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# PROGESTOGEN THERAPY FOR OVARIAN CARCINOMA

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**Summary**

Twenty-nine patients with advanced ovarian carcinoma were treated with a high-potency progestogen. A response was observed in 15 out of 23 who received adequate treatment with this hormone. It is suggested that progestogens offer a safe alternative to non-hormonal chemotherapy for the advanced case and that further trials should be undertaken.

THERE are few references to the use of progestogen therapy for ovarian carcinoma. Hiller (1960) reported a reduction in the speed with which malignant effusions formed in a patient treated with 17-α-ethinyl-19-nortestosterone (norethindrone, Norlutin). Jolles (1962) reported that three patients gained objective benefit and one gained symptomatic benefit out of ten treated with 17-α-hydroxyprogesterone 17-n-caproate (Primolut Depot, Delalutin). Varga and Henriksen (1964) treated eight patients with the same compound and out of six who received adequate dosage one had an objective remission lasting three months and two had symptomatic improvement. Kaufman (1966) reported a remarkable objective remission lasting three years when a patient was treated with 17-α-hydroxy-6-α-methylprogesterone acetate (medroxy-progesterone acetate, Provera) but ten other patients received no benefit. Briggs, Caldwell and Pitchford (1967) summarized the results in 80 patients with ovarian carcinoma treated by progestogens. In 23 patients there was objective remission.

## PATIENTS, MATERIALS AND METHODS

Twenty-nine patients with ovarian carcinoma were treated. Four of these had received no previous treatment and twenty-five had recurrent carcinoma after surgery or radiotherapy or both. Some patients had already received radiotherapy or chemotherapy for recurrent carcinoma. The immediately antecedent treatment and the time lapse before commencing progestogen therapy are noted in Table I which lists only the 23 patients who received a total of more than 600 mg. of progestogen. All patients received 17-α-hydroxy-19-norprogesterone-17-n-caproate (Gestronol hexanoate, Gestonorone caproate, Depostat, SH 582). The earlier patients in the series received this substance in combination with oestradiol valerate in the proportions of ten to three by weight as this was the only preparation available at the time. This combination is designated SH 834. Both preparations were given by intramuscular injection. SH 582 is a pure progestogen having no androgenic, oestrogenic nor corticosteroid-like activity. According to Heckmann (1966) the progestational activity of SH 582 is 20 times that of progesterone.

## RESULTS

The condition of six patients who received not more than 600 mg. of SH 582 steadily deteriorated. Their survival times were 2, 10 and 11 days, 4, 8 and 10 weeks. It was felt that this dosage was inadequate and hence those patients are excluded from Tables I and III. Table I lists the patients in the order of their presentation for progestogen therapy and summarizes the results. There were no side effects from the treatment save that two patients complained that the injections were painful. In Table II the results are classified according to the drug preparation and dosage given.

When treatment was continued for at least a

TABLE I

*Case summaries*

| Case no. | Ages | Histology | Time lapse from end of previous treatment | SH no. | Weekly dose × no. of weeks | Response | Duration of response (months) | Subsequent treatment | Survival time from first dose of SH (months) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 71 | Papillary adeno-carcinoma | 8 weeks after radiotherapy | 834 | 300×9 | Deteriorated | — | Cyclophospha-mide | 20 |
| 2 | 66 | Adeno-carcinoma | 10 months after radio-therapy | 834 | 400×4 | Felt much better and had less pain. Stopped SH because of thrombo-phlebitis | 1 | Cyclophospha-mide | 12 |
| 3 | 48 | Cystadeno-carcinoma | 7 months after radio-therapy | 834 | 300×13 then 600×15 | Pelvic mass stopped grow-ing and became softer | 6 | Radiotherapy | 21 |
| 4 | 52 | Anaplastic papillary adeno-carcinoma | 17 months after radio-therapy | 834 | 400×5 | Deteriorated | — | None | 2 |
| 5 | 51 | Papillary cystadeno-carcinoma | 6 months after radio-therapy | 834 | 200×5 | Deteriorated | — | None | 2 |
| 6 | 19 | Well differentiated papillary adeno-carcinoma | No time lapse after stopping chlorambucil | 834 | 400×8 | Frequency of paracentesis reduced from every 3 days to every 14 days | 2 | Radiotherapy | 4 |
| 7 | 59 | Poorly differentiated carcinoma | 12 days after stopping cyclophospha-mide | 834 | 400×3½ | Felt better but ascites increased | 1 | Radiotherapy | 5 |
| 8 | 55 | Poorly differentiated adeno-carcinoma | 1 month after radiotherapy | 834 | 300×5 | Deteriorated | — | None | 2 |
| 9 | 62 | Poorly differentiated adeno-carcinoma | 2 months after radio-therapy | 582 | 300×9 | Abdominal mass stopped growing and ascites remained unchanged | 1 | None | 3 |
| 10 | 73 | Well differentiated adeno-carcinoma | 3 months after radio-therapy | 582 | 200×4 | Deteriorated | — | Cyclophospha-mide | 8 |
| 11 | 60 | Serous cystadeno-carcinoma | No time lapse after cyclophospha-mide | 582 | 200×6 | Felt much better. Appetite improved. Ascites became less | 7 | None | 15 |

TABLE I (*continued*)

