NORETHISTERONE ACETATE (SH_{420}) IN ADVANCED BREAST CANCER

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Norethisterone acetate (SH. 420) has been used in 154 patients with advanced breast cancer, and a 41% objective remission obtained. Certain clinical factors enable selection of patients most likely to respond. Hence, those with predominantly local disease showed an 82.6% benefit while bony or visceral deposits did poorly. Rapidly evolving disease (disease-free interval under 2 years) benefitted in 21.3% whilst of those with longer time factors 59.6% responded. Patients under 55 years showed a 27.0% response rate compared with 48.0% over this age. By combining these factors groups of patients with response rates ranging from 96% down to 8% could be identified. Norethisterone would thus seem to be the agent of first choice in certain advanced breast cancers and without value in others.

THE TREATMENT OF ADVANCED BREAST CANcer commands an impressive literature abounding with endocrine and cytotoxic regimes of greater or lesser merit. This addition is justified by the fact that progestogens, probably the least appreciated of the hormone groups, may merit a more important role in management than they presently occupy.

Twenty years have passed since the first reports that the basic compound progesterone might benefit 20% of women with this disease.[12,13]

Virilization constituted a disadvantage, but potent 19-nortestosterone derivatives possessing higher progestational and lower androgenic activity have been synthesized; norethisterone acetate belongs to this group. Its value was demonstrated by Curwen[6] and Notter,[19] whilst Briggs,[3] in a review, collected 178 patients with 39% remission, and recently Curwen[7] reported 67% benefit.

PHARMACOLOGY

Progesterone has a low oral potency, but synthetic substances with similar actions generally effective by this route have now become available. One, norethisterone acetate, is a 19-nortestosterone derivative with potent progestational activity. This can be determined experimentally by the Clauberg assay which measures progestational transformation of the estrogen-primed endometrium of the rabbit. In this test norethisterone acetate displays a potency 25 times as great as that of progesterone, when both hormones are given subcutaneously. Given orally, norethisterone acetate is more than 300 times as potent as progesterone and about 3 times as potent as norethisterone.

This method of action is uncertain but may be through suppression of gonadotrophin secretion, as demonstrated by Martin and Cunningham,[17] Chow,[4] Netter,[18] and Curwen. A proportion may be converted to an estrogen as there are reports that urinary estrogen excretion increases after administration of norethisterone,[1,14,15,20] though Breuer[1] now considers these levels an extraction artifact.

TOXICOLOGY

Norethisterone, the first orally effective-progestogen, was synthesized in 1938. This testosterone derivative had a comparatively low progestational activity and was also relatively androgenic.

Esterification produced norethisterone acetate which proved to have only one-third of the androgenicity of the free compound when assessed by the seminal vesicle test and by studies on fetal intra-uterine masculinization.

Thus in clinical use, it had the advantage over androgen preparations in that symptoms of virilization rarely occur even at doses as high as 60 mg per day.

Uterine bleeding, a side-effect of estrogen administration, is rarely encountered. The

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TABLE 1. Overall Results with Norethisterone Acetate

Total patients in series		154
Not assessable:		29
(a) Died under 1 month	17	
(b) Intolerant of drug	4	
(c) No valid criteria	8	
Assessable		125
Objective response		52 (41.6%)

hormone is well tolerated by the gastro-intestinal tract, while occasionally, limited cholestatic liver changes have been observed.

CLINICAL DATA

Norethisterone acetate, 10 mg orally, 4 times daily, was used in any patient with breast cancer considered incurable by conventional measures.

Previous surgery and radiotherapy had been used in 91 patients, surgery in 25, radiotherapy in 15, while 23 had been too advanced initially for measures other than systemic. Previous hormone therapy had been used in 87 individuals.

As the hormone initially was employed terminally, 17 of the early patients included in the series were in poor physical condition, dying within 1 month. Following evaluation, it has been used earlier in disease, and 154 consecutively-treated patients (Table 1) are reported.

DEFINITION OF OBJECTIVE REMISSION

Disease status was recorded by measurement, photography, radiology, or isotope scan. Classification as an objective remission required 3 criteria: (1) Measurable regression of at least 50% in the dominant lesion; (2) that this be maintained for at least ten weeks; and (3) no evidence of cancer progression in any other situation.

The nature of disease treated is reflected by 17 deaths from advanced cancer within 1 month of commencing therapy. In calculating the objective remission rate these have been excluded as were 4 who were unable to tolerate the agent, because of severe nausea and vomiting. This leaves 125 patients assessable with an objective remission rate of 41.6%.

The duration of remission obtained is of limited significance, as life quantity is no indication of its essential quality, but it does help in evaluating the hormone. As many patients have been on the drug for less than 9 months, no relevant figures can yet be produced. Some responses are in excess of 1 year; the longest exceeds 2 years.

TABLE 2. Site of Disease (Predominant) and Response

Site	Total in group	Objective no.	Response %
Local	46	38	82.6
Bone	45	9	20.0
Visceral	34	5	14.7

χ^2 = (Local vs. Blood borne) = 50.38 $P < 0.001$

SELECTION FOR NORETHISTERONE ACETATE

One problem in advanced breast cancer is prompt selection of the approach appropriate to the individual patient. This has been undertaken by a retrospective search for clinical details common to patients responding to norethisterone acetate and absent among the failures.

