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SYNERGISTIC CYTOTOXIC AND CYTOSTATIC INTERACTIONS BETWEEN INTERFERON-ALPHA AND CHEMOTHERAPEUTIC DRUGS IN HUMAN MYELOID LEUKAEMIA CELLS.

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Interferon-alpha (IFN-alpha) showed significantly better median survival rate in chronic myeloid leukaemia patients, therefore current studies are focusing on the identification of the proper chemotherapeutic drug with the most effective synergistic interaction with IFN-alpha for the elimination of the human myeloid leukaemia cell clone. The cytostatic and cytotoxic effects of combining IFN-alpha with each of the three chemotherapeutic drugs: Carboplatin, Daunorubicin and Cytarabine were evaluated in three human myeloid leukaemia cell lines representing different stages of differentiation: MHH225 (CD34 positive multilineage), HL-60 (promyelocytic) and U937 (monoblastic) in both liquid suspension and agar clonogenic cultures. The ED90 (the concentrations of chemotherapeutic drug required for 90% inhibition of colony formation or cell death) in myeloid leukaemia cells were in the following order: Daunorubicin > Carboplatin > Cytarabine. Whereas IFN-alpha failed to significantly decrease the ED90s of Cytarabine in the three human myeloid leukaemia cell lines, it significantly decreased the ED90s of Carboplatin and to less extent Daunorubicin but not cytarabine in both liquid suspension and agar clonogenic cultures.The present results are in line with the previous negative interaction between IFN-alpha and Cytarabine both in vitro in K562 human leukaemia and in vivo in L1210 murine leukaemia, and the synergistic cytostatic interaction between IFN-alpha and Carboplatin in K562 cells. The significant synergism between IFN-alpha and Carboplatin was consistent in all four human myeloid leukaemia cell lines with various stages of differentiation and confirmed in both serum-free and serum-supplemented cultures applying different in vitro assays: liquid suspension, agar clonogenic and capillary agar microclonogenic cultures. In addition, significant antileukaemic activity of both IFN-alpha and Carboplatin were reported in several clinical studies for myeloid leukaemia patients. Thus, the clinical use of the combination of IFN-alpha and Carboplatin in the treatment of CML patients could prolong the complete haematologic and cytogenetic responses and consequently improve the survival rate. On the other hand, the present negative interaction between IFN-alpha and Cytarabine in myeloid leukaemia cells, together with the inferior cytogenetic responses observed in CML patients treated with IFN-alpha plus Cytarabine, cautions against the continous clinical use of the IFN-alpha plus Cytarabine and suggests instead the use of Carboplatin in combination with IFN-alpha for the treatment of myeloid leukaemia patients.

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THE COMBINATION OF INTERFERON-ALPHA, ALL-TRANS RETINOIC ACID AND TOPICAL MECHLORETHAMINE IN THE TREATMENT OF CUTANEOUS T-CELL LYMPHOMAS

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Cutaneous T-cell lymphomas have two major variants including mycosis fungoides (MF) and the Sezary syndrome (SS). The malignant cells are mature, thymic-dependent lymphocytes with striking convoluted or cerebriform nuclear contours. Clinically, the disease presents with an indolent course with cutaneous manifestations and lymphadenopathy. Several therapeutic modalities have been applied to produce partial clearing of lesions, but not curative. We administered interferon-alpha (IFN), all-trans retinoic acid (ATRA) and topical mechlorethamine (HN_2, topical application) as a combination to 2 male patients with MF and 1 female patient with SS. The ages of the three patients were 51,64 and 57. All were newly diagnosed without receiving chemotherapy previously. The INF was given subcutaneously for 2 months at a dose of 2 million IU daily, then 3x2 million IU weekly for 4 months. ATRA was given 1mg/kg daily for 2 months, then 0.5mg/kg daily for 4 months. The topical application consisted of HN_2 dissolved in 50ml of water applied daily to skin lesions for 6 months. A six month was considered as one cycle. The side effects included multiple cutaneous toxicities (dryness, atrophy, keratosis and hyperpigmentation) and flu-like symptoms. The female patient with SS had moderate myalgia which was easily brought under control with medication. Complete response was observed in the 51 old patient with MF with complete clearing lesions. This response began in the first trimester of therapy. Partial response occurred in 1 patient with MF and 1 with SS with reduction of plaques and less erythema. All patients' lymphadenopathies were improved and Sezary cells disappeared in the patient with SS. It is the authors' opinion that this regimen combines the effects of three different pharmaceutical agents and could serve as an active therapeutic modality. Rebound of lesions and reappearance of Sezary cells between cycles should be solved.

