i.v. His urine pH was kept above 7.0 with i.v bicarbonate. No CNS toxicity was observed. The 2nd patient was treated with PEI for testicular cancer, containing only Ig IFO for 4 days because of preexisting renal failure. On day 1, he developed paranoia, agitation and disorientation (CTC grade 3). IFO was continued together with MB and bicarbonate as described. All CNS symptoms resolved within 48 h. We conclude, that iv administration of MB might be effective against IFO-related CNS toxicity. A phase II trial is currently being conducted.

1249 PUBLICATION

OPTIMAL COMBINATION THERAPY IN THE PREVENTION OF ACUTE AND DELAYED EMESIS INDUCED BY HIGHLY EMETOGENIC CHEMOTHERAPY (CT)

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In an attempt to improve the control of both acute and delayed nausea and emesis for patients (pts) receiving combination CT, we designed a combination of antiemetic drugs as follows: day (d) 1: granisetron 3 mg IV + methylprednisolone (MPL) 240 mg IV + alprazolam (A) 0.5 mg tid per os (po), then po d2: MPL 48 mg + A 0.5 mg tid + Métoclopramide (M) 20 mg tid, d3: MPL 32 mg + M 20 mg tid, d4: MPL 16 mg + M 20 mg tid, d5: M 20 mg tid. Pts with or without previous CT were eligible if CT included cisplatin (P) >75 mg/m^2 or carboplatin >300 mg/m^2 or cyclophosphamide >1 g/m^2 on d1 and no highly emetogenic drugs on the following days. 318 pts were included: 59% male; mean age 57 y; 59% non naive pts (60% had prior emesis experience: EE). Main primary tumor sites were lung 49%, ovary 19%, head and neck 11%. 81% pts received P at a mean dose of 95 mg/m^2 (75–180). Mild adverse effects occurred in 31%: 12% headache, 9% drowsiness, 6% insomnia, 7% agitation, 5% hiccough. Outcome are summarized below:

Day	D_1	D_2	D_3	D_4	D_5	D_6	D_7
No Nausea % cumulative	82	70	59	53	50	48	47
No vomiting % cumulative	85	78	71	66	65	60	60

For non naïve pts with RC (no EE, no or mild nausea) and not RC at previous course, RC was recorded at day 1 respectively 91% and 56%. *Conclusion:* This combination appears feasible and effective with promising results in overall control of the emesis but delayed emesis remains a significant problem despite specifically designed antiemetic protocol.

1250 PUBLICATION

AN OPEN RANDOMIZED STUDY OF GRANISETRON (G) VERSUS GRANISETRON PLUS DEXAMETHASONE (G + D) IN THE TREATMENT OF CYTOSTATIC-INDUCED EMESIS

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The effectiveness and tolerability of the 5-HT$_3$ antagonist, granisetron (G) has been compared in an open randomized study with G + dexamethasone (G + D) in patients (pts) receiving high dose cisplatin (>100 mg/m^2). G was given as a single dose of 3 mg i.v. over 5 minutes or combined with D (D 8 mg i.v. and 4 mg orally bid on day 2–4). One hundred pts: 22 males, 28 females received G; 29 males, 21 females received G + D. Median age of pts were 60 yrs and 62 yrs in G and G + D arm. Tumor types are lung, cervical, head and neck, ovarian and unknown primary cancer. During the first 24 hrs, of 50 pts treated with G 66% had complete (no nausea, no vomiting (v)) + major response (1 episode of vomiting). Of 50 pts treated with G + D 80% had complete + major response. Response during day 2 to 7 for G vs G + D group were 28 vs 50, 28 vs 60, 58 vs 74, 64 vs 82, 82 vs 90 and 82 vs 100% respectively. Adverse effects consisted of headache, lightheadedness, diarrhoea.

This study in an Asian population treated with high dose cisplatin confirm and extends the observation that steroids enhance the antiemetic activity of 5-HT$_3$ antagonists.

1251 PUBLICATION

CEFTRIAXONE (CRO) PLUS GENTAMYCIN (GEN) AND G-CSF, VERSUS CIPROFLOXACIN (CPR) PLUS GEN AND G-CSF, IN FEBRILE PATIENTS (PTS) WITH CHEMOTHERAPY INDUCED NEUTROPENIA

