in the presence of good hemometry values. To date fifty-three pts entered into the study and 32 are evaluable for response and toxicity. The main characteristics of the evaluable pts were: median age 50 yrs; median Karnofsky PS 90; dominant site of disease: viscera 21 (62%), bone 4 (12%), soft tissue 9 (26%) of which 2 pts with locally advanced breast cancer (LABC), multiple site of disease 22 (65%). Globally 4 CR and 19 PR were observed for an ORR of 68%; there were 8 SD and 3 PD. Both the LABC pts achieved a PR and underwent to the surgery. Median duration of response was 9 months (range 4+–17+). A total of 188 cycles were administered: in 107 cycles (57%) it was possible to increase the mitoxantrone dosage and in 28 cycles (15%) the maximal dosage of 18 mg/mq was reached. In 43 cycles (23%) the interval among cycles was reduced. Toxicity was mild and gastrointestinal and hematological toxicity of grade (G) 3–4 was not observed. At nadir the most important hematological toxicity was leucopenia (85%), followed by anemia (76%) and thrombocytopenia (53%). Alopecia of grade G3 was seen in only 3 cases. The study is ongoing, but preliminary data show the F-FNC combination as a well tolerated and effective form of palliative treatment in ABC.

380 PUBLICATION

## PHASE I STUDY WITH WEEKLY PACLITAXEL (1 H) INFUSION IN HEAVILY PRETREATED ADVANCED BREAST CANCER AND OVARIAN CANCER PATIENTS

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*Introduction:* With the introduction of Paclitaxel (P) severe acute hypersensitivity reactions (HSR) attributed to the drug during phase I clinical trials led to subsequent changes. First, premedication was initiated prior to treatment and second, the duration of paclitaxel infusion was lengthened mostly up to 24 h. Recently in randomised trials the 3 h schedule and as well the 1 h schedule have proven to be safe there was no significant difference in acute HSR's, but a significant reduction of myelosuppression with the shorter infusion schedules. The optimal dose and schedule of P remained undefined especially with regard to combination chemotherapy. Therefore we performed a phase I study with a weekly 1 h infusion of P in heavily pretreated breast and ovarian cancer patients.

*Treatment:* Patients (pts) were treated with P (1 h infusion) once weekly. Each treatment cycle comprised of six weeks followed by two weeks rest. All pts were treated under outpatient conditions. Predmedication: dexamethason 8 mg p.o. 12 h and 6 h prior to each paclitaxel infusion and 30 min before treatment 400 mg cimetidine and 2 mg clemastine i.v. During Phase I we chose the following dose levels (dl): dl1 70 mg/m$^2$, dl2 80 mg/m$^2$, dl3 90 mg/m$^2$, dl4 100 mg/m$^2$. Maximal tolerable dose was defined: neutropenia 4°, thrombopenia $\geqslant$ 3°, other organ toxicity >2° according to WHO criteria.

*Patient characteristics:* 19 pts entered this trial (15 pts with advanced breast cancer, 4 pts with ovarian cancer): dl1 7 pts [86 single weekly doses (SWD) of P], dl2 5 pts (51 SWD), dl3 3 pts (37 SWD), dl4 4 pts (12 SWD). The characteristics were: age 54 yrs (32–73). WHO performance status 1 (0–2), metastatic disease sites 2 (1–4). Pts had a median number of 3 pretreatment regimens (1–4). All pts had anthracycline refractory disease in case of breast cancer and cisplatinum refractory disease in case of ovarian cancer.

