Current Status of High-Dose Progestins in Breast Cancer

Jeffrey S. Abrams, Howard Parnes, and Joseph Aisner

Progestins at standard doses have compared favorably with tamoxifen for the front-line treatment of women with metastatic breast cancer. Attempts to further enhance the role of progestins have centered on dosage escalation, based on European data suggesting a dose-response effect. A phase I/II pilot trial at the University of Maryland demonstrated that doses of megestrol acetate up to 1,600 mg/d were well tolerated for prolonged periods. Responses were seen in patients whose disease was refractory to both standard doses of megestrol acetate and to tamoxifen. Different mechanisms of progestin action on breast tumors are theorized at the higher doses, which could account for the dose-response effect. Two large multi-institutional dose comparison trials of megestrol acetate in metastatic breast cancer have been undertaken in the United States. The Piedmont Oncology Association recently reported a significant benefit for megestrol acetate 800 mg/d compared with the standard 160 mg/d in terms of response and disease-free and overall survival. The largest trial is currently ongoing in the Cancer and Leukemia Group B. They are comparing 800 and 1,600 mg/d with standard doses, and results from this study are eagerly anticipated.

SYNTHETIC PROGESTINS have a well-established role in the palliation of metastatic breast cancer. The two most widely tested progestins, megestrol acetate (Megace, Bristol-Myers, Evansville, IN) and medroxyprogesterone acetate, have demonstrated overall response rates of about 30% in unselected patients,[1-3] a rate similar to that associated with other commonly used hormonal therapies. In addition, several randomized trials have shown that megestrol acetate and the antiestrogen tamoxifen induce comparable response rates in untreated patients with metastatic disease, with no differences in response duration or survival.[4-7] Although the side effects of both megestrol acetate and tamoxifen are mild, close scrutiny of their toxicity profiles reveals significant differences: weight gain and increased appetite are the most common side effects of megestrol acetate, while tamoxifen more frequently causes tumor flare, vaginal bleeding, and hot flashes.[2]

Unlike tamoxifen, progestins have not yet been adequately tested in the adjuvant setting. They have, therefore, generally been reserved for use in patients whose disease has relapsed on adjuvant tamoxifen therapy and who have non–life-threatening disease. For those women whose disease progresses after tamoxifen, progestins are the treatment of choice when further hormonal therapy is indicated. Progestins may be preferable to tamoxifen as first-line therapy in women with metastatic disease who are underweight or anorexic. The proven effectiveness of the progestins in advanced breast cancer has encouraged efforts to further exploit these drugs by increasing their dosage.

HIGH-DOSE PROGESTIN THERAPY

Although very low doses of progestins have been effective in some patients,[8] European studies conducted in the early 1980s indicated an improved response rate with increased doses of medroxyprogesterone acetate.[9] These single-arm trials provided the impetus for further exploration of the dose-response question of progestin therapy in breast cancer. The Swiss Group for Clinical Research conducted the largest randomized trial evaluating this issue[10]: they compared medroxyprogesterone acetate 1,000 mg intramuscularly (IM) given Monday through Friday for 4 consecutive weeks with 500 mg IM given twice weekly for 4 weeks. Responding patients were maintained on 500 mg IM once weekly until progression. In that trial, 30 of 91 (31%) patients on the high-dose arm responded compared with 14 of 93 (15%) on the low-dose arm ($P = .004$). There were no differences between the two groups, however, in median duration of response, time to progression, or survival. Although other randomized trials did not confirm such a difference in response according to dose, all of those trials had small numbers of patients and the dosage differentials were never more than two-fold.[11-13]

Interestingly, despite its better gastrointestinal absorption and bioavailability, megestrol acetate

From the Division of Medical Oncology, Department of Medicine, University of Maryland Cancer Center, Baltimore.

Address reprint requests to Jeffrey S. Abrams, MD, Assistant Professor of Medicine and Oncology, University of Maryland Cancer Center, 22 South Greene St, Baltimore, MD 21201.