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In a prospective randomized study, 63 episodes of fever (>38°C) and granulocytopenia (absolute neutrophil count, ANC < 1000/mm^3), occurring in 63 cancer pts, were empirically treated with CRO 2 g/d IV, once daily [arm A = 31 pts], or CPR 400 mg IV, every 12 hours [arm B = 32 pts]. All pts received GEN 5 μg/kg/d IV, in a single dose, during the first 3 d, and G-CSF 5 μg/kg/d SC beginning on the day of neutropenia and until ANC recovery. In the A and B arms respectively, median age (range) was 61 (25–83) and 62 (27–83) years, 16/31 (52%) and 18/32 (56%) were men, 25/31 (80%) and 22/32 (69%) had ANC < 500/mm^3. Bacteremia, clinically documented infection and possible infection were documented in 4, 5 and 13 pts [arm A] and in 3, 6 and 14 pts [arm B]. Neutropenia lasted 4 days on average (range 1 to 10 days) in both arms. At 72 h, response without treatment modification occurred in 25/31 (80%) pts [arm A] and in 25/32 (78%) [arm B]. Days on the study drug (CRO or CPR) were 5 (2–10) for both arms. For bacteremic infections, responses were 2/4 for arm A and 2/3 for B. No adverse events or superinfections occurred. 2 pts in arm A died, because of treatment failure. The survival rate was 100% for arm B. In conclusion, CRO and CPR (both with GEN and G-CSF), were equally effective and safe as initial therapy in these febrile neutropenic pts.

1252 PUBLICATION

ONDANSETRON (ODS) + METOCLOPRAMIDE (MTP) + DEXAMETHASONE (DXM) VS ONDANSETRON + DEXAMETHASONE DURING CDDP BASED CHEMOTHERAPY (CT)

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During high dose (>50 mg/m^2) CDDP based CT, 51 pts randomized to either regimen A (ODS 40 mg IV d 1–2 & 8 mg PO q 8h d 3–5, MTP 20 mg IV q 4h d 1–2 & 20 mg PO q 4h d 3–5 plus DXM 32 mg IV d 1 or regimen B (as above exempting MTP). Pts randomized to A were given B during the 2nd course & vice versa, followed by alternating A&B thereafter. Vomiting & nausea was evaluated for each 24 h & the first 5d. *Results.* 147 courses were given 70 of A & 77 of B. Vomiting: With A, CR (no vomiting) was achieved in 62 (88%), 39 (56%), 48 (69%), 60 (86%) & 64 (91%) of 70 courses each 1, 2, 3, 4 & 5 d, respectively vs 55 (71%, $P < 0.025$), 19 (25%, $P < 0.001$), 22 (29%, $P < 0.001$), 46 (60%, $P < 0.001$) & 61 (79% – p < .05) of 77 courses with B. For all 5 d, CR was achieved in 35/70 (50%) courses with A vs 14/77 (18%) with B ($P < 0.001$) Nausea: With A, nausea was observed in 14 (20%), 24 (34%), 20 (29%), 14 (20%) & 4 (6%) of 70 courses each 1, 2, 3, 4 & 5 d, respectively vs 26 (34%, P = NS), 51 (66%, $P < 0.001$), 46 (60%, $P < 0.001$), 32 (42%, $P < 0.001$) & 15 (19%, $P < 0.025$) of 77 courses with B. For all 5 d, nausea was observed in 32/70 (46%) courses with A vs 58/77 (75%) with B ($P < 0.001$). The intrapatient comparison in 38 pts who received so far both A&B, demonstrated significantly better control of vomiting & nausea with A. Delayed emesis was also less with A. Toxicity was comparable in A&B regimens.

1253 PUBLICATION

EFFICACY OF MEGESTROL ACETATE ON ANOREXIA IN PATIENTS WITH ADVANCED NON HORMONE-RELATED TUMORS: A DOUBLE-BLIND PLACEBO CONTROLLED CLINICAL TRIAL

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Megestrol acetate (MA) was reported to induce weight gain and increase of appetite in cancer patients.

Methods: Out-patients of the "Divisione Terapia del Dolore" of the "Istituto Nazionale per la Cura dei Tumori" (Milano) with advanced non hormone-responsive tumors and loss or absence of appetite, who didn't assume any corticosteroid were randomized for a Phase III trial, that

consisted of two consecutive phases: a double-blind placebo controlled phase of 14 days (phase A) and an open phase of 76 days (phase B). During phase A patients were treated with MA 2 tablets × 160 mg/day (a low dose for this indication) or placebo. In phase B all patients received different dosages of MA according to the response to treatment.

A patient was considered responsive if his appetite, evaluated by means of a categoric-numeric scale, increased by 2 or more points.

Other parameters investigated were: food intake, body weight, Performance Status (Karnofsky), mood state (POMS) and pain.

Results: Forty-two patients were enrolled in this trial. Thirty-three patients were evaluable for efficacy: 13/16 MA patients were responsive for appetite vs 5/17 placebo patients. This result is clinically and statistically significant ($P < 0.003$). No relevant toxicity occurred during the study.

Conclusions: MA showed a remarkable effect on appetite with a low dose (2 tablets × 160 mg/die) already after 14 days, without side-effects of relief.

This result is of great importance considering the relevance of the quality of life and the low life expectancy of these patients and the low daily therapy costs of this treatment.

