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Papers

A Randomised Study to Compare the Effect of the Luteinising Hormone Releasing Hormone (LHRH) Analogue Goserelin With or Without Tamoxifen in Pre- and Perimenopausal Patients With Advanced Breast Cancer

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The use of goserelin with or without tamoxifen was investigated in a randomised multicentre study involving 318 pre- and perimenopausal advanced breast cancer patients. With a median follow-up of 93 weeks, 31% of goserelin-treated patients had objective responses (UICC criteria) compared with 38% of goserelin plus tamoxifen-treated patients ($P = 0.24$). There was a modest benefit in favour of combination therapy in time to progression ($P = 0.03$) but not in survival ($P = 0.25$). Median follow-up for survival was 117.5 weeks. Median times for disease progression and survival were 23 and 127 weeks in the goserelin alone group and 28 and 140 weeks in the combination group, respectively. In 115 patients with skeletal metastases only, significant differences in favour of combination therapy were seen in response rate, time to progression and survival. Both treatments were well tolerated and no additional safety issues were associated with combination therapy.

Key words: breast cancer, goserelin, randomised trial, tamoxifen, endocrine therapy
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INTRODUCTION

FOR NEARLY a century, oophorectomy has been used as an endocrine manipulation to produce regression of breast cancer in premenopausal women [1–4]. In recent years, the anti-oestrogen tamoxifen has been established as an effective endocrine manipulation for the treatment of breast cancer in both pre- and postmenopausal women. Studies directly comparing tamoxifen with oophorectomy for the treatment of premenopausal advanced breast cancer showed comparable results in the management of the disease [5, 6]. More recently, the luteinising hormone releasing hormone (LHRH) agonist goserelin (Zoladex) has been shown to suppress ovarian function and produce clinical responses in pre- and perimenopausal women with advanced breast cancer, which are comparable to those previously reported for other hormonal therapies [7–10].

Suppression of ovarian production of oestradiol via goserelin, combined with the antagonism of oestradiol at target tumour tissue level plus the additional non-oestradiol mediated effects of tamoxifen [11], may be anticipated to provide additional control of tumour growth compared to that associated with suppression of ovarian oestrogen production alone. It has been demonstrated that there is no endocrinological antagonism associated with the use of goserelin plus tamoxifen in pre- and perimenopausal women with breast cancer [12]. A preliminary study reported an increase in time to disease progression and a prolongation of survival in patients receiving goserelin plus tamoxifen when compared to historical controls treated with goserelin alone [13].

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The potential advantages of the combination of the LHRH analogue goserelin plus the anti-oestrogen tamoxifen compared to goserelin alone has been investigated in a randomised multicentre study in pre- and perimenopausal patients with advanced breast cancer.

PATIENTS AND METHODS

Between 1988 and 1991, 318 pre- and perimenopausal patients with histologically confirmed locally advanced (stage III) or metastatic (stage IV) breast cancer were randomised to receive goserelin or the combination of goserelin plus tamoxifen (Nolvadex). Patients randomised to receive goserelin alone were to have tamoxifen added following first disease progression. Exclusion criteria for entry into the study were adjuvant hormone, anti-hormone or adjuvant cytotoxic therapy within the previous 6 months, concurrent invasive malignancy, pre-existing sex endocrine disorder and pregnancy. Postmenopausal status was defined as last menstrual period more than 1 year ago. Informed consent was obtained from all patients participating in the study and local ethics committee approval was obtained from each of the centres.

Treatment

Goserelin was administered as a 3.6-mg depot injected subcutaneously into the anterior abdominal wall once every 28 days by a prefilled applicator. Tamoxifen was administered as a 40-mg dose taken as 2 × 20-mg tablets once daily.

Clinical trial

All patients were assessed every 3 months. Assessment of objective clinical response was based on UICC criteria [14] and was graded as one of the following: complete objective regression (CR), partial objective regression (PR), no change (NC), progression (PROG). An objective response was defined as either CR or PR. Objective clinical assessments included measurement of the local lesion, chest X-ray, limited skeletal survey and isotope bone scan, as appropriate.

