582 ORAL

THE ROLE OF BETA-INTERFERON AS A RADIOSENSITIZER IN THERAPY-REFRACTORY METASTASES FROM SOLID TUMORS—A PHASE-II-STUDY

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Type-I-Interferons appear, by current data, to be a potent radiosensitizer in solid tumors. They act directly antiproliferative and antiangiogenetic by enhancing both tumor necrosis factor-α activity, induced by radiotherapy itself, and basic fibroblast growth factor. Interferons may also play a role in radiotherapy-induced apoptosis enhancing p53 oncogen activity in the cell cycle. *Patients (pts) characteristics:* 21 pts, 12 male, 9 female, median age 52 years (range: 18–80); 8 pts had head and neck cancer (ca), 7 pts soft-tissue sarcomas, 2 pts breast ca, 2 pts colorectal ca, 2 pts esophageal ca; all pts refractory to chemo-, radio- or hormonotherapy; pretreatment: chemotherapy 16/21 pts, radiotherapy 21/21 pts; median tumor size 8 cm (range: 3–25). *Treatment schedule:* week (wk) 1–12 natural β-interferon (IFN) was given 3 times per wk intratumorally, wk 3–7 or 8 radiotherapy was given additionally (1.8–2 Gy single dose, 20–30 Gy total dose). *Results:* 1 CR, 11 PR, 2 MR, 5 NC, 2 PD; median duration of response 5 months (range: 2–28). *Conclusion:* Beside its direct antiproliferative effects IFN given intratumorally plus radiotherapy in therapy-refractory metastases from solid tumors seems to be an excellent radiosensitizer by interacting with various parts of cell cycle and several kinds of cytokines respectively.

583 ORAL

TREATMENT OF INTERFERON-ALPHA 2A(IFN)-INDUCED THROMBOCYTOPENIA BY THE PINEAL NEUROHORMONE MELATONIN (MLT)

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Cytokines may induce thombocytopenia, perhaps at least in part by activating macrophages, which are responsible for platelet peripheral destruction. Previous studies showed that IL-2- and TNF-induced platelet decline may be neutralized by the pineal indole MLT. On this basis, a study was performed to evaluate MLT effects in 10 patients (pts) showing persistent thrombocytopenia under IFN therapy for neoplastic disease (n = 8) or chronic hepatitis (n = 2). IFN was given SC at 3 million U thrice/week. MLT was given orally at 20 mg/day in the evening. A normalization of platelet number occurred in 6/10 pts after at least 1 month of MLT therapy. Moreover, most pts experienced a relief of IFN-induced asthenia and depression. This preliminary study would suggest that MLT may antagonize IFN-induced thrombocytopenia. Further studies will be required to confirm these data and to establish which is the influence of MLT on IFN therapeutic activity.

584 ORAL

MESOTHELIOMA: TREATMENT WITH A NEW IMMUNOMODULATOR—AS101

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Previous studies with AS101 (ammonium trichloro[dioxyethylene-0,0′]tellurate) have shown it to have significant immunostimulatory and tumoricidal effects with minimal toxicity. Nineteen consecutive patients with malignant mesothelioma were entered into protocol using AS101 at 3 mg/m^2, I.V., three times a week. Males (13) predominated, the median age was 50 years (range 30–72). Seven patients were heavily pretreated. Median number of treatments was 10+ weeks (wks) with a range of 3–136+ wks. One patient had a CR (136+ wks), one had a PR (48 wks), and one a minimal response (39+ wks). All responding patients were previously treated with chemotherapy with no response and with progressive disease. Side effects included halitosis (14) and fever spikes (4). We conclude that AS101 is a promising agent in the treatment of mesothelioma and plan further studies in combination with chemotherapy.

