6 complete responses (16.6%) and 22 partial responses (61.1%) for an overall RR of 77.7%. Responses were observed at all dose-levels.

Conclusions: The alternating administration of D and M is feasible and safe. This schedule allowed a dose intensification of mitoxantrone up to 108% without reaching yet the MTD.

683 POSTER

Endocrine effects of toremifene (TOR) at the level of CNS in advanced breast cancer patients

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Purpose: To differentiate the antagonistic and agonistic effect of TOR (Fareston[R]) at the level of the hypothalamus-hypophysis (HT-HP) axis, LHRH test was performed during a phase II clinical trial.

Methods: In 15 postmenopausal patients with advanced breast cancer FSH, LH and PROL release – induced by LHRH agonist (Suprefact[R] 0.5 mg sc) – was monitored during a 16-week TOR treatment (60 mg/day po). The functional test was carried out prior TOR therapy and then 4, 8, 12, 16 weeks afterwards. Hormone levels were measured by RIA method.

Results: TOR sensitizes the HP to the action of gonadotrophins, the LHRH induced FSH and LH release has a considerable increasing tendency during the therapy. The fall of the base levels of FSH and LH in postmenopausal patients may be due to a partial agonostic activity on the HT or an antagonistic activity on the HP. An increased LH secretion was characteristic to the responders. Non-responders did not show a normal response to LHRH. It seems that a very sensitive HP function would predict the patients sensitivity to TOR treatment. The PROL release, induced by LHRH, was more pronounced in responders.

Conclusion: The antagonistic effect of TOR seems to be more dominant than the agonistic property. The LHRH test proved that TOR exerts its effect at the level of the HP. TOR did not affect adversely the normal endocrine regulation of breast cancer patients at the level of CNS.

684 POSTER

Navelbine (NVB) plus mitomycin (MMC) or mitoxantrone (MTZ) as salvage regimen in metastatic breast cancer (MBC): A randomized trial

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NVB is a new semisynthetic vinca alkaloid that shows a 24% response rate (RR) in previously treated MBC cancer. As anthracyclines are often used as initial treatment for advanced disease, new drugs and combinations are required for relapsed or refractory patients. Between 4/93 and 4/95, 86 patients were included in a randomized trial to receive NVB 25 mg/m^2 days 1 and 8 IV plus MMC 7 mg/m2 IV (A) or MTZ 8 mg/m^2 IV (B). The 3 drugs each 21 days. Characteristics of population: (A/B) evaluables: 40/40, mean age: 56.2/55, number of metastatic sites: 1 = 14/11, 2 = 19/24 3 = 10/8. Dominant metastatic pattern: nodes-bone-soft tissue: 27/27 visceral: 13/13. Previous hormono: 36/37. Previous chemo: advanced disease (40/40), adjuvant: (8/8) all anthracyclines. RR: A: 50% (20/40 PR) B:50% (2/40 CR 18/40 PR). Survival: (median): A:7 m B:7.2 m (p 0.667) Mean N° of cycles A:3 B:3 Toxicity G3–4 (by cycles) A/B:153/153 cycles Neutropenia A = 18 B = 14 (p0.65). Thrombocytopenia A:2 B:1 (p:0.72) Alopecia A:2 B:0 (p0.0045). There were no drug related deaths.

Conclusion: 1) A and B were similar in RR, survival and toxicity 2) Both schedules are easy to administer with low toxicity profile.

685 PUBLICATION

Preliminary results from an early phase II combination of gemcitabine and taxol in metastatic breast cancer

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Purpose: Gemcitabine, a nucleoside analog, has single agent activity in breast cancer with a 25% response rate in phase II trial. The different toxicity profiles and mechanisms of action of gemcitabine and paclitaxel suggested their use in combination, and 22 patients with pretreated metastatic breast cancer have received a biweekly gemcitabine-paclitaxel treatment.

