Response after withdrawal of tamoxifen and progestogens in advanced breast cancer

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Summary. Tumor response after withdrawal of endocrine therapy for advanced breast cancer with estrogens and androgens is well described. There have been few reports of withdrawal responses (WRs) after cessation of treatment with the newer antiestrogens and progestogens. We assessed WR in women after cessation of adjuvant therapy at first relapse, and after progression on first, second or third line endocrine therapy for advanced disease. One of seven patients (14%) responded after cessation of tamoxifen adjuvant therapy at relapse. Sixty-five of 72 patients were evaluable for WR after cessation of tamoxifen as first line therapy for advanced disease. There were five partial responses (8%) and 14 (22%) 'no change' with a median duration of WR of 10 months (range 3–40 months). WR were seen mainly in soft tissue disease but there were two responses in lung and two in bone. Four of 21 (19%) patients had a WR after cessation of norethisterone acetate (3) and tamoxifen (1), all used as second line therapy. WR are therefore demonstrable after cessation of tamoxifen and norethisterone acetate with durations of response similar to those found with additive therapy. Assessment of WR may represent a way of prolonging the overall response duration in patients with relatively indolent metastatic breast cancer, particularly in soft tissues.

Key words: breast cancer, tamoxifen, withdrawal response (WR)

Introduction

Withdrawal responses or 'rebound regressions' of breast cancer were first described in 1949 in a group of patients who had initially responded to androgens. When the tumor eventually progressed on androgen therapy a further response was obtained when treatment was stopped [1]. WRs were later reported after cessation of therapy with estrogens in patients who had initially responded [2]. WRs in patients who failed to respond to first line treatment with estrogens were first described in 1956 [3]. In these early studies all WRs were seen after treatment with either estrogens or androgens and none were reported after cessation of corticosteroids or the progestogens in use at that time [4].

The first reported WR after cessation of tamoxifen was seen in a patient with parenchymal lung metastases [5]. There was no evidence of an initial response to tamoxifen in this patient, indeed the growth rate of the metastases appeared to be stimulated by treatment. Withdrawal of tamoxifen resulted in a partial response which lasted for at least six months. However, clinicians doubted that WRs were observable after tamoxifen since, in another study, no WRs were seen in 19 patients [6]. Since that time there have been two case reports [7, 8] and two series [9, 10] indicating that WRs do occur after stopping tamoxifen therapy. One study is particularly important since it gives some indication of the incidence of WR after tamoxifen [9]. Sixty-one consecutive patients were assessed for WR and there were six (9.8%) responses.

We began to assess WR in our clinic in 1980 and now report several new examples of WR after initial response or no response to tamoxifen. There have been no previous reports of WR after cessation of second endocrine therapy and we present evidence for this phenomenon and also evidence that WR can occur after cessation of progestogens.

Patients and methods

Patients

The first evaluation of WR was in January 1980 and the final one included in this analysis was in December 1988. Seven patients were assessed for WR after progression on adjuvant tamoxifen, 72 after failure of first endocrine therapy for advanced disease and 21 after failure of second or third line therapy for advanced disease. Patients were selected for assessment of WR because they had relatively indolent disease and it was thought unethical to assess all patients in this way. Therefore during the period of study a further 194 patients were treated with immediate second line additive endocrine therapy and 128 were treated immediately with chemotherapy after failure of first endocrine therapy.

Pretreatment characteristics

The characteristics of patients assessed for WR after failure of first line endocrine therapy are shown in Table 1. Compared with patients

Table 1. Characteristics of patients at the time of second therapy.

