Basil A. Stoll, London (Editor)

Endocrine Management of Cancer

2 Contemporary Therapy

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3 figures and 20 tables, 1988

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Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Preface

The approach of this book differs from that of others on this topic. It is not divided into sections dealing separately with the endocrine management of cancers of the breast, prostate, uterus and so on, because such reviews can be found in specialist journals and books. Instead, the book discusses the clinical role and pharmacological characteristics of several new groups of hormone-modulating agents which have become commercially available in recent years. The new agents have come at a time of incredible advances in our knowledge of the molecular biology of the cancer cell and in our ability to recognize biological mechanisms which make tumours behave in a particular manner in the individual patient.

Clinically, it is an ideal time to collate such knowledge because the new agents have now completed extensive clinical trials in cancers of the breast, prostate and endometrium especially. Many have yielded a significant degree and duration of tumour regression in patients with the advanced disease, and evidence of delayed recurrence when used as adjuvant therapy in the high-risk patient after primary surgical treatment. Their ability to prolong survival has been less clearly proved.

Combinations of endocrine agents or combination chemo-endocrine therapy have a greater potential to prolong remissions and thereby increase survival, but, in the past, selection of combinations was empirical. The introduction of biological assays of tumour receptors, and biological indices of tumour aggressiveness and tumour burden, should now permit more rational selection of suitable subsets of patients for such treatment. Metabolic disposition of agents in the body also needs to be considered in selecting patients for treatment.

The book reviews the principles underlying the use of the new hormone-modulating agents in the treatment of breast, prostatic and uterine cancers. In this aim, the writers distinguish between the effects of an endocrine agent which are specific for a particular tumour, as distinct from those which may apply to all hormonally responsive tumours. This is an innovative approach, as the literature has previously made no attempts to establish parallels

between the tumours in their rates and duration of primary response, likelihood of response to secondary therapy, significance of flare, path to autonomy and so on.

It is hoped that the insights into new agents and treatment approaches, together with an up-to-date account of the biological characteristics of tumours likely to respond, will lead clinicians to institute new clinical trials of hormonal modalities based upon rational, rather than empirical principles.

London, 1988

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Contents

1 Progestins in Cancer Treatment

Aman U. Buzdar[1]

There are currently a number of progestins in clinical use, including progesterone, hydroxyprogesterone caproate, medroxyprogesterone acetate, ethynodiol diacetate, norethindrone, norethynodrel, megestrol acetate, and norgestrel [1]. Medroxyprogesterone acetate, hydroxyprogesterone caproate, and megestrol acetate are the major agents shown to have significant antitumor activity in breast cancer, prostate cancer and endometrial cancer.

Pharmacology of Progestins

Most patients tolerate progestin therapy well, and a significant percentage of patients even experience a subjective sense of well-being during therapy. There is no evidence that this sense of well-being is due to the conversion of progestins to corticosteroids. Pharmcological doses of progestins have no androgenic or corticosteroidal side effects but, occasionally, patients treated with medroxyprogesterone acetate show Cushingoid features, suggesting altered metabolism in these individuals.

Progestin administration is not associated with hot flashes but infrequently, they cause increased perspiration and night sweats, which may be due to increased body temperature. Progestins can cause a significant weight gain, which is not due to fluid retention in most patients. It is most marked in patients who are initially overweight and such patients should be instructed to watch their calorie intake in order to avoid excessive overweight.

Progestins do not alter sodium metabolism or inhibit adrenocortical activity but, occasionally, progestin therapy may unmask latent diabetes

[1] The author would like to thank Vickie E. Richard for secretarial assistance and Carol Kakalec for editorial assistance.

Table I. Progestin therapy in advanced breast cancer

Number of patients	Response CR + PR %	Reference No.
Megestrol acetate trials		
18	50	4
39	44	5
48	31	6
160	30	7
160	30	8
20	30	9
Medroxyprogesterone acetate trials		
39	44	10
105	20	11
32	47	12
91	35	13
23	22	14
26	27	15

CR = Complete remission; PR = partial remission.

mellitus [2]. The injectable form of progestin may be associated with local soft tissue reactions which may result in sterile abscesses. In a small percentage of patients with osseous metastases, endocrine therapies can induce hypercalcemia within the first few days to two weeks of therapy but with supportive symptomatic therapy, continuation of progestin can result in objective response in a high percentage of these patients.

