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Letter to the Editor

Absence of Antitumor Activity of ORG 5895, a 11β-Aziridinylmethyl Derivative of Estradiol, on the MXT Mammary Tumor and the P388 Leukemia

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The presence of estrogen receptors in human breast cancers led to the concept of using estrogen-linked cytotoxic agents for the treatment of the disease. An 11 β-(1-aziridinylmethyl) derivative of estradiol has recently been synthesized (ORG 5895; formula in Fig. 1) [5]. This compound displays a significant binding affinity for the estrogen receptor (± 5% of estradiol) [4, 5]. Moreover, its estrone analog slightly modulates the in vitro growth of the MCF-7 breast cancer cell line (stimulation at 10^{-7} and 10^{-8} *M*; inhibition at 10^{-6} *M*) [4]. These observations led us to investigate the potential antitumor activity of the compound on the in vivo growth of the hormone-dependent MXT mouse mammary tumor [2, 6].

Six-week-old MXT mammary tumors were minced in minimum essential medium. Pieces of ± 15 mm^3 were inoculated into 60 BDF_1 female mice (8–10 weeks old). Animals were randomized and distributed into four groups of 15 mice each (3 treated and 1 control groups). The treated groups received ORG 5895 SC twice a week at 0.5, 5, and 50 mg/kg, respectively (suspension in physiological saline + Tween 80); the control group received the vehicle only. Administration started at the time of transplantation and was continued for 10 weeks. Tumor size, expressed as the product of two perpendicular diameters, was measured every 2 weeks. Animals were weighed at the time of measurement.

Examination of the animals revealed that ORG 5895 did not delay the appearance of palpable tumor nodules. After 4 weeks of treatment tumors were found in all animals, indicating that the compound did not reduce the tumor take. With regard to the tumor size, ORG 5895 also appeared totally devoid of antitumor activity. Figure 1 shows that its sole effect was a stimulation of tumor growth, which was only significant at 50 mg/kg after 8 and 10 weeks of treatment ($P < 0.002$ and 0.005, respectively; Mann-Whitney U-test). This effect was associated with a shortening of the survival of the animals (animals still living after 10 weeks: controls, 15; 0.5 mg/kg, 13; 5 mg/kg, 14; 50 mg/kg, 10). No loss of body weight was recorded. Notably, a control experiment run in parallel allowed verification of the expected hormone-dependent properties of the tumor transplants used [2, 6]. Thus ovariectomy produced a significant reduction of tumor growth; administration of estradiol and medroxyprogesterone acetate abolished this effect.

At the end of the experiment, the uterus and vagina were taken at random from three animals of each group. A marked gain in uterine weight was found in the group treated with ORG 5895 (mean weight: controls 217 mg; 0.5 mg/kg, 313 mg; 5 mg/kg, 670 mg; 50 mg/kg, 560 mg). Vaginas and uteri from animals treated with 5 or 50 mg/kg of the compound showed a histological pattern indicative of a strong estrogenic impregnation (keratinized vaginal epithelium, distended uterus with hypertrophic cystic gland). Controls and animals treated with the lower dose did not share this disturbed pattern.

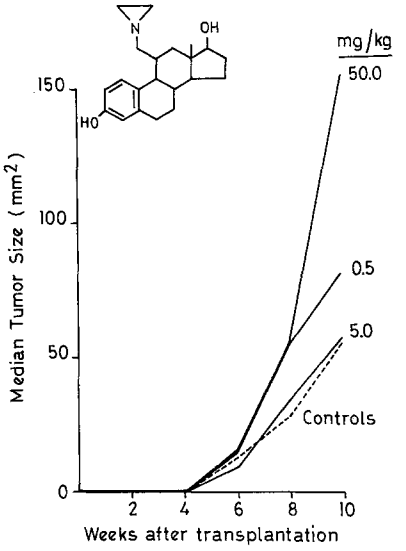

Fig. 1. Effect of ORG 5895 on the take and growth of the MXT mouse mammary tumor

The potential antitumor activity of ORG 5895 was further characterized in CDF_1 mice bearing the ascitic P388 leukemia, which were treated according to the protocol designed by the U.S. National Cancer Institute [3]: A dose of 200 mg/kg was administered IP and daily on days 1–5 post implant. The compound did not increase the survival of the animals, since a minimal T/C of 125% was not reached (T/C = 93%). Notably, a mean body weight reduction of −0.16 g was recorded, indicating that we were in the range of doses producing a reasonable antitumor effect for active drugs.

The present results seem to preclude the potential effectiveness of ORG 5895 for the treatment of breast cancer. The presence of only one aziridine group in the compound probably explains its lack of antitumor activity. In fact, it has been reported that the presence of at least two alkylating groups is necessary to produce an antitumor effect [1]. On the

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other hand, one may speculate that in the MXT mammary tumor model the slight stimulatory effect of the compound might be associated with its estrogenicity.

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References

1. Connors TA (1975) Mechanism of action of 2-chloro-ethylamine derivatives, sulfur mustards, epoxides and aziridines. Sartorelli AG, Johns DG (eds) In: Antineoplastic and immunosuppressive agents. II. Springer, Berlin, p 18
2. Devleeschouwer N, Gangji D, Leclercq G, Heuson JC (1980) In vitro and in vivo assessment of hormone dependence in the MXT murine mammary tumor. Cancer Chemother Pharmacol [Suppl] 5: 14
3. Geran RI, Greenberg NH, MacDonald MM, Schumacher AM, Abbott BJ (1972) Protocols for screening chemical agents and natural products against animal tumors and other biological systems. Cancer Chemother Rep 3 : 1
4. Leclercq G, Devleeschouwer N, Legros N, Heuson JC (1980) In vitro screening for cytotoxic estrogens of potential therapeutic activity. In: Raus J, Martens H, Leclercq G (eds) Cytotoxic estrogens in hormone receptive tumors. Academic Press, London, p 165
5. Schönemann KH, Van Vliet NP, Zeelen FJ (1980) Potential antitumor agents: 11β-(1-aziridinylmethyl) derivatives of oestradiol and oestrone. Eur J Med Chem 15: 333
6. Watson C, Medina D, Clark JH (1979) Characterization and estrogen stimulation of cytoplasmic progesterone receptor in the ovarian-dependent MXT-3590 mammary tumor line. Cancer Res 39: 4098

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