585 POSTER

A PHASE II STUDY WITH 13 CIS RETINOIC ACID α INTERFERON AND CDDP IN 28 SQUAMOUS CELL CARCINOMA

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28 pts, median age 56 years, were treated for an advanced or metastatic epidermoid carcinoma by 13 cis retinoic acid 1 mg/kg/d D1 to D84 INFα 6 MUI/d D1 to D84 and CDDP 40 mg/m^2/d D1, D28 and D56. 8 had cervix carcinoma, 16 head and neck carcinoma, 3 lung and 1 oesophagus. Toxicities were grade OMS > 2: neutropenia 29%, thrombopenia 11%, anemia 21%, nausea vomiting mucositis 4%, fatigue 11% and 14 pts developed cutaneous toxicity. 15 pts received the planned treatment (7/8 cervix) and 4 head and neck carcinoma did not receive all the schedule for intolerance. 18 pts are evaluable, 10 are in PD, 3 in SD, 5 in PR (28%). The association of CDDP to INFα and 13 cis retinoic acid seem to not increase the overall response, there is a modest but definit anti tumor activity on this pretreated pts with a mild moderate and manageable toxicity. It will be interesting to evaluate the impact of this treatment earlier in the disease.

586 POSTER

CONCOMITANT INTERLEUKIN-2-DOXORUBICIN (ADR) SCHEDULE IN PATIENTS (PTS) WITH ADVANCED SOFT TISSUE SARCOMAS (ASTS): A PHARMACOKINETIC STUDY

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Adult patients (pts) with ASTS who relapse or fail to respond to a first line ADR-containing chemotherapy regimen are candidates for investigational treatment. Based on a concept of possible antitumor interactions and anticipated biochemical and pharmacological synergism between cytokines and cytotoxic drugs, we designed a phase II study in which ADR was concurrently administered with subcutaneous (SC) r-IL2 in ADR-refractory or resistant ASTS. Pts received one injection of ADR alone (70 mg/m^2) and three weeks later a combination of r-IL2 (18 MIU/m^2 dl to d5 SC) and ADR at the same dose either 1) 3 hours after the first r-IL2 injection (d1) or 2) at lymphocyte rebounds (d8). The same combination was repeated every 4 weeks according to the status of the disease. The main objective of this trial was to evaluate the impact of r-IL2 on ADR pharmacokinetic parameters. In this ongoing study, started in 6/94, 11 pts have been included, of whom, nine have received the two planned courses (c). As expected, in these 9 heavily ADR-pretreated pts, both local relapses and metastatic lesions remained unchanged (3 pts) or exhibited progression (6 pts) after ADR alone. Interestingly, 2 pts achieved a PR after 4 and 2 IL2/ADR c (1 PR in both arms), 2 a MR after 1 c (pts still on treatment), and 1 pt a dissociated response. The toxicity (T) of the combination was more substantial than with ADR alone: grade 3–4 leukoneutropenia (7 pts), grade 3–4 thrombocytopenia (2 pts) and mucitis (5 pts). Total dose of ADR was reduced by 25% in all subsequent c. ADR infusion on d1 IL2 c prevents lymphocyte rebounds in all pts. The evaluation of the impact of r-IL2 on ADR metabolism, the determination of immunological profiles in the two treatment arms and an analysis supporting a modulation of resistance to ADR by r-IL2 will be presented.

587 POSTER

MODULATION OF HUMAN MALIGNANT EFFUSION—DERIVED MACROPHAGES BY CYTOKINES

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The role of tumor-associated macrophages (TAM) as potential effector cells for eradicating malignant cells is not yet entirely clarified. In the present study TAM were isolated from malignant effusions of ovarian, breast and lung cancer patients by gradient separation and phenotypically and functionally characterised by the following parameters: surface epitopes (moAb 27E10, 25F9), respiratory burst activity, cytotoxicity and cytokine production (TNF-α,TGF-β,) measured in culture supernatants by bioassay, ELISA/RIA. Additionally mRNA of these cytokines was detected in TAM by in situ hybridisation. Incubation of TAM with