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

rh-GM-CSF and rh-IFN-γ resulted in an augmentation of cytotoxicity. Furthermore, cell-bound TNF-α was detectable by immunohistochemistry and correlated with mRNA (in situ hybridisation). In contrast, GM-CSF, as well as IFN-γ reduced the production of TGF-β by TAM, verified by ELISA assay as well as by in situ hybridisation. Our studies show that TAM obtained from malignant effusions of cancer patients can be stimulated by GM-CSF and IFN-γ for cytotoxicity and cytokine production. Though, TGF-β release was reduced. Whether this observation is of therapeutical relevance has to be determined by further studies.

588 POSTER

TUMOR NESCROSIS FACTORα PRODUCTION BY MONOCYTES FROM LUNG AND COLORECTAL CANCER PATIENTS

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Tumor Necrosis Factor (TNFα) is a monocyte (MO) derived cytokine which plays an essential role in host defense mechanisms against cancer. In the present work we evaluate levels of TNFα (by ELISA Test), in culture supernatants of MO from untreated lung (L) and colorectal (C) cancer (C) patients and healthy controls (HC) spontaneously (SP) or LPS stimulated.

Results expressed as pg/ml (range) were LCP: Sp = 450 $\pm$ 113 (53–1000) LPS = 588 $\pm$ 134 (59–1000); CCP; Sp = 84 $\pm$ 30, (36–304). LPS = 430 $\pm$ 110 (61–1000); HC: Sp = 72 $\pm$ 20 (10–189) LPS = 573 $\pm$ 82 (168–1000).

Conclusions: No significant differences were observed in CCP but MO from LCP release high levels of TNFα Sp. ($P < 0.01$) vs HC.

589 POSTER

DO PATIENTS WITH CANCER TREATED WITH INTERFERON PRODUCE ANTIBODIES?

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Production of antibodies to Interferon-a (INF-a) has been described in certain cases. In the present study the evaluation of antibody production was tested in cancer patients treated with INF-a.

Material-Methods: Twenty five cancer patients that have been on therapy with interferon-a were included. The type of cancers were multiple myeloma, chronic myelogenous leukaemia hypernephroma, melanoma and colon carcinoma. All the patients had been on INF-a treatment for over 6 months. 9 other patients with malignancies that had not been on INF-a were also tested as control. The dose of INF-a varied from 5 mU to 9 mU per time given every 2d day subcutaneously. Elisa technique was used for the antibody demonstration.

Results: No patient with INF-a therapy nor the control produced antibodies to INF-a.

Comment: The lack of antibody production is discussed on whether it is due to immunosuppression of cancer patients, to the insensitivity of the technique or to the real lack of production.

590 POSTER

SOLUBLE IMMUNOLOGICAL PARAMETERS IN PATIENTS TREATED WITH INTERLEUKIN-2 (IL-2) PLUS INTERFERON-α (IFN)

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We evaluated the haematological and immunological changes in 4 patients (pts) with advanced melanoma and 6 pts with advanced renal cell carcinoma treated with IL-2 (s.c.) and IFN-α-2b. Serum samples taken before and during six weeks courses of IL-2 plus IFN-α were assayed for the presence of IL-2, soluble IL-2-receptor (sIL-2R), IFN-α, tumor necrosis factor (TNF)-α, soluble intercellular adhesion molecule-1 (sICAM-1), IL-6 and IL-8. Whole blood counts were taken weekly during treatment. Eosinophilia occurred in all pts, lymphocytosis in 8 pts. The median survival of the pts with higher eosinophil and lymphocyte counts tended to be short. The higher maximum level of IL-2 during treatment was connected to longer survival: it was a median of 578 pg/ml in the pts with a median survival of 7 months, and 1025 pg/ml in the pts who survived a median of 15 months. Conversely, an increase in sIL-2R was an unfavourable sign: it was a median of 8-fold and 3-fold, respectively, in the pts with a median survival of y and 16 months, respectively. The sICAM-1 level was a median of 296 ng/ml before treatment; during treatment sICAM-1 levels paralleled with those of sIL-2R. Serum TNF-α and IFN-α concentrations were measured only occasionally; mostly they remained low. There was major intraindividual and interindividual variation in serum IL-6 and IL-8 levels. It can be concluded that treatment with IL-2 plus IFN-α caused remarkable changes in immunological mediators; their prognostic value should be further evaluated in future trials.

591 POSTER

GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) ADMINISTRATION FOR CHEMOTHERAPY-INDUCED NEUTROPENIA

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Neutropenia due to cytotoxic chemotherapy causes significant morbidity and mortality. In this study G-CSF (Granulocyte colony stimulating factor) was given to 37 patients treated with intensive combined chemotherapy, who developed absolute neutropenia after 51 chemotherapy cycles were evaluated. The patients were also analysed in two groups as for solid (ifosfamide and etoposide combined regimen) and hematological (mitoxantrone—cytarabine regimen) malignancies. G-CSF was initiated following the onset of neutropenia. Solid tumor patients included total 12 patients and hematologic malignancies consisted of 9 patients. Control group was available for the leukemia group and included 31 acute myeloid leukemia patients. G-CSF was started on the first day on absolute neutropenia and was given for one hour intravenous infusion in 100 cc %5 dextrose solution at the dose of 5 μg/kg/day until absolute neutrophil count was above 1000/ml for two consecutive days. G-CSF was found to be effective for the early recovery of neutrophil count. Expected response was achieved within 14 days in 91.5% of course on median fifth (range 2–14 days) day of G-CSF treatment. Duration of neutropenia was significantly shorter in the study group. The incidence of febril episodes and documented infection rates were not found to be significantly decreased. The incidence of fungal infections was not found to be decreased as well when compared to the control group. In conclusion, administration of G-CSF patients receiving intensive combination chemotherapy at the onset of neutropenia was found to be effective in shortening the period of neutropenia but did not reduce the incidence of febrile episodes and the rate of documented infections.

592 PUBLICATION

IN VITRO CD2 EXPRESSION MODULATION BY IL-1 IN CANCER PATIENTS

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In this study results are presented showing that interleukin-1 (IL-1) modulates the expression of CD2 molecule tested by using sheep erythrocyte roseting assay.

Lymphocytes from 110 patients with solid malignant tumors (breast cancers, melanomas, colonic, carcinomas), leukemias and lymphomas were analyzed for its CD2 antigen expression after 60 min. incubation, at 37°C, with IL-1 in comparison with lymphocytes from patients with clinical evidences of immunodeficiency, autoimmune diseases and normal controls. *In vitro* exposure of lymphocytes from healthy subjects to IL-1 significantly depressed their ability to form active E-rosettes. Results are presented showing that the same monokine significantly enhanced CD2 antigen expression in immunodeficient cancer patients (% Δ = 198.04 $\pm$ 29.13) and in active stages of immune diseases (% Δ = 199.81 $\pm$ 35.92).

The correlation of regulatory effect of IL-1 to the prognosis of the cancer patients is examined.

Functional investigation of CD2 modulation by IL-1 could provide perspectives for future pharmacological interventions into the immune system.