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## CELLULAR BIOLOGY OF RETINOIDS

Bollag W.
F. Hoffmann-La Roche Ltd., Basle, Switzerland

Inhibition of cell proliferation, induction of differentiation, suppression of viral oncogene expression and inhibition of angiogenesis are among the most important properties of retinoids contributing to their antitumor effect. In transformed human hemopoietic cell lines all-trans, 13-cis and 9-cis retinoic acids, and various other retinoids induce a variable degree of differentiation. In cell proliferation experiments, the inhibitory effect varies markedly depending on the human transformed epithelial cell line tested. In HPV containing cervical carcinoma cell lines, viral oncogene expression was substantially decreased. Retinoids inhibit also tumor cell-induced angiogenesis considered to be necessary for tumor growth beyond a certain size. These activities of retinoids can be substantially enhanced by their combination with cytokines and growth factors, as well as by combination with 1,25-dihydroxy-vitamin $D_3$ and analogs. This leads to additive, synergistic or potentiating effects. Every compound and every combination has its own specific profile of properties. Since there is ample evidence that cell differentiation, cell proliferation, viral oncogene expression as well as angiogenesis play a role in tumor induction and/or progression of tumor growth, retinoids and particularly their combination with cytokines and vitamin D analogs may be useful in chemoprevention and chemotherapy of neoplastic diseases.

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## RETINOIDS IN CANCER PREVENTION.

Ugo Pastorino. Thoracic Surgery, Istituto Nazionale Tumori, Milan, Italy.

Human cancer chemoprevention research is rapidly developing, due to recent biological achievements. A considerable number of potentially active agents are being tested in clinical trials involving "healthy subjects" as well as cancer patients. Among these, retinoids play a dominant role due to their specific ability to modulate cell growth and differentiation in the various experimental systems. On the scientific ground, it is essential to assess the nature and extent of biological effect on human carcinogenesis, in terms of reduction and/or delay of new primary tumors in the target field. On the clinical ground, it is important to define the overall benefit of prevention measures, in terms of overall survival, having adjusted for confounding factors such as smoking and dietary habits, comorbidity, and mortality unrelated to cancer.

A number of clinical trials have been activated in the United States and Europe to investigate the preventive potential of retinoids, alone or in combination. The majority of these studies are ongoing, but a few of them have been concluded with very promising results in terms of cancer prevention. Other trials are negative or inconclusive, and emphasize the need for optimal study design with respect to selection of target populations, choice and combination of preventive agent(s), dose and duration of treatment, and definition of specific endpoints. In recent studies, various genetic and molecular biology investigations have been performed to identify specific and consistent changes in the various steps of carcinogenesis. Based on this finding, we will hopefully design a new generation of clinical trials using genetic biomarkers to identify optimal candidates for specific chemoprevention programs, and also to monitor the results of intervention in the short and intermediate term.

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## THERAPY OF SOLID TUMOUR WITH RETINOIDS, MONOTHERAPY AND COMBINATION THERAPY.

G J S Rustin, Mount Vernon Hospital, Northwood, Middlesex, UK

In vitro and animal studies indicated that several retinoids had anti proliferative activity against a variety of tumour prompting clinical trials. When isotretinoin or etetrinate were used as single agents, partial response rates as high as 70% were seen in patient with basal cell carcinomas and 62% with cutaneous T cell lymphomas. A few complete responses have been seen in patients with cutaneous squamous cell carcinoma but responses were only seen in only 30% of head and neck tumours and only 1 of 45 patients for non small cell lung cancer. Combinations of retinoids and cytotoxics have not led to improved response rates and neither did an initial study of interferon and etetrinate in patients with melanoma. However the combination of interferon with isotretenion produced 7 (25%) complete and 12 (43%) partial responses in patients with advanced squamous cell carcinoma of skin and 12 partial and one complete response among 26 women with untreated squamous cell carcinoma of the cervix but was ineffective against recurrent disease. A programme to test the most active of the polyaromatic derivatives of vitamin A, has led to the discovery of the arotenoid RO 40-8757. This agent is active against DMBA induced rat mammary carcinoma in vivo and some breast and squamous human tumour xenografts. Syngersistic activity has been seen with cytotoxics and cytokines and chemoprotection has been noted. Phase I trials as single agents in combination in patients with breast and lung carcinoma are ongoing.

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## THERAPY OF ACUTE PROMYELOCYTIC LEUKEMIA WITH ALL-TRANS RETINOIC ACID.

Gillis, S., Ben-Yehuda, D., Rachmilewitz, E.A. Dept. of Hematology, Hadassah University Hospital, Jerusalem, Israel.

We have used ATRA in the treatment of 7 patients with APL, 4 females and 3 males with a mean age of 36 years. WBC count ranged from $1.1x10^9$/L to $90x10^9$/L. Platelet counts ranged from $5.0x10^9$/L to $155x10^9$/L. Six patients had a mild to moderate bleeding tendency and two had laboratory evidence of DIC. All patients received ATRA orally at a daily dose of $45mg/m^2kg$ for 90 days. Daunorubicin and Cytosar was given for a brief period (1-5 days) and was stopped as soon as the counts began to fall. The coagulopathy was treated by daily transfusions of fresh frozen plasma, cryoprecipitate and platelets. A low molecular weight Heparin - Enoxaparin was administered to all of the patients. Fibrinogen degradation products peaked within 1-9 days and returned to normal by day 12 in all patients. Complications of treatment included intracerebral hemorrhage (1), pulmonary hemorrhage (3) and "retinoic acid syndrome" (1). ATRA was stopped in one patient on day 84 because of pseudotumor cerebri. Three patients are in complete remission up to 12 months after diagnosis. One patient successfully underwent allogeneic BMT. One patient relapsed after 12 months and one patient died in remission from sepsis following chemotherapy. Conclusions: 1. The dose of chemotherapy during induction with ATRA must be tailored specifically for each case. 2. All patients are followed by serially B.M. examinations with the polymerase chain reaction (PCR) for detection of rearrangement of the retinoic acid receptor and PML genes. In the patient who relapsed the PCR became positive 6 weeks before clinical signs of relapse occured. 3. Enoxaparin shows promise in the management of the coagulopathy in APL.

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## RETINOIDS IN THE TREATMENT OF NEUROBLASTOMA.

LIE, S.O.- Dept. Pediatrics, University Hospital, Oslo, Norway.

Neuroblastoma is one of the most aggressive childhood malignancies. In spite of increasingly intensive treatment protocols - the survival rate of children with advanced disease remains less then 20 % New treatment modalities are therefore constantly being searched for.

Retinoids have in several in-vitro-systems been shown to induce maturation of neuroblastoma cells and stop the malignant cell division in in-vitro culture systems. Since 1988 the European Neuroblastoma Study Group have conducted a double blind placebo controlled trial investigating the effect of 13-cis retinoic acid in children having achieved a complete or very good partial remission after intensive induction chemoterapy. Patients are randomized to receive a placebo or the active drug in a dose of approximately 0,75 mg per kilo per day. Length of therapy being 4 years.

In USA the Children Cancer Group (CCG) have recently initiated a similar study also using 13-cis retinoic acid. The drug is given in high doses ($160 mg/m^2$/day) two weeks on and two weeks off x 12 months.

Neuroblastoma is a disease with many late relapses and it will therefore take more time before any conclusions as to the possible effect on survival can be reached.

Keywords: neuroblastoma, retinoids, children.