Hormonal Therapy of Human Endometrial Adenocarcinoma in a Nude Mouse Model

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ABSTRACT

The hypothesis that 17β-estradiol or tamoxifen (TAM) can potentiate clinical response of endometrial cancer treated with progestin was tested in an ovariectomized nude mouse system, using a sex steroid receptor-positive and a receptor-negative human endometrial carcinoma. Animals were divided into three groups: control; 17β-estradiol-treated; and TAM-treated. When tumors of a group reached about 1 cm in diameter, subgroups were given either 0.9% NaCl solution (saline) or medroxyprogesterone acetate (MPA). The receptor-negative tumor grew rapidly in all three groups, and several animals were dead before or during progestin treatment. The growth rate of receptor-containing carcinoma was significantly increased in TAM-treated mice compared to controls (p < 0.02) but significantly less than that in 17β-estradiol-treated animals (p < 0.01). Endometrial carcinoma in 17β-estradiol-saline-treated animals continued to grow rapidly, and all animals were dead by 11 weeks. The growth of tumors in the 17β-estradiol-progestin group was suppressed at 11 weeks, and some of these animals lived 20 weeks. Administration of progestin to TAM-exposed animals resulted in a remarkable regression of the tumor compared to TAM-saline-treated group. The growth rate of tumors in control animals (no implants) was unaffected by progestin treatment. We conclude that, in this nude mouse model, treatment with TAM and MPA is superior to MPA alone, or 17β-estradiol plus MPA for sex steroid receptor-positive endometrial carcinoma.

INTRODUCTION

Progestins are routinely used in the treatment of patients with recurrent or metastatic endometrial carcinoma with about 30% response rate (4). It has been widely assumed that the effectiveness of progestin on endometrial carcinoma may be directly related to the presence of PR in the tumor (1, 2, 5). Unfortunately, progestin treatment leads to depletion of PR within the target tissue. Therefore, any agent that increases PR concentrations in these tumors may be expected to potentiate the effectiveness of progestins.

Antiestrogens are known to counteract the actions of estrogens in various experimental systems (3). The nonsteroidal antiestrogen, TAM, is currently used in the management of patients with estradiol receptor-positive mammary carcinoma with a 55% response rate (7). We have reported previously that TAM augments PR concentrations in endometrial carcinoma (9). Based on this finding, we postulated that TAM may increase the degree and duration of response of endometrial carcinoma to progestin therapy. This prediction was tested in our experimental model of human endometrial carcinoma grown in athymic nude mice.
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Hormonal therapy of uterine cancer was investigated in receptor-positive tumor, EnCa-X (8). The growth rate was also increased significantly by 17β-estradiol compared to controls (p < 0.02), but was significantly less than that observed in the presence of 17β-estradiol (p < 0.01). While the control tumors reached a geometric mean diameter of 1 cm by the ninth week, the tumors in 17β-estradiol- and TAM-treated animals reached this dimension by the fourth and sixth weeks, respectively (Chart 1).

Within the control group, there was no difference in the rate of tumor growth between saline- and progestin-treated subsets. The geometric mean diameter of these tumors reached about 3 cm by the 26th week following transplantation (Chart 1A).

The endometrial carcinoma grew rapidly during continuous exposure to 17β-estradiol, and all animals in the 17β-estradiol/saline-treated subset were dead by 11 weeks. For the first 2 weeks following administration of MPA in the presence of 17β-estradiol, the tumors continued to grow at the same rate as 17β-estradiol plus saline group. However, beginning at the third week, the tumor growth was suppressed for a 10-week period (Chart 1B).

Weekly administration of MPA to TAM-exposed animals resulted in a dramatic decrease in tumor growth (Chart 1C). During the first 3 weeks of progestin treatment, the tumors continued to grow essentially at the same rate as in TAM plus saline group. This was followed by an arrest of tumor growth for about 4 weeks, after which there was a decrease in tumor size for the next 5 weeks (p < 0.05). Subsequently, tumor growth returned to a rate approximating that in animals treated by TAM plus saline.

DISCUSSION

In this study, MPA therapy alone had no effect on the growth of EnCa-X tumor. The lack of response to progestin may be due to the absence of PR at 9 weeks when MPA treatment was initiated, as demonstrated in our prior studies (8).

Since both 17β-estradiol and TAM increase PR in EnCa-X, we investigated progestin therapy in combination with 17β-estradiol or TAM in this tumor. Although 17β-estradiol plus MPA temporarily arrested tumor growth, combination of TAM and MPA resulted in a regression in tumor mass. Further, the tumor volume in this latter treatment subset was less than that of any other group. For example, 10 weeks after initiation of progestin treatment, the geometric mean diameter of tumors in the TAM plus progestin group was significantly less (p < 0.05) than that in mice given progestin alone. However, after a 12-week period of response in the TAM plus MPA group, the tumors began to grow again in these animals at the same rate as in controls.

The reason for regrowth of tumors following a period of regression during treatment is unknown. Variable expression of steroid receptor synthesis within tumor subpopulations with selective proliferation of receptor-negative cells could explain the emergence of tumor cells resistant to therapy. Simultaneous treatment with TAM and MPA might also result in a tumor...
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comprised of ER- and PR-negative cells because of down regulation of ER and PR by MPA.

In contrast to the hormonal modulation of growth identified in steroid receptor-positive EnCa-X, rapid growth of receptor-negative EnCa-V was noted in all treatment groups. These observations reinforce the need for identifying nonhormonal modalities for effective treatment of receptor-negative endometrial carcinoma.

Progestin therapy results in an objective response in about 30% of women with recurrent or metastatic endometrial adenocarcinoma. Combination therapy with a progestin and 17β-estradiol or TAM has been proposed, since progestin treatment leads to depletion of PR within target tissues. Because 17β-estradiol markedly stimulated tumor growth, the reluctance to use this agent in the management of patients with endometrial carcinoma may be justified. Mortel et al. (6) proposed therapy with TAM plus MPA, since TAM increased tumor levels of PR but did not stimulate ornithine decarboxylase, an indicator of cell proliferation. Our current study has demonstrated an initial increase in growth rate with TAM, but significantly less than that with estradiol. Reduction in tumor size followed the addition of MPA to TAM. Therefore, the prediction that TAM plus MPA would be superior to MPA alone for the treatment of receptor-positive endometrial adenocarcinoma is supported by our present investigation.

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REFERENCES

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