Specific questions on tolerability were asked at each follow-up visit to assess the effect of treatment on hot flushes, vaginal discharge, vaginal soreness and sexual activity.

All adverse events occurring during treatment were recorded; routine haematology and clinical chemistry measurements were made at follow-up visits.

The oestrogen and progesterone receptor status of the primary tumour, measured according to local practice, was recorded where known.

Statistical methods

All analyses were completed on an intention-to-treat basis, i.e. all patients were grouped according to randomised therapy and no patients were excluded. All available data up to and including 31 October 1992 (up to 31 January 1994 for survival) were included. Comparisons were made between the two treatment modalities.

Kaplan–Meier survival curves for the time to progression and overall survival were calculated for each treatment modality from the time of start of therapy. The estimates were compared, using either the log-rank test or the Wilcoxon test, which ever was most appropriate judged on the shape of the survival curve. The proportion of patients responding to treatment, up to their first progression, was calculated for each treatment modality and compared using a two-sided Mantel–Haenszel χ^2 test.

The effects of the following prognostic factors on the efficacy endpoints were assessed: age, disease-free interval, previous adjuvant therapy, previous cytotoxic therapy, hormone receptor [oestrogen receptor (ER) and/or progesterone receptor (PR)] status of the primary tumour, ER status of the primary tumour and site of disease at entry. The aim of these analyses was to see if there were particular sub-groups of patients within which the response to each of the treatments was different. The study was not designed to look at the effect of these prognostic factors within each treatment group.

A separate analysis of patients with skeletal metastases only, at entry to the study, was also performed using the statistical methods described above.

RESULTS

Demographic details

A total of 318 patients were recruited; 159 patients were randomised to each treatment group. Treatment groups were comparable for menopausal status, age, weight, disease-free interval, hormone receptor status (ER and/or PR) and grading of the primary tumour, and site of disease at entry (Table 1). An 8% higher proportion of patients in the combination group had advanced disease at first diagnosis while 8% more patients in the goserelin alone group had previously received cytotoxic adjuvant therapy. Of the 159 patients randomised to receive goserelin alone, only 71 patients had tamoxifen added after first disease progression. The reasons for patients not receiving tamoxifen after disease progression were rapidly progressing disease/other treatment required (43 patients), lost to follow-up/refused tamoxifen (7 patients), death (4 patients), protocol violation/deviation (3 patients), received wrong treatment (2 patients), adverse event (1 patient) and other (18 patients). 10 patients had not progressed at the time of the analysis.

At entry to the study, 115 patients had skeletal metastases only, of which 62 patients were in the goserelin alone group and 53 patients were in the combination group. Treatment groups were also comparable with regard to demographic characteristics for this sub-group of patients, although this was not a prospective stratification factor (Table 2).

Efficacy results

The objective response, time to progression and overall survival are shown in Table 3.

At a median follow-up of 93 weeks, 247 patients (78%) had had progression of disease at the time of the analysis; 130 patients in the goserelin alone group and 117 patients in the combination group. For the 71 patients who had not had disease recurrence at the time of the analysis, the date last seen without disease progression was used in the analysis. The two Kaplan–Meier curves, compared using the log-rank test, are shown in Figure 1.

Of the 71 patients who had tamoxifen added at first disease progression, 13 patients (18%) had an objective response (CR + PR) to treatment and 29 patients (41%) showed stable disease. The median time from the addition of tamoxifen to second disease progression was 20 weeks (range 2–148).

198 patients (62%) had died at the time of the analysis; 99 patients in each of the treatment groups. The majority of these deaths were due to breast cancer alone; 89 patients (90%) in the goserelin alone group and 92 patients (93%) in the combination group. The Kaplan–Meier survival curves, compared using the Wilcoxon test, are shown in Figure 2.

