was 54 (25–73), sex ratio 15 male/5 female, Performance status (WHO) means 1 (0–2). All pts were treated according to the schedule and were asked for a written informed consent. The main side effect is thrombopenia, probably dose-related. We observed thrombopenia grade 3–4 in 1/5 pts at 40 mg/m$^2$, 3/9 pts at 50 mg/m$^2$ and 2/4 pts at 60 mg/m$^2$. Three pts needed platelet transfusions. Grade 3–4 neutropenia was observed in 2/10 pts at 50 mg/m$^2$ and 1/4 pts at the 60 mg/m$^2$ dose level. No febrile neutropenia was noted. Nausea and vomiting were moderate. The 60 mg/m$^2$/w level was actually explored and could be the MTD. We observed a stabilisation of disease in 7 patients. One may conclude that Cystemustine can be used in a weekly schedule at a higher dose-intensity than previously reported, with tolerable toxicity.

961 POSTER

## PHASE I STUDY OF DOCETAXEL AND IFOSFAMIDE IN PATIENTS WITH ADVANCED SOLID TUMORS

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The activity of docetaxel in our Phase II trial in sarcoma (Ann. Oncol 1994; 5: 539–542) prompted a phase I trial of docetaxel and ifosfamide in patients with advanced solid tumors. Docetaxel is administered as a 1-hr infusion on day 1 followed by ifosfamide as a 24-hr infusion. The doses are to be escalated from a starting dose of 60 mg/m$^2$ and 2.5 g/m$^2$ for docetaxel and ifosfamide respectively. All patients are premedicated with oral steroids, hydration and mesna. All cycles are repeated every 21 days. Dose Limiting Toxicity (DLT) is defined as $\geq$ 3/6 pts with > gr. 2 major toxicity, nadir to < 500 ANC for > 7 days or nadir to < 1000 ANC with fever > gr. 2 more than 3 days. Preliminary results are available on 6 patients.

*Patients characteristics:* median age, 58 yr (range 51–67); median WHO P.S., 1 (range 0–1) ; sex: 2 Male, 4 Female; Tumor type: 2 colon carcinoma, 2 mesothelioma, 1 cervix uteri, 1 leiomyosarcoma; 3 pts had prior chemotherapy for advanced disease, 1 pt had prior adjuvant chemotherapy.

*Results:* to date 6 patients received 11 cycles. No DLT has been observed.

| Dose Level | Docetaxel | Ifosfamide | Toxicity |
|---|---|---|---|
| 1 | 60 | 2.5 | 0/3 pts with DLT |
| 2 | 75 | 2.5 | 0/3 pts with DLT |

*Toxicity:* WBC nadirs occurred at day 7 with an average duration of neutropenia < 7 days. Only 1/11 cycles (9%) required patient's hospitalization for fever and neutropenia gr. 2 . All cycles were administered on day 22 . Extra-hematologic toxicities were mild and consisted in gr. 1 or 2 asthenia, alopecia, anorexia, myalgia, diarrhea, nausea. No acute hypersensitivity reaction and urotoxicity (hematuria) has been observed. Patients are being accrued at the next dose levels.

962 POSTER

## BONE MARROW PROTECTION BY AMIFOSTINE (AMI) IN PATIENTS TREATED WITH CARBOPLATIN (CARBO): A PHASE I STUDY

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*Background:* The cytoprotective properties of AMI and the pharmacokinetic data of both CARBO and AMI and their respective metabolites led us to perform a phase I study with CARBO and 3 divided doses of AMI in solid tumor patients (pts).

*Objectives:* To determine the maximum tolerated dose (MTD) of CARBO, when combined with 3xAMI, and to determine the qualitative and quantitative toxic effects of 3xAMI.

*Methods:* AMI is given 15 min before, 2 hr after and 4 after the start of CARBO. Both AMI and CARBO are given iv over 15 min. Starting dose of CARBO was 400 mg/m$^2$ (escalation steps 25%→20%), and of AMI 910 mg/m$^2$. All pts needed to have normal hematologic parameters and a creatinine clearance $\geq$ 80 ml/min at the start.

