Correspondence and Short Communications

Comments on published articles, short communications of a preliminary nature, case reports, technical notes and the like are accepted under this heading. The articles should be short and concise and contain a minimum of figures, tables and references.

PLASMA ESTRONE AND ESTRONE SULPHATE IN BREAST CANCER PATIENTS TREATED WITH THE AROMATASE INHIBITOR CGS 16949A

Aromatase is a key enzyme in the synthesis of estrogens (1). The main postmenopausal estrogen, estrone (E_1) is produced mainly in peripheral tissues by aromatization from androstendione (4-A) (2). Recently, estrone-sulphate (E_1-S) has received considerable interest as a source of estrogens for breast cancer cells (3). The plasma level of E_1-S is 5–10 times higher than the plasma E_1 (4–6). As both sulphatase (3) and dehydrogenase (7) are found in breast tumors, E_1-S might be an important source of estrogens in breast cancer cells.

The successful use of aminoglutethimide (AG) as endocrine treatment of breast cancer has suggested that aromatase inhibition will be an important new treatment alternative for this disease (8). However, as AG frequently causes side effects, there is a need for new and less toxic aromatase inhibitors (9, 10).

Recently, imidazole derivatives have been shown to be aromatase inhibitors (9). CGS 16949A (Ciba-Geigy), 4-(5, 6, 7, 8-tetrahydroimidazo-[1, 5]-pyridin-5-yl)-benzonitrile monohydrochloride is in clinical phase I and II trials (11). Animal investigations have suggested that this drug is a more potent aromatase inhibitor than AG (12) and promotes regression in mammary tumors in rats (13).

In this communication we report on acute (hours) and long-term (0–57 days) changes in plasma E_1 and E_1-S in 7 postmenopausal women with advanced breast cancer (Table), receiving CGS 16949A treatment. They had all received tamoxifen previously. Three patients had received either additional endocrine or cytotoxic therapy. None had been treated with AG or other aromatase inhibitors. The patients were randomized to 2 dose levels of CGS 16949A, either 0.3 mg b.i.d. (n = 4) or 0.3 mg t.i.d. (n = 3), as part of a multicenter phase I–II study. The UICC criteria for response were used (14). The study was approved by the regional ethical committee. All patients gave their informed consents to participate in the study.

Blood samples for estrogen measurements were obtained before start and at regular intervals during therapy. The blood samples were drawn before the morning dose at 8 a.m., after an overnight fasting. For short, acute-term effects blood samples were obtained 4 h after the morning dose. Long-term effects were evaluated after 1, 2, 7, 30 and 57 days of treatment.

The blood samples were allowed to coagulate for 1 h, serum separated and stored at −20°C until analysis. All samples from each patient were analyzed in the same run, each sample was assayed in duplicate.

E_1 and E_1-S were quantitated with an RIA batch method, as described in detail elsewhere (6). The sensitivity for E_1 was

Table

Patient characteristics

No.	Age (years)	Dose (mg)	Metastasis	Response
1	71	0.3 × 3	Bone	SD (>16 months)
2	60	0.3 × 2	Lung	PD
3	70	0.3 × 2	Local/regional	PR (2 months)
4	62	0.3 × 3	Bone	SD (3 months)
5	69	0.3 × 3	Local/bone	PD
6	73	0.3 × 2	Regional/pleura	PD
7	72	0.3 × 2	Local	SD (7 months)

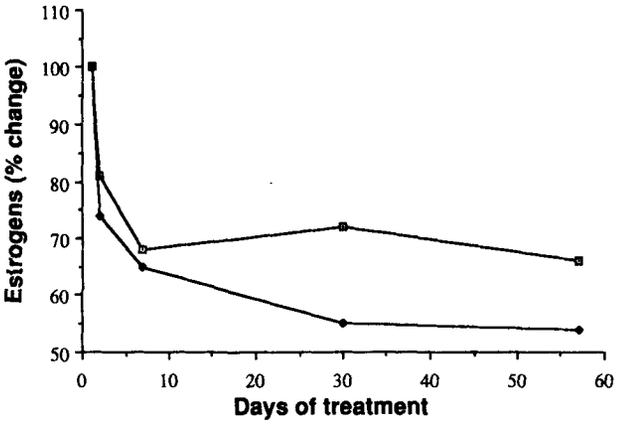
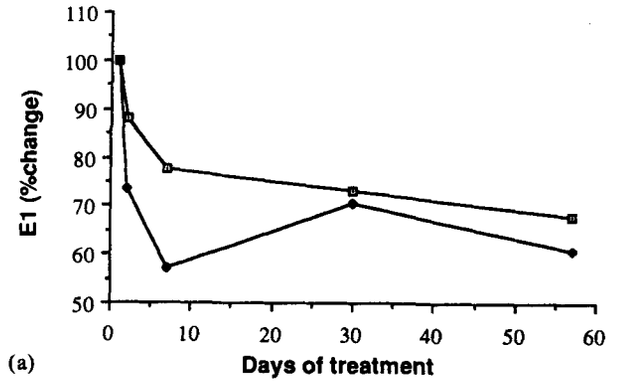
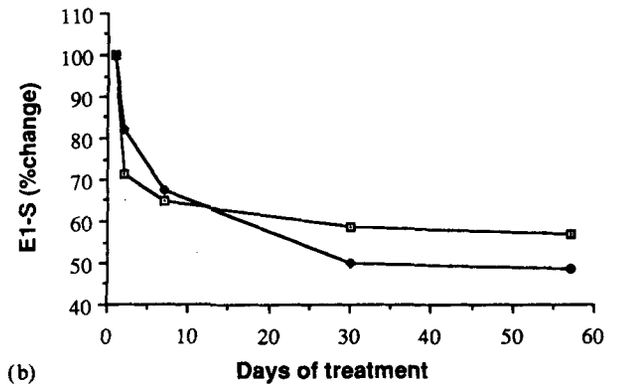