Table 1. Demographic details

	Randomised treatment	
	Goserelin alone (n = 159)	Goserelin plus tamoxifen (n = 159)
Premenopausal, n (%)	151 (95)	148 (93)
Age, years		
Mean (range)	41 (24–55)	42 (28–55)
Weight, kg		
Median (range)	63 (43–114)	63 (42–103)
Advanced disease at first diagnosis, n (%)	18 (11)	31 (19)
Previous adjuvant therapy, n (%)*	84 (53)	76 (48)
Tamoxifen	4 (3)	4 (3)
Cytotoxics	52 (33)	39 (25)
Radiotherapy	45 (28)	44 (28)
Oestrogen receptor (ER) status, n (%)		
Positive	90 (57)	91 (57)
Negative	28 (18)	36 (23)
Unknown	41 (26)	32 (20)
Grading of primary tumour, n (%)		
High	10 (6)	7 (4)
Medium	54 (32)	58 (36)
Low	42 (26)	37 (23)
Not assessed	53 (33)	57 (36)
Site of disease, n (%)		
Local only	24 (15)	25 (16)
Visceral only	19 (12)	20 (13)
Skeletal only	62 (39)	53 (33)
Multiple	49 (31)	57 (36)
Not assessed/not evaluable	5 (3)	4 (3)
DFI (months)		
Median (range)†	24 (4–170)	27 (4–120)

*Some patients appear in more than one category. †Disease-free interval (DFI) excluding patients who had advanced disease at first diagnosis.

Table 2. Demographic details for patients with skeletal disease only

	Randomised treatment	
	Goserelin alone (n = 62)	Goserelin plus tamoxifen (n = 53)
Age, years		
Mean (range)	41 (24–53)	43 (31–55)
Weight, kg		
Median (range)	62 (47–86)	63 (48–103)
Advanced disease at first diagnosis, n (%)	9 (15)	9 (17)
Previous adjuvant therapy, n (%)	35 (56)	29 (55)
DFI, months		
Median (range)*	22 (5–97)	26 (4–120)
Oestrogen receptor (ER) status, n (%)		
Positive	36 (58)	32 (60)
Negative	13 (21)	10 (19)
Unknown	13 (21)	11 (21)

*Disease-free interval (DFI) excluding patients with advanced disease at first diagnosis.

Table 3. Objective response, time to first progression and survival

	Randomised treatment		
	Goserelin alone (n = 159)	Goserelin plus tamoxifen (n = 159)	P value
Objective response (CR + PR), n (%)	50 (31)	60 (38)	0.24
Complete response	8 (5)	12 (8)	
Partial response	42 (26)	48 (30)	
No Change, n (%)	51 (32)	42 (26)	
Progression, n (%)	49 (31)	47 (30)	
Median duration of response, weeks (range)	59 (12–216)	88 (8–196)	
Median time to first progression, weeks (range)	23 (0–216)	28 (0–196)	0.03
Median survival, weeks (range)	127 (0–303)	140 (0–298)	0.25