*Toxicity and results:* No dose limiting toxicities occurred during dl1–3. With regard to the reduced premedication program in order to avoid corticosteroid side effects using the weekly schedule, it must be emphasized, that neither mild nor severe HSR's occurred. The following toxicities could be observed in 15 pts (dl1–3), 29 treatmeant cycles and 174 weekly doses of paclitaxel [grade WHO (number of cycles)]: neutropenia 3° (1), 2° (5), nausea/vomiting 1° (3); myalgia 1° (3); peripheral neuropathy 1° (6); mucositis 1° (7). After the second weekly application of paclitaxel at dl4 in 3 out of 4 pts the next infusion had to be postponed for 1 week because of neutropenia grade 4 WHO. So far no hospitalisations must be performed. Pts received a median of 2 treatment cycles. At all dl's responses could be observed, dl1: PR 1, SD 5, PD 1; dl2: PR 1, SD1, PD 3; dl3: PR 1, SD 1, PD 1; dl4: PR 1 not evaluable 3. MTD was reached using dl4, Dl 3 is recommended for phase II.

*Conclusions:* As with other antineoplastic agents, P is likely to make an impact when used in combination therapy. Our phase I study underlines that P, given in a weekly 1 h infusion, is safe and active in heavily pretreated breast cancer and ovarian cancer patients. Its moderate toxicity, especially with regard to myelosuppression, should lead to further studies using dl3 in order to better define the value of this schedule for the use in combination protocols.

381 PUBLICATION

## HIGH DOSE CHEMOTHERAPY (HDC) WITH G-CSF AND PERIPHERAL BLOOD STEM CELL SUPPORT (PBCS) IN ADVANCED BREAST CANCER (ABC)

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There is a dose-response relationship in ABC. HDC with autologous bone marrow transplantation, after conventional induction chemotherapy enhance complete response rate, but we still ignore the long term survival benefit. Another approach is to use very HDC at induction with PBCS.

We have begun a trial with epirubicin (100 mg/sqm) and cyclophosphamide (3000 mg/sqm) q 2 week × 4. PBCS were collected after the 1st course and reinfused after course 3 and 4.

As for February 1995, 12 ABC pts have received 42 courses. Relative dose-intensity was 92%. Median duration of grade 4 leukopenia lasted 3, 5, 8 and 8 days after successive courses with a median duration of fever of 3–5 d. However rehospitalization for IV antibiotics was required in less than 33 % of pts. Grade 3–4 thrombocytopenia appeared after cycle 3. Other side effects were grade 0–3 and manageable. 6/18 pts achieved a PR. This treatment appears feasible and further pts will receive 6 courses. Actualized results will be presented.

382 PUBLICATION

## PRELIMINARY EFFICACY AND TOLERANCE RESULTS OF DOCETAXEL (TAXOTERE) (TXT) IN HEAVILY PRETREATED METASTATIC BREAST CANCER PATIENTS (MBC)

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The activity/safety profile of TXT in heavily pretreated MB pts is of interest to the practicing oncologist. *Pts char:* From Aug 1994 to Feb 1995, 29 women with heavily pretreated MBC, have received TXT: 24 pts with 100 mg/ and 5 pts with 70 mg/sqm q 3 weeks given with steroids premedication: median age 53 years [42–75]; PS (WHO) 0–1: 16 pts (55%), 2: 9 pts (31%), 3: 4 pts (14%), median time diagnosis first relapse: 28 months (m) [1–216]; median time first relapse/TXT: 40 m [1–164]; Metastatic Sites: liver: 17 pts (58%), bone: 16 pts (55%), lung: 14 pts (48%), skin: 12 pts (41%), lymph nodes: 2 pts (6%), CNS: 4 pts (14%), miscellaneous: 1 (3%). Number of sites/pt: 1: 6 pts (20%), 2: 13 pts (45%), $\geqslant$3: 9 pts (31%); CA 15-3 was increased in 20 pts (68%). Median nb previous chemotherapy (CT) lines: 4 [2–11], with anthracyclines 27 pts (93%); 16 pts (55%) had also Mitoxantrone; previous hormonotherapy in 25 pts (86%). *Toxicity:* 123 cycles (cy); median (cy) nb/pt: 4 [1–10]; 84 (cy) and 28 (pts) evaluable for hematol Tox, 13 cy (23%) grade III and 44 cy (52%) grade IV neutropenia, 5 cy (6%) grade III–IV thrombocytopenia; 106 cy and 28 pts evaluable for non hematol Tox: asthenia (100%); 5 episodes of mucositis grade III, other Tox: edema: 15 pts (53%) (1 severe); nail changes: 12 pts (42%). *Activity:* 22 pts evaluable (2 early death and 5 too early): 4 PR (6+, 7+, 7+, 8), 11 Minor Response, 7 PD. Median TIP (all pts) 3 months (1–8). Encouraging results and acceptable toxicity in a multitreated cohort confirm the value of TXT and its interest as second or first line treatment in MBC.