Treatment	Withdrawal (1)	Additive endocrine (2)	p (1 vs. 2)	Chemo-therapy (3)	p (1+2 vs. 3)
Patient numbers	72	194		128	
Median age at presentation	63	60	NS	53	NS
(range)	(32–90)	(25–87)		(25–84)	
Histology					
Infiltrating duct	50 (70)*	138 (71)		99 (77)	
Infiltrating lobular	6 (8)	14 (7)	NS	8 (6)	NS
Other types	16 (22)	42 (22)		21 (16)	
Receptors					
ER+ve	47 (82)	108 (79)		42 (45)	
−ve	10 (18)	29 (21)	NS	52 (55)	<0.0001
NK	15	57		34	
PR+ve	37 (66)	78 (58)		32 (34)	
−ve	19 (34)	57 (42)	NS	62 (66)	<0.0001
NK	16	59		34	
Dominant site of disease					
Locally advanced	12 (17)	25 (13)		6 (5)	
Recurr. soft tissue	26 (36)	34 (17)		23 (18)	
Bone	17 (24)	70 (36)	0.007	27 (21)	<0.0001
Lung	15 (21)	47 (24)		49 (38)	
Liver	2 (3)	18 (9)		21 (16)	
Brain	–	–		2 (2)	
Number of sites of disease					
1	32 (44)	76 (39)		31 (24)	
2	25 (35)	70 (36)	NS	55 (43)	0.0007
3	12 (17)	37 (19)		22 (17)	
3+	3 (4)	11 (6)		20 (16)	

* (%).
NS = not significant.

Table 2. Response to first endocrine therapy in all patients.

Second therapy	Withdrawal (1)	Additive endocrine (2)	p (1 vs. 2)	Chemo-therapy (3)	p (1+2 vs. 3)
Patient numbers	72	194		128	
Response to 1st endocrine therapy					
Complete (CR)	8 (13)	12 (8)		0 (0)	
Partial (PR)	20 (32)	37 (24)		8 (8)	
No change (NC)	21 (34)	31 (20)	0.004	13 (12)	<0.001
Progression (PD)	13 (21)	72 (48)		85 (80)	
Not evaluable (NE)	10	42		22	
Time in months					
Surv. from presentation	73	63	NS	42	<0.0001
Disease free interval	31	28	NS	25	0.05
Time to progression (on 1st therapy)	13	8	0.006	3	<0.0001
Survival from 1st therapy	44	31	0.002	19	<0.0001
Duration of response	15	14	NS	11	<0.0001

who were treated with additive second line endocrine therapy they were significantly more likely to have soft tissue disease only. Patients given chemotherapy as second treatment were significantly more likely to be receptor negative, to have liver and lung as dominant sites of disease and to have multiple sites of disease compared with the endocrine treated groups. The response to first endocrine therapy in the three groups is shown in Table 2. The WR group had a significantly higher response rate (79%: CR + PR + NC) than those treated later with second line additive endocrine therapy (52%) or with chemotherapy (20%). The WR group also had a significantly longer time to progression and survival from first therapy than the other two groups.

Assessment of response

The criteria used for assessment for tumor responses were those defined by Hayward et al. for the UICC [11]. Patients were examined monthly after withdrawal of therapy. Lung metastases were assessed by monthly chest x-rays and bone changes at two monthly intervals. The duration of response was taken from the start of treatment to the date of objective tumor progression. For WR this time was taken from the cessation of tamoxifen to the time of progression; to be defined as 'no change' (NC) the disease had to be stable for a period of at least six months. We have previously shown that patients who have NC for at least six months have the same survival and steroid hormone receptor characteristics as those with a PR [12]. For these reasons we believe that NC for 6 months is a 'response'.

Statistical methods

Time to progression and survival curves were calculated according to the method of Kaplan and Meier [13] and compared using the log rank test [14]. The Chi-square test was used to compare tumor response categories.

Other methods

Estrogen (ER) and progesterone receptors (PR) were assayed as previously described [15].

Results

Withdrawal response after adjuvant tamoxifen

One of 7 patients had a WR when adjuvant tamoxifen therapy was stopped at the time of relapse. All relapses were in soft tissues. The responder was a 70-year-old woman who relapsed on the chest wall and axillary lymph nodes 11 months after mastectomy; she had NC for 10 months and then progressed again; tumor steroid receptor status was not known.

