Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study

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Abstract

Objectives. The objectives of this study were to estimate the clinical response rate and toxicity of daily tamoxifen combined with intermittent weekly medroxyprogesterone acetate (MPA).

Methods. This study reports the results of 61 patients with measurable advanced or recurrent endometrial carcinoma enrolled on this study to be treated with tamoxifen 40 mg p.o. daily plus alternating weekly cycles of MPA 200 mg p.o. daily.

Results. One patient was excluded and two patients did not receive study treatment. The percent of patients responding (6 complete and 13 partial) was 33% (95% confidence interval [CI]: 21–46%) among 58 eligible patients who received therapy. Median progression-free survival (PFS) was 3 months and median overall survival (OS) was 13 months.

Conclusion. The combination of daily tamoxifen and intermittent weekly medroxyprogesterone acetate is an active treatment for advanced or recurrent endometrial carcinoma. Further investigation of this combination is appropriate.

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Introduction

A variety of progestational agents has long been known to be effective in the treatment of recurrent and metastatic endometrial carcinoma [1,2]. These include hydroxyprogesterone caproate, response rates of 9–34% [3–5]; medroxyprogesterone acetate (MPA), response rates of 14–53% [6–8]; and megestrol acetate, response rates of 11–56% [9,10]. The more recent Gynecologic Oncology Group (GOG) experience suggests that this proportion may only be on the order of 15–20% [7,8]. In any event, such responses are usually of short duration, with a median of approximately 4 months, though an occasional prolonged response is seen [11]. Tamoxifen alone has produced modest response rates of 10–20% [12–14].

Estrogenic compounds such as tamoxifen have been shown to increase progesterone receptors (PRs) in human endometrial cancers [15,16] and, therefore, could theoretically increase the effectiveness of progestational agents in the treatment of endometrial carcinoma. In order to test this hypothesis, in 1991 the GOG activated a phase II study of daily tamoxifen and intermittent weekly dosing of the progestational agent medroxyprogesterone acetate in the outpatient management of recurrent or metastatic endometrial carcinoma. The goals of the study were to evaluate the activity and assess the side effects of this combination of treatments.

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Materials and methods

To be eligible for this study, patients must have had any grade of histologically confirmed recurrent or metastatic endometrial carcinoma considered incurable by local therapy. Tissue samples from recurrent or metastatic lesions were required for quantitative assessment of estrogen and progesterone receptor status. Required slides were reviewed by the GOG Pathology Committee to confirm primary site, histological type, and tumor grade. All patients were to have measurable disease defined as lesions measurable in two dimensions by palpation or imaging. Lesions measurable by CT scan or ultrasound had to be greater than 3 cm in diameter. The lesion(s) being followed must not have been treated with radiation within 3 months before the entry date. Normal hematologic, renal, and hepatic functions were required. Patients had to be free from infection and have a GOG performance status of 0–2 to be eligible. Patients with other previous or concomitant cancers except non-melanoma cancer of the skin were not eligible for this study. Patients with a history of systemic therapy for endometrial cancer, including cytotoxic drugs and hormone therapy, were ineligible. Eligibility was confirmed by the review of submitted records, forms, and operative reports by the GOG Gynecologic Oncology Committee. Written informed consent con-
unexpected adverse effects were to be reported immediately to the GOG Administrative Office and to the study chair.

Progression-free interval (PFI) was defined as the time from study entry to clinical or radiographic evidence of disease progression or to the date the patient was last seen. Overall survival (OS) was defined from study entry to death or date last seen. Progression-free survival (PFS) is equal to the PFI if the patient progressed; otherwise, it is equal to the survival time. Life tables were computed using the method of Kaplan and Meier.

This study utilized a standard two-stage phase II design to allow for early termination due to inactivity. For the purpose of study design, agents with a true probability of response (complete or partial) 0.15 or less were considered to have insufficient activity to warrant further investigation. On the other hand, a true probability of response 0.30 or higher would be clinically significant and indicates that further investigation of the regimen is appropriate. The interim decision rule for this study required three or more responses out of 20 patients to continue to the second stage of accrual. The sample size of 58 patients provides an 85% chance of correctly classifying an active agent while type I error was limited to 5% [18]. A confidence interval (CI) adjusted for the two-stage design is reported [19].

### Table 4
Response \( (n = 58) \)

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>6</td>
</tr>
<tr>
<td>Partial</td>
<td>13</td>
</tr>
<tr>
<td>No response*</td>
<td>39</td>
</tr>
</tbody>
</table>

*Three patients were not evaluable for response.

Results

Between June 1991 and February 1996, 61 patients were entered into this study. One patient was ineligible because at central pathology review, the primary was not felt to be an endometrial carcinoma. The remaining 60 eligible patients constitute the basis of this report.

Patient characteristics are displayed in Table 1. Most patients were postmenopausal and had good performance status. Tumor characteristics were predominantly adenocarcinomas of high histological grade (23% were papillary serous carcinomas) and most were from recurrent lesions. Sixty percent of the patients had received prior radiation therapy. The sites of measurable disease at entry are outlined in Table 2. Thirty-seven of the 60 patients had disease within the pelvis, of which 25 had received prior pelvic radiotherapy. Moreover, there were 32 with vaginal disease only. Extra-pelvic disease occurred in 23 patients, with the most common site of involvement being lung.

Table 3 depicts toxicity for the 57 patients who received study therapy and were evaluated for toxicity. The reported toxicities were typical of those encountered with standard dose hormonal therapy. None of the deaths was attributed to the study treatment. Two patients, who did not receive any study treatment, are not included in the summary of response or toxicity. One patient was never treated and the other received 4 days of MPA only and had no baseline measurements of measurable disease. One patient refused further therapy after 1 day and was not evaluated for toxicity.

