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ORIGINAL ARTICLE

Duration of remission to ICI 182,780 compared to megestrol acetate in tamoxifen resistant breast cancer

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SUMMARY. Recently we reported that treatment with the specific (pure) antioestrogen, ICI 182,780, in 19 patients with advanced breast cancer resistant to tamoxifen resulted in a high response rate and a long median duration of remission (> 22 months). In order to assess the relative value of ICI 182,780 in this clinical situation we have compared its activity with that of megestrol acetate, the standard second-line endocrine therapy in a group of similarly selected patients.

Each ICI 182,780 treated patient was matched with three patients who received megestrol acetate ($n = 57$). Both groups were previously treated with tamoxifen. Patients were matched for age, site of metastases, prior tamoxifen therapy (for adjuvant or advanced disease) and therapeutic response to tamoxifen where given for advanced disease and therapeutic response to second-line therapy (i.e. ICI 182,780 or megestrol acetate). The duration of remission (PR or SD) was significantly longer for patients treated with ICI 182,780 compared to megestrol acetate (26 months and 14 months respectively, $P = 0.04$). These findings support further clinical comparison between ICI 182,780 and established endocrine agents.

INTRODUCTION

The antioestrogen, tamoxifen, has become established as the initial endocrine therapy of choice in postmenopausal patients with advanced breast cancer. In some patients the cancer shows primary resistance whilst in the remainder, although initially responsive, the cancer eventually develops acquired resistance to tamoxifen. The choices for further endocrine manipulation most commonly are either a synthetic progestin (e.g. megestrol acetate, medroxy-progesterone acetate) or an aromatase inhibitor (e.g. aminoglutethimide, 4-hydroxy androstenedione, anastrozole or letrozole).

We have recently reported a phase II study of the new specific antioestrogen ICI 182,780 used as second-line endocrine therapy in 19 patients with tamoxifen-resistant advanced breast cancer.[1,2] Rather surprisingly for a second antioestrogen, not only did most patients respond but the median duration of remission (> 22 months) was longer than expected for a second-line endocrine agent such as megestrol acetate[3] or aminoglutethimide.[4–7]

The Notingham Breast Unit previously reported on a large series of patients with advanced breast cancer treated with megestrol acetate. Interestingly, in patients who had shown disease remission (stable disease or objective response) on tamoxifen, 62% subsequently showed a remission to megestrol acetate – a figure similar to that reported for ICI 182,780. However, the median duration of remission in patients treated with megestrol acetate was only 15 months.[3] We therefore decided to compare the duration of remission to ICI 182,780 versus megestrol acetate in matched tamoxifen-resistant patients. For this comparative study we identified patients from the Nottingham and Manchester units treated with megestrol acetate as second-line endocrine therapy after tamoxifen and selected a group of patients with similar clinical characteristics to those reported in our recent phase II study of ICI 182,780.

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PATIENTS AND METHODS

A detailed description of 19 patients treated with ICI 182,780 has been published.[1,2] All were postmenopausal, less than 81 years and had advanced histologically proven breast cancer. The patients were selected as having endocrine responsive tumours based on their previous treatment with tamoxifen:

(1) If they had been treated with tamoxifen as adjuvant therapy for more than 2 years before disease relapse; or

(2) If they had been treated with tamoxifen for advanced disease and had shown a complete or partial remission, or static disease by International Union Against Cancer (UICC) criteria[8] for at least 6 months[3,9] and subsequently progressed.

For each of the 19 patients treated with ICI 182,780 we matched three control patients who had received megestrol acetate. Patients were matched on the basis of age, site of disease, response to prior tamoxifen therapy and response to second-line therapy (i.e. ICI 182,780 or megestrol acetate) (Table). It was not possible to match for oestrogen receptor (ER) or progesterone receptor status owing to lack of data concerning tumour hormone receptor content on a large number of the historical control group of patients.

