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Factors Predicting the Response of Patients with Advanced Breast Cancer to Endocrine (Megace) Therapy

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Abstract—*We have treated* 238 *patients with advanced breast cancer with megestrol acetate (Megace, Bristol-Myers):* 221 *were assessable for response at* 6 *months by UICC criteria. Thirty-six* (16%) *patients responded,* 54 (25%) *were static and* 131 (59%) *progressed. Survival from the time of starting Megace calculated by log-rank analysis showed no significant difference in survival between patients showing response and static disease at* 6 *months. Patients with progression of disease within* 6 *months survived significantly shorter than patients who showed response or static disease at* 6 *months. Categorizing response at* 6 *months appeared to identify patients who had static disease of worthwhile duration.*

ER status of the primary tumour correlated significantly with survival from the time of commencing Megace. However, when Megace was used as a second-line hormone therapy the assessment of response or static disease on prior hormone therapy was a better predictor of the effect of Megace than ER status of the primary tumour.

INTRODUCTION

THE USE of progesterones in advanced breast cancer is still being evaluated. While the use of the progestogen megestrol acetate (Megace, Bristol-Myers) has been reported both in retrospective [1] and prospective [2] comparison with Tamoxifen as first-line therapy it has in the main been used as second-line therapy following Tamoxifen [3–6].

We have examined Megace in 238 patients with advanced breast cancer. We have used it either as first-line therapy in a small group of patients with oestrogen receptor (ER) negative tumours or, in the majority of patients, as second-line therapy after Tamoxifen. We have (1) assessed the effectiveness of Megace, (2) reviewed the role of previous response to therapy and of ER and progesterone receptor status of the primary tumour in predicting response to Megace as second-line hormone therapy and (3) assessed the best time to define the static disease category by comparing duration of static disease and subsequent survival with the survival of patients in the response category.

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PATIENTS AND METHODS

Two hundred and thirty-eight patients (median age 64 years: range 29–91) with histologically proven breast carcinoma have been treated with Megace, 160 mg b.d. All had either locally or systemically advanced disease. No patient had received systemic adjuvant therapy. Two hundred and twenty-one patients were assessable for response to Megace by UICC criteria [7] at 6 months. Of the 17 unassessable patients five were lost to follow-up, three were withdrawn from the study and nine had clinically unassessable disease.

Of the 221 patients, 189 received Megace as second-line therapy after Tamoxifen (175 patients), oophorectomy (9) or Zoladex (LHRH agonist) (5). Of the 175 Tamoxifen-treated patients only 163 were assessable for response to Tamoxifen. ER status was known in 93 of the 163 patients.

A small group of 32 patients with ER negative tumours received Megace as first-line therapy as a study because of the previously reported low response rate of ER negative tumours to Tamoxifen [8].

ER and progesterone receptor status were measured on specimens of primary tumour at the Tenovus Institute, Cardiff, by the dextran charcoal method [9]. Values below 5 fmol/mg cytosol protein were reported as negative.

Survival curves have been calculated from the time of starting Megace therapy using the log-rank method. Where other statistical tests have been used these are clearly indicated.

Assessment

Patients were assessed for response, static disease and progression according to UICC criteria [7]. As recommended by the British Breast Group (BBG) it is our policy to categorize patients as showing response or static disease at a minimum of 6 months after commencing hormone therapy. Patients are reviewed at least every 2 months during the first 6 months of therapy with a view to early change of therapy in patients showing progressive disease.

The clinical and radiological criteria for static disease are clearly defined by the UICC criteria but no indication is given as to how long patients should fulfil these criteria to be categorized as having static disease. We have assessed the value of categorizing patients for static disease at 6 months by comparing the survival of four groups of patients—patients who progressed within 2 months of commencing Megace therapy, patients with static disease at 2 months but with progression at 6 months, patients with static disease at 6 months and patients showing a response at 6 months.

RESULTS

Of the 221 patients assessable for response to Megace, 36 (16%) showed a response (2 CR + 34 PR), 54 (25%) remained static and 131 (59%) progressed. Response rates by major site(s) of disease are shown in Table 1. Time to progression for each group of patients is shown in Table 2.