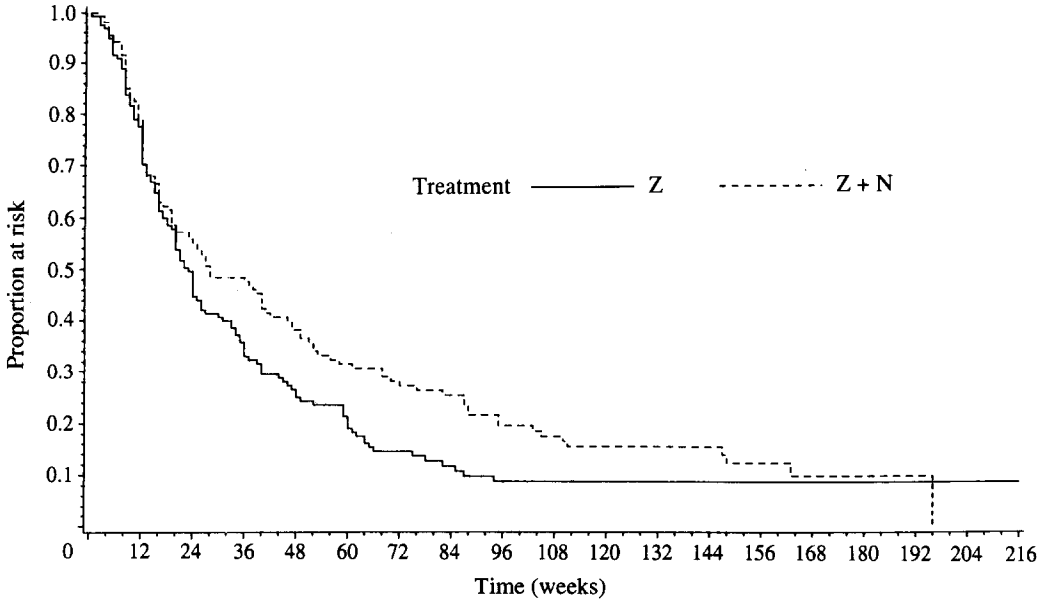

Figure 1. Kaplan-Meier survival curves, compared using the log rank test.

Prognostic factors

There was no significant difference between the two treatments in response rate, time to disease progression and overall survival for any of the prognostic factors, except for disease-free interval (DFI) which showed inconsistent effects (for survival only) across the range of DFI assessed.

For ER status, patients with ER-positive tumours showed a significant benefit over patients with ER-negative tumours in terms of response rate (34 versus 11% in goserelin group; 42 versus 25% in combination group), median time to progression (24 versus 12 weeks in goserelin group; 37 versus 18 weeks in combination group), and median survival (146 versus 75 weeks in goserelin group; 161 versus 86 weeks in combination group), respectively.

Skeletal disease only

For the 115 patients with skeletal metastases only, there was a statistically significant difference between the treatments in response rate, time to disease progression and overall survival in favour of the combination therapy (Table 4). When adjusting for the ER status of the primary tumour in this skeletal analysis, there was still a significant difference between treatments in terms of these efficacy endpoints. Patients with ER-positive tumours compared to patients with ER-negative tumours had objective response rates of 19 versus 23% in the goserelin group and 44 versus 10% in the combination group, median time to progression of 27 versus 15 weeks in the goserelin group and 52 versus 24 weeks in the combination group, and median survival of 142 versus 78 weeks in the goserelin group and median not reached versus 138 weeks in the combination group, respectively.

Tolerability and safety

Fifty-nine adverse events were reported in 34 patients of which 16 patients (10%) were in the goserelin alone group and 18 (11%) in the combination group. Adverse events led to the

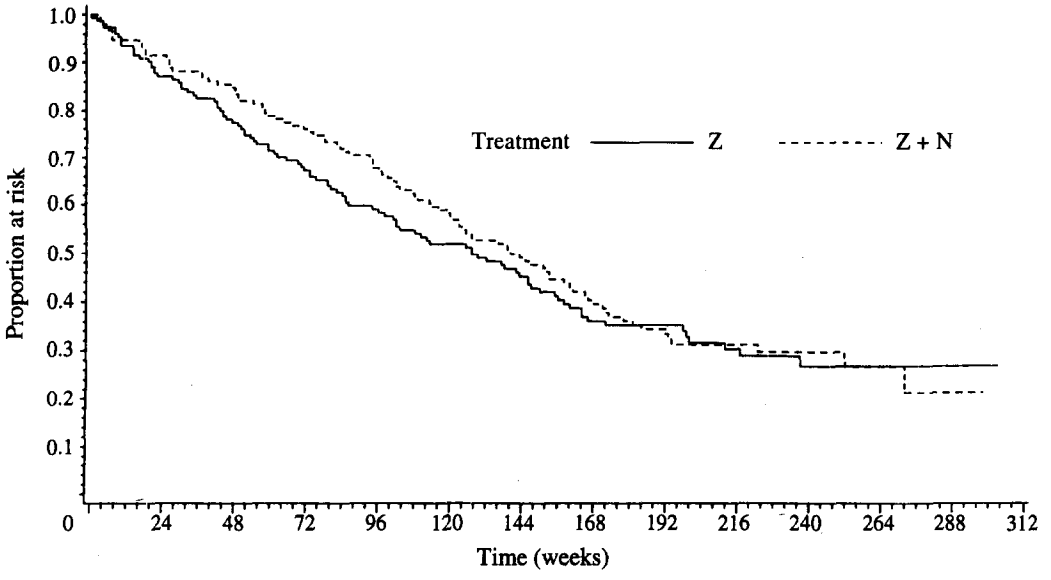

Figure 2. Kaplan-Meier survival curve compared using the Wilcoxon test.

