Medroxyprogesterone Acetate (Depo-Provera) Vs. Hydroxyprogesterone Caproate (Delalutin) in Women with Metastatic Endometrial Adenocarcinoma

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A prospective trial was initiated in 1972 utilizing Depo-Provera in women with metastatic or recurrent endometrial adenocarcinoma to evaluate if the objective response and survival would be significantly improved in comparison to patients previously treated with Delalutin at a similar dose. One hundred fourteen patients were included in the study: 70 received Delalutin and 44 Depo-Provera. There was no significant increase in the objective response or survival between the Delalutin or Depo-Provera patients. Of the 114 patients, 15.8% achieved an objective response, with 7.0% being complete responders. There was no significant increase in objective response to Delalutin or Depo-Provera in relationship to the size of the tumor masses, the number of metastases, site of metastases, histologic grade of the primary, histologic grade of recurrence or metastases, or prior radiation therapy. The only significant correlate was that patients whose disease recurred 3 or more years after the initial therapy had a significant ($P = 0.01$) increase in response (33.3%) compared to those with recurrence less than 3 years after their original treatment (8.3%).

Cancer **45:268–272, 1980.**

PROGESTERONE THERAPY remains the preferred treatment for women with metastatic endometrial adenocarcinoma that is not amenable to surgery or radiation therapy. In July of 1972, we initiated a prospective trial of Depo-Provera (6-methyl 17α-hydroxyprogesterone acetate) at a dose of 1 g intramuscularly weekly to all patients with metastatic endometrial adenocarcinoma to evaluate if the objective response and survival would be significantly improved in comparison to patients previously treated at Roswell Park Memorial Institute with Delalutin (17α-hydroxyprogesterone caproate) at a similar dose.

Materials and Methods

One hundred fourteen evaluable patients were included in the study. Forty-four patients with metastatic endometrial adenocarcinoma received Depo-Provera over a 5½-year period compared to 70 controls who received Delalutin over the previous 11½ years. Patients have been followed from 2–17 years. Fifty-one women received Delalutin alone and 19 received localized palliative radiation therapy to the pelvis in addition to Delalutin during and after radiation therapy. Similarly, 37 patients received Depo-Provera alone and seven received pelvic radiotherapy in addition to Depo-Provera. All patients had measurable disease after completion of localized radiation therapy.

Response rates, median duration of response, and survival were evaluated for Delalutin alone, Depo-Provera alone, Delalutin + radiation therapy, and Depo-Provera + radiation therapy. In addition, response rate and duration of survival were evaluated for the entire group of patients receiving Delalutin and similarly for those receiving Depo-Provera. Other parameters studied with the Delalutin group and the Depo-Provera group separately include response in relationship to (1) size of tumor, (2) age of the patient, (3) number of metastatic sites, (4) site of metastasis, (5) grade of primary, (6) grade of recurrence or metastasis, (7) time to recurrence, and (8) previous therapy. Statistical evaluation was performed comparing the pretherapy characteristics of Delalutin vs. the Depo-Provera patients for metastatic sites, number of metastases, prior treatment, concomitant radiation therapy and histologic grade of the primary, and the recurrences or metastases. For the 70 Delalutin pa-

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Medroxyprogesterone acetate was kindly supplied by the Upjohn Company, Kalamazoo, MI.

Accepted for publication February 19, 1979.

0008–543X/80/0115/0268 $0.75

tients, 64 or 91.4% had the grade of the recurrence or metastases known as compared to 81.8% (36) of the Depo-Provera patients. The groups were not significantly different except that more of the Depo-Provera patients had pulmonary metastasis ($P < 0.05$), while more of the Delalutin patients had grade 1 lesions of the primary ($P < 0.05$), and of the recurrence or metastases ($P < 0.001$) (Table 1).

A complete response to progesterone therapy consisted of complete regression of all x-ray and clinical evidence of tumor for at least 3 months. Partial response consisted of a decrease by 50% or greater in the product of the perpendicular diameters of the tumor masses for 3 months or longer. Stable disease consisted of no change or less than 50% decrease in the size of measurable disease, while progression consisted of increase in the size of the tumor masses. There were no responses that lasted less than 3 months.