Of the 131 patients with progressive disease, 51 progressed within 2 months of commencing Megace therapy while the remaining 80 patients fulfilled the criteria for static disease at 2 months but had progression of disease at 6 months. Survival from commencing Megace therapy was calculated for four groups of patients: (1) 36 patients showing a response at 6 months, (2) 54 patients with static disease at 6 months, (3) 80 patients with static disease at 2 months but with progression of disease at 6 months and (4) 51 patients with progression of disease within 2 months. There was a significant difference in survival between the four groups (Fig. 1) ($\chi^2 = 57.60$, 3 d.f.: $P < 0.001$: χ^2 for trend $= 44.72$, 1 d.f.: $P < 0.001$). There was no significant difference in survival between patients showing response or static disease at 6 months ($\chi^2 = 1.62$, 1 d.f.: $P > 0.2$). Patients with static disease at 6 months survived significantly longer than patients who fulfilled the static disease criteria at 2 months but had progression of disease at 6 months ($\chi^2 = 28.05$, 1 d.f.; $P < 0.001$). Patients fulfilling the static disease criteria at 2 months but with progressive disease at 6 months survived significantly longer than patients who had progressive disease within 2 months of commencing Megace therapy ($\chi^2 = 9.177$, 1 d.f.: $P < 0.01$).

ER status was known in 143 patients: 80 patients had ER positive tumours and 63 ER negative

Table 1. Major sites of disease and response rates (in 221 patients treated with Megace)

Major sites of disease	Number of patients	Percentage response rate
Local	84	46
Bone	72	43
Lung	23	30
Liver	5	20
Bone and liver	7	14
Bone and lung	24	37
Others	6	17

Table 2. Time to progression in 221 patients assessable for response to Megace

	Mean (months)	S.D.	Median (months)	(Range)
Response ($n = 36$)	15.4	+32.3	14	(6–42)
Static ($n = 54$)	13.3	+31.0	11.5	(6–44)
Progression ($n = 131$)	3.8	+3.9	3	(1–6)

Response vs. progression: $P < 0.01$.
Static vs. progression: $P < 0.01$.
Response vs. static: not significant.

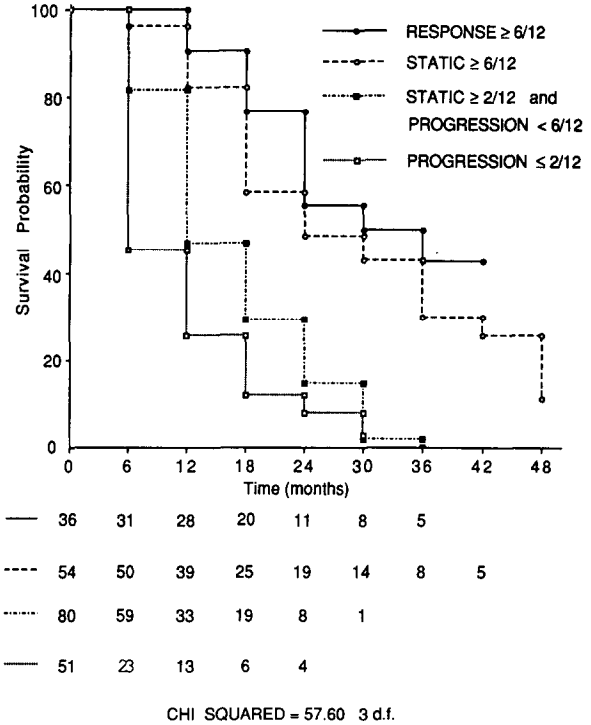

Fig. 1. Survival by response to Megace therapy (221 patients).

tumours. Progesterone receptor status was known in 98 patients: 45 patients had progesterone receptor positive tumours and 53 progesterone receptor negative tumours. Response rates by ER and progesterone receptor status are shown in Table 3. Neither ER nor progesterone receptor status correlated significantly with response + static disease at 6 months ($P > 0.10$ and $P > 0.50$ respectively; 1 d.f.: chi-squared test). Survival from the time of commencing Megace was significantly longer in the group of patients with ER positive tumours (Fig. 2). There was no significant difference in survival from commencing Megace between patients with progesterone receptor positive and negative tumours (Fig. 3).

Combined ER and progesterone receptor status was known in 98 patients who were divided into four groups: ER+/PR+, ER+/PR−, ER−/PR+ and ER−/PR−. Survival was similar between the four groups ($\chi^2 = 0.191$, 3 d.f.: $P > 0.9$). Of the 98 patients with combined receptor status 68 had received Tamoxifen as first-line therapy prior to Megace therapy: 21 patients had responded to Tamoxifen, nine had static disease at 6 months and 38 had progressed within 6 months. Response to Megace by combined receptor status in these 68 patients is shown in Table 4. All patients showing a response to second-line Megace had positive receptor status for ER or PR or both. No patient with ER negative/PR negative showed an objective response at 6 months although 4/15 patients had static disease at 6 months.

