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NEUROENDOCRINE STRATEGY WITH THE PINEAL HORMONE MELATONIN(MLT)TO ENHANCE THE ANTITUMOR ACTIVITY OF INTERLEUKIN-2(IL-2).

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It is known that the immune functions change during the day and the period of the year. The pineal gland has been shown to play an essential role in the chronobiology of the immune system through the secretion of MLT,which has been proven to stimulate several immune reactions. On the basis of the immunomodulating properties of MLT,a study was carried out to evaluate its influence on the antitumor activity of IL-2. The tumor used was the CL26 murine colon cancer cell line.This tumor was induced in C57BL/6 mice by intravenous injection of 2 x 10^5 cells.A first group of animals was treated with rIL-2(Euro-Cetus) alone,given intraperitoneally at a dose of 40,000 U/day from day 3 to 7. A second group of mice was treated with IL-2 plus MLT,which was given subcutaneously at a daily dose of 0.25 or 50 mg/kg b.w. in the afternoon,starting 3 days before IL-2 injection. Mice were sacrified 13 days after,and metastatic pulmonary nodules were measured. The association with MLT at both dosages significantly reduced the number of lung colonies in respect to that seen with IL-2 alone(MLT 0.25 mg/kg: $p < 0.01$; MLT 50 mg/kg: $p < 0.005$).These data show that a pretreatment with the pineal hormone MLT enhances the antitumor activity of IL-2.

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MELATONIN AS A TREATMENT OF HUMAN ADVANCED MALIGNANCIES: A PHASE II STUDY. Farina G.°,Scaglione F.*,Dugnani S.*,Ferrara F.*,Maccarinelli G.*,Perrone S.°,Tomirotti M.°,Fraschini F.*,Scanni A.° - °Dep.Med.Oncology and Chemoth.-Fatebenefratelli Opht.Milan - *Dep.of Pharmacology,Chemoth and Toxicol.Univ.of Milan. Italy.

The present study was undertaken to evaluate the antineoplastic activity and the tolerability of Melatonin in pts. bearing advanced malignancies resistant to the conventional therapies. 14 pts. (6 ♀ and 8 ♂),mean age 61,3 (range 33-77)were included in this investigation:9 had colorectum cancer, 2 breast cancer, 2 stomach cancer, 1 lung adenocarcinoma. In these pts. intramuscolar Melatonin was given (20 mg /day at 3 p.m.)for at least 2 months, followed by oral administration (10 mg/day) in case of response or stabilization of the disease. All required examinations were performed in order to evaluate the response. Besides, the natural killer cell (NK) activity and the phagocyte activity were regularly assayed on days 0,15,30,45,60 after the beginning of treatment (data in processing). The evaluable pts. were 12; we achieved 11 PROs and 1 RP> 50% (4+ mos). The inevaluable ones were 2: 1 went off protocol because of toxicity (nausea, vomiting, severe asthenia since the beginning of treatment) and 1 was lost to follow-up. We also observed the following individual effects: improvement in PS (3/14); increase of appetite (4/14); reduction of asthenia (6/14); improvement in morale (3/14). 1 pt. showed severe asthenia following the end of treatment. The pt. showing a PR (basal NK activity= 14%; after 15 days= 21%; 30 days= 26,7%; 45 days= 20,6%; 60 days=27%) was the only one contemporarily treated with slow-relmease morphine (120 mg. twice per day). This result might be related to a favourable interaction between opioids and Melatonin (Cancer 62: 494-499, 1988).

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PRE-CLINICAL EVALUATION OF HUMAN RECOMBINANT GM-CSF ON HUMAN BREAST ADENO-CARCINOMA CELLS IN VITRO.

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Granulocyte and Monocyte Colony Stimulating Factor (GMCSF) has a clinical potential in patients with leucopænia induced by chemo- or radiotherapy. Prior to any extensive use of this compound, assessment of its effect on non-hæmatopoietic tumor cell growth is essential.
Colony forming assays (CFAs), MTT colorimetric assays and tritiated thymidine (^{3}H-Thd) uptake on MCF-7 human breast adenocarcinoma cells were performed using human recombinant GMCSF kindly provided by Glaxo Institute for Molecular Biology, Geneva, Switzlerland (Dr. J.J. Mermod).
Doses of 0.1, 1, 10 and 100 ng/ml were tested in media containing 5% Fœtal Calf Serum.
CFAs did not show significant differences (Student's t test) between GMCSF-treated and control cells, survival rates being less than 125% of control: 123±7, 109±11, 109±9 and 113±8%, respectively (mean values ± SD, n=12 for each dose).
MTT assays after 4-day incubation with GMCSF confirmed these data with survival rates of 124±3, 100±2, 103±2 and 103±1%, respectively (n=4), as did ^{3}H-Thd uptake: 111±6, 112±4, 115±4, 113±2%, respectively (n=4).
These results allowed us to conclude on the non-proliferative activity of GMCSF on MCF-7 adenocarcinoma cells.
Extended cooperative studies are in progress with EORTC Clonogenic Assay Screening Study Group (Dr. M.S. Aapro, Chairman) on cell lines from different anatomical origin.
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ACCELERATED HEMATOPOIETIC RECONSTITUTION INDUCED BY GM-CSF ALLOWS SHORT-TERM HIGH DOSE CHEMOTHERAPY IN SMALL CELL LUNG CANCER (SCLC)

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Although SCLC is highly susceptible to chemotherapy, severe myelosuppression limits application of cytotoxic drugs. We provide evidence that application of GM-CSF subcutanously from day 4 to day 12 after a 3-day chemotherapy with AIO and PE in alternating cycles shortens the period of neutropenia even after an increased dose of chemotherapy. As a result, these patients could be treated in 2 weeks intervals.
Cytotoxic treatment was started with adriamycin (A) 50 mg/m² day 1, vincristine 2 mg day 1, and ifosfamide 2 g/m² days 1-3 in cycle (C) 1 and 3, alternating with cisplatinum (P) 90 mg/m² day 1, and etoposide (E) 200 mg/m² days 1-3 in cycle 2 and 4. According to randomization, patients were treated with or without GM-CSF 250 µg/m² sc day 4 to 12. Start of the next cycle on day 15 would require at least 3500 leucocytes / cmm and 100000 platelets / cmm. A dose-escalation of ifosfamide in 0.5 g/m² steps and of etoposide in 50 mg/m² steps after every 10 patients (5 with and 5 without GM-CSF) was planned, provided that in the preceeding dose step at least 3 patients in each group had fullfilled the criteria for application of the next cycle on day 15. The effect of GM-CSF was demonstrated in dose level 2: in 5 / 5 patients treated with GM-CSF chemotherapy could be continued on day 15. In contrast, in the group of the 4 patients not treated with GM-CSF no patient could be retreated on day 15.
Short-term aggressive chemotherapy in combination with GM-CSF might be a new approach possibly leading to improvement of treatment results in SCLC in the future.