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## Research paper

# Vorozole (Rivizor™): an active and well tolerated new aromatase inhibitor for the treatment of advanced breast cancer patients with prior tamoxifen exposure

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**Vorozole (Rivizor™) is a potent and stereospecific inhibitor of aromatase having shown promising endocrine effects in phase I studies. In the present trial, 27 postmenopausal patients with advanced breast cancer, measurable lesions, presumably hormone responsive (ER or PR+, or ER? with disease-free survival longer than 1 year, or prior documented response to tamoxifen), were treated with vorozole one tablet 2.5 mg daily. All had been previously treated with tamoxifen as adjuvant (two patients) or for advanced disease (24 patients), or both (one patient). Objective remissions were observed in eight patients (30%) with two complete responses (CR) and six partial responses (PR) lasting for a median of 14.3 months (range 6.8–40.6); nine stabilizations were also recorded (median 7.9 months; range 3.7–40.1). Median time to progression for the 27 patients was 5.9 months. Sites of response were skin (three patients), lymph nodes (two patients), lung (two patients) and chest wall plus lymph nodes (one patient). Treatment was very well tolerated: mild hot flushes (four patients), gastrointestinal complaints (four patients) and no significant toxicity (common toxicity criteria grade above 2) or drug-related severe adverse event. It is concluded that vorozole is an active second-line endocrine treatment, deserving consideration for randomized comparison with other agents such as aminoglutethimide, megestrol acetate or medroxyprogesterone acetate. [© 1998 Rapid Science Ltd.]**

*Key words:* Aromatase, breast cancer, metastatic, phase II, postmenopausal, vorozole.

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## Introduction

Commonly utilized endocrine therapies in postmenopausal women with metastatic breast cancer include antiestrogens, progestational agents and aromatase inhibitors. Agents of these three different classes have similar overall response rates and response duration in the advanced disease setting, but are associated with different toxicity profiles.[1] Mainly due to its excellent tolerability, tamoxifen is usually considered as the first-line agent; aromatase inhibitors and progestins being generally prescribed in second or third line. It has been suggested in the literature—notably in two randomized trials comparing aminoglutethimide with tamoxifen[2,3]—that use of aromatase inhibitors may be associated with higher response rates in bone.

Aromatase inhibitors, of which aminoglutethimide is the classical example, decrease circulating estrogens by inhibiting the peripheral conversion of adrenal-derived androstenedione and testosterone into estrone and estradiol. In postmenopausal women, this pathway represents the main source of estrogen biosynthesis. The conversion of androgens into estrogens, which occurs through a series of three hydroxylations, is dependent on the multicomponent enzyme complex, aromatase, which is a cytochrome P450-containing enzyme.

Certain aromatase inhibitors, such as aminoglutethimide, lack specificity in also reacting with other

cytochrome P450-containing hydroxylases. Aminoglutethimide, for example, inhibits enzymatic systems involved in cholesterol side-chain cleavage in the adrenal gland, thereby reducing adrenal corticosteroid production and necessitating the co-administration of replacement corticosteroid, at least at highest dosage levels (1.0 g daily), in order to avoid an Addisonian syndrome.

Because of this need for corticosteroid replacement and other potential toxicities (central nervous system depression, cutaneous rash, thyroid insufficiency and hematological dyscrasia) associated with the use of aminoglutethimide, there has been great interest in developing less toxic and more specific aromatase inhibitors for the hormonal treatment of postmenopausal women with breast cancer.

Vorozole (Rivizor™) (R083842, see Figure 1), the dextroisomer of the racemic mixture R076713, is a new non-steroidal aromatase inhibitor which has been demonstrated to be both a specific and potent inhibitor of aromatase *in vitro* and *in vivo*.[4-7] The aromatase inhibiting activity of R076713 has been shown to reside almost entirely in vorozole.[6] In a phase I trial performed in 28 heavily pre-treated postmenopausal patients, the vorozole racemate showed both activity and excellent clinical tolerability.[8] Daily doses of 2.5 or 5.0 mg were associated with an equivalent level of plasma estradiol suppression below 10 pmol/l without any impairment of glucocorticoid or mineralocorticoid biosynthesis.

Using a more sensitive assay for plasma estradiol, Johnston *et al.*[9] found a significant trend to increasing estradiol ($E_2$) suppression with increasing dose of vorozole, from 1.0 to 5.0 mg. At daily doses of 1.0, 2.5 and 5.0 mg, the proportions of patients with $E_2$ values below the detection limit (3 pmol/l) were 5/38, 12/39 and 17/42, respectively. It was concluded that 1.0 mg was inferior to higher dosages with regard to estrogen suppression. The differences between 2.5 and 5.0 mg were, however, not significant, and plasma estrone and estrone sulfate were similarly suppressed at these dose levels. Objective remissions and excellent tolerance were also observed in this trial.