Megace as first-line endocrine therapy in ER negative tumours

Thirty-two patients with ER negative tumours received Megace as first-line therapy. Four patients had a response and five were static giving a response and static disease rate of 28%. Of the nine patients, eight had bone metastases as the major site of disease, the remaining patient having lung metastases.

Megace as second-line endocrine therapy

Fourteen patients received Megace after either surgical oophorectomy or treatment with the luteinizing hormone releasing hormone (LHRH) agonist Zoladex: nine had responded and five had progressed. On second-line Megace two patients showed a response, three were static and nine progressed.

Table 3. Response rates to Megace by ER and PR status

	ER status		PR status	
	(+) ($n = 80$) (%)	(−) ($n = 63$) (%)	(+) ($n = 45$) (%)	(−) ($n = 53$) (%)
Response	15 (19%)	6 (10%)	9 (20%)	3 (6%)
Static	18 (22%)	11 (17%)	5 (11%)	11 (20%)
Progression	47 (59%)	46 (73%)	31 (69%)	39 (74%)

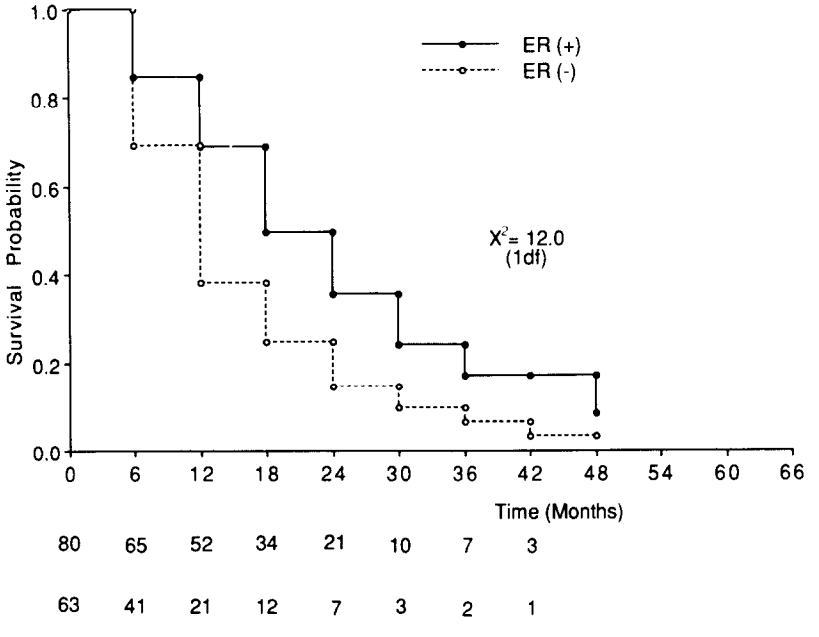

Fig. 2. Survival by ER status (143 patients).

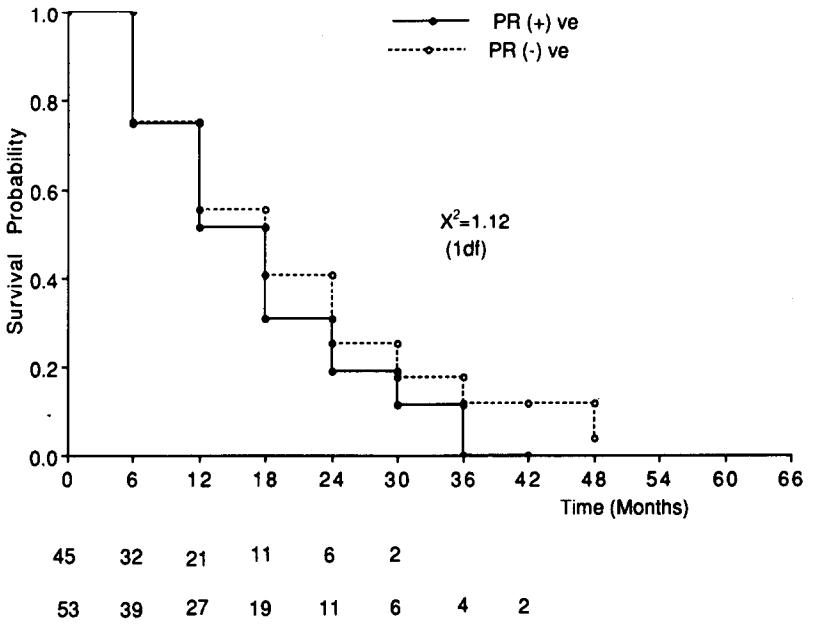

Fig. 3. Survival by PR status.