Withdrawal response after first additive endocrine therapy for advanced breast cancer

Seventy-two patients were assessed for a WR after progressing on first line endocrine therapy for advanced disease. Of these, 65 were evaluable for response. Non-evaluability was due to the presence of sclerotic bone metastases or insufficient observations made. Five (8%) of the assessable patients had a partial response (PR) for 28+, 22, 8, 6 and 3 months, respectively, while a further 14 (21%) showed no change (NC) in tumor size for a period of more than six months. The median duration of PR was 8 months and for NC the median was 11 months.

The first endocrine therapy in all patients was either tamoxifen alone (64), tamoxifen in combination with

(3); one patient was assessed after withdrawal of megestrol acetate. One WR was seen after cessation of tamoxifen and medroxyprogesterone acetate (NC); the remainder of WRs were seen after cessation of tamoxifen treatment alone. The details of all the WRs seen after first endocrine therapy are shown in Table 3. Responses were mainly seen in advanced primary tumors and in skin or nodal metastases. However there were 2 responses in parenchymal lung metastases and 2 in bone metastases. ER status of the primary tumor was known in 17 responders and was positive in 15 (88%). PR status was known in 17 and was positive in 12 (71%).

Table 3. Characteristics of responders to withdrawal of first endocrine therapy.

Age (yrs)	Site(s) of disease	ER (f.mols/mg cyt. protein)	PR	Response to 1st ther.	Duration (mths)	Response to WR	Duration (mths)
77	Lung parenchyma	NK	NK	PR	32	PR	28+
54	ST, bone (NE), PE	38	300	NC	12	PR	22
47	ST, PE	12	242	PD	2	PR	08
79	ST	79	0	NC	8	PR	6
69	Adv. primary+ST	12	0	PR	35	PR	3
71	Lung parenchyma	118	231	PR	57	NC	40
74	ST	89	9	CR	27	NC	32
56	ST, bone (NE)	0	67	NE	14	NC	22
86	Adv. primary+ST	23	26	NC	8	NC	20
67	ST	50	10	NC	22	NC	15
77	Adv. primary	33	16	PR	16	NC	14
75	Adv. primary	20	19	NC	7	NC	12
85	Adv. primary+ST	88	670	NC	9	NC	11
58	Bone, PE	585	80	CR	27	NC	10
47	ST, bone	NK	NK	NE	–	NC	08
56	ST	0	0	PD	4	NC	08
61	ST	190	93	CR	55	NC	07
57	Adv. primary+ST	21	0	PD	4	NC	07
75	ST, bone (NE)	217	0	NE	19	NC	06

CR = Complete response; PR = Partial response; NC = No change for >6/12; PD = Progressive disease; ST = skin or node recurrences; PE = Pleural effusion; NE = Not evaluable; NK = Not known.

Relationship of response to WR to response to first endocrine therapy

WRs were seen after all types of response to first therapy. Eight complete responders to first therapy were assessed for WR; of whom 5 were evaluable: 3 of the evaluable patients had NC for 32, 10, and 7 months, respectively. Eighteen of 20 partial responders to first therapy were evaluable; there were two PRs of 28+ and 3 months, and 2 NC of 40 and 14 months. Twenty of 21 patients with NC on first therapy were evaluable; there were 2 PRs of 22 and 6 months and 4 NC of 20, 15, 12, and 11 months duration. All 13 patients with PD on first therapy were evaluable; there was one PR of 8 months and 2 NC of 8 and 6 months, respectively. Three NC withdrawal responses of 22, 8 and 6 months duration were seen in 10 patients not evaluable for first endocrine therapy. The proportion of WR in each group were not significantly different.