The matching appeared to be satisfactory on all criteria (Table). Matching for the main sites of disease (i.e. bone, lung and viscera) was perfect while for age of patient (± 5 years) it was good. Matching for prior therapeutic response was perfect in 10 patients who received tamoxifen for advanced disease. The matched patients who received megestrol acetate were treated initially with megestrol acetate up to 12 years ago. The routine use of tamoxifen as an adjuvant therapy prior to this time was not standard therapy. Matching the nine ICI 182,780 treated patients who more recently received tamoxifen as adjuvant therapy with a similar group of megestrol acetate treated patients proved more difficult. In order to weigh the matching in favour of the megestrol acetate treated group we matched megestrol acetate treated patients whose tumours had shown disease remission on tamoxifen for advanced disease (i.e. endocrine sensitive) as controls for the ICI 182,780 treated patients who received tamoxifen as adjuvant therapy: it is more difficult to be certain that a tumour is responsive to adjuvant therapy. The overall rate of disease remission (objective response + static disease) to second-line therapy was 13 out of 19 (69%) for the ICI 182,780 treated patients compared to 36 out of 57 (63%) for megestrol acetate treated patients.

The ICI 182,780 and the megestrol acetate treated patients were followed up regularly at similar intervals in the same outpatient clinics in each of the two centres (Nottingham and Manchester).

Table Matching megestrol acetate treated patients with ICI 182,780 treated patients

	ICI 182,780 ($n = 19$)	Megestrol acetate ($n = 57$)
Site of metastases matched	19	57
Age (± 5 years)	13	39
(± 10 years)	3	9
(> 10 years)	3	9
Prior tamoxifen therapy		
Advanced disease		
– therapeutic remission matched	10	30
Adjuvant therapy – matched	9	10
		17*
Second-line therapy		
Therapeutic remission (OR + SD)	13	36
Progressive disease	6	21

*It was not possible to match megestrol acetate treated patients for prior adjuvant tamoxifen therapy ($n = 17$). We matched for tamoxifen therapy in advanced disease where patients had shown disease remission (objective response [$n = 13$] and static disease [$n = 4$].

STATISTICS

Duration of remission and overall survival between the two groups was compared using the Lee-Desu statistic – a modification of Gehan's generalized Wilcoxon test. The analysis was carried out using SPSS for Windows (SPSS UK Ltd).

RESULTS

The disease stabilization rate (objective response + static disease) was 13 out of 19 (69%) for ICI 182,780 and 36 out of 57 (63%) for megestrol acetate. The duration of remission was significantly longer in the group of patients treated with ICI 182,780 (26 months) compared to megestrol acetate (14 months) (Fig. 1, $P = 0.04$). The survival curves diverge in a similar pattern to the duration of remission but as yet there is no significant difference in survivial between these two groups, although it should be emphasised that the number of patients in each group is small (Fig. 2).

Ten of the ICI 182,780 treated patients have gone on to receive megestrol acetate as third-line endocrine therapy. None showed an objective response. Nine patients progressed within 6 months of starting megestrol acetate and the remaining patient had static disease at 6 months.

DISCUSSION

The development of specific antioestrogens has resulted in a new class of endocrine agents for the treatment of breast cancer. Experimental work using either the lead compound ICI 164,384, or ICI 182,780, which has greater affinity for the ER, suggested that these compounds were more potent than tamoxifen at inhibiting oestradiol stimulation of hormone responsive breast cancer cell lines.[10,11] It was recently reported that for endocrine naive MCF-7 xenografts grown in nude mice the time to progression using ICI 182,780 was double that obtained with tamoxifen (200 and 104 days respectively).[12] Other studies have also shown that even where breast cancer cell lines have developed acquired resistant to tamoxifen they may still be sensitive to the pure antioestrogens.[13]

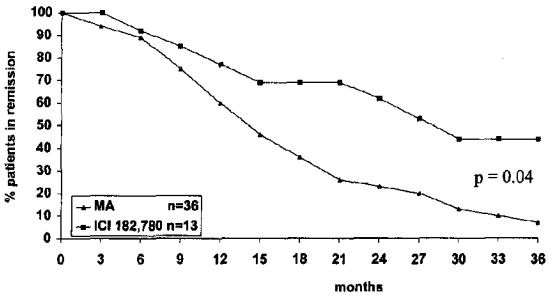

Fig. 1 DoR in patients achieving OR or SD on MA or ICI 182,780. MA = megestrol acetate, DoR = duration of remission, OR = objective response, SD = static disease.