Breast Cancer

Since the initial report of their effectiveness in causing regression of advanced breast cancer [3] numerous studies have confirmed the value of progestins in its management (table I). Used as first-line therapy for metastatic breast cancer, a number of studies show a response rate comparable to that of tamoxifen (table II). The length of remission following their use as first-line therapy is also similar to that of tamoxifen. The median duration of remission is 9–12 months, and the mean objective response rate is 38%.

Table II. Comparative trials of progestins and tamoxifen in advanced breast cancer

Drug trial	Objective response, %	Reference No.
T vs. MPA	47 vs. 54	16
T vs. MPA	27 vs. 37	17
T vs. MPA	28 vs. 25	18
T vs. MA	14 vs. 26	19
T vs. MA	35 vs. 31	20
T vs. MPA	27 vs. 37	21
T vs. MA	21 vs. 29	22
T vs. MA	42 vs. 35	23

T = Tamoxifen; MPA = medroxyprogesterone acetate; MA = megestrol acetate.

However, in another 15–30% of patients, growth rate is stabilized by progestin therapy and such patients have a similar duration of control of disease to that of patients with clear objective response.

Progestins given as second-line therapy for breast cancer are reported to give a response rate of 30–40% in patients who respond to first-line endocrine therapy (mostly by antiestrogen). In these studies again, an additional 15–30% of patients achieved stable disease. The median duration of response for second-line therapy was in the range of 6–9 months. Antitumor activity of progestins has also been evaluated before and after treatment with cytotoxic drugs, and the data indicate that the likelihood of response to progestins is independent of prior treatment with cytotoxic drugs [6].

Both estrogen and tamoxifen induce the synthesis of progesterone receptors in hormone-dependent breast cancer. Several studies utilizing short cycles of estrogen or tamoxifen alternating with progestins have been reported (table III). The number of patients treated is too small to evaluate the merit of this cyclic approach (see chapter 9).

Progestins have been combined with various chemotherapeutic regimens but the available data show no evidence of synergism between the two treatment modalities (table IV). Response rates achieved in combined hormonochemotherapy studies were not superior to those from chemotherapy alone, nor were the length of remisson and of survival with the combined modality. Thus, concurrent administration of combined progestin and cytotoxic drugs offers no advantage, while sequential administration of progestins and chemotherapy will palliate the patient for a duration similar

Table III. Tamoxifen or estradiol followed by medroxyprogesterone acetate in advanced breast cancer

Sequence of drugs	Number of patients	Response CR + PR %	Reference No.
T → MPA	30	56	24
T → MPA	25	24	25
Estradiol → MPA	23	65	26

T = Tamoxifen; MPA = medroxyprogesterone acetate; CR = complete remission; PR = partial remission.

Table IV. Chemotherapy vs. hormonochemotherapy in advanced breast cancer

Drug trial	Objective response, %	Reference No.
CAMF vs. CAMT + MPA	45 vs. 61	27
FAC vs. FAC + MPA	55 vs. 75	28
CMFVP vs. CMFVP + MPA	63 vs. 53	29
Mitomycin + MA	27	30

C = Cyclophosphamide; A = adriamycin; M = methotrexate; F = fluorouracil; V = vincristine; P = prednisone.

to the combination, and patients will experience fewer side effects during the hormone-only phase of the treatment.

Some studies of combined hormonochemotherapy have suggested that progestins reduced the toxicity of the cytotoxic drug by reducing the degree of myelosuppression. In one study, progestin combined with mitomycin C did not cause the significant weight loss that is usually observed with mitomycin therapy [30]. This could be attributed to the anabolic effect of progestins.

Progestins have been evaluated in a small number of male patients with breast cancer, and significant antitumor activity was observed in advanced disease. Antitumor activity was observed in patients without prior surgical castration [10].