In 9 patients the duration of the WR was longer than the duration of the response to first therapy and in 9 the duration of the first response was longer. In one patient the duration of first response was not clear because of missing evaluations. There was no significant correlation between the duration of response to first therapy and duration of the WR.

Comparison of WR with response to immediate second additive endocrine therapy after failure of first endocrine therapy

During the period that the above 72 patients were assessed for WR after progression on first endocrine therapy for advanced disease, a further 196 patients were treated with second additive endocrine therapy immediately after progression on first line treatment. There was no significant difference between the ER and PR receptor distribution of the tumors from the two groups but the second additive therapy group were significantly more likely to have distant metastases (Table 1). Although the two groups are not strictly comparable because they are selected, it is of interest that the overall response to second additive endocrine therapy was significantly greater in the group not assessed for WR (response rates 30% vs. 35% [CR + PR + NC], $p = 0.03$ (Table 4). No CRs were seen after assessment of WR but there were 6 (4%) with additive second endocrine therapy. However, there were no significant differences in time to progression or duration of response between the two groups. The survival from the start of second therapy was significantly poorer in the additive group, which is presumably a reflection of their more extensive disease.

Table 4. Response rate and response duration to WR, compared with second additive endocrine therapy.

Second therapy	Withdrawal	(%)	Additive endocrine	(%)	p
n	72		194		
CR	0	(0)	6	(4)	
PR	5	(8)	26	(19)	
NC	14	(22)	17	(12)	0.03
PD	46	(70)	91	(65)	
NE	7		54		
Surv. from 2nd therapy (mths)	25		16		0.004
Time to progression (mths)	3		3		NS
Duration of response (mths)	10		10		NS

Endocrine therapy after assessment of WR

Fifty-three of the 72 patients assessed for WR went on to have further endocrine therapy. Forty-two of the 53 were assessable for response. The reasons for failure to give further additive therapy were death of the patient (n = 9), treatment with chemotherapy (n = 9) and a

continuing WR one patient with lung metastases after 28+ months of follow up. Eighteen (42%) of patients responded to second additive endocrine therapy (6 PR and 12 NC). Ten patients who had a WR were assessable and eight (80%) responded to further endocrine therapy. Six of these 8 had responded to first additive endocrine therapy. Thirty-one patients did not have a WR and of these 10 (32%) responded to further endocrine therapy. Nine of these 10 had responded to first additive therapy. The median duration of response to third endocrine therapy was 12 months. A flow chart of the outcome of all of this group of patients is shown in Fig. 1.

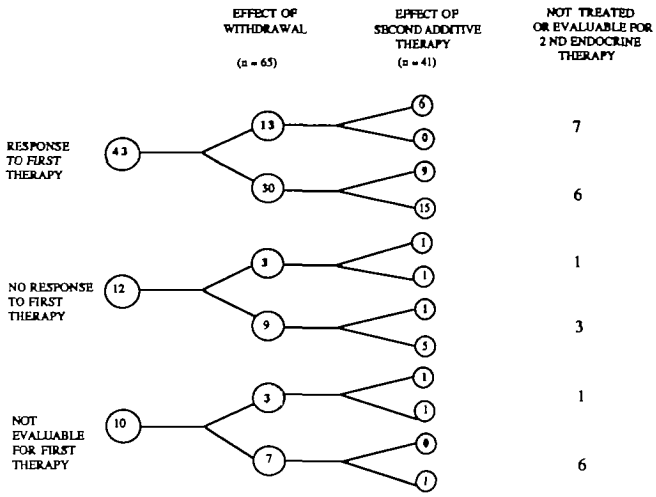

Fig. 1. Overview of responses to first additive therapy, to withdrawal of tamoxifen, and to second additive therapy. Upper figures = ○ responders; Lower figures = ○ progressors.