0093-7754/90/1706-9008$05.00/0

was not tested as extensively as medroxyprogesterone acetate in Europe.[14] Standard doses of megestrol acetate (160 mg/d) have been found to result in blood levels five to ten times higher than those seen with high doses of medroxyprogesterone acetate given either orally or IM,[15] and it has been estimated that 160 mg of oral megestrol acetate is equivalent to 1,000 mg of oral medroxyprogesterone acetate. Peak plasma levels of megestrol acetate occur 2 to 3 hours after a single oral dose, and the serum half-life is 15 to 20 hours.[16]

Alexieva-Figusch et al[17] were among the first to study increased doses of megestrol acetate in patients with breast cancer. They administered consecutive 6-week treatments of 90, 180, and 270 mg megestrol acetate in random sequence to 18 patients. Ten of the 18 patients responded, but plasma accumulation of megestrol acetate rendered the dose-response effect inevaluable. These researchers did note, however, that megestrol acetate at doses of 180 and 270 mg/d, but not at 90 mg/d, produced complete suppression of the hypothalamic-pituitary-adrenal axis, and only the highest dose significantly increased basal insulin levels. This selective pharmacologic hypophysectomy leading to complete suppression of adrenal steroid secretion (including secretion of estradiol) also has been noted with medroxyprogesterone acetate[18] and may represent an important mechanism of action of the progestins. As early as 1983, a pilot study was conducted to evaluate even higher doses of megestrol acetate (800 mg/d), but no definite conclusions were reached.[16] However, results of a recent, large, randomized study appear to indicate an advantage for higher doses (800 mg/d) compared with standard-dose treatment.[19] This has renewed interest in the mechanism of action of high-dose progestins.

Potential Mechanisms of Action

Precise explanations of the way in which progestins combat breast cancer remain elusive, but it is likely that several mechanisms are involved (Table 1). It also is probable that the predominant effect of these semisynthetic progesterone derivatives varies with the drug dose. Several investigators have hypothesized that low doses may decrease the concentration of the estrogen receptor, thereby diminishing the ability of tumor cells to respond to endogenous estrogen[20] while higher doses are capable of blocking adrenal production of sex hormones[17] and also may cause direct cytotoxicity.[21] This provides a rationale for the effectiveness of higher doses of progestins in patients whose disease has progressed on lower doses.

Table 1. Potential Mechanisms of Progestin Activity in Breast Cancer

Endocrinologic effects
Suppression of adrenal production of estradiol and androstenedione
Interference with steroid hormone receptors (estrogen, progesterone, androgen, and glucocorticoid)
Direct cytotoxicity
Suppression of growth in hormone-sensitive cell lines
Regulation of autocrine growth factors
Stimulatory or inhibitory effects on production of growth factors (TGF-α, TGF-β, EGF, IGF-1)
Regulation of growth factor receptors

Abbreviations: TGF, transforming growth factor; EGF, epidermal growth factor; IGF, insulin growth factor.

Using two human breast tumor lines, one sensitive to hormones (MCF-7) and the other resistant (MDA-231), Allegra and Kiefer[21] demonstrated in vitro that progesterone and megestrol acetate caused direct cytotoxicity and were capable of inhibiting the mitogenic effects of estradiol in the hormone-sensitive tumor cell line. No effect was seen in the hormone-resistant cell line. The concentration of progestin used was 10^{-5} mol/L, which is attainable in plasma. Lower doses (10^{-6} to 10^{-12} mol/L) were ineffective, while higher concentrations of these agents were found to be "nonspecifically cytotoxic."

Using oral doses of medroxyprogesterone acetate ranging from 500 to 1,500 mg/d, Blossey et al[18] showed that differential endocrinologic effects in women with metastatic breast cancer depended on the dose. Medroxyprogesterone acetate doses of 1,000 mg/d or greater were necessary to completely suppress endogenous cortisol secretion, with a concomitant decrease in follicle-stimulating hormone, luteinizing hormone, and estradiol. It is also instructive that megestrol acetate has been substituted successfully for prednisone in combination with aminoglutethimide treatment.[22] The weak corticoid effects of high-dose progestins, their ability to compete for the glucocorticoid receptor,[23] and their suppression of adrenal steroid production in postmenopausal

Table 2. Overall Response to Megestrol Acetate by Dose Level

Dose (mg/d)	No. Patients	CR	PR	SD	PD
480	3	1	1	1	0
800	3	2	0	1	0
1,280	3	1	0	1	1
1,600	48	2	5	20	21

Abbreviations: SD, stable disease; PD, progressive disease.

women all may play a role in the mechanism of action of these compounds.