Table 4. Objective response, time to disease progression and survival in patients with skeletal disease only

	Randomised treatment		
	Goserelin (n = 62)	Goserelin plus tamoxifen (n = 53)	P value
Objective response (CR + PR), n (%)	15 (24)	23 (43)	0.03
Median duration of response, weeks (range)	60 (15–159)	111 (11–193)	
Median time to progression, weeks (range)	24 (4–159)	70 (4–193)	0.005
Number of deaths, n (%)	35 (56)	18 (34)	
Median survival, weeks (range)	124 (5–238)	221 (4–236)	0.009

Table 5. Tolerability

	Treatment received	
	Goserelin alone (n = 154)	Goserelin plus tamoxifen (n = 160)
Symptoms appearing or worsening during treatment	n %	n %
Hot flushes	114 (74)	115 (72)
Vaginal discharge	20 (13)	27 (18)
Vaginal soreness	27 (18)	29 (18)
Adverse effect on sexual activity	23 (15)	16 (10)
Positive effect on sexual activity	3 (2)	5 (3)

withdrawal of therapy in 4 patients; 1 patient receiving goserelin alone (headache and hot flushes), 2 patients receiving goserelin after tamoxifen was added (menopausal symptoms; nausea, vomiting, irritability, constipation, chest tightness, light headedness and urinary hesitancy) and 1 patient receiving goserelin plus tamoxifen (hot flushes). The incidence of worsening of elicited pharmacological effects, i.e. hot flushes, vaginal discharge, vaginal soreness and sexual activity, was similar in both groups (Table 5). There were no clinically significant differences in the haematology or biochemistry parameters between the two treatment groups.

DISCUSSION

Since the time of Beatson, methods to reduce serum oestrogen levels have been used in the treatment of premenopausal advanced breast cancer. The hypothesis of providing maximal oestrogen blockade by combining the use of a LHRH analogue with an anti-oestrogen, both of which have been shown to be efficacious as single agents, is therefore an attractive approach. Other studies are in progress which also address this approach [15, 16].

With a median follow-up of 93 weeks (117.5 weeks for survival), the results of this study showed a similar objective response rate for the two treatment groups. In addition, a significant prolongation of time to disease progression in favour of the combination therapy was observed supporting the preliminary results of Dixon and associates [13]. Unlike previously reported studies [13, 17], this comparative study has not shown a survival benefit for combination therapy over goserelin alone. There were more patients who had received previous cytotoxic adjuvant therapy in the goserelin alone group and more patients who presented initially with advanced disease at first diagnosis in the combination group. The impact, if any, of these slight differences on the overall results are unknown.

Less than half (45%) of the patients in the study who received goserelin alone as initial therapy had tamoxifen added following disease progression, as stipulated by the protocol. The main reason for this was that the majority of patients had rapidly progressive disease which was considered by the clinicians to require alternative therapy. It is noteworthy, however, that a useful clinical benefit was achieved in those patients who did receive tamoxifen following disease progression, with 18% having an objective response to treatment and stable disease being achieved in 41% of the patients. There is evidence that ER are present in bone [18, 19]. It was considered appropriate, therefore, to perform a separate analysis on patients who had skeletal metastases only at entry to the study, on the basis that skeletal disease may be particularly responsive to endocrine therapy, and that there might be a difference between combination therapy and the use of goserelin alone. The statistically significant differences in objective response rate, time to disease progression and overall survival in favour of the patients treated with combination therapy, along with the finding that this difference was not due solely to the ER status of the primary tumour, are interesting. However, before any conclusion can be reached, a prospective study is required to confirm any possible benefit for the use of this combination in this specific group of patients.

Both treatments were well tolerated and no additional safety issues associated with the use of this combination therapy were identified.

