of adjuvant levamisole versus control in resectable Duke's C colon cancer** (Study Coordinator : J.P. Arnaud, Strasbourg).
Objective : determine the effect of levamisole on survival of patients who received curative surgery for colorectal cancer.
Treatment schedule : two to five tablets of 50 mg levamisole versus placebo daily, depending on body weight, for one year.
Results : from 1978 to 1987 297 patients were entered. Levamisole was generally well tolerated, with only four reversible cases of agranulocytosis reported among 129 patients. There was no benefit from levamisole on disease-free survival or on survival. The final results will be published in the "British Journal of Surgery".

40833 : **Randomized phase II study of a combination of cisplatin (DDP), 5-fluorouracil (5FU) and allopurinol (HPP) versus 5FU in advanced colorectal carcinoma** (Study Coordinator : H. Bleiberg, Brussels).
Objective : Improve the therapeutic index of fluorouracil by combination with cisplatin as enhancing agent and to allopurinol as toxicity modulator.
Treatment : Patients with measurable colorectal carcinoma, previously untreated by chemotherapy were randomised to receive either 5FU alone 500 mg/m$^2$ push IV d 1-5 or allopurinol 3x300 mg p.o., d 1-5, 5FU 800 mg/m$^2$ push IV, d 3-5 and DDP 50 mg/m$^2$ d 6. Treatment was repeated every 4 weeks.
Results : Six partial responses seen in each treatment group (15%) and the median survival was 7 months. Hematologic toxicities comparable in both treatment groups. Patients in the allopurinol group had less diarrhea (33 vs 43%) and stomatitis (10 vs 43%).

2.0 Active trials

2.1 Colon

40872 : **Randomised phase II study of low dose methotrexate (LD-MTX) plus high dose 5-fluorouracil (HD-FU) versus HD-FU in advanced or metastatic colorectal carcinoma** (Study Coordinator : G. Blijham, Maastricht).
Objective : To assess the response rate of high dose 5FU combined with low dose MTX.
Treatment : Patients randomised to receive 5FU 60 mg/kg IV as a continuous 48 h infusion every week for a total of 4 doses, then every other week for another 4 doses with or without MTX, 40 mg/m$^2$ IV push before and 48 hrs infusion with 5FU.
Results : Up to September 1988, 66 patients have entered the trial. Toxicity grade 3 was noted in 2 patients in the high dose arm and in 3 patients in the low dose arm. No data available yet concerning response rates.

40863 : **Pilot study on the regional treatment of colorectal liver metastases by intermittent arterial ischaemia with degradable starch microspheres (DSM) and arterial and portal infusion with mitomycin-C plus 5FU** (Study Coordinator : Civalleri).

Objective : Evaluate the therapeutic value of combination arterial and portal chemotherapy with mitomycin C bolus infusion plus 5FU continuous infusion associated with arterial embolization with DSM.
Treatment : Before starting chemotherapy the arterial catheter perfusion of the liver and the vascularity of metastases are evaluated by an intraarterial perfusion scan.
DSM administration is monitored using a sodium-iodine detector connected to a one-channel analyzer and the pulses collected are further processed using a computer with a printer.
Mitomycin C 10 mg/$m^2$ is given on day 1 2/3 by arterial route mixed with DSM, 1/3 by portal route. 5FU 500 mg/$m^2$ to be given as a continuous infusion from day 1 to 5.
Results : Fourty patients entered in this study. Major difficulty due to portal catheter mobilisation occurred. A new study excluding the portal route will be designed.

2.2 Hepatocarcinoma

**40861 : Double blind clinical trial of an antiandrogen therapy versus a placebo in unresectable hepatocellular carcinoma** (Study Coordinator : H. Bleiberg).
Objectives : To test the activity of anti-androgen therapy in terms of tumor response and survival.
Treatment : Patients to be randomised to receive Ananandron + placebo or Zoladex + placebo, which will all be administered with the same schedule.
Results : Up to September 1988, 49 patients have been randomised. No major side effects were reported.