Recent evidence has shown that progestins also down regulate their own receptors and stimulate production of autocrine growth factors and their receptors.[24] These growth factors are proteins produced by normal and malignant breast cancer cells. In vitro experiments have demonstrated that transforming growth factor-α, epidermal growth factor, and epidermal growth factor receptors tend to increase with progestin stimulation, while transforming growth factor-β and insulin growth factor-1 are decreased by progestin treatment. No consensus has been reached yet as to the precise role these factors play in the regulation of breast cancer growth. It is likely, however, that progestins have direct effects on the genome and corresponding gene products.

Recent and Ongoing Trials

Fifty-seven patients (56 postmenopausal women and 1 man) with biopsy-proven metastatic breast cancer, positive or unknown estrogen or progesterone receptors, and measurable or evaluable disease, were treated in a phase I-II trial at the University of Maryland Cancer Center. Megestrol acetate, in escalating dosages ranging from 480 to 1,600 mg/d, was given as specially formulated 160-mg tablets (Bristol Myers Oncology Division, Evansville, IN). All patients had chemotherapy or hormonal therapy before entering the trial; 37 had measurable disease, and 20 had evaluable but nonmeasurable disease.

Toxicity in this trial was notable for increased appetite and weight gain, especially at the highest dose (1,600 mg/d). For those treated longer than 6 weeks, weight gain occurred at all dose levels and ranged from 1 to 20 lb (median, 2.5). Pharmacokinetic modeling of this drug effect demonstrated that the weight gain was best described by a function in which there was an initial lag time followed by an asymptotic increase in weight to a maximal weight gain.[25] This side effect has been turned to advantage in patients suffering from cancer cachexia, as described by Aisner et al elsewhere in this issue (pp 2-7). Additional side effects included hyperglycemia and hypertension, which occurred in 16% and 12% of patients, respectively. Insulin, oral hypoglycemic agents, and antihypertensive drugs were occasionally needed to counteract these effects; however, all patients so affected had baseline hypertension or glucose intolerance before starting therapy, and most were being treated for these problems before entering the study.

The overall response rate, including complete response (CR) and partial response (PR), was 32% in patients with measurable tumor; responses, including CRs, were seen at each dose level (Table 2). Responses were fairly equivalent in patients with predominantly soft tissue, bone, or visceral tumors, with the exception of those with hepatic metastases (Table 3): all five patients with liver disease progressed rapidly on this study. This finding is similar to results noted by others with conventional megestrol acetate doses.[26]

In 27 of these study patients, disease progression had previously occurred during treatment with standard doses of megestrol acetate, including 9 patients whose tumors demonstrated primary refractoriness to conventional doses of the hormone. A 15% response rate (1 CR, 3 PRs) was noted with high-dose megestrol acetate, and 10 patients (37%) had stable disease lasting a median of 5.4 months (range, 3 to 11.5). Two of the objective responses occurred in women whose tumors had previously not responded to standard megestrol acetate doses. In addition, 2 of 14 patients with primary resistance to initial treatment with tamoxifen had objective responses (1 CR and 1 PR) on the high-dose treatment. These

Table 3. Results With High-Dose Megestrol Acetate by Dominant Lesion

	No. Patients	CR	PR	SD	PD
Soft tissue	9	3	0	3	3
Bone	24	0	4	15	5
Viscera					
Liver	5	0	0	0	5
Other	19	3	2	5	9
Total	57	6	6	23	22

Table 4. CALGB Megestrol Acetate Trial

Stratification		Megestrol Acetate Dose (mg/d)
ER and PgR status		160
Prior adjuvant chemotherapy	Randomize	800
Prior hormonal therapy		1,600

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

provocative initial findings indicate that a dose-response effect might exist for megestrol acetate.

The Piedmont Oncology Association recently reported preliminary results of their randomized phase III trial comparing high-dose (800 mg/d) with conventional-dose (160 mg/d) megestrol acetate in patients with metastatic breast cancer.[19] All patients in this trial had undergone at least one prior course of treatment with a nonprogestin hormone; tamoxifen accounted for the vast majority. Positive or unknown estrogen or progesterone receptor status was required for study entry. Toxicity in the trial was minimal, with weight gain (mean, 17 lb) reported as the major side effect. The results demonstrate an impressive benefit for the high-dose arm, with a 26% overall response rate compared with 11% in the standard-dose arm. The significant differences in progression-free interval (7.8 *v* 3.2 months) and median survival (18 *v* 11 months) for the high- and standard-dose arms, respectively, also reflect the dose-response effect.