Statistical methods utilized included the actuarial method for calculating life tables[1] from which the median survival (or median response times) were calculated.[5] Statistical comparisons of median survival times were actually made by comparing the total survival curves calculated from the life tables using the method of Breslow for censored data.[2]

TABLE 1. Characteristics of Patients Treated with Progestogens

Characteristic	Delalutin group No.	Delalutin group %	Depo-Provera group No.	Depo-Provera group %	Total No.	Total %
Metastatic sites						
Pelvis	43	61.4	21	47.7	64	56.1
Vagina	39	55.7	19	43.2	58	50.9
Lung*	19	27.1	22	50.0	41	36.0
Lymph nodes	19	27.1	13	29.5	32	28.1
Abdomen	17	24.3	6	13.6	23	20.2
Bone	12	17.1	5	11.4	17	14.9
Other	11	15.7	5	11.4	16	14.0
Number of metastatic sites						
1	16	22.9	11	25.0	27	23.7
2	26	37.1	23	52.3	49	43.0
3	21	30.0	7	15.9	28	26.4
≥4	7	10.0	3	6.8	10	8.8
Prior treatment	62	88.6	34	77.3	96	84.2
Surgery alone	12	17.1	10	22.7	22	19.3
Radiation alone	8	11.4	7	15.9	15	13.2
Surgery & radiation	42	60.0	17	38.6	59	51.8
Concomitant radiation therapy	19	27.1	7	15.9	26	22.8
Histologic grade of primary*						
I	33	47.1	10	22.7	43	37.7
II	24	34.3	22	50.0	46	40.4
III	13	18.6	12	27.3	25	21.9
Histologic grade of recurrence or metastases†						
I	23	35.9	3	8.3	26	26.0
II	12	18.8	17	47.2	29	29.0
III	29	45.3	16	44.5	45	45.0

* $P < 0.05$.
† $P < 0.001$.

Results

Delalutin vs. Depo-Provera with or Without Radiation Therapy: Response

As seen in Table 2, the objective response to Delalutin alone (complete + partial responders) was 13.7% as compared to 18.9% for Depo-Provera for an overall response rate of 15.9%. These were not statistically different. The addition of localized radiation therapy resulted in a 15.8% response rate for the Delalutin patients as compared to 14.3% for the Depo-Provera patients, for an overall response to progesterone + radiation therapy of 15.4%.

The median duration of objective response for the Delalutin patients was 22.4 months compared to 19 months for the Depo-Provera patients, which was not statistically significant. The median duration of objective response for patients receiving Delalutin + radiation therapy was 9.5 months. There was only one objective responder among the seven patients receiving Depo-Provera + radiation therapy and this response lasted 48 months. For those who had objective responses, the median duration of survival for the pa-

TABLE 2. Response to Progesterone with or without Radiation Therapy*

Treatment	Patients No.	Patients %	Response: Objective No.	Objective %	Stable No.	Stable %	Progression No.	Progression %
Delalutin	51	72.9	7	13.7	10	19.6	34	66.7
Depo-Provera	37	84.1	7	18.9	11	29.7	19	51.4
TOTAL	88	17.2	14	15.9	21	23.9	53	60.2
Delalutin + R.T.*	19	27.1	3	15.8	7	36.8	9	47.4
Depo-Provera + R.T.*	7	15.9	1	14.3	1	14.3	5	71.4
TOTAL	26	22.8	4	15.4	8	30.8	14	53.8

* R.T. = Radiation therapy.

TABLE 3. Median Duration of Response and Survival

Treatment	Patients	Response (Mos)		Survival (Mos)		
		Objective	Stable	Objective	Stable	Progression
Delalutin	51	22.4	6.0	59.8	12.0	2.8
Depo-Provera	37	19.0	8.7	28.8	11.0	3.8
TOTAL	88	23.1	7.0	47.9	11.8	3.1
Delalutin + R.T.	19	9.5	32.7	12.3	33.5	3.5
Depo-Provera + R.T.	7	48.0*	6.0*	48.0*	6.0*	4.8
TOTAL	26	17.0	15.8	24.3	21.3	5.0

* One patient in this group.
R.T. = Radiation therapy.

tients receiving Delalutin alone was 59.8 months as compared to 28.8 months for those receiving Depo-Provera. However, this difference was not significantly different. Similarly, the median duration of survival for the patients receiving Delalutin + radiation therapy who had objective response was 12.3 months. As mentioned above, there was only one objective responder to Depo-Provera + radiation therapy and this patient was still alive at 48 months (Table 3). Those patients achieving an objective response to Delalutin alone had a significant increase in median length of survival (59.8 months) as compared to those women with stable disease (12.0 months) or progression (2.8 months) ($P < 0.001$). A similar correlation was seen in the Depo-Provera alone patients with a median survival of 28.8 months for those achieving an objective response as compared to 3.8 months for progression ($P < 0.001$). However, the survival of the objective responders was not significantly different from that of the patients with stable disease (11 months).