**40871 : A simple large scale, randomised phase III trial on hepatic perfusion of 5FU and heparin in resectable cancer of the colon and rectum**
Objectives : To determine if adjuvant therapy with portal vein perfusion of 5FU + heparin improves survival and/or time to disease recurrence in patients with colorectal cancer after potentially curative surgery. The treatment hopes to detect an improvement of 70 to 80% over surgery alone.
Treatment : Patients randomised to the control group will receive no further treatment after surgery. Patients randomised to the treatment group will receive 500 mg 5FU/$m^2$ + 5000 IU of heparin per 24 hrs for a total of 7 consecutive days.
Results : Up to September 30, 1988, 209 patients were registered. Contacts were taken with other groups which could enter patients in this trial.

3. New protocols

Dr. J. Jeekel (Rotterdam) presented a draft protocol for patients with pancreatic cancer who underwent a pancreatectomy with a curative aim. Patients to be randomized after surgery between a control arm and an arm combining radiotherapy (2x 20 Gy with an interval of 2 weeks) and 5-FU (25 mg/kg/day during days 1 to 4 of radiotherapy). The final version of this protocol will be submitted to the next session of the PRC.

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## REPORT EORTC HEAD AND NECK CANCER COOPERATIVE GROUP MEETING
## PARIS, SEPTEMBER 28, 1988

Chairman : G. Snow (Amsterdam)

1. Review of ongoing studies

**24842 : Phase II trial of cisplatin, methotrexate, bleomycin and vincristine (CABO) vs cisplatin and 5-fluorouracil (CF) v s cisplatin alone (C) in patients with advanced squamous cell carcinoma of the head and neck** (Study Coordinator : M. Clavel).
Three hundred eighty two patients entered the trial up to the last EORTC Head and Neck meeting when the study was closed for accrual. Three hundred sixty nine patients were reviewed ; 18 not eligible. Thirty not evaluable for response. Three hundred twenty one patients fully evaluable. Fourty five patients were not pretreated. No patient received prior chemotherapy. The overall response is summarized :

| % | CABO | CF | C |
|---|---|---|---|
| CR | 11%<br>C1* (5-18) | 1%<br>(8-4) | 4%<br>(0-8) |
| PR + CR | 37%<br>(27-47) | 33%<br>(22-43) | 14%<br>(6-21) |

C1* is the 95% confident interval.

The comparison between the 3 arms shows a significant difference. CABO and CF are significantly better than C for the overall response. There is a trend in favour of CABO versus CF in regard to CR rate. No difference was found in either hematological or non hematological toxicity.

**24844 : Randomized trial of 5-fluorouracil/cisplatin as induction chemotherapy followed by surgery and postoperative irradiation versus surgery and postoperative irradiation alone in the treatment of advanced squamous cell carcinoma of the lateral oropharynx and the lateral posterior oral cavity, a phase III study** (Study Coordinator : G.B. Snow).
Until now nearly 80 patients have been entered. The study coordinator will prepare an interim report early next year to be presented at the Spring meeting of the group. On quite a few patients, however, data are still missing and the participating institutions are once more requested to send the missing data to the Data Center at their earliest convenience.

**24851 : Phase II study of 4'-epidoxorubicin in recurrent or metastatic adenoid cystic carcinoma of the head, and neck** (Study Coordinator : J.B. Vermorken).
Seventeen patients have now been entered of whom 16 are evaluable. Complete or partial responses were not noted, so that according to WHO criteria epirubicin is not active in this disease. However, 3 patients had symptomatic improvement, one of whom is now without symptoms for more than 2 years. This study is now closed (see for next study on adenoid cystic carcinoma under report of subcommittee on chemotherapy).

**24871/08871 : EUROSCAN : intensive screening and/or chemoprevention, with vitamin A and/or N-acetylcysteine, of second primary cancer in patients curatively treated for carcinomas of the larynx, oral cavity and lung** (Study Coordinators : U. Pastorino, N. de Vries, N. van Zandwijk).
Until now 25 patients have been entered, although 30 institutions in the European countries have been provided with medication. Ethical committees, regulations and initial organization within the participating centers are the main causes of the delay in accrual. By this time most of these problems have been solved and it is hoped that many patients will be entered in 1989.

**24872 : Randomized phase II trial of methotrexate vs 10-EdAM, a new methotrexate analogue, in patients with advanced squamous cell carcinoma of the head and neck** (Study Coordinator : J. Schornagel).
The entry rate of patients in this protocol is very satisfactory. Fifty-seven patients have been randomized. Responses have been seen in both arms (MTX or 10-EDAM). Sending in of forms is of major importance. If promising in December a decision will be made to continue as a phase III trial.