Since June 1987, Cancer and Leukemia Group B has been conducting the largest trial to date testing the dose-response concept with megestrol acetate. This three-arm trial for patients with metastatic breast cancer is comparing standard-dose (160 mg) megestrol acetate with both five (800 mg) and ten times (1,600 mg) the standard dose. The study is projected to accrue 315 patients and should meet this goal by the fall of 1990. Patients are randomized for treatment after stratification according to estrogen or progesterone receptor status, prior hormonal therapy, and prior adjuvant chemotherapy (Table 4). Patients in this trial may have had only one prior hormonal maneuver (including both adjuvant and metastatic treatment) and cannot have received chemotherapy except for adjuvant treatment, in which case they must be disease-free for at least 1 year from the end of therapy. Interim analysis of 163 patients with the blind still in effect reveals an overall response rate (CR and PR) of 29%, although 49% of the patients have stable disease and could yet respond. With 100 patients per arm, when completed, this trial will have sufficient power to correlate response with estrogen and progesterone receptor levels and disease sites. It should also provide an answer to the dose-effect question for megestrol acetate in this population of patients with advanced breast cancer.

CONCLUSIONS

In an era in which new biologic features (such as cell-proliferative indices, DNA ploidy, and cathepsin D levels) of primary breast tumors are increasingly influencing therapeutic decisions in the adjuvant setting, it is noteworthy that less attention has been paid to these factors in metastatic disease. Studies with conventional megestrol acetate doses have indicated some pretreatment characteristics that influence treatment with progestins (Table 5).[6,7,10,12,27,28] However, as with most hormonal treatments, multivariate analysis shows that estrogen and progesterone receptor levels have correlated most closely with response, and in several studies, progesterone receptor levels have proven to be the most important prognostic indicator for successful progestin treatment.[26,29-31] Yet, as the described trials indicate, patients with hormone-resistant disease as well as those who progress on standard progestin doses may respond to high-dose megestrol acetate. These initial findings obligate (1) clinical investigators to elucidate other features of these tumors that might predict response and (2) laboratory researchers to pursue the mechanism of action of high-dose progestins.

Trials comparing high-dose megestrol acetate with tamoxifen are already under way. Better understanding of how progestins work in breast cancer could lead to more innovative trials. It is possible that high-dose progestin therapy could be combined or alternated with antiestrogens or

Table 5. Clinical Prognostic Factors for Response to Progestins

Previous response to hormone therapy
Disease-free interval
Menopausal status (and time from menopause)
Metastatic site (nonvisceral *v* visceral)

aromatase inhibitors to allow more complete blockade of the sex hormones and increase interference with their receptors. Another avenue of benefit might result from combining progestin therapy with chemotherapy, since breast tumors are heterogeneous and possess cells with different growth kinetics that might be preferentially sensitive to one or the other modality.

