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PUBLICATION

EFFECT OF OM-163, A NEW BIOLOGICAL RESPONSE MODIFIER ON THE IMMUNO-SUPPRESSION CAUSED BY CYTOSTATICS AND IONIZING RADIATION

D. Gaál, H.R. Hendriks¹

National Institute of Oncology, Budapest, Hungary

¹EORTC-NDDO, Amsterdam, The Netherlands

Immunosuppression induced by antitumor agents and ionizing radiation is an undesirable side effect of cancer chemo- and radiation therapy. The dose- and time dependent stimulatory effect of OM-163 (cell wall protein extract of *E. coli* from Lab. OMS. A., Meyrin, Switzerland) on the humoral and cellular immune response was measured and verified by using the plaque forming cell- and rosette forming cell assay. The compensatory effect of OM-163 on the diminished immune response of mice treated with different cytostatic agents (VCR, 5-FU, CisPt) or Co⁶⁰ irradiation was studied. OM-163 was generally able to compensate the immunosuppressive effect of cytostatics and radiation treatment without interfering with their antitumor activities. On the basis of our experiences OM-163 may be a potent agent in cancer therapy.

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MODULATION OF SPONTANEOUS RELEASE OF LDH ACTIVITY BY R H TNF α FROM PBL OF LYMPHOMA PATIENTS. AND HEALTHY CONTROLS

V. Jurišić¹, G. Konjević, I. Spužić

Institute of Oncology and Radiology, Beograd

¹School of Medicine, Kragujevac, Yugoslavia

Spontaneous *in vitro* release of lactic dehydrogenase (LDH) from peripheral blood lymphocytes (PBL), 8×10^6 /ml culture medium RPMI 1640 without phenol red (CM), of patients with Hodgkin's and Non Hodgkin's Lymphomas in advanced clinical stage was significantly increased compared to controls. After an *in vitro* treatment of the same concentration of PBL of lymphoma patients and controls with 100 U/ml CM r h TNF α an increase in the release of LDH activity was determined by the spectrometric method after reduction of the appropriate substrate. This increase was greater from PBL of controls, values of absorbance/min. changing from 19.13 to 38.68 nm, while for the lymphoma patients it was from 63.16 to 75.83 nm. These results suggest that PBL of lymphoma patients are altered in comparison with healthy PBL with respect to LDH release.

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PRONOUNCED DERMATOLOGICAL SIDE EFFECTS FOLLOWING IRRADIATION (RT) GIVEN WITH INTERFERON ALPHA-2A (IFN) PLUS RETINOIC ACID (RA)

A. Rahn¹, S. Moss¹, I.A. Adamietz¹, W. Hoffmann², B. Schilcher¹, H.D. Böttcher¹

¹J. W. Goethe-University School of Medicine, Department of Radiation Oncology, D-60590 Frankfurt, Germany

²Eberhard-Karls-University Tübingen, School of Medicine, Department of Radiotherapy, D-72076 Tübingen, Germany

Phase II studies revealed increased response rates in patients with skin or cervical tumors treated with IFN plus RA as compared to conventional chemotherapy. We are currently applying combined RT and IFN (3 Mill. I.U. s.c. three times per week) plus RA (0.5 mg/kg/d p.o.) in patients with squamous cell carcinoma.

In 1/4 patients (68 year old woman with locally disseminated cervical cancer) we observed at 42/50 Gy of pelvic RT (2 Gy daily, five times per week, 42 MV photons) moist desquamation and pronounced erythema (WHO grade III). Symptoms occurred at exit portals. IFN plus RA were postponed and RT finalized. During next 3 weeks symptoms disappeared except for dry skin.

IFN plus RA might increase skin reaction beyond 40 Gy; therefore, higher RT doses given with BRM substances warrant special observation.