Methods: Paclitaxel was given at a dose of 135 mg/m2 over 3 hours days 1 and 15, followed gemcitabine at a dose of 2500 mg/m2 over 30 min. dayus 1 and 15. To date 22 patients have been included evaluable for response. Median age is 51 (44–69), performance status (0–1) in 19 patients and 2 in 4 patients. Every women have been received previous salvage chemotherapy treatment; 20 patients have received antracycline based chemotherapy and 8 have received paclitaxel for metastatic disease. Metastases were localized in lung (9), liver (6), bone (6), pleura (3) and lymph nodes (4).

Results: Analysis of toxicity data (WHO grade) after 116 cycles is a follow: neutropenia grade 3 or 4 occurred in 28% of cycles –3% grade 4 with one neutropenic fever episode- and thrombocytopenia grade 3–4 in 5%. In general hematological toxicity was moderate. Non-hematological toxicity included mild nausea and peripheral neuropathy. One reversible episode of cardiac toxicity grade 3 has been observed. Of the 22 patients enrolled so far there are 2 CR, 7 PR, 6 SD and 7 PRO with an OR rate of 41%.

Conclusion: These results indicate that the association of gemcitabine-paclitaxel biweekly is well tolerated and highly effective in anthracyclin-resistant pretreated metastatic breast cancer. Patients accrual is still ongoing and definitive results will be presented.

686 PUBLICATION

Taxotere in the treatment of patients with advanced breast cancer

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Methods: Twenty eight pts with morphologically proven advanced breast cancer were treated with taxotere. Taxotere was administered in dose 100 mg/m^2 every 3 weeks. The prophylactic medication with methylprednisone 32 mg per os has to be given 13, 7 and 1 hour before the infusion and should be continued on the day of administration and for 96 hours after at the same dose twice daily (b.i.d.). The average age pts was 49.3 (32–67), WHO PS 0–2, 19 pts previously operated. 22 pts have received previously chemotherapy: neoadjuvant – 2, adjuvant – 13 (5 with anthracyclines, 9 – CMF), curative – 8 (7 with anthracyclines, 1 – CMF). Taxotere was used as the first line of treatment in 20 pts, as the second line in 8 pts.

Results: The results of treatment were the following: overall response was 15/28 (53.7%), CR – 3/28, PR – 12/28, SD – 3/28, PD – 10/28. The best results (OR – 11/20) were observed in pts who had only adjuvant chemotherapy, or previously untreated. 3 pts had the improvement of results after the study termination. The toxicity in 184 cycles were the following: anemia 22.8% (Gr II – 16.3%), neutropenia 57.6% (Gr III–IV – 37.5%), but only in 4 cases the dose was reduced, because of febrile neutropenia. All cases of neutropenia were reversible and had short duration (<7 d). There were no cases of trombocytopenia. We did not observed any nausea and vomiting. The incidence of mucositis was 66/184 (35.8%), Gr II 14/184 (7.6%), diarrhea – 37/184 (20.1%), Gr II – 7/184 (3.8%), fluid retention syndrome 38/184 (20.7%) Gr II 2/184 (1.0%), neurotoxicity 43/184 (23.3%) Gr II 15/184 (8.2%), myalgia, arthralgia 16/184 (8.7%). Skin toxicity Gr I 23/184 (12.5%).

Conclusion: Taxotere as a single agent is a high effective cytostatic agent against advanced breast cancer.

687 PUBLICATION

Experiences with thermoradiotherapy of locally recurrent breast cancer

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Background: In inoperable or R1/2 resected recurrent breast cancer thermoradiotherapy is established. We analysed acute side effects of thermoradiotherapy in locally recurrent breast cancer depending on duration, applicator arrangement, electric field parameters, bolus temperature, placement of temp. probes and applicators.

