SOCIEDAD VENEZOLANA DE DERMATOLOGIA

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ORAL CONTRACEPTIVES - SKIN CANCER RISK

RESPONSE

ue to coincident increases in melanoma and in oral contraceptive use in recent deca des, questions have arisen about a potential link between the two. Green (1991) reviewed the epidemiologic literature concerning the association between oral contraceptive use and the occurence of melanocytic nevi and melanomas. Two reports were cited which evaluated the occurrence of melanocytic nevi in oral contraceptive users and neither of these demonstrated a significant association. With regard to melanoma occurrence rates, one report was cited which showed no relative change in the occurrence ratess between males and females over a 10 - year period after oral contraceptives became available. Also, among 9 case - controlled studies no increased risk due to oral contraceptive use was found. The author noted that the issue of subtypes of melanoma may be an important factor in detecting an increased risk due to oral contraceptive use, and cited one study where analysis controlling for histologic subtype found a significant increase in superficial spreading melanoma among oral contraceptive users, although other confounding variables were not controlled for.

CONCLUSION

No significant association has been found between oral contraceptive use and the occurence of melanocytic nevi and melanomas.

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LEVAMISOLE THERAPY OF CANCER

RESPONSE

EVAMISOLE, is an orally active agent which has attracted attention becasuse it was found to possess IMMUNOTROPIC PROPERTIES. It seems, to restores inefficient host defense mechanisms and thus its usefulness as an adjunct in the treatment of certain types of human CANCER as well as other conditions is being explored.

In most animal cancer models, levamisole does not influence the growth of primary tumur but prolongs the remission period after chemotherapy. In vitro, levamisoles was found to restore azathioprine suppressed T-cell function. In patients with cancer, levamisole restores skin reactivity to 2, 4 dinitro-chlorobenzene (DNCB) and purified protein derivative (PPD). In those patients with Hodgkin's disease, levamisoles restores the ability to form E rosettes (Verhagn et al, 1977; Anon, 1975). A ll of the above are indications of enhancement of cellmediated immunocompetency.

A long-term, multicenter doubleblind study in patientes undergoing operations for primary bronchial carcinoma was designed to test the immunotropic effects of levamisole (Anon,1975). The patientes received levamisole or placebo for three days every two weeks, starting threee days before surgery. Unless there was clinical evidence of recurrence, cytostatic drugs, corticosteroids, and radio-therapy were prohibited. In the 111 patientes who had been followed for one year, the incidence of side effects were similar in both the placebo and drug treatment groups. Recurrence occurred in ten out of 51 patients (seven deaths) that received levamisole and in 20 out of 60 (twelve deaths) that received placebo. The difference appearss not to be due to chance alone. In the levamisole group, there were fewer recurrences in patients with squamous cell carcinoas and medium and large primary tumors, and fewer suspected and proved recurrences and deaths from metastases in patients with extended tumors. Distant recurrences (in bone, brain, and liver) tended to be less common in the levamisole group, whereas the disease-free interval-(time between surgery and evidenpe of recurrence) in a relapsing patients was almost identical in the two groups.

Rojas et al (1976) conducted a clinical trial of levamisole in women with primary inoperable BREAST CANCER (stage III).

After being rendered clinically disease free by radiotherapy to the brasst, supraclavicular area, and axillia, patients were allocated alternately to a control group (no further treatment) or to a levamisole-treated group. The follow-up in 43 patients (20 levamisole treated and 23 controls) indicated significant prolongation of the median diseasefree interval (25 vs 9 months) and survival (90% vs 35% alive at least 30 months) in the levamisole-treated group compared with the controls. Levamisole treatment was also associated with an increase in the perpentage and intensity of delayed hypersensitivity skin reactions and in the absolute lymphocyte counts. No significant toxicity of levamisole was observed in this study except for a slightly higher incidence of nervousness, gastric intolerance and fever.