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Post-Marketing Surveillance Study on the Treatment of Solid Tumors with Filgrastim

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In Germany, filgrastim (Neupogen®, r-metHuG-CSF) has been approved inter alia for use in shortening the duration of neutropenia and in reducing the frequency of neutropenic fever in patients undergoing myelo-suppressive chemotherapy at customary doses. We give below an interim evaluation of a post-marketing surveillance study carried out in 346 patients suffering from solid tumors.

The patients were observed over a maximum of 6 cycles of therapy comprising chemotherapeutic agents and filgrastim. Tumor type, duration of treatment, daily dose, blood count, infectious complications and adverse events were documented.

23.1% of the study subjects were suffering from breast cancer, 19.4% from testicular cancer, 15.7% from ovarian cancer, 15.4% from small-cell lung cancer, 7.4% from non-small-cell lung cancer, 3.1% from bladder cancer and 15.9% from other tumors.

Filgrastim was administered on an average of 6.2 days per cycle at an average dose of 377 µg per day. In 88% of evaluable patients it was possible to administer the planned dose of chemotherapeutic agents and in 79.8% the planned interval between cycles was maintained. Neutrophil recovery under filgrastim was considered good or very good by 86.3% of assessing physicians. Compared with previous cycles without filgrastim, patients' quality of life was considered by 57.4% of physicians to have improved and by 38.6% to have remained stable. Adverse events were observed in 2 patients, one of whom experienced severe bone pain and the other a swelling in his right arm.

Treatment with filgrastim enables chemotherapy to be administered as planned in the vast majority of patients. The treatment is very well tolerated and a significant improvement in patients' quality of life is observed in chemotherapy cycles with filgrastim support.

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Effective treatment of radiotherapy-induced thrombocytopenia with Interleukin-3 (IL-3)

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A 40-year old woman suffering from Hodgkin's disease (stage III A) underwent myelotoxic chemotherapy (5x COPP and 5x ABVD). After radiotherapy (40 Gy) for mediastinal tumor mass, the patient exhibited severe persistent thrombocytopenia requiring 5 thrombocyte transfusions (HLA-matched) and 2 erythrocyte transfusions. No signs of spontaneous bone-marrow recovery could be observed even 4 weeks after radiotherapy. Therapy with granulocyte-stimulating factor (G-CSF) over 12 days increased granulocyte counts only. Therefore it was decided to start IL-3 (5 µg/day/kg) for 5 days followed by 7 days G-CSF (5 µg/day/kg). The thrombocyte count in the course of platelet and erythrocyte treatment dropped from 184.000/µl to 10.000/µl. An increase in the thrombocyte count from 18.000/µl to 34.000/µl was observed nine days after starting IL-3. The rise continued steadily to a thrombocyte count of 124.000/µl after 16 days and remained almost constant on that level. Side effects due to IL-3 administration (flu-like symptoms) were typical for growth factors and could be treated effectively with Paracetamol. These data support efficacy of IL-3 treatment in radiotherapy-induced thrombocytopenia. A cumulative effectiveness through combination of the early acting IL-3 with later acting growth factors (G/GM-CSF) is still under discussion.