*Results:* So far 33 pts entered the study: 19 male, 14 female, median age 55 yrs (range 36–66 yrs), median ECOG performance status 1(0–4), 21 without prior chemotherapy (CT). Nonhematologic toxicity (NHTOX) in the first 2 pts forced to dose reduction of AMI (740 mg/m$^2$). The MTD in pts with prior CT was CARBO-500/3xAMI-740 mg/m$^2$ (grade 4 WBC, ANC, platelets), but has not been reached in pts without prior CT (so far 1/4 pts showed grade 4 myelosuppression at CARBO-720/3xAMI-740 mg/m$^2$). With vigorous antiemetic protection CTC grade 3 or 4 nausea and vomiting did not occur. Hypotension occurred in 20 pts (36/76 cycles) and required further dose modifications of AMI in 6, but never led to complications. Other NHTOX (sneezing, flushing, dizziness (4 pts with grade 3), hypothermia, fatigue, lethargy, myalgia) were not dose-limiting. There were 2 partial responses and 1 minor response (colon 1, head and neck 2).

*Conclusion:* 3xAMI-740 mg/m$^2$ is safe and seems to protect the bone marrow.

963 POSTER

## EXEMESTANE IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER: A DOSE-FINDING STUDY

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Exemestane (6-methylenandrosta-1.4-diene-3.17-dione) is a new type I aromarase inhibitor, which is active by the oral route. In a previous experience, we documented the drug's effectiveness in reducing serum oestrogen levels at daily doses ranging from 25 to 2.5 mg and, for this reason, we initiated this further study to determine the minimum effective dose. Exemestane was orally administered to 20 postmenopausal patients with metastatic breast cancer, at daily doses of 5, 2.5, 1 or 0.5 mg. The doses were randomly given under double-blind conditions (5 pts for each dose), and the changes in $E_1$, $E_2$, $E_1S$, LH, FSH, SHGB and DHEAS serum levels were evaluated on days 0, 7, 14, 28 and 56. The pts were considered evaluable providing they had received at least two months of therapy. The hormone analysis is still ongoing, but here we report the data concerning clinical efficacy and tolerability. All of the pts had received previous hormonal therapy for metastatic disease (9 pts >1 treatment) and 18 had also received chemotherapy (7 as adjuvant treatment and 11 for metastatic disease). The other characteristics of the pts were: median age 56 yrs (range 47–82); ER+/PgR+: 14 pts; DFI $\geq$ 2 yrs:15 pts. Soft tissue involvement was documented in 7 pts, bone in 12 and viscera in 14. Irrespective of the dose, 2 PR were obtained on soft tissue and liver; SD with a median duration of 6 months (range 3–14) was observed in 14 pts. Exemestane was very well tolerated, with nausea and asthenia (grade 1 WHO) being reported in 3 and 2 pts respectively. The hormonal data will be provided at the Congress.

*Data management by I.T.M.O. (Italian Trials in Medical Oncology) Scientific Service.*

964 PUBLICATION

## ASSOCIATION OF MITOTANE TO ETOPOSIDE, ADRIAMYCIN AND CISPLATIN COMBINATION CHEMOTHERAPY IN ADVANCED ADRENOCORTICAL CARCINOMA (ACC)

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Mitotane (MIT) has been recently found to be able to reverse *in vitro* the multi drug resistance mediated by the MDR-1/P-glycoprotein, providing the rationale for its clinical use in combination with non specific cytotoxic drugs in the treatment of ACC. We report on the association of MIT to a etoposide, adriamycin and cisplatin chemotherapeutic regimen (EAP) in 7 patients (pts) with advanced/metastatic ACC. 3 of them were previously submitted to radical surgery and recurred after 29, 11, 7 months, respectively. 4 pts presented with locally advanced or metastatic disease *ab initio*, maximal debulking was pursued in 2 and primary tumor was judged as inoperable in the remaining.

| Pt | Age(yr) /Sex | Surgical resection | Disease localizations | Hormone secretion | N° of courses | Tumor response | Response duration |
|---|---|---|---|---|---|---|---|
| 1 | 45/M | A | adrenal+liver | F | 5 | SD | 6 months |
| 2 | 29/F | A | liver+adrenal | F + An | 8 | PR | 7 months |
| 3 | 18/F | RA | lung+mediastinum | F | 6 | PR | 27 months |
| 4 | 47/F | RA | liver+lung+adrenal | F+An | 6 | SD | 3 months |
| 5 | 62/F | - | liver+adrenal | An | 4 | SD | 10 months |
| 6 | 44/F | RA | lung | An | 5 | 3 months | |
| 7 | 46/F | - | adrenal | An 3 P | - | | |

F: cortisol; An: androgens; SD: stable disease; PR: partial response; P: progression; Horm: Hormone; secret; secretion.

All pts had clinical and/or biochemical evidence of hormone hypersecretion. A median of 5 EAP cycles was administered. Oral MIT was