REFERENCES

1. Schacter L, Rozencweig M, Canetta R, et al: Megestrol acetate: Clinical experience. Cancer Treat Rev 16:49-63, 1989
2. Sedlacek SM: An overview of megestrol acetate for the treatment of advanced breast cancer. Semin Oncol 15:3-13, 1988
3. Henderson IC: Endocrine therapy in metastic breast cancer, in Harris JR, Hellman S, Henderson IC, et al (eds): Breast Diseases. Philadelphia, PA, Lippincott, 1987, pp 398-428
4. Ettinger DS, Allegra J, Bertino JR, et al: Megestrol acetate v tamoxifen in advanced breast cancer: Correlation of hormone receptors and response. Semin Oncol 13:9-14, 1986
5. Muss HB, Paschold EH, Black WR, et al: Megestrol acetate v tamoxifen in advanced breast cancer: A phase III trial of the Piedmont Oncology Association (POA). Semin Oncol 12:55-61, 1985 (suppl 1)
6. Ingle JN, Ahmann DL, Green SJ, et al: Randomized clinical trial of megestrol acetate v tamoxifen in paramenopausal or castrated women with advanced breast cancer. Am J Clin Oncol 5:155-160, 1989
7. Morgan LR: Megestrol acetate v tamoxifen in advanced breast cancer in postmenopausal patients. Semin Oncol 12: 43-47, 1985 (suppl 1)
8. Stoll BA: Progestin therapy of breast cancer: Comparison of agents. Br Med J 3:338-341, 1967
9. Tchekmedyian NS, Tait N, Aisner J: High-dose megestrol acetate in the treatment of postmenopausal women with advanced breast cancer. Semin Oncol 13:20-25, 1986
10. Cavalli F, Goldhirsch A, Jungi F, et al: Randomized trial of low- versus high-dose medroxyprogesterone acetate in the induction treatment of postmenopausal patients with advanced breast cancer. J Clin Oncol 2:414-419, 1984
11. Della Cuna GR, Calciati A, Strada M, et al: High dose medroxyprogesterone acetate treatment in metastatic carcinoma of the breast: A dose-response evaluation. Tumori 64: 143-149, 1978
12. DeLena M, Brambilla C, Valagussa P, et al: High-dose medroxyprogesterone acetate in breast cancer resistant to endocrine and cytotoxic therapy. Cancer Chemother Pharmacol 2:175-180, 1979
13. Pannuti F, Martoni A, DiMarco AR, et al: Prospective, randomized clinical trial of two different high dosages of medroxyprogesterone acetate in the treatment of metastatic breast cancer. Eur J Cancer 15:593-599, 1979
14. Martin F, Adlercreutz H: Aspects of megestrol acetate and medroxyprogesterone acetate metabolism, in Garattini S, Brendes HW (eds): Pharmacology of Steroid Contraceptive Drugs. New York, NY, Raven, 1977, pp 99-115
15. Canetta R, Florentine S, Hunter H, et al: Megestrol acetate. Cancer Treat Rev 10:141-157, 1983
16. Morgan LR, Donley PJ, Savage J: High dose megestrol acetate in advanced breast cancer: Bioavailability, toxicity and response. Proc Am Assoc Cancer Res 28:19, 1983 (abstr)
17. Alexieva-Figusch J, Blankenstein MA, Hop WCJ, et al: Treatment of metastatic breast cancer patients with different dosages of megestrol acetate; dose relations, metabolic and endocrine effects. Eur J Cancer Clin Oncol 20:33-40, 1984
18. Blossey HC, Wander HE, Koebberling J, et al: Pharmacokinetic and pharmacodynamic basis for the treatment of metastatic breast cancer with high-dose medroxyprogesterone acetate. Cancer 54:1208-1215, 1984
19. Muss H, Case D, Cates-Wilkie S, et al: High vs standard dose oral progestin therapy (megestrol acetate) for metastatic breast cancer: A phase III trial of the Piedmont Oncology Association. Proc Am Soc Clin Oncol 8:22, 1989 (abstr)
20. Tseng L, Gurpide E: Effects of progestins on estradiol receptor levels in human endometrium. J Clin Endocrinol Metab 41:402-404, 1975
21. Allegra JC, Kiefer SM: Mechanisms of action of progestational agents. Semin Oncol 12:3-5, 1985
22. Nagel GA, Wander HE, Blossey HC: Phase II study of aminoglutethimide and medroxyprogesterone acetate in the treatment of patients with advanced breast cancer. Cancer Res 42:3338-3444, 1982 (suppl)
23. Lippman M, Bolan G, Huff K: The effects of glucocorticoid and progesterone in hormone-responsive human breast cancer in long term tissue culture. Cancer Res 36:4602-4609, 1976
24. Meeting report: Progestin action and progesterone receptors in breast cancer. Cancer Res 49:7176-7179, 1989
25. Parnes H, Tait N, Aisner J: The potential of megestrol acetate in the treatment of cancer cachexia. Nutrition 5:206-209, 1989
26. Haller DG, Glick JH: Progestational agents in advanced breast cancer: An overview. Semin Oncol 13:2-8, 1986
27. Alexieva-Figusch J, Van Glise HA, Hop WCJ: Progestin therapy in advanced breast cancer. Cancer 46:2369-2372, 1980
28. Ansfield FJ, Kallas GH, Sinson JP: Clinical results with megestrol acetate in patients with advanced carcinoma of the breast. Surg Gynecol Obstet 155:888-890, 1982
29. Bonomi P, Johnson P, Anderson K, et al: Primary hormonal therapy of advanced breast cancer with megestrol acetate: Predictive value of estrogen and progesterone receptor levels. Semin Oncol 12:48-54, 1985
30. Gregory EJ, Cohen SC, Oines DW, et al: Megestrol acetate therapy for advanced breast cancer. J Clin Oncol 3: 155-160, 1985
31. Johnson PA, Bonomi PD, Anderson KM, et al: Megestrol acetate: First-line therapy for advanced breast cancer. Semin Oncol 13:15-19, 1986