2. New protocols

**24873 : Phase II study of pirarubicin (THP) in patients with advanced squamous cell carcinoma of the head and neck** (Study coordinator : P.J.M. de Mulder).
This phase II protocol has now been approved by the PRC. This is second line chemotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck, progressing after first line chemotherapy (like 24872). Patients can be entered.

**24881 : Phase II study of epirubicin and cisplatin in advanced nasopharyngeal carcinoma (NPC)** (Study coordinator : F. Cognetti).
Has also been approved by the PRC. Patients can be entered into the study.

**24882 : Phase II study of mitoxantrone in recurrent or metastatic adenoid cystic carcinoma of the head and neck** (Study coordinator : J. Verwey). Has been accepted by the PRC pending several modifications. As soon as the final version of this protocol has been finalized, it will be mailed to the members of the group.

3. Reports of subcommittees

Subcommittee on chemotherapy

- Amongst the members of the subcommittee a phase II study of 5-fluorouracil given by continuous I.V. infusion (C.I.V.I.) in patients with advanced squamous cell cancer of the head and neck is being carried out (this is not an official EORTC study). It has been shown at the previous meeting that CIVI 5-FU is not active in patients with pretreated lesions. As responses have been observed in patients with non-pretreated lesions further evaluation will be done in that category of patients (up to a total number of 25 evaluable patients).

- A protocol has been designed by Dr. P. de Mulder for a "Phase II study of loco-regionally injected recombinant interleukin-2 (rIl-2) in locally far advanced non-pretreated head and neck squamous cell carcinoma (H&NSCC) (Study coordinator : P.H.M. de Mulder). This study is being carried out amongst the Dutch members of the subcommittee. It is at present not an official EORTC study.

- Quality Control : it was decided that this would be connected to the pirarubicin study in a prospective manner. It includes data control, visits at the different institutes, check-lists for patient follow-up, check on informed consent, etc.

- A master protocol for phase II studies in squamous cell carcinoma of the Head & Neck has been prepared by Dr. P. de Mulder and been submitted to the PRC.

Subcommittee on Radiotherapy

Again a phase III study together with the EORTC Radiotherapy Group : comparing radiotherapy alone with upfront chemotherapy followed by radiotherapy in patients with T3 laryngeal carcinoma has been discussed. Very few members of the group would support this study in terms of active participation. It has been decided to await the discussion on this study within the EORTC Radiotherapy Group. The Radiotherapy Group in the meantime has discussed this proposal at its Autumn meeting in Besançon. Also in the Radiotherapy Group too little support exists for this study. It is therefore concluded to be not feasible.

4. Business meeting

- The minutes of the previous meeting, Rome April 29, 1988, were approved.
- Concern has been brought forward about the group at the moment not having a statistician assigned by the Data Centre to the Group. Action will be taken on this point by contacting Dr. Staquet, Director of the Data Centre.
- At the next meeting Dr. Snow and Dr. Clavel will step down as chairman and secretary according to the statutes. Unanimously, Dr. J.L. Lefebvre from Lille, France and Dr. Cognetti from Rome, Italy were elected and approved by the membership as he next chairman and secretary. They will both take office at the next meeting.
- The next meeting will be on May 13th, 1989, in the Institut Jules Bordet, rue Héger-Bordet, 1, Brussels, Belgium. Our host will be Dr. P. Dor

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## REPORT EORTC EARLY CLINICAL TRIALS GROUP MEETING LUGANO, OCTOBER 27-28, 1988

Chairman : F. Cavalli

1. New drugs presented to the Group

**Benzothiopyranoindazole CI-958 (Warner-Lambert)**
The benzothiopyranoindazoles differ structurally from the anthrapyrazoles in that the carbonyl at the 6-position has been replaced with a sulfide linkage. These compounds are potent inhibitors of both DNA and RNA synthesis to an equal extent at approximately the same drug concentration and are similar in this respect to doxorubicin and mitoxantrone. They cause DNY SSBs and DSBs in a time and concentration-dependent manner. These breaks were tightly associated with protein. The benzothiopyranoindazole induced breaks were very slowly repaired.

These compounds induced far less (50 to 70-fold) superoxide dismutase-sensitive oxygen consumption than doxorubicin in the rat liver microsomal system, a property which can be related to the reduced cardiotoxicity.