Progestins have not been evaluated as adjuvant therapy in operable breast cancer in randomized trials, but in one uncontrolled clinical trial,

megestrol acetate was claimed to delay recurrence following local therapy in high-risk breast cancer patients [31]. Preliminary results of this study were comparable to those from tamoxifen, but prolongation of survival was not evident. To evaluate the adjuvant role of progestational agents, randomized studies are needed.

Efficacy of Various Progestins and Dose Schedules

Medroxyprogesterone acetate and megestrol acetate show similar activity in breast cancer and there are no data on cross-resistance between the two progestins in this disease. Megestrol acetate has been utilized at doses of 160 mg/day orally while medroxyprogesterone acetate has been evaluated at 400–800 mg/day orally, but in the injectable form at much higher doses. There has been no clear therapeutic superiority shown for injectable therapy, but it has an advantage in patients who have compliance problems with oral administration.

Endometrial Cancer

Approximately 80% of localized endometrial cancer is cured by local therapy such as surgery or radiotherapy or their combination. Studies have shown significant antitumor activity of progestins in advanced disease, and patients with well-differentiated tumors have a higher probability of response. Approximately 60% of patients with endometrial cancer show progesterone receptor-positive assays, and presence of such receptors is related to the degree of differentiation. Among well-differentiated tumors, more than 80% show positive progesterone receptor assays, while only 33% of undifferentiated tumors have positive receptor assays [32, 33].

The presence of progesterone receptors has been correlated with response to progestin therapy in a few studies of advanced disease. In progesterone receptor-positive tumors, approximately 70% response rate has been reported from pooled data while in progesterone receptor-negative tumors, the response rate is less than 10% [32]. In unselected patients without receptor information, response to progestin therapy is in the range of 30–40% and the duration of response from initiation of therapy is in the range of 16–19 months. Patients with well-differentiated tumors and long disease-free intervals have a higher probability of response to progestin therapy.

Progestin therapy can be used also in earlier stages of the disease. In approximately 60% of the patients with in situ endometrial carcinoma who

were treated only with systemic progestins, no residual cancer could be detected; however, in stage I disease these agents caused complete response in only 20% of the patients. Progestin therapy administered either prior to radium therapy or surgery, or postoperatively, is claimed to reduce the risk of local recurrence, and preliminary data suggest a survival advantage.

Endometrial carcinoma in younger women carries a better prognosis than in older patients. In younger women who wish to have families, early stage disease can be effectively treated with progestins alone but these patients must be followed closely at 2-month intervals until there is complete remission. Surgery should be reserved for patients with persistent tumor or those who fail to achieve complete remission with progestin therapy [34]. Progestin therapy should be continued for as long as the disease remains in remission, because discontinuing therapy is said to be associated with rapid relapse.

In a few studies, progestins have been evaluated as adjuvant therapy at an earlier stage of endometrial cancer [33, 35–42] but their use in this role remains controversial. Certain high-risk groups can be identified, and they include patients with myometrial invasion and nodal metastasis. The impact of adjuvant progestin therapy on length of survival in such high-risk patients is not clear, although the small gains do favor such therapy. To evaluate its effect adequately requires larger clinical trials.

Efficacy of Various Progestins and Dose Schedules

The most commonly used progestins in the treatment of endometrial cancer have been hydroxyprogesterone and medroxyprogesterone, but recent studies with megestrol acetate have produced similar results. The usual doses of medroxyprogesterone acetate and hydroxyprogesterone caproate are 1–3 g/week for the initial dose, and then maintenance doses of 400–800 mg/week. Megestrol acetate has been used in doses of 160 mg/day. A review of several studies of advanced endometrial cancer show no significant differences in response rates between medroxyprogesterone acetate, hydroxyprogesterone and megestrol acetate. A few studies suggested that higher response rates could be achieved with higher doses of drug, but others have observed no dose-dependent response.

Combined progestin therapy with tamoxifen (which increases the progesterone receptor level) has been evaluated but the combined modality was not more effective than progestins alone [43]. Combined hormonochemotherapy (mostly with single agents) was not significantly better than sequential administration of the two treatment modalities [44–47].