Table 4. Response to second line Megace by prior response to Tamoxifen and by ER and progesterone receptor status

	Response to Tamoxifen (n = 21)			Static disease on Tamoxifen (n = 9)			Progression on Tamoxifen (n = 38)		
Response to Megace	Resp. (n = 5)	Stat. (n = 5)	Prog. (n = 11)	Resp. (n = 2)	Stat. (n = 5)	Prog. (n = 2)	Resp. (n = 2)	Stat. (n = 4)	Prog. (n = 32)
ER/PR Status									
+/+	2		3	1	2	1	1	3	14
+/−	1	3	5	1	2	1			6
−/+	2		1				1		4
−/−		2	3		1			1	8

Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; Resp., response at 6 months' therapy; Stat., static disease at 6 months' therapy; Prog., progression of disease at 6 months' therapy.

One hundred and sixty-three patients were assessable for response both to Tamoxifen as first-line therapy and to Megace as second-line therapy. Survival curves calculated from the time of starting Megace according to response to Megace for this subgroup of patients are shown in Fig. 4. There was no significant difference in survival between patients showing a response or static disease at 6 months (χ^2 = 3.6, 1 d.f.: $P > 0.05$). Patients with progression of disease within 6 months survived for a significantly shorter time than patients showing a response or static disease at 6 months (χ^2 for trend = 52.3, 1 d.f.: $P < 0.001$).

Of these 163 patients, 26 (16%) showed a response, 45 (28%) remained static and 92 (56%) progressed on second-line Megace. Response to prior first-line Tamoxifen and subsequently to Megace are shown in Fig. 5. Response rates to Megace were similar whether patients had shown a response or static disease at 6 months on Tamoxifen; patients showing progression of disease on Tamoxifen had a significantly lower response and static disease rate on Megace (Fig. 5). Of 97 patients showing response or static disease at 6 months on Tamoxifen, 60 (62%) subsequently had non-progressive disease (response or static disease) at 6 months on Megace (Fig. 5): of 66 patients with progression of disease within 6 months of Tamoxifen therapy, 11 (17%) had non-progressive disease (response or stable disease) at 6 months on Megace (Fig. 5) ($P < 0.001$: chi-squared test).

Of the 163 patients assessable for response to first-line Tamoxifen and second-line Megace, 93 also had ER status measured. ER status of the

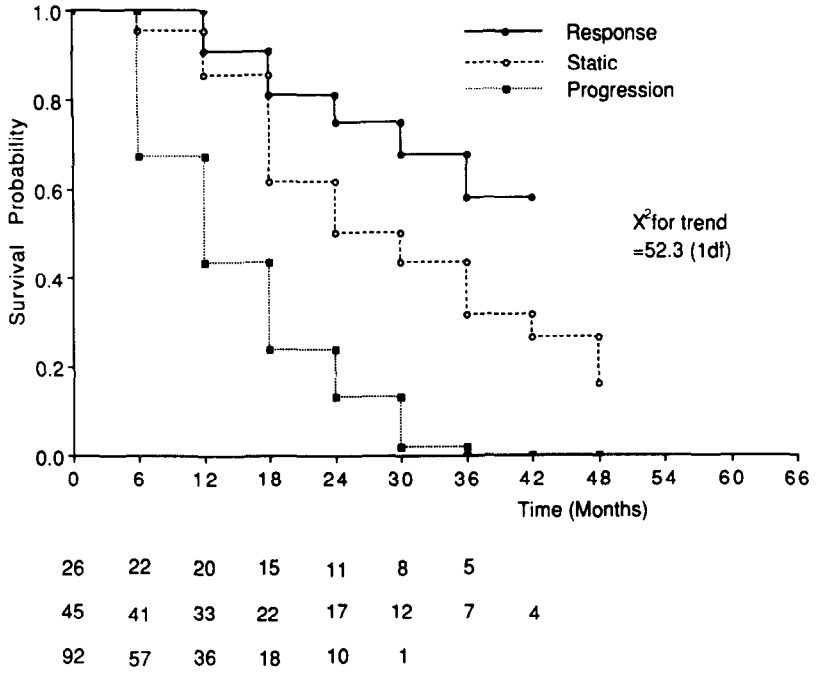

Fig. 4. Survival by response to Megace therapy in 163 patients who had previously received tamoxifen therapy.