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IMMUNOMODULATING EFFECT OF T-ACTIVIN THERAPY IN MELANOMA PATIENTS

N. Stanojević-Bakic, D. Milosevic, Lj. Vuckovic-Dekic, M. Sasic, Lj. Markovic

Institute for Oncology and Radiology of Serbia, Beograd, Yugoslavia

Many of the unconventional therapeutical approaches in malignant melanoma include immunomodulating agents. In this study we investigated the *in vivo* effects of thymic agent T-activin on several cellular immunity parameters in early stage melanoma patients. The criterion for selection of immunodepressed patients for immunotherapy was *in vitro* effect of T-activin in E-rosette assays and lymphoproliferative response to mitogen. In addition to these assays, the monitoring of *in vivo* effects also included the determination of various lymphocytes subsets (CD3, CD4, CD8, CD38, CD16, CD21 positive cells) by monoclonal antibodies. *In vivo* administration of T-activin did not affect the number of T cells and their subsets. However, T-activin therapy significantly improved lymphoproliferative response, indicating better predictive value of this *in vitro* functional T cell assay, and its potential usefulness in optimising the immunological treatment of cancer patients.

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EOSINOPHILS AND CLINICAL RESPONSE TO THE THERAPY WITH IL-2 PLUS INF- α IN PATIENTS WITH KIDNEY CANCER

F. Tacconi, E. Mainardi, M. De Amici¹, M. Confalonieri, C. Bianchessi, E. Bobbio Pallavicini

Divisione di Medicina, Ospedale Maggiore, 26013 Crema, Italy

¹IRCCS Policlinico S. Matteo, 27100 Pavia, Italy

In a group of 5 patients (pts.) affected by kidney cancer (3 of these reached a complete remission (CR), 2 reached a stabilization (S) of the disease), the treatment with low doses IL-2 s.c. plus IFN- α caused an increment of 11% (mean value) of eosinophils. The aim of our study is to evaluate if the eosinophils' increment and their activation could have a correlation with the clinical response. We have assessed the following parameters: percentage and total number of eosinophils, serum ECP (Eosinophil cationic protein), serum EPX (Eosinophil protein X) before and during the treatment course. The comparison between the results of CR and S pts. showed a statistical significance only for these ECP values: ECP (μ g/l) (basal serum level): S = (3697 ± 830) versus CR (1945 ± 77) $P = 0.028$; basal ECP % / WBC: S = (2.06 ± 0.431) versus CR (0.51 ± 0.26) $P = 0.01$; serum ECP difference after therapy: S = -1280 vs. CR = -130 ($P = 0.0024$). Our preliminary data suggest that a stable serum level of ECP during the treatment could have a correlation with the good outcome of the therapy. A randomized controlled study is necessary to clarify the possible role of eosinophils and their basic proteins as mediators and/or predictive factors of the clinical response to IL-2 therapy.

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STIMULATION OF HUMAN NEUTROPHILS FUNCTIONS IN VITRO AND AFTER ORAL ADMINISTRATION OF A POLYENZYME PREPARATION

E. Zavadova, L. Desser, T. Mohr

Institute for Tumorbiology/Cancer Research, University of Vienna, Austria

Polymorphonuclear neutrophils (PMN) can be primed for enhanced release of reactive oxygen species (ROS) by exposure to cytokines and biological response modifiers. ROS are considered to possess tumoricidal activity. The polyenzyme preparation Wobenzym^R (WE) contains pancreatin, papain, bromelain trypsin and chymotrypsin and is used in adjuvant tumor therapy. We investigated killing of WE exposed PMN against tumor cells and analyzed WE influence on ROS production in a chemiluminescence assay in PMN *in vitro* and *in vivo*. Depending on dose WE stimulates the cytotoxic capacity of PMN *in vitro* against tumor cells (50μ g/ml: $P < 0.01$). Exposure of PMN to Wobenzym caused a time-dependent significant ($P < 0.02$) increase in release of ROS. Similarly, oral administration of Wobenzym to healthy volunteers ($n = 28$) resulted in significant increases ($P < 0.01$) in ROS production, depending on dose (peak with 20 tablets) and time (peak 4 hours after Wobenzym administration). In contrast, ROS production was not elevated in the PMN of healthy volunteers receiving placebo ($n = 8$) or no treatment ($n = 16$). These findings point to an immunomodulatory capacity of WE in adjuvant tumor therapy.