First investigated was the behavior pattern of the growth (Table 2). Recurrent breast cancer may develop in one of three predominant ways:[8]

1. Local disease: Grows extensively in breast, on chest wall and in regional lymph nodes. While occasional distant deposits may be present, its local nature predominates. Eighty-two percent responded to norethisterone acetate.

2. Blood-borne metastases: Though possibly associated with local recurrence, this group possesses the ability for hematogenous dissemination. Two sub-groups exist: A. Osseous: Predominantly bony lesions with a 20.0% response; and B. Visceral: Predominantly involving brain, lungs or liver with 14.7% response.

The pattern of disease had significant bearing on the incidence of response, local recurrence being favorable.

The second factor investigated was the rate of tumor progression estimated by the disease-free interval (D.F.I.) between therapy and clinical recurrence (Table 3).

Two conditions have been considered: rapidly progressive cancer with a D.F.I. under 2 years; and a slowly progressive variety with a longer period. The latter group did best with norethisterone acetate (Table 3), 59% responding, compared with 21%.

The third factor considered is age at time of therapy (Table 4), with an arbitrary division

TABLE 3. Disease-Free Interval

Time (months)	Patient total	Remission No.	Remission %
0–24	61	13	21.3
25+	47	28	59.6

(not ascertainable in all patients)
$\chi^2 = 16.5$ $P < 0.001$

TABLE 4. Age of Patient

Age	Patient total	Remission No.	Remission %
55–	48	13	27.0
55+	77	37	48.0

χ^2 (under 55's vs. over 55's) = 5.4 $0.05 > P > 0.01$

into 2 groups, below and above 55 years. The younger group had a poorer response (27.0%) than did the older (48.1%). There was little difference between subsequent decades.

Response to prior endocrine therapy was also examined but the multiplicity of agents available made firm conclusions impossible.

Information about the probability of response to norethisterone acetate may thus be gained from 3 factors, namely age, "D.F.I.", and predominant recurrence pattern.

It should be possible to increase predictive accuracy by considering these factors in combination, but the resulting large number of sub-groups would preclude meaningful analysis. Selection, however, may be improved by considering the factors merely as favorable or unfavorable (Table 5).

Where all factors were unfavorable, 8.3% of patients responded while groupings with 1 favorable gave a result of 20.8%, 2 favorable gave 58.6%, and where all were favorable the figure rose to almost 96%.

DISCUSSION

In this study 17 patients died within 1 month of commencing treatment. In all instances this was attributable to progression of advanced cancer, and there was no suggestion that the hormone possessed an adverse effect upon either tumor progression or the patient generally.

Some degree of intolerance, usually gastrointestinal, consisting of nausea and vomiting, was observed in possibly 30 patients, but this responded to temporary dose reduction and antiemetics in all but 4 instances, in whom persistence of these symptoms rendered treatment impossible.

Norethisterone acetate would seem to be a safe and well-tolerated agent capable of benefitting a significant proportion of patients, in this series 41%. Such a figure accords well with the 44% of Notter and Wicklund,[19] the 50% of Clavel and Bourdin,[5] and the review by Briggs,[3] which produced a figure of 39%. It falls short of the 67% claimed by Curwen, but this discrepancy is possibly explained by the type of disease treated.

It has been shown that locally-recurrent cancer has a greater likelihood of responding to treatment, a point noted by the above workers. Such patients make up almost two-thirds of Curwens series, here amounting to one-third. This could account for the varying figures obtained and makes the point that series comparisons between different centers can be misleading if not indeed dangerous.

Norethisterone acetate is a valuable agent, principally because of the ready ability to select patients likely to respond. The most significant indicator is the behavior pattern of cancer, this reinforcing the point that the disease is not one entity but several. There is that which grows extensively through the breast, over the chest wall, and in local lymphatics. This often indolent pattern exhibits certain differences from that which spreads by the blood stream.

Thus, thyroid function measured by radioiodine studies is reduced,[10] there is poor response to hypophysectomy,[9] and thiotepa,[16] while cyclophosphamide is of benefit.[8]

It is these locally recurrent patients who consistently respond to Norethisterone acetate, while those with bony deposits do badly in contrast to their good outcome with hypophysectomy. Visceral disease carries a gloomy future with any endocrine procedure.

Other favorable factors are slowly evolving disease and an older patient, both of value in hypophysectomy selection.

TABLE 5. Combinations of Factors and Response to Norethisterone Acetate

Factors Favorable	Factors Unfavorable	Number in group	Response No.	Response %
2 or 3	none	24	23	95.8
2	1	29	17	58.6
1	1 or 2	48	10	20.8
none	2 or 3	24	2	8.3

In certain cases the D.F.I. could not be determined.

Although a controlled clinical trial comparing Norethisterone acetate with other endocrine therapies has not been undertaken, it would appear not unreasonable to suggest that this is the hormone of choice in locally recurrent breast cancer in the older patient with slowly evolving disease. Lacking the side effects of other hormones, cytotoxic agents, and endocrine ablation, it represents a useful addition to the therapeutic armamentarium.

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