383 PUBLICATION

## COMPARATIVE STUDY: PIRARUBICIN VS DOXORUBICIN IN COMBINATION WITH CYCLOPHOSPHAMIDE AND FLUOROURACIL IN THE TREATMENT OF BREAST CANCER

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Pirarubicin, an anthracycline antibiotic without significant cardiotoxicity in preclinical and clinical trials, showed equal antineoplastic effect but less alopecia than doxorubicin in patients with breast cancer. A prospective, randomised phase III study of FPC versus FAC in the treatment of advanced breast cancer was carried out in Croatia in 9 clinical centres during 2 years. A total of 94 patients was entered into the trial and 87 patients were evaluable for responses. The patients characteristic were

well balanced: age < 72; PS 0–3; evaluable lesions; no prior anthracycline therapy; absence of cardiopathy. Patients were given cyclophosphamide and 5-fluorouracil 500 mg/m$^2$ each and either doxorubicin or pirarubicin 50 mg every three weeks-6 cycles.

Efficacy: FAC group: CR −6/44, PR −15/44;

FPC group: CR −7/43, PR −12/43; statistically N.S.

Toxicity (myelosupression, nausea-vomiting, cardiotoxicity) was similar in both groups. Alopecia: FAC group: gradus 2 −8/43, gradus 3 −29/43;

FPC group: gradus 2 −10/44, gradus 3 −11/44;

$P < 0.0000001$ significantly favouring FPC.

Pirarubicin gives better life quality to patients with advanced breast cancer and should be an anthracycline of choice in young, high risk patients with early breast cancer submitted to the adjuvant chemotherapy, causing less alopecia.

384 PUBLICATION

## PILOT STUDY OF TAXOTERE IN TAXOL-RESISTANCE METASTATIC BREAST CANCER (TRMBC)

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Ten patients (pts) with MBC who had primary/secondary resistance to Taxol (135–250 mg/m$^2$ over 3–24 hours) were treated with Taxotere 100 mg/m$^2$ every 21 days. *Pts characteristics (10):* med age, 47 yrs (37–61); med Zubrod PS, 1 (0–2); med # sites 3 (2–5); disease sites: liver 9/10, bone 4/10, soft tissue/LN 7/10; med # of prior CT was 2 (1–3); 9/10 had prior anthracycline therapy. *Results:* 10 pts were evaluable for response. Responses: 1 MR, 4 NC and 4 PD. *Toxicity:* to date, 10 pts received 30 cycles. *Hematological:* med nadir granulocytes ($\times 10^3$)/dl: 0.3, med nadir platelet count ($\times 10^3$)/dl: 236,000. 4 pts had 8 cycles complicated with neutropenic fever. *Other toxicity (grade 2 or greater) by # pts (# cycles):* stomatitis 3 (5), diarrhea 4 (5), fatigue 8 (14), myalgias 7 (12), skin 5 (9), paresthesias 7 (13). *Conclusion:* The preliminary data of this ongoing trial showed that Taxotere has activity in TRMBC.