Material and Methods: Thermoradiotherapy was performed in 17 pat. with median dose of 58 Gy (30–60 Gy) combined with twice weekly hyperthermia applications (BSD 2000, MA150, MA120, SA115). In group 1 (6 pat.) skin cooling by bolus temp. of 15–20°C and intratumoral and epicutaneous temp. mapping was performed. Group 2 (11 pat., 2 × patchwork) with cutaneous lymphangiosis or infiltrated skin or R1-resection received bolus temp. of 40°C, monitored by epicutaneous temp. mapping.

Results: In group 1, median intratumoral temp. of 41.5°C (41.1–42.3°C) and max. temp. of 42.6–44.0°C were recorded in a median of 8 (2–12)

applications with 20–160 W over 75 min. In group 2, median epicutaneous temp. of 41.2°C (40.0–42.0°C) and max. temp. 41.9–44.0°C were recorded in a median 10 (3–23) applications with 10–45 W over 60 min. In group 1 2/6 pat. presented with blisters/necrosis whereas no blisters were seen in group 2. Moist desquamation occurred in 2/6 pat. and 3/11 pat. in group 1 and 2, respectively.

Conclusion: To avoid hyperthermia induced blisters/necrosis epicutaneous temp. mapping is most important. In case of lymphangiosis cutis or infiltrated skin, bolus temp. of 40°C provide homogeneous heating of the chest wall. Large applicators increases the risk of "hot spots" and blisters/necrosis.

688 PUBLICATION

Taxol (T) and mitoxantrone (M) as first line treatment in advanced breast cancer (ABC) patients. A phase II study of the Southern Italy oncology group (GOIM)

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Purpose: In phase I/II studies the combination of T with anthracyclines yielded response rate ranging from 63% to 94%, sometimes with significative cardiotoxicity. In prospective randomized trials, M has shown a clinical activity only slightly inferior to that of anthracyclines, but with less incidence of alopecia, nausea/vomiting and cardiotoxicity. In view of these considerations, in April 1996 we started a phase II study with the combination of T and M as first line treatment of ABC.

Methods: Patients with histologically proven diagnosis of ABC, age between 18 and 65 years, adequate haematologic and normal renal, hepatic and cardiac functions, were elegible for the study. T was administered as a 3-hour intravenous infusion after standard premedication with steroid, antihistamine and H_2-blockers at a dosage of 175 mg/m^2; M was administered intravenously at a dosage of 12 mg/m^2. Courses were repeated every 3 weeks.

Results: To date, 23 patients were enrolled in the study and 16 are fully evaluable for clinical efficacy and toxicity. We obtained 4 CR, 7 PR and 5 SD for a total of 11 OR (69%) with a median duration of response of 6+ months and a median duration of survival of 7+ months. Toxicity was mild and mainly of grade I–II according to WHO criteria.

Conclusion: From our preliminary data of this ongoing study, the combination of T and M seems to be an effective and safe chemotherapy regimen for patients with ABC.

689 PUBLICATION

Factors predicting response to chemo-endocrine treatment in advanced breast cancer

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Purpose: Chemo-endocrine treatment as used in our institution is well tolerated even by heavily pretreated patients with advanced breast cancer. In a retrospective study the response rate and duration of response to this treatment regime was evaluated to find factors that predict good response to this treatment.

Methods: Response (CR, PR, NC) of 129 patients with metastatic breast cancer to chemo-endocrine treatment using Cyclophosphamide (100 mg/d p.o.), Methotrexate (25 mg/week i.v.), 5-Fluorouracil (500 mg/w i.v.), Prednisone (10 mg/d p.o.) and Methenolone (300 mg/w i.m.) was evaluated in correlation to steroid receptor status, prior disease-free interval, site of metastatic disease and previous treatement.

Results: Response rates were higher in patients with estrogen-and/or progesterone receptor positive tumors (80% vs. 37% in hormone-receptor negative), with long disease-free interval (78% in patients >2 years vs. 66% in patients <2 years), and with endocrine pretreatment (85% vs. 35% with chemotherapeutic pretreatment). Patients with bone metastasis showed better response (77%) than women with other metastatic sites (61%). Response rates were 73% with two and 68% with three previous treatment regimes.