1. Beatson GT. On treatment of inoperable cases of carcinoma of the mamma. *Lancet* 1896, **2**, 104–107,162–165.
2. Taylor GW. Evaluation of ovarian sterilization for breast cancer. *Surg Gynaecol Obstet* 1939, **68**, 452–446.
3. Veronesi U, Di Fronzo G, Galluzzo D, *et al.* A reappraisal of oophorectomy in carcinoma of the breast. *Ann Surg* 1987, **205**, 18–21.
4. Conte CC, Nemoto T, Rosner D, *et al.* Therapeutic oophorectomy in metastatic breast cancer. *Cancer* 1989, **64**, 150–153.
5. Ingle JN, Krook JE, Green SJ, *et al.* Randomised trial of bilaterial oophorectomy versus tamoxifen in pre-menopausal women with metastatic breast cancer. *J Clin Oncol* 1986, **4**, 178–185.
6. Buchanan RB, Blamey RW, Durrant KR, *et al.* A randomised comparison of tamoxifen with surgical oophorectomy in pre-menopausal patients with advanced breast cancer. *J Clin Oncol* 1986, **4**, 1236–1330.
7. Kaufmann M, Jonat W, Kleeberg U, *et al.* Goserelin, a depot gonadotrophin-releasing hormone agonist in the treatment of pre-menopausal patients with metastatic breast cancer. *J Clin Oncol* 1989, **7**, 1113–1119.
8. Kaufmann M, Jonat W, Schachner-Wunschmann E, *et al.* The depot GnRH analogue goserelin in the treatment of pre-menopausal patients with metastatic breast cancer—a 5-year experience and further endocrine therapies. *Onkologie* 1991, **14**, 22–30.
9. Blamey RW, Jonat W, Kaufmann M, *et al.* Goserelin depot in the treatment of pre-menopausal advanced breast cancer. *Eur J Cancer* 1992, **28A**, 810–814.
10. Blamey RW, Jonat W, Kaufmann M, *et al.* Survival data relating to the use of goserelin depot in the treatment of premenopausal advanced breast cancer. *Eur J Cancer* 1993, **29A**, 1498.
11. Jordan CV. A current view of tamoxifen for the treatment and prevention of breast cancer. *Br J Pharmacol* 1993, **110**, 507–517.
12. Robertson JFR, Walker KJ, Nicholson RI, *et al.* Combined endocrine effects of LHRH agonist ('Zoladex') and tamoxifen ('Nolvadex') therapy in pre-menopausal women with breast cancer. *Br J Surg* 1989, **76**, 1262–1265.
13. Dixon AR, Nicholson RI, Blamey RW. Combined LHRH agonist ('Zoladex') and tamoxifen therapy in pre-menopausal advanced breast cancer: current controversies in the treatment of breast cancer. The Nottingham Proceedings, 1st Nottingham International Breast Cancer Meeting, 22–28 September 1990; 1991, **2**, 41–49.
14. Hayward JL, Carbonne PP, Heuson JC, *et al.* Assessment of response to therapy in advanced breast cancer. *Eur J Cancer Clin Oncol* 1977, **13**, 89–94.
15. Klijn JGM. LR-RH agonists in the treatment of metastatic breast cancer: ten years experience. *Recent Results Cancer Res* 1992, **124**, 75–90.
16. Nicholson RI, Walker KJ, McClelland RA, *et al.* Zoladex plus tamoxifen versus Zoladex alone in pre- and peri-menopausal metastatic breast cancer. *J Steroid Biochem Mol Biol* 1990, **37**, 989–997.
17. Klijn JGM, Foekens JA. Long-term peptide hormone treatment with LH-RH agonists in metastatic breast cancer. Proceedings of the International Symposium on Endocrine-dependent Breast Cancer: Critical Assessment of Recent Advances 1987. 14th International Cancer Congress, Budapest, 23 August 1986. Bern, Hans Huber, 92–102.
18. Ernst M, Schmid CH, Froesch ER. 17β-estradiol stimulated proliferation and type I procollogen gene expression in primary osteoblasts. International Symposium on Osteoporosis, Aalborg. Copenhagen, Osteopress, 1987, **1**, 198–201.
19. Eriksen EF, Berg NJ, Graham ML, *et al.* Multiple sex steroids receptors in cultured human osteoblast-like cell. International Symposium on Osteoporosis, Aalborg, 1987, abstract 67.

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