Fig. 1. Changes (%) in estrogens related to days (d) of treatment. Data are given as mean values for E_1 (–⊡–) and E_1-S (–◆–).



(a)



(b)

Fig. 2. Changes (%) in individual estrogens (a) E_1, estrone; (b) E_1-S, estrone-sulphate related to days (d) of treatment and dose given. Gr. 1: Patients receiving 0.3 mg × 2 (–⊡–), Gr. 2: Patients receiving 0.3 mg × 3 (–◆–).

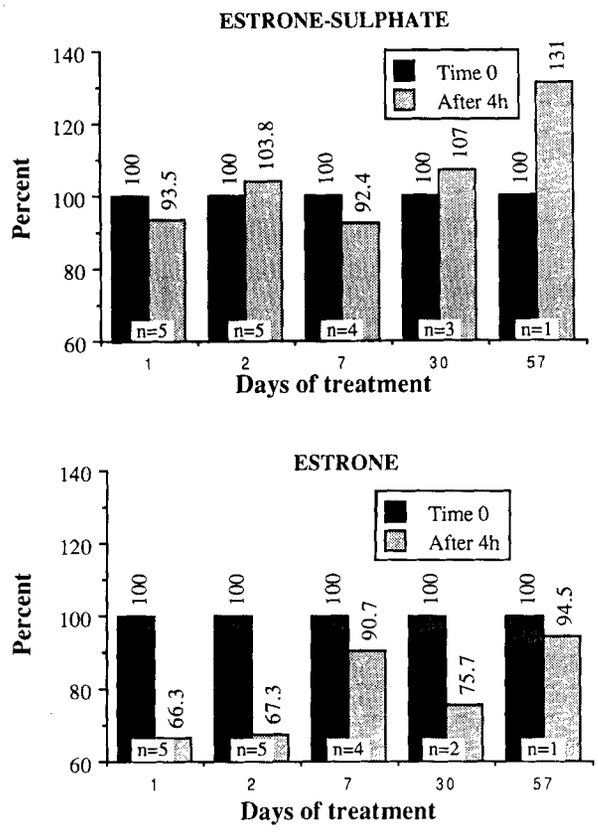


Fig. 3. Mean changes (%) in individual estrogens 4 h after the morning dose of CGS 16949A, related to days (d) of treatment.

approx. 20 pmol/l and for E_1-S 45 pmol/l. Intra- and interassay coefficients of variation (C_v's) for both steroids were less than 10%.

A partial remission was observed in 1 patient, in another 2 patients long-lasting (>6 months) stabilizations were observed, one patient is still on therapy after 16 months (Table). No side effects have been observed so far.

The pretreatment mean values for E_1 and E_1-S were 85.4 pmol/l and 426.7 pmol/l respectively. A 30 and 45% mean reduction in plasma E_1 ($p < 0.05$) and E_1-S ($p < 0.02$) levels were seen (Fig. 1). Most of the changes seen appeared during the first week of treatment, only minor variations in estrogen levels were seen after 7 days of treatment. CGS 16949A administered at the 2 dose levels did not seem to affect E_1 and E_1-S to a different degree (Fig. 2).

In 5 of the patients in whom estrogen levels were measured 4 h after intake of the morning dose (Fig. 3) a significant reduction in plasma E_1 ($p = 0.01$) but not in E_1-S was found between the 8 a.m. and 12 a.m. values.

While a 30–35% reduction in the level of E_1 found in this study corresponds to what may be found during treatment with AG (15), plasma E_1-S seems to be differently affected by the 2 drugs. E_1-S was reduced by a mean of 45% during CGS 16949A treatment. In contrast, treatment with AG seems to cause a 65–70% reduction in this estrogen (5, 6). This difference might be due to the AG promoted stimulation of the metabolism of E_1-S (15, 16). Further studies are needed both to establish the absolute difference in E_1-S levels, and to evaluate the possible clinical implications of this difference.