As shown in Table 4, 19 of 58 patients (33%; 95% CI: 21–46%) with study drug exposure achieved a response,

![Graph](image-url)
with 6 patients achieving a complete response and 13 patients attaining a partial response. Thirty-six patients had no evidence of response during protocol therapy. Three patients were not evaluable for response for the following reasons: one patient refused further therapy after 1 day, another patient refused treatment after one course and was never evaluated for response, and the third patient discontinued therapy after 3 weeks due to hospitalization and surgery for a previously reported bowel obstruction. These patients were classified as having no response. At the time of this report, 54 patients are dead from their disease, 3 are alive with disease, and only 1 is alive without any clinical or radiographic evidence of disease. Among four patients who died while on study, two were classified as not responding and died from endometrial cancer 9 and 24 days, respectively, into study therapy. One patient whose best response was stable died 60 days into protocol therapy from endometrial cancer, and another patient died as a result of Alzheimer’s disease after completing nearly 18 courses of study therapy and achieving a PR. Median PFS is 3 months and median OS is approximately 13 months. Survival curves are shown in Fig. 1.

Discussion

Progestational agents have been the most commonly used form of hormonal therapy for patients with advanced or recurrent endometrial carcinoma [1–8]. Although response rates have been reported in the range of 30–35%, more recent studies suggest even lower frequencies of objective response, on the order of 15–25% [7,8].

Because the uterus is a sex steroid responsive organ, many investigators have explored the usefulness of measuring progesterone receptor (PR) concentrations in endometrial cancers to predict hormone responsiveness in patients with these tumors [20–24]. In fact, the few studies of receptor status in metastatic endometrial cancer and hormonal response do indeed point to a strong predictive value for the level of progesterone receptor concentration expressed in the tumor tissue. However, the responses are often of short duration, approximately 4 months. Because progestins have been shown to have a negative effect on progesterone receptor concentration (downregulation), Mortel et al [15] proposed that the reduced effectiveness of these agents and the short duration of response may, at least in part, be attributed to depletion of PR in these tumors treated with progestational agents. They also postulated that any agent that augments PR concentrations within the tumor (upregulation) might be expected to potentiate the effectiveness of progestin therapy.

Estrogenic compounds are known to increase progesterone receptor concentration in normal and malignant endometrium. Tamoxifen binds to estrogen receptors and translocates with the receptor complex to the nucleus where its estrogenic and antiestrogenic activity is tissue- and species-dependent. In the human endometrium, it does increase progesterone receptors. At a dose of 40 mg/day, tamoxifen was also shown by Mortel et al [15] to increase PR concentrations in endometrial carcinoma in vivo. Long-term treatment of human endometrial carcinoma in nude mice has also been shown to significantly increase PR in the tumor tissue [25]. Additionally, the combination of MPA and tamoxifen was found superior to MPA alone in the treatment of endometrial cancer in the nude mouse model [26]. Based on these clinical and laboratory factors, the current study was undertaken. The overall response rate of 33% in this study is consistent with the initial hypothesis. Whether this result is actually superior to the previous GOG experience with MPA [7,8] will require a randomized trial to assess. Although pooled data indicated a 22% response rate for tamoxifen [27], a GOG study of 68 patients reported by Thigpen et al. [14] demonstrated a response rate of only 10% for patients treated with single agent tamoxifen at a dose of 20 mg p.o. twice daily. Pandya et al. [28] reporting for the Eastern Cooperative Oncology Group (ECOG) did not find sufficient evidence to suggest a difference between megestrol acetate as a single agent versus tamoxifen and megestrol acetate. In that phase II study of 42 patients, response rates were similar for the combination and megestrol acetate alone: 19% and 20%, respectively. Fiorica et al. [29] in the GOG studying alternating tamoxifen and megestrol in the treatment of advanced or recurrent endometrial carcinoma. That study of 56 women first treated patients with megestrol 80 mg twice daily for 3 weeks, followed by tamoxifen 20 mg twice daily for 3 weeks, using the rationale that the initial dose of megestrol would destroy cancer cells and the subsequent doses of tamoxifen would recruit further cancer cells that would then be susceptible to further doses of megestrol. The overall response rate was 26% (21% complete and 5.4% partial responses). That study had a much smaller percentage of papillary serous carcinomas (7% vs. 23%) and perhaps a more favorable patient population than the current study. Historically, papillary serous tumors are not considered hormonally responsive. However, a requirement for tissue from a metastatic site in this protocol could have introduced a potential bias toward patients with more responsive disease. In this study, the majority (52%) of patients had measurable disease limited to the vagina. This is much higher than that reported by Fiorica et al., which was not more than 25%.

In this study, the median PFS was 3 months and median survival was 13 months. These results are similar to those reported for progestins alone [4,5,7]. In the GOG study reported by Fiorica et al., the patients exhibited a median PFS of 2.7 months and a median overall survival of 14 months. Adverse effects were similar to other series of patients treated with hormonal therapy for advanced or recurrent endometrial cancer.

Hormonal therapy for advanced or recurrent endometrial carcinoma remains an attractive option for selected patients. Low toxicity with the potential for response makes proges-
tional agents a suitable therapeutic first choice for many patients, particularly for those with hormone receptor tumors. A future manuscript will address the relationship between steroid receptors, their isoforms, and response to treatment, using this regimen. The 33% response rate reported herein is among GOG’s most positive experiences with hormonal therapy for women with advanced or recurrent endometrial carcinoma. Indeed, it approaches that seen with active single agent cytotoxic chemotherapy [11,30,31].

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