The most active compounds of this series - including CI-958 - exhibited in animal models a broad spectrum of antitumor activity. CI-958 showed high levels of activity in P388 and L1210 leukemia, M5076 sarcomas, colon adenocarcinoma 11a, mammary adenocarcinoma 13c and the Ridgway osteogenic sarcoma.

Toxicity studies were done in mice, rats and dogs. A dose-related transient leukopenia associated with thrombocytopenia only at the higher doses, was observed after single and five day IV administration in rats and single IV administration in dogs.

A dose-related hypocellularity of bone marrow and lymphoid depletion of the spleen were observed in all high-dose animals. All the effects on the bone marrow and lymphoid tissues were reversible. Warner-Lambert/Parke-Davis has proposed to the Group, through the NDDO, to perform phase I studies with two different schedules (single intermittent every 3 wks and d x 5 every 3 wks). These studies could possibly start within April 1989.

**Somatostatin analog (BMY-41606) (Bristol-Myers)**

The cyclic tetradecapeptide somatostatin is widely distributed in the body, and it has been found in high concentrations in the CNS, GI tract, pancreas. Somatostatin has a broad spectrum of biological actions, including inhibition of anterior pituitary secretions, inhibition of exocrine and endocrine secretions, modulation of peptide growth factors such as EGF, IGF-1. The compound has shown some efficacy in the treatment of acromegaly, diarrhea, pancreatitis, and in the control of carcinoid syndrome due to ectopic tumors like gastrinomas and vasoactive intestinal peptide (VIP) producing tumors.

Its clinical use has been hampered by its multiple actions and the short duration of the antisecretory effects, the half-life in the circulation being about 3 minutes. Therefore, the main prerequisites for developing somatostatin analogs were a selectivity of action, longer half-life and an increased potency.

BMY-41606 the octapeptide analog of somatostatin was selected for clinical studies on the account of the higher potency in the inhibition of growth hormone release in vivo in rats (the potency of the analog being 120 fold that of the parent compound), its almost selective action on the suppression of GH secretion, its prolonged duration of action (of at least 3 hours).

The proposed mechanism of antitumor effect of the somatostatin analogs could be a direct antiproliferative effect, via somatostatin receptors or via other hormonal receptors. High levels of membrane receptors for somatostatin have been found in the endocrine tumors of the gastroenteropancreatic system, in which the use of somatostatin has been associated with a prompt and sustained relief of the symptoms in a high percentage of the patients.

The indirect mechanism of antitumor effect includes :

1. The inhibition of the release of the GH and, under certain conditions, of prolactin, which may contribute to the growth inhibition of breast and prostate tumors.
2. The modulation of growth factors like IGF-1 and EGF, either reducing their levels, either reversing the stimulatory effect of EGF on the phosphorylation of the tyrosine kinase portion of the EGF receptor.
3. Interference with the synthesis of autocrine growth factors by tumor cells.

In addition, somatostatin analogs can suppress the release or action of gastrointestinal hormones which could be involved in the growth of pancreatic and colorectal cancers.

The antitumor activity of the somatostatin analog BMY-41606 has been shown in vitro in the human breast cancer MCF-7, in the pancreatic carcinoma MiaPaCa, in the Gerlil fibroma. In vivo antitumor activity has been reported in the Dunning R3327 prostate carcinoma, MT/W9A mammary carcinoma and pancreatic tumors of rats and hamsters.

The efficacy/toxicity of the somatostatin analogs might be influenced by the specific analog used, the schedule applied, the dose administered, the tumor type tested and the presence of somatostatin membrane receptors. From the in vivo preclinical studies it appears that the best antitumor effect is achieved with the administration of the drug as a continuous infusion or as a depot form, and that the somatostatin receptors are not always required for an antiproliferative response.

Pilot phase I-II studies have been done in Villejuif with s.c. doses of 100-400 ug BID or TID in patients with pancreas, carcinoid and lung small cell tumor. The side effects observed were represented by steatorrhea, abdominal cramps, weight loss. A phase I study with the IV continuous infusion schedule is ongoing in Bellinzona in patients with solid tumors. The drug is administered for at least 28 days from a starting dose of 1000 ug/m$^2$. In this study also the hormonal suppression induced by BMY-41606 will be evaluated, through repeated assessments of the serum levels of GH, IGF-1, EGF and prolactin. The optimal dose, derived from the results of this phase I, will be defined not only on the basis of the dose-related toxicity but taking into account also the existence of a dose-response relationship and the correlation observed between the biological activity and the antitumor effect.