Klefstrom et al (1985) reported the benefits of levamisole in significantly prolongign disease-free and total survival in stage II postmenopausal breast cancer patients when combined with radiotherapy. Miwa et al (1980) described a potential role for levamisole in gastric cancer. However, most recent reports have not demonstrated any efficacy of levamisole when used in combination chemotherapy or with radiation in the treatment of malignant melanoma (Costanzi et al, 1974), lung cancer (Davis et al, 1982; Krauss et al, 1984; Ainslie et al, 1983; White et al, 1982), ovarian cancer (Khoo et al, 1984), breast cancer (Anon, 1980) and acute nonlymphocytic leukemia (van Sloten et al, 1983). In fact, negative effects of levamisole therapy have been reported. A higher recurrence rate of breast cancer was described with combined levamisole and radiation therapy, as compared to radiation therapy alone, by the Danish Breast Cancer Cooperative Group (Anon, 1980); other studies have reported a significantly shorter survival in patients treated with levamisole, as opposed to patients not receiving levamisole, for lung cancer and ovarian cancer (Khoo et al, 1984; Davis et al, 1982; Krauss et al, 1984; Ainslie et al, 1983).

In addition, the toxicity of levamisole appears to be more frequent and severe than previously suggested. A high incidence of leukopenia, agranulocytosis, severe skin rashes, fever and gastrointestinal intolerance has been reported frequently resulting in discontinuation of therapy (Anon, 1980; Gunderson & Fossa, 1980; Drew et al, 1980; Klefstrom et al, 1985; Teerenhovi et al, 1978; Veys et al, 1978; Krauss et al, 1984). In one large study (Anon, 1980), leukopenia was observed in 20% of postmenopausal patients with breast cancer during therapy with levamisole; agranulocytosis was observed in 3,6% of patients (premenopausal and postmenopausal).

Some investigators feel levamisole lacks the potency and specificity required of an active immunotherapeutic agent (Krauss et al, 1984).

CONCLUSION

Levamisole appears capable of stimulating the cell-mediated immune response, however the majority of studies have not demonstrated the efficacy of the drug as an adjunct in the treatment of human cancers. In addition, the toxicity of levamisole, primarily granulocytopenia, will limit its use as an immunotherapeutic agent. Further clinical trials should evaluate levamisole as an adjunctive therapy in more established chemotherapy regimens. However, at present, available studies do not suggest levamisole will have a major role in the treatment of cancers.

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RETINOID THERAPY OF SKIN CANCER

RESPONSE

Vitamin A and its natural and synthetic derivatives, collectively termed RETINOIDS, are being studied as cancer chemoprophylactic and chemotherapeutic agents. It has long been known that VITAMIN A deficiency is associated with reversible epithelial dysplasia and metaplasia, which is characterized by increasing cell proliferation and hyperkeratosis of a variety of epithelia. Epidemiologic data suggest that normal serum vitamin A levels protect against the development of epithelial malignancies. Yet, little is known about the precise mode of action of vitamin A in epithelial tissues, and even less about its role in opposing neoplasia (Wolbach et al, 1925; Peto et al, 1981).

MECHANISM OF ACTION

Several molecular mechanisms have been proposed to explain the action of retinoids. It is believed that retinoids act similar to steroids, initially binding to cytosol receptors, which then translocate to the nucleus, there after altering messenger RNA and protein systhesis. Another theory suggest that retinoids act as tumor anti-promoters, either by inhibiting agents that stimulate polyamine synthesis (which may, in turn, lead to unchecked DNA synthesis) or by direct interference with expression of the oncogene. Also, retinoids may have an effect on cell membranes by destabilizing lysosome membranes via their detergent-like activity at high concentrations (Elias et al, 1981). Results of a study conducted by Hendrix et al (1990) indicated that retinoic acid inhibited tumor cell invasion through a basement membrane-like matrix by suppressing matrix degradation and by altering cell surface receptors.

TRETINOIN

Bollag & Ott (1970, 1975) described the effect of tretinoin in BASAL CELL CARCINOMA and ACTINIC KERATOSES. In the first study, 11 patients with 16 basal cell carcinomas were treated with 0.1% and 0.3% tretinoin ointments applied once daily under occlusion for three to five weeks. Treatment with 0.1% tretinoin ointment on six tumors led to 3 complete and 3 partial responses (defined as a size reduction of greater than 50%). Treatment with 0.3% tretinoin ointment on ten lesions resulted in 2 complete and 7 partial responses. Two of the 5 completely responding tumors recurred 8 and 10 months after discontinuation of treatment.