Conclusions: Combined chemo-endocrine treatment is most effective in patients bone metastasis, positive receptor status and after response to prior endocrine therapy and is showing good response rates even in pretreated patients.

690 PUBLICATION

Phase II study of i.v navelbine (NVB) and doxorubicin (DOX) in previously untreated advanced breast cancer (ABC)

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Promising results have previously been obtained with the combination of NVB and DOX. 74% of the 89 patients (pts) responded with 21% CRs (JCO, 1994 Spielmann). A phase II study was conducted in South Africa in order to confirm these results with I.V NVB 25 mg/m^2 D1 & D8 + DOX 50 mg/m^2 IV on D1, every 21 days, for 8 cycles maximum. Forty chemotherapy-naive pts with ABC were treated. Up to now, 24 pts are evaluable for tolerance and response. Median (m) age was 47.7 y (25–69). All pts had Good PS: 0–1. At the inclusion, 77% pts had metastatic disease and 70% had extensive loco regional disease (m. size of local disease = 80 mm Ø, (range 20–140). 60% pts had ≥3 metastatic sites of which 45% were visceral (38% liver and 7% lung). In total, 223 cycles were administered (m per pts: 5, range 1–8). The overall response rate was 54% (CR 8%, PR 46%/95 CI 34–74%). 2 further pts obtained an objective response but were not available for confirmation. Pt's WHO grade 3 toxicity was as follows: Alopecia 69%, nausea/vomiting 15%, stomatitis 11.5%, phlebitis 4%. WHO grade 3 neutropenia was observed in 27% pts and grade 4 in 15% pts (2 of whom died). Grade 1 peripheral neuropathy was only observed in 4 pts (15%). No cardiac impairment was observed. Given the large tumor bulk of local disease in these patients, very good results and tolerance were documented.

691 PUBLICATION

The LHRH analogue triptoreline (TRP) with or without the aromatase inhibitor formestane (4-OHA) in premenopausal advanced breast cancer: A study by the I.T.M.O. group

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Purpose: This pilot study was undertaken by our group with the aim of acquiring information on the feasibility and toxicity of combined TRP and 4-OHA treatment in premenopausal patients (pts) with previously untreated advanced breast cancer.

Methods: 28 consecutive pts were randomised; 15 pts received TRP 3.75 mg i.m. monthly alone, and 13 pts received it in combination with 4-OHA 500 mg i.m. fortnightly. Eligible pts had to have measurable lesions, ECOG PS 0–2, and ER and/or PgR positive tumours. Postmenopausal status was defined as last menstrual period more than 1 year ago. Blood samples for measuring serum oestrogen and gonadotrophin levels were taken before and during treatment.

Results: There was no difference in terms of age, DFI, and PS between the two groups; 32% of pts had multiple disease sites. The intent-to-treat analysis showed objective responses in 27% of pts (2 CR + 2 PR) on TRP and in 31% (1 CR + 3 PR) on TRP + 4-OHA. The median duration of response in the two groups was 16+ months (range, 7+–21) and 11+ (range, 7–16), respectively. The sites of response were soft tissue (3 CR) and viscera (5 PR); SD occurred in 5 pts on TRP, and in 4 on TRP + 4-OHA. Local and systemic tolerability was highly satisfactory in both treatment groups. The endocrine evaluations are in progress.

Conclusion: In our experience, the concurrent use of TRP and 4-OHA proved to be a feasible and well tolerated approach in the management of premenopausal advanced breast cancer.

692 PUBLICATION

Are new anthracycline dose recommendations needed for patients with liver dysfunction?

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Purpose: To investigate whether U.K. oncologist follow current anthracycline dose modifications when treating patients with liver dysfunction.

Methods: One hundred and seventy oncologists replied to a questionnaire asking the % of full dose doxorubicin or epirubicin they would prescribe