There was a small group of 6 patients who were assessable for all three therapies and who responded to all three. Two of these are of particular interest since they had a second response to tamoxifen after a period of no treatment during which a WR was assessed. Both had slowly progressive chest wall disease which responded completely to the first treatment with tamoxifen. After progression and cessation of tamoxifen, WRs were seen (NC) for 11 and 20 months, respectively; both patients then went on to have another response to tamoxifen when it was reintroduced at the same dosage of 20 mg per day but did no respond to a second withdrawal of tamoxifen.

Withdrawal responses after second or third line endocrine therapy

Eighteen patients were assessed for WRs after cessation of second therapy and 3 after withdrawal of third therapy. There were 4 NC (22%) for 14, 14, 9, and 7 months after withdrawal of second line additive endocrine therapy but no responses were seen after withdrawal of third line endocrine therapy. Three stabilisations were seen after withdrawal of norethisterone acetate. The durations of responses after cessation of norethisterone acetate were 14, 14, and 7 months, respectively. A fourth patient was treated with 20 mg of tamoxifen per day as first therapy and had a complete response for 12 months; the dose was increased to 40 mg per day at progression and she had a further period of no change for 26 months. Tamoxifen was then withdrawn and she had a WR of 9 months duration.

Discussion

This study confirms that WRs are detectable after cessation of additive therapy with tamoxifen used as first line endocrine therapy for advanced breast cancer [5, 6–10]. There is only a single previous report of WR after no initial response to tamoxifen [5] and we report 3 further examples. In addition we report for the first time WR after norethisterone acetate and after cessation of second line endocrine therapy.

Five of the 24 WRs reported here were partial remissions and the remainder were in the 'no change' category. Although 'no change' is regarded by international criteria as a 'response' [11] a question remains as to whether this is justifiable. Since short periods of NC may be difficult to distinguish from slowly progressive disease we have taken a minimum period of six months of NC for a patient to qualify for this category of response. In previous studies we and others [12, 16, 17] have shown that, if this period is taken, the patients with NC have similar durations of response and survival to those with an objective PR and their tumours have similar ER and PR positivity [12]. All 19 NC had signs of objective progression on additive therapy before it was stopped and the period of NC lasted from 6 to 40 months.

Incidence of withdrawal response

Because of patient selection for assessment of WR this study gives only a broad indication of the true incidence of WR in a population of women failing first line endocrine therapy for advanced disease. In this regard the paper by Canney et al. [9] is important since it is the only one, to our knowledge, where consecutive patients were assessed. They detected 6 responses (9.8%; 1 CR, 4 PRs and 1 NC) in 61 patients studied; all responses were in soft tissue disease and occurred in patients who had previously responded to first endocrine therapy. This figure is lower than the overall WR rate after first endocrine therapy of 30% reported here. However our rate falls to 6.2% (19/308) when the total number of evaluable patients for all types of second therapy in the whole study population is considered as the denominator. It is possible that this figure would be higher if all of our patients, particularly those treated with second line additive endocrine therapy, were assessed for WR.

In the earlier reports of WRs following cessation of treatments with estrogens and androgens WRs were re-

Table 5. Withdrawal responses after first endocrine therapy.

Additive treatment	WR	Total assessed	(%)	Total study population	(%)	Reference
Androgens	7	11	(64)	Not known	–	Escher 1949 [1]
Estrogens	9	14	(64)	100	(9.0)	Huseby 1954 [2]
Andr. & estr.	15	88	(17)	674	(2.2)[a]	Kaufman 1961 [4]
Estrogens	7	22	(32)	97	(7.2)	Baker 1972 [19]
Estrogens	8	32	(25)	83	(9.6)	Nesto 1976 [18]
Tamoxifen	6	61	(10)	61	(9.8)	Canney 1987 [9]
Tamoxifen	19	65	(29)	308	(6.2)[a]	This study

[a] Includes additional WR seen after no response to first therapy.

ported only in a subset of the total study population (Table 5). For example Huseby [2] reported WR after cessation of estrogens in 9 of 14 initial responders to estrogen but did not report assessment of WR in the remaining 86 patients in the total study population of 100 patients. When these are included in the analysis the overall rate of WR is 9%. We show in table 9 the proportion of WR in relation to total patient numbers in all the reported series. The overall absolute incidence of WR ranges from 3 to 10%. It is probable that 3% is an underestimate due to failure to assess all potential responders for withdrawal of additive endocrine therapy. As judged by the consecutive series of Canney et al. [9] the figure may be nearer 10% of the total number of patients who fail first line endocrine therapy.