The authors concluded that topical tretinoin was not useful as a routine treatment of basal cell carcinomas because it was inferior to standard therapy.

In the second study, 0.1% and 0.3% tretinoin ointments were used twice daily without occlusion for 3 to 8 weeks in 60 patients with multiple actinic keratoses. Of the 20 patients receiving 0.1% tretinoin ointment applications, 7 (35%) had complete responses and 8 (40%) had partial responses. Treatment of 31 patients with 0.3% tretinoin ointment resulted in 17 (55%) complete responses and 12 (39%) partial responses. No complete responses were observed in actinic keratoses of the hands and forearms in patients treated with either 0.1% of 0.3% tretinoin ointments. Of the 24 patients with completely responding facial actinic keratosess, 8 recurred within 12 months after therapy ended. The authors concluded that topical tretinoin was inferior to other modalities, such as 5-fluorouracil in this application.

Robinson & Kligman (1975) reported synergistic effects with 5fluorouracil 5% cream and tretinoin in 20 patients with actinic keratoses. Epstein (1986) also concluded that tretinoin used in combination with 5fluorouracil was effective in the treatment of precancerous lesions on the forearms and hands.

Levine & Meyskens (1980) reported the use of tretinoin in the treatment of cutaneous metastatic melanoma in 2 patients. One drop of 0.05% tretinoin solution applied once daily under occlusion for 12 weeks was used. Complete regression of the treated lesions was noted in one patient and a partial response was seen in the other. Histological evidence from both cases revealed that the activity of tretinoin was limited to the upper regions of the dermis, suggesting that tretinoin may only penetrate to a certain depth and that this may be limit its antineoplastic activity.

In a pilot study of 3 patients with multiple dysplastic nevi, Meyskens et al (1986) reported encouraging results following treatment with topical tretinoin 0.05% therapy. Following 10 to 12 weeks of treatment and after several months, biopsed lesions demonstrated either benign compound nevi without dysplastic changes or only minimal residual dysplasia.

ISOTRETINOIN

Peck et al (1982) performed a two-stage study of the treatment of basal cell carcinoma with oral isotretinoin. In the first treatment stage an initial high-dose chemotherapy was used. Twelve patients with a total of 270 basal cell carcinomas due to chronic sunlight exposure, x-ray irradiation, arsenical insectivide exposure, and nevoid basal cell carcinoma syndrome received an average maximum dosage of 4.5 milligrams/kilogram/day of oral isotretinoin. Mean treatment duration at these dosages was approximately eight months. In this series, approximately 10% of the tumors underwent complete clinical and histologic remission. Smaller tumors responded better to highdose isotretinoin; 23% of 3 to 5 mm tumors achieved complete response, in contrast to only 7% of tumors 10 mm or larger. Because these results compared unfavorably with standard therapy, this stage of the study was stopped. The second stage of the study involved using lower-dose isotretinoin as a chemoprophylactic agent. This phase of the study included only 3 of the 12 patients involved in the chemotherapeutic phase. Initially, an average isotretinoin dosage of 1.5 milligrams/Kilogram/day was used for a mean duration of 34 months. After the study was underway, the dosage was reduced to 0.5 milligram/kilogram/day. While each of the 3 previously studied patients had varying complete responses (3%, 12%, 34%) to isotretinoin during che-motherapy, none developed new tumors within the next 2 to 8 years. Among patients who withdrew from the trial due to mucocutaneous toxi-

cities observed at the high dosage, preexisting lesions enlarged and new tumors began to appear at varying intervals after therapy ceased. This indicates that the chemoprophylactic effects of retinoids require chronic maintenance therapy. Peck (1987) indicated similar results regarding isotretinoin as a chemoprophylactic agent in bassal cell carcinoma.