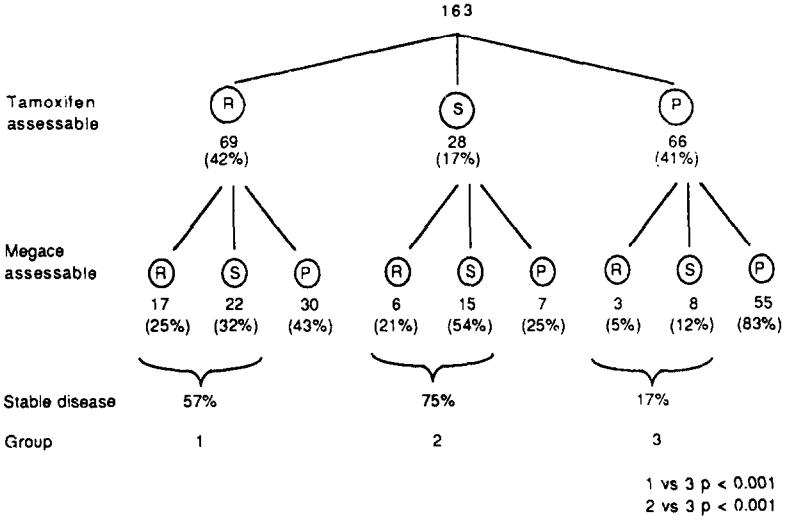

Fig. 5. Response to first-line Tamoxifen and second-line Megace therapy in 163 patients.

primary tumour was compared with previous response or static disease on Tamoxifen as predictors of response or static disease on Megace (Table 5). Response or static disease on prior Tamoxifen therapy was a significantly better predictor of response or static disease on Megace than ER status of the primary tumour.

Toxicity and side-effects of Megace were minimal. The most common side-effects were increased appetite and weight gain. In only 10 patients was the weight gain sufficient to require reduction in the dose of Megace from 160 mg b.d. to 80 mg b.d. In many patients increased appetite and weight gain were welcome results of Megace which is now being examined for its anti-cachectic effects. There were no cases of hypercalcaemia or cardiac failure due to fluid retention. Two patients developed deep venous thrombosis and in both cases Megace was stopped.

DISCUSSION

There are four categories of response by UICC criteria—complete response (CR), partial response (PR), static disease, and progression. Many studies report CR and PR together as one group. The place of static disease has remained uncertain. Studies

Table 5. ER status and first line Tamoxifen as predictors of response to second line Megace in 93 patients

	ER positive			*ER negative*		
	No. 60	Resp. + stat. on Megace	Prog. on Megace	No. 33	Resp. + stat. on Megace	Prog. on Megace
First line Tamoxifen (TAM)						
Resp. + stat.	33	21 (64%)	12 (36%)	14	7 (50%)	7 (50%)
Progression	27	3 (11%)	24 (89%)	19	3 (16%)	16 (84%)

Patients

ER positive: Resp. + stat. (TAM) vs. progression (TAM) as predictor of Resp. + static (Megace) $P = 0.0003$, Fisher's exact test.

ER negative: Resp. + stat. (TAM) vs. progression (TAM) as predictor of Resp. + static (Megace) $P = 0.0418$, Fisher's exact test.

TAM Resp. + static: ER positive vs. ER negative as predictor of Resp. + static (Megace) $P = 0.2909$, Fisher's exact test.

TAM progression: ER positive vs. ER negative as predictor of Resp. + static (Megace) $P = 0.4843$, Fisher's exact test.

reporting static disease at 2 months on endocrine therapy have reported no significant difference in mean duration of response [3, 4, 10] or survival [3, 10] between patients with responding (PR) and static disease while others have reported that patients with static disease at 2 months survived significantly shorter than patients who showed an objective response [5]. In all these studies patients with static disease at 2 months survived significantly longer than patients with progression of disease within 2 months of commencing therapy [3, 5, 10].

Howell *et al.* have tried to establish how long a patient needs to maintain static disease to have statistically no difference in survival from patients with partial response and reported that the minimum time for endocrine therapy was 5 months [11]. Our results with Megace therapy assessed after 6 months support these conclusions as patients with static disease at 6 months had similar survival to patients showing objective response at 6 months and significant longer survival than patients fulfilling the UICC criteria for static disease at 2 months but with progression of disease at 6 months. The period of 6 months would appear to identify patients with static disease of worthwhile duration.