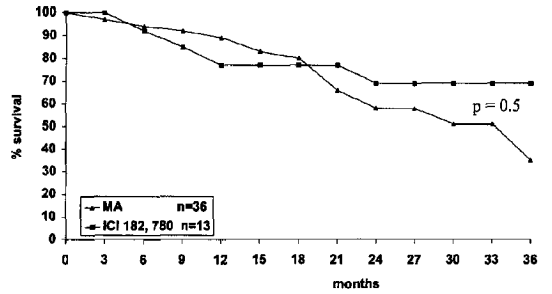

Fig. 2 Survival of patients achieving OR or SD on MA or ICI 182,780. MA = megestrol acetate, OR = objective response, SD = static disease.

An initial phase I study using ICI 182,780 reported biological evidence of antioestrogenic effects on endocrine naive human breast cancers in vivo even after only 7 days treatment. Furthermore, in contrast to tamoxifen, there was no evidence of agonist activity.[14] A subsequent phase II study showed that ICI 182,780 produces responses in patients with tamoxifen resistant breast cancer.[1] These clinical studies matched the preclinical experimental data and confirmed that ICI 182,780 appeared to act as a specific antioestrogen without agonistic activity and while human breast cancers might develop tamoxifen resistance this should not be equated to resistance to pure antioestrogens. These results with ICI 182,780 in tamoxifen resistant breast cancer are in contrast to other new antioestrogens, such as toremifene and idoxifene.[15]

In patients with tamoxifen resistant breast cancer it will require a randomized study to determine whether the response rate is significantly different for ICI 182;780 compared to other endocrine agents as second-line therapy. Nevertheless, by matching the megestrol acetate treated controls closely to the ICI 182,780 treated patient we have obtained two groups with similar characteristics in relation to the patient (age), the disease (site of metastases), previous endocrine therapy (tamoxifen) and endocrine sensitivity (response to first and second-line therapies). Comparison of duration of remission (Fig. 1) suggested that ICI 182,780 may maintain breast tumours in remission for significantly longer than megestrol acetate. The majority of randomized clinical studies have reported therapeutic equivalence of tamoxifen and megestrol acetate as first-line endocrine therapy[16–18] suggesting indirectly that ICI 182,780 may be a therapeutic advance over not only megestrol acetate but also current antioestrogenic agents. The only direct comparison on remission times between the pure antioestrogens and tamoxifen is the experimental data from breast cancer xenograft studies. Remission durations in mice treated with ICI 182,780 were more than twice as long as mice treated with tamoxifen.[12] It is of great interest that in both the experimental and the clinical studies the duration of remission to ICI 182,780 has been twice that seen with currently available endocrine agents (tamoxifen and megestrol acetate respectively). Since the first prospective randomized clinical trial comparing ICI 182,780 with an established endocrine agent has yet to start it will be at least 5 years before a comparison can be made of duration of remission. The matched comparison presented in this paper may therefore be an important early identification of a potential clinical benefit of ICI 182,780 over other endocrine agents.

None of the 10 patients who developed acquired resistance to ICI 182,780 subsequently showed an objective response to metestrol acetate as third-line therapy. This particular group of patients did have endocrine sensitive tumours (to first and second-line antioestrogen therapies). Therefore, while the number of patients ($n = 10$) was small a proportion might have been expected to show an objective response to a third-line endocrine agent. Clearly the confidence limits must be large with such a small number of patients but this early finding raises the hypothesis as to whether acquired resistance to ICI 182,780 may be equivalent to developing an endocrine resistant phenotype. This finding also needs to be addressed in a larger study.

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