Goldberg et al (1989) used iso-tretinoin to treat a pair of identical twins with vasal cell nevus syndrome (a precurssor of basal cell carcinoma). The twins received isotretinoin 0.4 milligram/kilogram/day orally for 1 year. After 1 year, both patients had a significant decrease in the number of new lesions. At this time, the dosage was lowered to 0.2 milligram/kilogram/day in one of the twins (twin A). Four years later the twins were evaluated and twin B had developed only 12 new basal cell carcinomas, while twin A developed almost four times as many new lesions. The authors concluded that isotretinoin was a useful adjunct in the treatment of patients with basal cell nevus syndrome. Also, the dosage of 0.2 milligram/kilogram/day isotretinoin was significantly less chemoprotective than the 0.4 milligram/ kilogram/day dose. Kessler et al (1987) administered isotretinoin to 25 patients with extensive MYCOSIS FUNGOIDES (T-cell lymphoma). The first 16 patients received isotretinoin 2 milligrams/kilogram/day. Subsequent patients received 1 milli-gram/kilogram/day. The median time to response was 2 months and the median response duration was eight months longer. There was a 44% (11 patients) objective clinical response rate with 3 complete clinical reponses without convincing evidence of pathologic clearing of the disease. An additional 24% (six patients) showed a minor degree of clinical improvement. Chronic toxic reactions consisted primarily of drying of the skin and mucous membranes which resulted in dose reductions in 14 of the 16 patients who initially received 2 milligrams/kilogram/day. The authors concluded that isotretinoin is of sig-

nificant clinical benefit, but topical steroids and PUVA should still be considered the primary treatment of mycosis fungoided. Kessler et al (1983) also reported successful treatment of mycosis fungoides with oral isotretinoin.

Kraemer et al (1988) reported the efficacy of isotretinoin 2 milligrams/kilogram/day orally for 2 years in the prevention of skin cancers in 5 patients with XERODERMA PIGMENTOSUM who had a history of multiple cutaneous basal cell or SQUAMOUS CELL CARCINOMAS. A total of 121 tumors were observed, with an average reduction in SKIN CANCERS of 63%. Tumor frequency again increased (mean of 8.5 fold) when isotretinoin was discontinued. Adverse effects were severe during treatment, including cutaneous toxicity, increases in triglycerides, abnormal hepatic function tests, arthralgias and skeletal toxicity. The investigators concluded that high-dose isotretinoin would probably be useful in preventing CUTANEOUS CARCINOMAS in patients with xeroderma pigmentosum. Use of etretinate (25 milligrams daily) was also reported useful in treating xeroderma pigmen-tosum (Berth-Jones, 1990).

ETRETINATE

Berreti & Grupper (1984) reported on the effects of etretinate in the treatment of KERATOACANTHOMAS, basal cell carcinomas, and actinic keratoses. Six large, solitary kerato-acanthomas underwent complete regression following etretinate 1 milli-gram/kilogram/day and a lower main-tenance dosage of 0.5 milligram/kilo-gram/day. Basal cell carcinomas were not found to respond as well. Only three of 42 tumors (7%) underwent complete regression. Re-lapse after discontinuation of therapy was noted inpartially responding basal cell carcinomas. In the treatment of actinic keratoses, 35 of 46 (76%) patients with multiple actinic keratoses cleared completely by using the above dosing schedule. Although relapses occurred following

the discontinuation of therapy, the authors stated that an intermittent dosage schedule of 1 milligram/kilogram/day for two moths at yearly intervals kept most patients free of actinic keratoses. Moriarty et al (1982), in a double-blind, crossover study, reported similar results with the use of etretinate in the initial treatment of actinic keratoses. Use of etretinate (25 milligrams daily) was also reported useful in treating xeroderma pigmentosum (Berth-Jones, 1990).

CONCLUSION

Oral and topical retinoids have been used in the treatment and prevention of cutaneous malignancies (chronic actinic dermatitis, NEVOID BASAL CELL CARCINOMA SYNDROME, basal cell carcinoma, xeroderma pigmentosum, cutaneous metastases of MALIGNANT MELANOMA, and cutanous T-cell lymphoma). In general, synthetic retinoids usually do not cure cutaneous tumors, but do produce variable degree of regression when administered in high doses. When combined with other chemotherapeutic agents, greater effectiveness than either individual agent alone has been demonstrated. Low-dose isotretinoin and etretinate may be of value in new skin tumor prophylaxis in susceptible patients. Discontinuation of therapy is often followed by relapse.

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