Key words: Breast cancer, aromatase inhibitor, plasma estrone.

R. KLEPP
P. E. LØNNING
S. KVINNSLAND

Department of Oncology
University of Trondheim
Trondheim

Department of Oncology
University of Bergen
Bergen
Norway

September 1989

ACKNOWLEDGEMENTS

The skilful technical assistance of Mr Dagfinn Ekse is highly appreciated. This work was supported by grants from the Norwegian Cancer Society.

Request for reprints: Dr Stener Kvinnsland, Department of Oncology, Regional Hospital, N-7006 Trondheim, Norway.

REFERENCES

1. McDonald PC, Rombout RP, Siiteri PK. Plasma precursors of estrogen. I. Extent of conversion of plasma androstendione to estrone in normal males and in nonpregnant normal, castrate, and adrenalectomized females. J Clin Endocrinol Metab 1967; 27: 1103–7.
2. Grodin JM, Siiteri PK, McDonald PC. Source of estrogen production in postmenopausal women. J Clin Endocrinol Metab 1973; 36: 207–14.
3. Santner SJ, Feil PD, Santen RJ. In situ estrogen production via the estrone sulfatase pathway in breast tumours: relative importance versus the aromatase pathway. J Clin Endocrinol Metab 1984; 59: 29–33.
4. Ruder HJ, Loriaux L, Lipsett MB. Estrone-sulfate: production rate and metabolism in man. J Clin Invest 1972; 51: 1020–33.
5. Samojlik E, Santen RJ, Worgul TJ. Plasma estrone-sulfate assessment of reduced estrogen production during treatment of metastatic breast carcinoma. Steroids 1982; 39: 497–507.
6. Lønning PE, Johannessen DC, Thorsen T, Ekse, D. Alterations in plasma estrone-sulfate not caused by aromatase inhibition in breast cancer patients receiving aminoglutethimide treatment. J Steroid Biochem 1989; (Accepted for publication).
7. McNeill JM, Reed MJ, Beranek PA, et al. A comparison of the in vivo uptake and metabolism of 3H-estrone and 3H-estradiol by normal breast and breast tumour tissues in postmenopausal women. Int J Cancer 1986; 38: 193–6.
8. Santen RJ, Santner SJ, Davis B, et al. Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. J Clin Endocrinol Metab 1978; 47: 1257–65.
9. Ayub M, Levell MJ. Structure-activity relationship of the inhibition of human placental aromatase by imidazole drugs including ketaconazole. J Steroid Biochem 1988; 31: 65–73.
10. Shaw MA, Nicholls PJ, Smith HJ. Aminoglutethimide and ketoconazole: historical perspectives and future prospects. J Steroid Biochem 1988; 31: 137–43.
11. Santen RJ. Methods of novel oestrogen deprivation. Proc. Oestrogens and the Human Breast, Edinburgh, 22nd–24th September, 1988.
12. Steel RE, Mellor L, Sawyer WK, Wasvary JM, Browne LJ. In vitro and in vivo studies demonstrating potent and selective estrogen inhibition with the nonsteroidal aromatase inhibitor, CGS 16949A. Steroids 1989; (In press).

13. Schieweck K, Bhatnagar AS, Matter A. CGS 16949A, a new nonsteroidal aromatase inhibitor: effects on hormone-dependent and independent tumors in vivo. Cancer Res 1988; 48: 834–8.
14. Hayward JL, Rubens RD, Carbone PP, Heuson JC, Kumaoka S, Segaloff A. Assessment of response to therapy in advanced breast cancer. Br J Cancer 1977; 35: 292–8.
15. Lønning, PE, Kvinnsland S. Mechanism of action of aminoglutethimide as endocrine therapy of breast cancer. Drugs 1988; 35: 685–710.
16. Lønning PE, Kvinnsland S, Thorsen T, Ueland PM. Alterations in the metabolism of estrogens during treatment with aminoglutethimide in breast cancer findings: preliminary findings. Clin Pharmacokinet 1987; 13: 393–406.

REVERSIBLE NAIL LOSS AFTER CANCER CHEMOTHERAPY

Most anticancer drugs act by inhibiting cell division. Therefore, rapidly proliferating tissues such as bone marrow, gastrointestinal mucosa, and hair follicles are especially susceptible to the toxic effects of these drugs. Clinical nail symptoms may occur but are rare. We now report a patient with a curious episode of reversible nail loss after cytotoxic treatment.