Delalutin vs. Depo-Provera

For the 70 women receiving Delalutin, the objective response was 14.3%, with 5.7% being complete responders. This was not dissimilar to the 18.2% objective response for the 44 Depo-Provera patients, 9.1% of whom had a complete response. Of the 114 women receiving progesterone therapy, 15.8% had an objective response with 7.0% being complete responders (Table 4). As seen in Table 5, even though the Depo-Provera study was started after the Delalutin study, the majority of the patients are already dead of cancer, with 75% of the Depo-Provera patients dying compared to 88.6% of the Delalutin patients; 7.2% of the patients are surviving who received Delalutin as compared to 25.0% receiving Depo-Provera, the latter patients having been followed for a shorter time period (Table 5).

Parameters Evaluated vs. Response to Progesterone Therapy

The proportion of objective responses achieved with smaller tumors did not differ significantly from that of larger tumors. Twelve percent of the patients with tumors less than 2 cm had an objective response as compared to 31.8% for those with tumors measuring 2.1–4 cm, and 11.9% for those with tumors greater than 4.1 cm ($P = 0.07$) (Table 6). Similarly, there was not a statistically significant increase in objective response when there were less than two metastatic sites (17.1%) as compared to three or greater metastatic sites (13.2%).

The median age of the patients achieving objective response was 60.5 years compared to 60.8 years for those having stable disease and 62.8 years for those having progression of the malignancy ($P = 0.6$). There

TABLE 4. Response to Delalutin or Depo-Provera with or without Radiation Therapy

Progesterone	Patients	Response					
		Objective		Stable		Progression	
		No.	%	No.	%	No.	%
Delalutin	70	10	14.3*	17	24.3	43	61.4
Depo-Provera	44	8	18.2†	12	25.3	24	54.5
TOTAL	114	18	15.8‡	29	25.4	67	58.8

Complete response: *5.7%, †9.1%, ‡7.0%.
$\chi^2 = 0.76$, not significant.

was no significant difference between the median age of the patients who had an objective response to Delalutin ($P = 0.9$) or Depo-Provera ($P = 0.14$).

As seen in Table 7, there was not a significant increase in objective response for those patients having a histologic grade 1 (well-differentiated) or grade 2 (moderately differentiated) primary lesion as compared to a grade 3 (poorly differentiated) with 16.8% and 13.0% objective response respectively. Similarly, the objective response in relationship to the histologic grade of recurrence or metastasis was not significantly better for the grade 1 or 2 lesions (20.0%) as compared to the grade 3 lesions (6.7%) ($P = 0.1$). There was a statistically significant difference in the objective response ($P = 0.01$) for those patients having a recurrence less than 3 years after the original therapy, with 8.3% responding as compared to 33.3% objective response for those having recurrence greater than 3 years after initial therapy (Table 8).

There was no statistically significant difference in response rate in relationship to the site of metastasis or recurrence. There was also not a significant difference in response rate for those women with prior or concomitant whole pelvis irradiation as compared to those who did not receive such therapy.

Discussion

In 1972, a prospective study was initiated to evaluate Depo-Provera in women with metastatic or recurrent endometrial adenocarcinoma not amenable to curative surgery and/or radiation therapy. The purpose of this study was to evaluate if a statistically significantly larger percentage of women responded to Depo-Provera and for a longer period of time than women previously treated with Delalutin. However, there was no significant increase in objective response to Depo-Provera (18.9%) as compared to Delalutin (13.7%). Moreover, the addition of localized radiation therapy to pelvic recurrences did not increase the response rate to Depo-Provera (14.3%) as compared to Delalutin + radiation therapy (15.8%). Of the 114 patients who received Progesterone therapy, 15.8% achieved an objective response, with 7.0% being complete responders. Also, the median duration of response was not significantly better in the Depo-Provera patients as compared to the Delalutin patients.

The only significant correlate in relationship to response to Delalutin or Depo-Provera was the time from original treatment to recurrence. Patients with recurrences 3 or more years after the initial therapy had a significant ($P = 0.01$) increase in response (33.3%) compared to those with recurrences less than 3 years after the original treatment (8.3%). There was no significant increase in objective response in relationship to the size of the tumor masses, the number of metastases, site of metastases, histologic grade of the primary, histologic grade of recurrence or metastases, or prior radiation therapy.