Sites of response

Although WRs may be of value in approximately 10% of patients they represent a subgroup who tend to have soft tissue disease. This observation also applies to the old studies with estrogens and androgens as well as the more recent studies with tamoxifen. However, there are exceptions to these observations. At least 6 WRs after tamoxifen have been reported in lung metastases [5, 7, 8, 10] (and 2 in this study) and WRs after androgens and estrogens have been reported in bone [3, 18], liver [18] and brain secondaries [4].

Comparison of WR with response to second line additive endocrine therapy

It is well documented that a proportion of patients will have a response to a second additive endocrine therapy. In the group of patients who had a second additive therapy in this study 35% responded compared to the 30% response rate in the potentially more favourable group who were assessed for a withdrawal response. Despite there being CRs and more PRs in the additive group the median durations of response and the times to progression of the two groups were not significantly different. It has to be emphasised, however, that the two groups are not strictly comparable because those assessed for WR were highly selected. However eight of the 10 patients who responded to additive therapy after failing to have a WR had also responded to first line endocrine therapy suggesting that there is a small group of highly endocrine responsive tumours which will not respond to endocrine withdrawal. Conversely there is a small group of patients who appear to be highly responsive in that they responded to withdrawal as well as to two additive therapies (Fig. 1).

The duration of WR for all patients in this series ranged from 3–40 months. A similar wide range of durations was reported after WR to androgen and estrogen therapy. Kaufman and Escher [4] pointed out that the average duration of response to withdrawal is similar to that seen in responders to additive therapy. The same appears to be the case for tamoxifen; the median duration of response to withdrawal of tamoxifen in this study was 10 months and was identical to the duration of response in the group of patients given immediate additive therapy as second line treatment.

WRs occur in patients who have not responded to first endocrine therapy. This phenomenon was reported first by Kaufman and Escher [4]. They saw 6 WRs after failure of patients to respond to estrogens and 4 after failure to respond to androgens: (no denominator was given). Baker and Vaitkevicius [19] noted WRs in 2 of 11 (18%) non-responders to estrogens. Legault-Poisson et al. [5] were the first to report WRs after failure to respond to first line therapy with tamoxifen in a patient with lung metastases. The basal doubling time of her lung metastases as measured on serial chest x-rays was 120 days. After starting tamoxifen there was tumor growth stimulation with a reduction in the doubling time to 52 days. Treatment was discontinued after 110 days therapy and the patient remained off all therapy; a PR occurred which lasted for more than 6 months. In the study reported here we found 1 PR and 2 NC in 13 evaluable patients for WR who had objective progression on first line therapy with tamoxifen.

WRs after stopping progestogens have not been previously documented. Kaufman and Escher [4] reported no responses after 71 trials of withdrawal to unspecified progestogens. Here we report three WRs after stopping norethisterone acetate given as a second line therapy.

Mechanism of withdrawal response

The early studies with androgens and estrogens and the more recent studies with antiestrogens and progestogens indicate that WR is a definite phenomenon which occurs in a subgroup of prognostically favourable patients. It appears that similar proportions of patients with similar clinical characteristics respond to withdrawal of each type of therapy.

It is tempting to suggest that because withdrawal of treatment results in a change from tumor growth to tumor regression or stabilisation, that under certain circumstances additive endocrine therapy may stimulate tumor growth. Removal of the growth stimulus by stopping treatment then results in growth inhibition because of absence of a 'trophic' hormone.

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