Patients assessed at 2 months as fulfilling the UICC criteria for static disease but with progression of disease at 6 months survived significantly longer than patients with progression of disease within 2 months of commencing therapy in keeping with previous reports [3, 5, 10]. However, the survival curve of these two groups of patients come together with time (i.e. at 30 months) while the survival curve of patients with static disease at 6 months continues to diverge with time from patients with static disease at 2 months but with progression of disease at 6 months (Fig. 1). Disease assessed as fulfilling the criteria for static disease at 2 months but showing progression at 6 months probably reflects slowly progressive disease which at 2 months was undetected by the UICC assessment carried out.

Of 93 patients showing an objective response or static disease after 6 months on Tamoxifen as a first-line endocrine therapy, 60 (62%) subsequently showed a response or static disease after 6 months on Megace; only 17% of 66 patients who progressed within 6 months on Tamoxifen showed a response or static disease on Megace ($P < 0.001$). Blackledge *et al.* reported on 37 heavily pretreated patients 25% of whom showed an objective response with a further 38% of patients showing static disease on Megace therapy [6]. This combined response and static disease rate of 63% on Megace following progression on prior hormone therapy is similar to our own reported combined response and static disease rate of 62%. Ross *et al.* reported on 48 patients treated by megestrol acetate all of whom had been treated initially by Tamoxifen; 45 patients had responded to Tamoxifen therapy [3]. Fifteen patients (31%) achieved a partial response and a further 16 patients (33%) were static on megestrol acetate, giving a combined response and static disease rate of 64%. Ross *et al.*, however, treated only three patients who had progressed on initial Tamoxifen therapy: we have shown that in this subgroup of patients there is a poor response (17% combined response and static disease rate) to megestrol acetate. We are unable to recommend Megace in patients who have progressed within 6 months on prior Tamoxifen therapy.

ER status correlated significantly with survival (Fig. 2) but not with response (Table 3). We have shown that response or static disease at 6 months on Tamoxifen was statistically a better predictor than ER status on the primary tumour of response or static disease at 6 months on Megace (Table 5). It would appear that when considering second-line hormone therapy the previous effect of first-line hormone therapy is a more direct and accurate

means of identifying patients with hormone sensitive tumours than ER status, which is an indirect measure of hormone sensitivity. The progesterone receptor status of the primary tumour did not correlate either with response rate (Table 3) or survival (Fig. 3) despite the fact that Megace is a synthetic progestogen. Gregory *et al.* previously reported no correlation between progesterone receptor status and response to Megace although they did find a correlation with ER status [5].

Combining ER and progesterone receptor did not improve the correlation of ER alone with survival although no patient with an ER negative, progesterone receptor negative tumour responded to second-line Megace. This supports the observation of Van Roenn *et al.* who also noted objective response to second line Megace only in patients with ER positive and/or progesterone receptor positive tumours [1]. However, of 163 patients who received Tamoxifen followed by Megace only 68 had both ER and progesterone receptor status measured. Of these 68 patients, 15 (22%) were ER negative and progesterone receptor negative, of whom 4/15 (26.6%) did show a worthwhile period of static disease. Previous non-progression (response and static) or progression on Tamoxifen appears a better predictor of non-progression (response and static) after 6 months on Megace (62% and 17% respectively) than either ER alone or combined ER and progesterone receptor status.

The major site of disease appeared to influence the response rate to Megace (Table 2). As expected the response rates were highest for local disease and bone metastases and lowest for visceral metastases. Series reporting treatment with megestrol acetate have however been conflicting, one reporting a higher response rate in bone [3] and another in viscera [4].

Tamoxifen remains our first-line endocrine therapy in post menopausal women with advanced breast cancer, since even in patients with ER negative tumours Megace does not appear to hold any advantage over Tamoxifen as first-line therapy. Patients with response or static disease at 6 months on Tamoxifen as first-line therapy are likely to benefit from further hormone therapy—62% having response or static disease at 6 months on second line Megace therapy.

Six months would appear an acceptable time to categorize response by UICC criteria—especially the static disease category. It allows identification of patients with static disease of worthwhile duration who have a survival similar to patients showing response at 6 months. This should provide a basis for combining response and static disease thereby leaving patients in one of two groups—non-progressive (response and static disease) or progressive disease which would simplify both patient treatment and assessment of the efficacy of therapeutic regimens.

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