TABLE 5. Survival of Patients Treated with Delalutin and Depo-Provera

Results	Delalutin No.	Delalutin %	Depo-Provera No.	Depo-Provera %	Total No.	Total %
Dead of cancer*	62	88.6	33	75.0	95	83.3
Dead of ICD†	3	4.3	0	0	3	2.6
Alive with cancer	2	2.9	5	11.4	7	6.1
Alive NED‡	3	4.3	6	13.6	9	7.9

* $\chi^2 = 2.7$, $P = 0.10$.
† Intercurrent disease.
‡ No evidence of disease.

Although there was only a 15.8% objective response, it is clear that those patients achieving an objective response live significantly longer than those with stable or progression of their disease. For patients treated with Delalutin, the median survival for the responders was 59.8 months as compared to 12 months for stable disease and 2.8 months for progression of disease. Similarly, for women treated with Depo-Provera achieving an objective response, the median duration of survival was 28.8 months, compared to 11.0 months for stable disease and 3.8 months for progression of disease.

It has been suggested that response to progesterone therapy can be predicted by the finding of high progesterone receptors in the tumor-cell cytoplasm. Until this becomes more predictive, methods for enhancing the effect of progesterone therapy should be sought. Adriamycin is an effective agent in metastatic endometrial adenocarcinoma. Thigpen and coauthors reported a 34% response rate (14% complete) among 44 women with metastatic endometrial adenocarcinoma.[9] Using a slightly lower dose of Adriamycin,

TABLE 6. Effect of Size of Tumor Mass on Response to Progestogens

Response	Size of tumor (cm) 0–2 No.	0–2 %	2.1–4.0 No.	2.1–4.0 %	>4.1 No.	>4.1 %
Objective	3	12.0	7	31.8	8	11.9
Stable	10	40.0	3	13.6	16	23.9
Progression	12	48.0	12	54.5	43	64.2

$\chi^2 = 8.7$, 4DF, $P = 0.07$.

TABLE 7. Response vs. Grade of Original and Metastatic Tumor

	Grade of primary				Grade of recurrence or metastases			
	1 or 2		3		1 or 2		3	
Response	No.	%	No.	%	No.	%	No.	%
Objective	15	16.8*	3	13.0	11	20.0*	3	6.7*
Stable	26	29.2	3	13.0	18	32.7	8	17.8
Progression	48	53.9	19	76.0	26	47.3	34	75.6
TOTAL	89		25		55		45	

* $\chi^2 = 2.63$, $P = 0.10$.

however, Horton and associates could achieve only a 19% (4.7% complete) response.[6] The addition of cyclophosphamide to Adriamycin increased the response to 45.5% (27.2% complete) among 11 patients in one study;[7] however, Smith achieved only a 7.1% response rate in 14 patients treated with this combination.[8]

Similarly, we have treated 12 patients with metastatic endometrial adenocarcinoma with this combination of Adriamycin + cyclophosphamide primarily at a slightly higher dose (Adriamycin 45 mg/M^2 + cyclophosphamide 1000 mg/M^2) and achieved two partial responses (16.6%) lasting 3 and 5 months respectively.‡

More recently, Bruckner *et al.* utilized Adriamycin, cyclophosphamide, 5-fluorouracil and Depo-Provera in seven women with metastatic endometrial carcinoma and reported a 100% response rate, none of which was complete.[3] Finally, Cohen and co-authors reported an 85.7% response rate (12.5% complete) utilizing melphalan, 5-fluorouracil, and Depo-Provera in seven patients with metastatic endometrial adenocarcinoma.[4]

‡ Piver, M. S., and Barlow, J. J.: Unpublished data.

TABLE 8. Response to Progesterone Therapy Related to Time to Recurrence from Initial Therapy

	Response						
	Objective		Stable		Progression		
Time	No.	%	No.	%	No.	%	Total
<3 yrs	5	8.3*	15	25.0	40	66.7	60
>3 yrs	8	33.3*	7	29.2	9	37.5	24
TOTAL	13		22		49		84

* $\chi^2 = 6.4$, $P = 0.01$.

The reported median duration response in the above series ranged from only 3+ to 10 months.

Although only one in six women in our study responded to progesterone therapy, the responders had a significant prolongation of life, and, therefore, progesterone therapy should remain an integral part of the therapy of metastatic endometrial adenocarcinoma. However, because of the low response rate, progesterone therapy should be combined with other active cytotoxic agents, the most active of which remains to be established.

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