228

EFFECT OF LIPOSOMAL ALLOGENEIC MELANOMA VACCINE WITH IL-2 ON CELLULAR IMMUNE RESPONSES

A. Adler[1], J.Schachter[1], A.Sulkes[1], Y.Barenholz[3], T.Klein[1], T. Prigozhina[1], Y.Cohen[2], I. Kedar[2]. [1]Institutes of Oncology, Beilinson Medical Center and [2]Soroka Medical Center, [3]Hadassah School of Medicine, Israel

This study was designed to assess the biological effects of allogeneic liposome-embedded human melanoma vaccine, combined with IL-2 (systemic vs low-dose-regional) and cimetidine in pts with metastatic melanoma. Membrane preparations from six human melanoma cell lines were used for vaccine. The cell lines were characterized by expression of MHC class I & II and of melanoma-associated antigens by MoAbs GD3 and p97; 12 pts have entered this protocol and their in vivo and in vitro cellular immune responses prior to - and following vaccine-treatment were measured. In vivo invigoration or de novo induction of Delayed Type Hypersensitivity (DTH) to liposomal vaccine was observed in the majority of patients following 4-5 weeks of vaccination, whereas DTH to membrane vaccine preparation (without liposomes) was induced only in 5 of vaccine-treated patients. The latter correlated with augmented in vitro proliferative responses of patients' PBMC stimulated by melanoma cell lines and membrane preparation (MLTI assay) and with augmented cytolytic activity against melanoma cell lines. Three of 8 patients treated with liposomal vaccine and regional (s.c.) low dose IL-2 had documented PR (partial responses) and two patients have SD (stable disease) . These clinical responses correlated with induction of DTH to melanoma-memebranes in vivo and with enhanced in vitro lymphoproliferative and cytolytic anti-melanoma responses.

229

ANTIPHOSPHOLIPID SYNDROME ASSOCIATED WITH IMMUNOTHERAPY FOR PATIENTS WITH MELANOMA

Jürgen C. Becker, Barbara Winkler, Sabine Klingert, and Eva-Bettina Bröcker

Department of Dermatology, University of Würzburg, Germany

Immunotherapy for patients with cancer are associated with severe side effects, including the possible induction of autoantibodies. The latter had been proven for antithyroid microsomal and antithyroglobulin antibodies. This study was designed to evaluate antiphospholipid antibodies (APA) in 30 patients receiving 3 different forms of immunotherapy for disseminated melanoma based on interleukin-2 (IL-2), interferon alpha or the combination of both. APA were detected in 0% (0/18) of patients treated with IL-2 alone, 50% (2/4) treated with interferon alpha alone, and 37.5% (3/8) treated with the combination of both. In the latter group, increasing concentrations of APA were already observed, when the patients were still receiving interferon alpha alone. In none of 10 control patients suffering from disseminated melanoma increased concentrations of APA could be detected. In those patients with increased APA, 100% (5/5) had a prolongation of the partial thromboplastin time and 60% (3/5) developed deep venous thrombosis, in one case followed by pulmonary embolism. The high incidence of therapy induced elevated APA concentrations suggests that these should be carefully monitored in all patients receiving immunotherapy based on interferon alpha.

230

ANTIPROLIFERATIVE EFFECT OF RETINOIDS AND INTERFERON α IN COMBINATION WITH IRRADIATION ON HUMAN TUMOR CELL LINES

Hoffmann W., Schiller U., Rodemann H.P., Essink M.*, Bamberg M. (Dept. of Radiotherapy / Radiobiology, University of Tübingen FRG; *Hoffmann-LaRoche, Grenzach, FRG)

Since the combination of BRMs and irradiation has recently gained increasing clinical interest in cancer treatment we analyzed the antiproliferative and/or differentiation inducing effect of retinoids (RA) and interferon α (IFNα) in combination with various irradiation (IR) schedules on established human tumor cell lines (transformed fibroblasts, squamous carcinoma cells of head and neck, cervix and lung, malignant glioma cells, T-cell lymphomas). Apparently, the combination of RA, IFNα and IR led to a pronounced synergistic amplification of growth inhibition measured by colony formation assay. The predescribed radiosensitizing effect of IFNα could also be demonstrated for retinoids. In addition, besides inducing mitotic cell death the antiproliferative effect of the combined treatment was predominantly based on the induction of terminal postmitotic differentiation as analyzed by cytomorphological (cell counts, colony size) and molecular parameters (e.g. oncogene expression). These data suggest that in combined treatment modalities, RA, IFNα and IR, may lead to an enhancement of therapeutic effects.