385 PUBLICATION

## PILOT STUDY OF CONTINUOUS INFUSION 5FU AND BOLUS DOXOCUBICIN AND CYCLOPHOSPHAMIDE FOR BREAST CANCER

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The therapeutic index of 5FU is improved with continuous iv infusion (ci) compared with bolus administration. We have combined 18 weeks ci5FU with 6 courses of bolus doxorubicin (50 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) q3/52, aiming to develop a regimen for neoadjuvant treatment of breast cancer. 25 patients have been treated 6 large operable tumours, 5 locally advanced disease, and 13 metastatic disease.

| 5FU mg/m$^2$/day | Patients treated | Neutropaenia grade 3 | Neutropaenia grade 4 | Mucositis grade 2 | Mucositis grade 3 |
|---|---|---|---|---|---|
| 100 | 6 | 4 | 1 | 4 | 0 |
| 150 | 4 | 1 | 2 | 3 | 0 |
| 200 | 14 | 5 | 7 | 7 | 2 |

The 3rd dose level produced tolerable toxicity. WHO grade 3–4 neutropaenia was frequent but short-lived in the majority. Mucositis required 5FU dose reduction in 2 patients. Two patients had neutropaenic sepsis and one died of unresolving pneumonia. Grade 2 plantar palmar skin toxicity occurred in 5 patients and grade 2 diarrhea in 2. Hickman line-associated proximal vein thrombosis occurred in 4 patients despite prophylactic warfarin (1–3 mg/d). The response rate in 20 evaluable patients was 5 CR, 9 PR, 3 SD, 2 PD. Patient accrual will continue to further define the response rate in neoadjuvant patients.

# Head and neck tumours

386 ORAL

## PREVENTION OF SECOND PRIMARY TUMORS WITH A SECOND GENERATION RETINOID IN SQUAMOUS CELL CARCINOMA OF ORAL CAVITY AND OROPHARYNX: LONG TERM FOLLOW-UP

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Retinoids exert a prophylactic action on the development of epithelial cancers when tested on human premalignant lesions, and are now used in the chemoprevention of epithelial cancers, in randomized trials. We prospectively studied 316 patients who developed squamous cell carcinoma of the head and neck, classified as T1/T2, N0/N1 ⩽ 3 cm, M0. Patients were randomly assigned to receive orally, either etretinate (a loading dose of 50 mg per day the first month, followed by a dose of 25 mg per day the following months) or a placebo for 24 months. Adjuvant treatment began no later than 15 days after surgery and/or the initiation of radiotherapy. The five-year survival rate and disease free survival rate are similar in the two groups. There are no differences regarding either local, regional and distant relapses (logrank NS). After a median follow-up of 65 months. forty two patients in the etretinate group and forty in the placebo group, developed a second cancer, with respectively 18 and 17 in the head and neck region. Adjuvant treatment was definitively discontinued mainly due to toxicity in 33% of patients in the etretinate group versus 23% in the placebo group ($P < 0.05$). Etretinate, a second-generation retinoids, does not prevent second primary tumors in patients who have been treated for squamous cell carcinoma of oral cavity and oropharynx.

387 ORAL

## CHROMOSOMAL ABNORMALITIES INVOLVING 11Q13 ARE ASSOCIATED WITH POOR PROGNOSIS IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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The karyotype is an independent prognostic factor in certain hematologic malignancies and solid tumors, but no such data have so far been reported in squamous cell carcinoma of the head and neck (SCCHN).

*Material & methods:* The present study included 116 patients. Samples were obtained from diagnostic biopsies or at operation 1987–1991. The samples were short-term cultured in 5–10 days before karyotyping. Due to karyotypic findings patients were divided into four groups: Normal karyotype (k1), numerical changes only (k2), simple structural rearrangements (k3) and complex karyotype (k4).

*Results:* Survival was significantly shorter in k4 than in k1–3 in the total material ($P = 0.02$), as well as among laryngeal carcinomas, the largest subgroup ($P = 0.045$). The most common breakpoint was 11q13 seen in 11 tumors, 10 of which also showed complex karyotypes. Survival was significantly shorter for patients with 11q13 rearrangements ($P = 0.001$).

*Conclusions:* Complex karyotype and 11q13 aberrations are independent prognostic factors in cases of SCCHN. The oncogene *prad1*, encoding for Cyclin D1, is located in 11q13, and studies regarding amplification of *prad1* and overexpression of Cyclin D1 are now initiated in our laboratory.