**2. Phase I studies**

**Anthrapyrazole CI-941**

Schedule : IV bolus, every 3 wks (Sutton).
The starting dose of 5 mg/m$^2$ has been escalated by 5 mg/m$^2$ increments up to 45 mg/m$^2$. Thirty three patients have been treated for a total of 65 courses administered. Grade 3-4 leukopenia was observed from 35 mg/m$^2$ (see table).

| Dose | No. courses / pts | Median WBC nadir (range) | Max. toxicity grade pts | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| 35 | 10 / 5 | 2.3 (0.4 - 3.5) | 5 | 1 | 2 | 1 |
| 40 | 15 / 6 | 2.9 (2.0 - 8.5) | 6 | 3 | . | . |
| 45 | 6 / 5 | 3.3 (1.4 - 7.7) | 5 | 1 | 2 | . |

The median time to nadir was 14 days. Thrombocytopenia gr 2 occurred only after one cycle at 30 mg/m$^2$. Mild to moderate nausea and vomiting and partial alopecia were observed from doses of 25 mg/m$^2$. Cardiac toxicity was never reported. The dose would be possibly escalated to 50 mg/m$^2$.

Schedule : IV bolus, weekly x 3, every 6 wks (Edinburgh, Glasgow).
Starting from 2 mg/m$^2$ the dose has been escalated up to 36 mg/m$^2$/wk. Forty one pts have been treated, 13 of them without a prior chemotherapy. In the 3 pts treated at 32 mg/m$^2$ the WBC nadir (X 10$^3$/ul) were : 0.9, 0.6, 1.1 on week 3. In the 2 evaluable pts treated at 36 mg/m$^2$, the WBC nadir were 1.0 and 0.4. Because of the hematologic toxicity observed this regime does not allow the administration of doses higher than those given with the single intermittent schedule and will not be further pursued.

**Elsamycin (Amsterdam)**

Schedule : IV 10 min infusion, every 4 wks.
Starting from 0.6 mg/m$^2$ (1/10 mouse LD 10) the dose has been doubled up to 19.2 mg/m$^2$ without any significant toxicity.

An analytical method has been recently developed at the Free University in Amsterdam and the AUC values achieved in animals and humans have been compared. The mouse AUC at the LD10 was 944'250 ug/ml X h and the human AUC at 9.6 mg/m$^2$ was 59'610 ug/ml X h, thus partly explaining the lack of toxicity observed. The drug is rapidly eliminated with a short ß half life.

**Esperamycin (Bellinzona, Nurnberg)**

Schedule : IV 10 min infusion, every 6 wks.
Starting from 1 ug/m$^2$ (1/10 mouse LD10) the dose has been escalated up to 3 ug/m$^2$. Twelve pts have been treated for a total of 19 courses administered. The non hematological side effects observed the day of the treatment were vomiting (starting from 1 up to 9 hrs after the administration), phlebitis (feeling of burning during the injection) and fever (starting from 2 up to 4 hrs after the administration). One patient treated at 3 ug/m$^2$ achieved a peak value of 39°C with generalized chills and dyspnea. The patient had a general history of allergy with bronchial asthma. After the second administration he rapidly developed rigors, severe dyspnea with bronchospasm, requiring a vigorous supportive therapy, followed, after 2 hrs, by pyrexia with a peak value of 39.7°C. Thrombocytopenia was observed in 2 among 3 pts treated at 1,5 ug/m$^2$ but not at the higher levels. Neither renal nor clearly drug-related hepatic toxicities were observed. The dose was going to be escalated to 4 ug/m$^2$.

**Duphar 113901 (benzoylphenylurea) (Amsterdam)**

Schedule : IV 0.3 mg/min, d X 5, every 4 wks.
This phase I study has been closed mainly because of coagulation problems, possibly related to the formulation used (the drug was given as microemulsion in Miglyol 812 neutral oil, a triglyceride of saturated fatty acids of medium chain length). The other observed side effects were shivers and headache. Since the compound might have a new mechanism of action, as a distorter of membrane, the drug company is developing a new formulation.