231

SOME CRITICAL APPROACHES TO NK ACTIVITY MODULATION IN PATIENTS WITH DIGESTIVE CANCER

J Shparyk
Department of Oncology, Medical Institute, Lviv, Ukraine.

106 cancer patients with tumor of digestive tract showed reduced natural killer (NK) activity and number of large granular lymphocytes (LGL). Progressive reduced NK activity and blood level LGL after operation, 5-fluorouracil chemotherapy, radiotherapy was observed. Pretreatment of patients' lymphocytes with interferon or indomethacin enhanced NK activity. We propose to use these and other biological response modifiers in vivo not only after (or during) immunosuppressive therapy (operations, chemotherapy etc.) but before this therapy. The above-mentioned approach allows to diminish the degree of temporary depressive influence of radical therapy. We propose also to carry out short repeated courses of immunotherapy (2-3 weeks with indomethacin, cimetidine etc.) after radical therapy for diminishing the risk of metastatic spreading and the progress of malignancy.

232

NEUROIMMUNOMODULATION(NIM)AND IL-2 IMMUNOTHERAPY:A NEUROENDOCRINE COMBINATION WITH IL-2 AND MELATONIN(MLT)IN ADVANCED SOLID TUMORS.

P.Lissoni,S.Barni,A.Ardizzoia,G.Tancini. Division of Radiotherapy,S.Gerardo Hospital,Monza,Italy.

The study of the NIM could allow to potentiate IL-2 anti tumor efficacy by using neurohormones involved in the regulation of immune cells.Pinealectomy has been shown to induce immunosuppression and to stimulate cancer growth. Therefore,the alterations in the pineal function observed in cancer patients(pts)could explain the low in vivo efficacy of IL-2 in respect to its great antitumor activity in vitro.On these bases,we decided to perform a clinical study with IL-2 and the pineal neurohormone MLT in cancer pts with very advanced solid neoplasms.The study included 64 pts(lung:20;colon:13;pancreas:9;stomach:8;liver:7;breast:4;pharynx:1;cholecystis:1;unknown:1).IL-2 was given subcutaneously at very low doses(3 M IU/day for 4 weeks); MLT was given orally at 50 mg/day at 8.00 P.M. Treatment was very well tolerated in all pts.Tumor objective regression was seen in 12/64(19%) (PR:10;CR:2); 22 pts had a SD,while the other 30 progressed.Survival was significantly higher in responder than in non-responder pts.

233

ADOPTIVE IMMUNOTHERAPY WITH INTERLEUKIN-2 (IL2) + α-INTERFERON (αIFN) + IL2-ACTIVATED LYMPHOCYTES (LAK) IN METASTATIC RENAL CELL CANCER

Goey, S.H.[1], Kruit, W.H.J.[1], Eggermont, A.M.M.[2], Bolhuis, R.L.H.[3], Stoter, G.[1]

1) Dept. Med. Oncol., 2) Dept. Oncol. Surg., 3) Dept. Immunol., Rotterdam Cancer Institute, Rotterdam, The Netherlands.

We performed a single institution phase II study of the combination of IL2 and αIFN and LAK. Treatment schedule: IL2 18 MIU/m²/day, continuous i.v. infusion days 1-5, αIFN 5 MU/m² i.m., days 1-5. Leukapheresis: days 7-9. LAK: days 12-14 with IL2 on days 12-16 and αIFN on days 12-15. The cycle was repeated on day 36. Patients with stable disease or response went on to maintenance treatment with 4 monthly cycles of IL2 18 MIU/m²/day and αIFN 5 MU/m²/day, days 1-4. Eligibility criteria: nephrectomy of primary tumor, performance status WHO 0-1 and normal organ function. Brain metastases were excluded. 46 Patients were entered. 60% Had metastatic involvement of 2 or more organs. Presently, 39 patients are evaluable for response and 43 for survival. 5 Patients achieved a CR (13%), 11 a PR (28%). The median duration of response is 10 months and the median survival of all treated patients is 28 months. In 75% of the patients, dose reductions and/or delays in the administration of the IL2 and αIFN were made as a result of hypotension, oliguria/anuria or severe diarrhea with metabolic acidosis.

In conclusion, this particular treatment regimen of IL2 + αIFN + LAK yields a high response rate (41%) and prolonged survival (median 28 months) as compared to 8 months in renal cell cancer patients treated with IL2 alone. The relative contribution of LAK will be evaluated in a randomized study.