Tumour markers

1254 ORAL

PREDICTIVITY OF CIRCULATING TUMOR MARKERS (CEA, MCA, CA 15.3, CA 549) IN BREAST CANCER RECURRENCE AFTER SURGERY

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Concomitant measurement of 4 serum markers (CEA, MCA, CA 15.3 and CA 549) were performed every 3–6 months in 128 breast cancer patients with no evidence of disease after surgery. After a median follow-up of 4 yrs (range 3–4 yrs) 29 pts (23%) relapsed. In 24 of these at least one marker was abnormal (sensitivity: 83%); the 5 pts with normal marker value at the time of relapse had only local recurrence (soft tissue metastases). The sensitivity of CEA and MCA (33% and 47%) was significantly lower than the sensitivity of CA 15.3 (79%) and CA 549 (80%) ($P = .02$). Ninety-nine pts did not relapse: 90 have normal marker values (specificity: 91%). The predictive value of a positive test and of a negative test is 73% and 95%, respectively. The combination of 2 or more markers does not increase the sensitivity ($P = .7$) and the positive predictive value of the test when compared to CA 15.3 or CA 549 alone. In conclusion a single marker determination (CA 15.3 or CA 549) is recommended in the follow-up of pts after surgery for breast cancer.

1255 ORAL

CEA, CA 15-3 AND MCA: COMPARATIVE CLINICAL RELEVANCE IN BREAST CANCER

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To comparatively investigate the clinical relevance of the serum tumor markers CEA, CA 15-3 and MCA simultaneous determinations of the serum concentrations of the three tumor markers CEA, CA 15-3 and MCA were performed in 419 sequential breast cancer patients. CEA and MCA were determined by means of enzyme-immuno-assays and CA 15-3 by a radio-immuno-assay.

Results: The serum concentration of all three tumor markers correlates with tumor activity and tumor mass. The receiver operating characteristics (ROC) curves show that CA 15-3 has the highest sensitivity and specificity. All three tumor markers do not show any dependence on age, but on the location of metastases; the median serum values decrease in the sequence osseous, visceral or soft tissue metastases. With a combination of tumor markers, the gain in sensitivity is associated with a loss of specificity; the combination of CA 15 + CEA appears to be the most favourable.

The combination of all three tumor markers does not have any advantage over the double combination CA 15-3 + CEA.

Conclusion: CA 15-3 has the highest sensitivity and specificity. As combinations of tumor markers CA 15-3 + CEA as well as MCA + CEA are recommended.

1256 ORAL

SERUM CYFRA 21-1 AS A PROGNOSTIC MARKER IN LUNG CANCER

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An immuno-radiometric assay was used to detect a fragment of the cytokeratin 19, referred to as CYFRA 21-1, in the serum of 405 patients with histologically proven lung cancer (314 non-small cell and 91 small cell lung cancers). This prospective study was conducted to evaluate the reliability of this immuno-radiometric assay, and to identify the relationship between serum CYFRA 21-1 and different features of lung cancer including prognosis. The reliability of the immuno-radiometric assay was demonstrated by the reproducibility of the dosage in intra-assay and inter-assay and the high sensitivity of the method in discriminating low CYFRA 21-1 concentrations. Using a threshold of 3.6 ng/mL, specificity was 0.96, and sensitivity was 0.55 and 0.36 for NSCLC and SCLC respectively. The sensitivity of the marker was highest in squamous cell carcinoma and lowest in small cell carcinoma. In non-small cell lung cancer patients, the marker varied significantly according to both stage of the disease, nodal status, weight loss, and performance status. A high serum CYFRA 21-1 level was strongly associated with advanced stages, mediastinal lymph nodes and poor performance status. NSCLC with serum CYFRA 21-1 over 3.6 ng/mL proved to have a significantly shorter overall survival than those with a normal serum level (log rank: $P = 0.0001$). A similar negative effect of a high serum CYFRA 21-1 on SCLC survival was found (log rank: $P = 0.004$). In Cox's model, performance status, stage grouping, lactate deshydrogenase and CYFRA 21-1 were significant determinants of survival.

1257 ORAL

TUMOR MARKERS AS PROGNOSTIC FACTORS FOR NON-SMALL-CELL LUNG CANCER (NSCLC)

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The prognostic value of CEA, SCCA, NSE, and LDH in 300 patients who had been irradiated for primary NSCLC was analysed retrospectively with univariate (Kaplan-Meyer, log-rank) and multivariate tests (Cox regression analysis).

Serum levels of the particular tumor markers were pathologically elevated in 25–36.5% of cases. Their values correlated with the stage of the disease. A normalization of increased marker levels 3 months after irradiation occurred in 37.5–67% of cases.

In univariate analysis survival with elevated CEA, SCCA, and LDH was significantly worse compared to normal levels. Normalisation after therapy was prognostically favourable.

In multivariate analysis the influence of tumor markers was meaningless. Independent factors were Karnofsky performance status, total dose, UICC-stage, and pretherapeutic weight-loss.