**Elliptinium chloride (9-hydroxydiethylaminoethyl ellipticine) ( SR 95156B) (Brussels)**

Schedule : 1 hr IV infusion, d X 3, every 3-4 wks.
(Some data were presented at the meeting of March 1988 in Geneva - see minutes of the general meeting).
Starting from 13 mg/m$^2$/d the dose has been escalated up to the currently tested level of 500 mg/m$^2$/d. Forty nine pts have been entered so far all pretreated but 1. At 400 mg/m$^2$ the median WBC nadir (x 10$^3$/ul) was 3.1 (range 1.9-14.4) occurring after 10-14 days and recovering about 3 wks after the treatment. Thrombocytopenia was unfrequent. Mild nausea and vomiting were frequently observed. The most important toxicity was represented by phlebitis, which was reduced by shortening the duration of the infusion from one hr to 30 min.

| Dose (mg/m$^2$/d) | Duration (h) | Number of cycles total | with phlebitis |
|---|---|---|---|
| < 220 | 1 | 81 | 3 |
| 220 | 1 | 3 | 3 |
| 220 | 0.5 | 7 | 3 |
| 300 | 0.5 | 7 | 3 |
| 400 | 0.5 | 11 | 6 |
| 500 | 0.5 | 1 | 0 |

The administration of 400 mg/m$^2$ as 10 min infusion was associated with hypotension. Hepatic toxicity, with pathological reversible modifications of the alkaline phosphatase and transaminases values, was observed in about 50% of the pts treated at 400 mg/m$^2$ and in the pt treated at 500 mg/m$^2$. Renal toxicity with slight reversible increases of the creatinine value, was also reported. No objective responses were seen. One previously untreated pt with NSCLC showed a NC of 18 +months. A minor response was seen in a previously treated pt with breast cancer. The study was still ongoing since the MTD had not been defined yet.

**Deoxyazacytidine (Nijmegen, Lyon)**

Schedule : 4 h infusion, d X 5.
The drug has been initially given as IV bolus to 27 pts from the starting dose of 0.35 mg/m$^2$/d to the highest dose tested of 5.60 mg/m$^2$/d. Because of the importance of the exposure time on the antitumor activity, the drug was then given as 4 h infusion at the dose of 11.2 mg/m$^2$/d. The MTD had to be defined yet.

**Aphidicolin glycinate (NSC 303812) (Bellinzona)**

Schedule : IV, 1 h infusion, d X 5, every 3 wks.
Nineteen pts have been entered and the dose has been escalated from 12 mg/m$^2$/d up to 1000 mg/m$^2$/d without any significant drug-related toxicity. The human AUC values at 1000 mg/m$^2$/d were 9.6 and 13.4 ug/ml x h, still far from the mouse LD10 AUC of 40.1 ug/ml x h. The dose was going to be escalated to 1500 mg/m$^2$/d.

**Pyrroloquinone GR 63178 A (Glaxo compound)**

The main preclinical features of the compound have been summarized in the minutes of the general meeting of March 1988.

Schedule : IV d x 5 every other wk (Edinburgh). The dose has been escalated from 40 to 120 mg/m$^2$.

IV weekly X 3 wks (1 cycle) for at least 2 cycles (Glasgow, Sutton). The dose has been escalated from 70 to 150 mg/m$^2$. The main side effects were headache, muscle pain, nausea and vomiting.

IV d X 3 every 3 wks for 3 wks (Rotterdam). The dose has been escalated from 50 to 100 mg/m$^2$. The main side effect was represented by nausea and vomiting.

**Dabis maleate (NSC 262666) (Rotterdam)**

Schedule : IV single bolus injection every 3 wks.
Starting from 50 mg/m$^2$, the dose has been escalated up to 900 mg/m$^2$. Seventeen pts have been treated all pretreated but 2. Nausea and vomiting were already present at the low levels, without any increase at the higher levels. Mild paresthesias were also observed. No leukopenia has been reported (the main animal toxicity was hematological). One cycle at 400 mg/m$^2$ was associated with thrombocytopenia. One patient with mesothelioma showed a > 50% tumor reduction in one site but had PD in the other sites. The MTD had still to be reached.