*Case summaries*

| Case no. | Ages | Histology | Time lapse from end of previous treatment | SH no. | Weekly dose × no. of weeks | Response | Duration of response (months) | Subsequent treatment | Survival time from first dose of SH (months) |
|---|---|---|---|---|---|---|---|---|---|
| 12 | 55 | Anaplastic papillary carcinoma | 9 months after radiotherapy | 582 | 200×9 | Felt better. Less pain and dyspnoea | 1 | None | 3 |
| 13 | 30 | Well differentiated papillary adenocarcinoma | 1 month after nitrogen mustard | 582 | 100×5 then 200 ×12 | Felt much better. Pleural aspiration required less often. Abdominal distension became less | 3½ | None | 4 |
| 14 | 52 | Poorly differentiated carcinoma | No time lapse after stopping chlorambucil | 582 | 200×9 | Deteriorated | — | Radiotherapy | 4 |
| 15 | 57 | Anaplastic carcinoma | 2 weeks after cyclophosphamide | 582 | 200×12 | Vomiting stopped and pain became less. Able to return to part-time work. Abdominal mass became smaller | 3 | Radiotherapy and then cyclophosphamide | 6 |
| 16 | 56 | Serous cystadenocarcinoma | 4 months after radiotherapy | 582 | 400×9 | Felt much better. Ascites reduced | 4 | Cyclophosphamide plus SH 582 | 12 |
| 17 | 64 | Poorly differentiated carcinoma | No previous treatment | 582 | 200×10 | Deteriorated | — | Radiotherapy | 4 |
| 18 | 64 | Poorly differentiated serous adenocarcinoma | 1 week after thiotepa | 582 | 200×4 | Pain less. Abdominal mass unchanged | 4 | None | 2 |
| 19 | 47 | Anaplastic carcinoma | 1 week after chlorambucil | 582 | 200 3 weekly for 3 months | Abdominal pain ceased | 11+ | None | Alive and well at 11 months |
| 20 | 45 | Anaplastic carcinoma | No previous treatment | 582 | 600×5 | Deteriorated | — | Cyclophosphamide | 3 |
| 21 | 64 | Anaplastic carcinoma | 9 weeks after cyclophosphamide | 582 | 200 weekly | Felt better Ascites less | 3+ | None | Still alive |
| 22 | 64 | Papillary adenocarcinoma | 5 months after radiotherapy | 582 | 200 weekly | Felt better. Ascites less. Abdominal mass much smaller | 3+ | None | Still alive |
| 23 | 31 | Papillary cystadenocarcinoma | No previous treatment | 582 | 200 weekly | Abdominal mass much smaller | 2+ | None | Still alive |

TABLE II

*Results classified by dose of progestogen and preparation used*

| Dose | SH number | Number of patients treated | Number who responded only symptomatically | Number who responded symptomatically and objectively |
|---|---|---|---|---|
| Total dose not exceeding 600 mg. | 582 | 6 | 0 | 0 |
| Total dose 800 mg. over 3 months | 582 | 1 | 1 | 0 |
| 200 mg. weekly for at least one month | 582 | 11 | 3 | 5 |
| 300 mg. weekly for at least one month | 582 | 1 | 0 | 1 |
| 300 mg. weekly for at least one month | 834 | 4 | 0 | 1 |
| 400 mg. weekly for at least one month | 582 | 1 | 0 | 1 |
| 400 to 600 mg. weekly for at least one month | 834 | 4 | 2 | 1 |
| 600 mg. weekly for at least one month | 582 | 1 | 0 | 0 |

month a total of 15 out of 23 patients responded either symptomatically or both objectively and symptomatically. A striking feature was a sense of well-being which patients often reported although they had advanced disease. Several patients said they were happy to accept the discomfort of injections because they felt so well while they were having them. If the injections were missed for only a week they would begin to feel unwell again. In Table III the results are classified according to the age of the patients and the histological appearances of the tumours.

TABLE III

*Number of patients responding and total number treated classified by age and histology of the tumour*

| Age in years | Well differentiated carcinoma | Poorly differentiated carcinoma | Anaplastic carcinoma | Total |
|---|---|---|---|---|
| Below 50 | 4/4 | 0 | 1/2 | 5/6 |
| 50 to 59 | 1/2 | 1/3 | 2/3 | 4/8 |
| 60 to 69 | 3/3 | 2/3 | 1/1 | 6/7 |
| Over 70 | 0/2 | 0 | 0 | 0/2 |
| Total | 8/11 | 3/6 | 4/6 | 15/23 |

## DISCUSSION

The results suggest that treatment with high dosage of a progestogen can play a useful part in the management of advanced ovarian carcinoma. Eight out of 11 patients who received 200 mg. of SH 582 weekly for at least a month responded favourably whereas with SH 834 it was only at higher dose levels that this response rate was matched. This suggests that progestogen was more effective alone than in combination with oestrogen but the number of patients treated is too small for any firm conclusion to be drawn. It seems likely that 200 mg. of SH 582 weekly is an adequate dose level.

The response rate was slightly better for well-differentiated tumours than for others but again the numbers are too small for any firm conclusion to be drawn. Apart from the lack of response in two patients who were over 70 years old the favourable responses are evenly distributed throughout all age groups.

These observations suggest that progestogen therapy for ovarian carcinoma is worthy of further trial and while surgical resection and radiotherapy should still be carried out when indicated the use of a high potency progestogen in adequate dosage is a reasonable and safe alternative to non-hormonal chemotherapy. This treatment is indicated regardless of the histological appearance of the tumour and the age of the patients.

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