In Mrs VA, aged 40 years, a left-sided breast cancer (T3N1M0) was diagnosed in January, 1985. She underwent simple mastectomy and received locoregional radiotherapy (50 Gy in 25 fractions). The patient was apparently well till September, 1988, when she presented with a local recurrence—a 3 × 4 cm mass in left outer upper quadrant—and a superclavicular lymph node metastasis. Fine-needle aspiration biopsy of the local mass confirmed recurrence of the disease. She received CMF (cyclophosphamide, methotrexate and 5-fluorouracil) (1). After 2 courses, the finger nails loosened from the nailbed and dropped off within a month. She also had marked alopecia. After the fourth course of CMF in January, 1989, her nails had regrown and they were now looking normal.

Comments. Symptoms and signs from the nails are uncommon manifestations of anticancer drug toxicity. Pigmentary changes (diffuse changes, pigmented bands or horizontal lines) are the most common. These may be seen after doxorubicin, cyclophosphamide, methotrexate, bleomycin, etc. (2). One of the authors has previously described two patients of non-Hodgkin's lymphoma with reversible nail loss after chemotherapy (3). Received drugs common to these two patients were cyclophosphamide, vincristine and prednisolone. Also the now reported patient had received cyclophosphamide, in addition to methotrexate and 5-fluorouracil. This suggests that cyclophosphamide might be mainly responsible for the observed reversible nail loss.

Key words: Cancer, breast, chemotherapy.

L. KUMAR
V. KOCHUPILLAI
Department of Medical Oncology
Institute Rotary Cancer Hospital
All India Institute of Medical Sciences
New Delhi
India

May 1989

Request for reprints: Dr. Lalit Kumar, Department of Medical Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi-110 029, India.

REFERENCES

1. Bonadonna G, Brussamolina M, Valagussa P, et al. The CMF programme for operable breast cancer with positive axillary nodes. Cancer 1977; 39: 2904.
2. Hood Antoinette F. Cutaneous side effects of cancer chemotherapy. Med Clin North Am 1986; 70: 187.
3. Kochupillai V, Prabhu M, Bhide NK. Cancer chemotherapy and nail loss (onychomadesis). Acta Haematol 1983; 70: 137.

A PROSPECTIVE PILOT STUDY ON THE EFFECT OF SUCRALFATE MOUTH-SWISHING IN REDUCING STOMATITIS DURING RADIOTHERAPY OF THE ORAL CAVITY

Radiotherapy in sufficient dose involving the oral cavity always causes stomatitis, the severity of which is dependent on primary diagnosis, age, oral status and whether concomitant chemotherapy is given or not (1).

The patients complain of oral discomfort, changes in taste, dry mouth, burning sensation and pain. Erythema and, if more pronounced, fibrinous exudation is seen. The radiation reaction may be complicated by local and systemic infections, especially in leukopenic patients (2).

Radiation stomatitis usually appears at a dose level above 20 to 25 Gy, when therapy is given with a daily dose of 2 Gy. After completing radiotherapy the stomatitis as a rule resolves in 2 to 3 weeks (1). Current treatment is ineffective and stomatitis may aggravate pre-existing malnutrition (1). Therefore, efforts are needed to reduce the severity of stomatitis or, if possible, to prevent it.

Sucralfate is a non-absorbable, basic aluminum salt of a sulfated disaccharide which has proven effective in the treatment and prevention of gastric and duodenal ulcers. Sucralfate forms polyvalent bridges to the positively charged proteins present in the mucosa and forms a pasta-like, adhesive substance (3–5), a protective barrier is thus formed against further mucosal damage. The binding of sucralfate is most effective at low pH but may still occur at higher pH (3, 5). In a former study, using sucralfate labeled with $^{99}Tc^{m}$, we found that 20–30% of the initially attached sucralfate remained bound to the oral mucosa $2\frac{1}{2}$ h after the swishing procedure (6).

Moreover, sucralfate has a cytoprotective effect probably mediated through prostaglandin release from the mucosa (7). The result is an increase in mucosal blood-flow, mucus production, mitotic activity and surface migration of cells (5, 8).

A few pilot studies (9, 10) and one randomized trial (6) indicate that patients treated with stomatotoxic chemotherapy may benefit from oral sucralfate suspension. Other pilot studies indicate that sucralfate may be helpful in reducing or preventing the radiation induced toxicity of the mucosal lining in the lower intestinal tract (11, 12).

Thus, mouth-swishing with a sucralfate suspension might be of value in stomatitis induced by radiotherapy.

The aim of the present pilot study was to assess whether mouth-swishing with sucralfate suspension might reduce oral radiation mucositis without disturbing side effects.

Material and methods. Patients receiving radiation therapy encompassing the oral cavity were considered for the study. Patients were not included if permanent systemic treatment with anti-inflammatory drugs was given. Mouth-swishing with the sucralfate suspension was started at the point of time when the patients complained of oral discomfort during radiotherapy, and when objective signs of mucositis were present. Written informed consent was provided by each patient. The trial was approved by the local Ethical Committee.