**3. Phase II studies**

**16864E Flavone acetic acid (FAA) in advanced non small cell lung cancer**
Among 21 pts entered (2 since the last meeting) 5 were not evaluable for response (early treatment discontinuation : 3 pts ; early death : 1 pt ; protocol violation : 1 pt) and 3 were too early. Since only 1 PR had been observed among 13 evalua

ble pts and it was orally reported that the 3 too early pts had not responded to the treatment, the study was closed.

**16864F Flavone acetic acid (FAA) (6 hr infusion) in advanced kidney cancer**
Among 21 pts entered (5 since the last meeting) 1 was ineligible (because of prior interferon), 7 were not evaluable (early treatment discontinuation) and 5 were too early for response evaluation. The study remained open.
N.B. : The study was closed on 9.1.1989.

**16864B Flavone acetic acid (FAA) (6 hr infusion) in advanced gastric cancer**
Six pts were entered (3 since the last meeting). Because of the very low accrual the study was closed.

**Pentostatin in malignant lymphoma**
16863 A (advanced Hodgkin's disease) = 3 pts entered (1 ineligible, 2 too early)
16863 B (intermediate, high grade T cell type NHD) = 7 pts entered (2 ineligible, 1 PR, 1 NC, 1 PD, 2 EP)
16863 C (low grade NHD) = 8 pts entered (3 too early, 3 NC, 1 PD, 1 EP).

**Current status of the phase II studies with DUP 785**

| Protocol number | Tumor type | Entered | Pts Inel/NE | too early | Eval. | Response | Status |
|---|---|---|---|---|---|---|---|
| 16871 C | Colorectal | 31 | 5/8 | 4 | 14 | 0 | closed |
| 16871 P | Pancreas | 6 | 1/1 | 3 | 1 | 0 | open |
| 16871 M | Melanoma | 11 | 1/3 | 0 | 7 | 0 | open |
| 16871 B | Breast | 6 | 1/1 | 3 | 1 | 0 | open |
| 16871 K | Kidney | 5 | 0/1 | 3 | 1 | 0 | open |

Among 29 eligible pts evaluable for hematological toxicity gr 3-4 leukopenia and/or thrombocytopenia after the first cycle were reported in 10% and 24% of the cases.
Among 39 eligible pts evaluable for non hematological toxicity the following gr 3-4 toxicities have been observed :

| | % of pts with toxicity |
|---|---|
| Nausea/vomiting | 8 |
| Oral | 20 |
| Skin | 13 |
| Diarrhea | 8 |
| Bleeding | 5* |

*1 pt died from bleeding

The phase II studies in patients with head and neck and non small cell lung cancer were activated in November 1988.

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## THE EORTC PROTOCOL REVIEW COMMITTEE

Chairman : J.G. McVie (Amsterdam, The Netherlands)

The Protocol Review Committee (PRC) consists of 17 reknowned specialists who represent the major EORTC Cooperative Groups, national Groups and each discipline involved in Oncology. Non EORTC members, at least 4, include an independent statistician who comments on all randomized protocols. In addition a panel of 20 consultants exists for referral of occasional protocols in highly specialized areas.

The PRC meets 4 times a year and reviews protocols submitted, according to agreed published guidelines for phase II and phase III protocols. Two or three members review protocols in depth, NCI Bethesda reviews all protocols, particularly with respect to repetition of work already done in the United States.

Routine phase II protocols, which are based on previously accepted master protocols are dealt with via a "quick procedure", which involves two medical oncologists and one pharmacologist reviewing the protocols within 2 weeks after submission. A special procedure has also been set up for phase I protocols in liaison with the New Drug Development Committee.
In 1988, 14 phase II protocols were submitted for the quick procedure, of which only 6 were accepted in the first round.

During full meetings of the PRC in 1988, 38 new protocols were seen and only 6 accepted without modifications, 21 were rejected and 23 were accepted pending modifications. A further 11 protocols were resubmitted, of which 6 were accepted and 13 protocols, which had previously been accepted pending modifications were amended to the satisfaction of the PRC.

A new task for the PRC, which has evolved in the last year, has been the review of all protocols failing to achieve 50% of predicted accrual in 2 consecutive years. After discussion with the chairman of the relevant Cooperative Groups 8 such protocols were stopped.

The overall impression of the PRC is that the quality of protocols has improved in the last few years, and that few fail now on technical grounds. This has led to a more critical ranking of priority based on scientific merit.

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