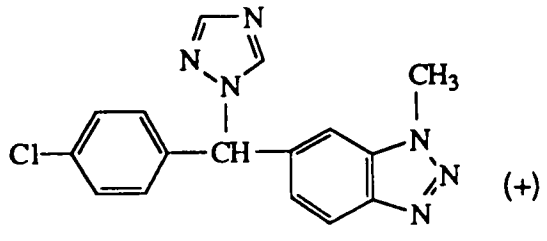


**Figure 1.** Chemical structure of vorozole.

The present phase II study was initiated in December 1991 and was designed to evaluate the antitumor activity of vorozole in postmenopausal breast cancer patients, when used as second-line treatment after tamoxifen exposure. The other aim was to characterize further the tolerability profile of the drug during long-term treatment, at a daily dose of 2.5 mg, chosen on the basis of the above-mentioned endocrine studies, indicating maximal estrogen suppression at this dose level. Endocrine and pharmacokinetic studies were additional features of special interest which will be reported separately.

## Patients and methods

Twenty-seven patients were accrued between December 1991 and February 1993. Six centers from Belgium, The Netherlands and the UK participated in the trial. The study was approved by the EORTC Protocol Review Committee and by the committee for medical ethics of each participating center. Eligible patients had histologically or cytologically verified breast cancer with uni- or bi-dimensionally measurable metastatic lesions. Tumors had to be receptor positive [estrogen receptor (ER) and/or progesterone receptor (PgR) at 10 fmol/mg protein or higher as determined by the dextran-coated charcoal method] or receptor status unknown, but in this case, relapse-free survival had to be 1 year or longer. Patients with receptor negative status were eligible only if they had a previously well documented response [complete response (CR) or partial response (PR)] under tamoxifen.

A postmenopausal status was mandatory and defined as absence of regular menses for a minimum of 12 months. Follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol levels were to be determined for women below the age of 56 years who had undergone hysterectomy before the onset of menopause, bilateral oophorectomy, radiotherapy castration or presented with amenorrhea after stopping oral contraceptives. In such cases, increased FSH and LH levels in the presence of postmenopausal plasma estradiol concentrations had to be documented. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less and a life expectancy of at least 3 months. The patients could have received prior chemo- or hormonal therapy as adjuvant systemic treatment. A maximum of one previous hormonal therapy for metastatic disease was allowed as long as

2 weeks had elapsed between the discontinuation of this treatment and the start of therapy with vorozole. If the most recent endocrine therapy was ovarian ablation, an interval of at least 3 months from the day of oophorectomy was required. Written informed consent was obtained from all patients. Patients with previous or current malignancies at other sites (with the exception of a second hormone receptor positive primary breast cancer, adequately treated cone-biopsied *in situ* carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin), patients with central nervous system metastases and patients with rapidly progressive life-threatening metastases, such as lymphangitic carcinomatosis of the lung and metastases occupying more than one-third of the liver with abnormal liver function tests, were not eligible. Patients with white blood counts less than $3 \times 10^9$/l or platelets less than $100 \times 10^9$/l, or with impaired renal function (creatinine above 2 mg/dl) were also excluded.

Prior to the start of treatment, patients underwent a complete physical examination. Blood sampling for routine hematology and biochemistry, as well as for hormonal parameters and urinanalysis were performed. A tumor work-up included a chest X-ray, bone scan and liver CT scan or ultrasound examination. Tumor parameters were assessed every 2 months. An electrocardiogram was also performed and was repeated after 2 months. All patients were seen 2 weeks after starting vorozole, and then 1 month, 2 months and every 2 months thereafter for toxicity evaluation. At the time of the clinical follow-up visit, further blood samples for hematology, biochemistry, hormonal profile, lipid profile and drug level measurements were taken. Vorozole was given orally, at the dose of 2.5 mg once daily, to be taken in the morning, until disease progression or excessive toxicity.

### Criteria of evaluation

Tumor response was assessed according to the Union Internationale Contre le Cancer (UICC) criteria.[10] CR was defined as the disappearance of all known disease, determined by two observations not less than 4 weeks apart. PR was defined as the decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by two observations not less than 4 weeks apart, in case of bi-dimensionally measurable disease, or a decrease by at least 50% of the sum of the largest diameters of all lesions for unidimensionally measurable disease. It was not necessary for all lesions to have regressed to qualify for a partial response, but no lesions should have progressed and no new lesions should have appeared. Serial evidence of appreciable change documented by radiography or photography was obtained for external review. The no change (NC) category corresponded to a less than 50% decrease and a less than 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions in case of bi-dimensionally measurable disease or in the sum of the diameters of all lesions for unidimensionally measurable disease maintained at least 2 months after treatment initiation. Progressive disease (PD) was defined as a 25% or greater increase in the size of at least one bi-dimensionally measurable lesion or the appearance of a new lesion.

### Toxicity

Toxicities were graded according to the NCI CTC scale. Briefly, grade 0 toxicity reflects no toxicity; grade 1, a mild toxicity; grade 2, a moderate toxicity; grade 3, a severe toxicity; and grade 4, a toxicity requiring hospitalization.

### Statistical methods

Descriptive statistics were used to assess response rate. The duration of response was computed from the date of start of treatment until documentation of progression. Time to progression was defined as the interval between treatment start and the date of documented progression.

## Results

The characteristics of the 27 patients are summarized in Table 1. The median age was 67 years. Most patients (22 out of 27) had ER+ tumors. The median DFI between initial tumor diagnosis and first recurrence was 4.2 years. Nine patients had received prior adjuvant systemic therapy and 25 had received prior tamoxifen for metastatic disease. The best response to first-line therapy with tamoxifen given for metastatic disease was a CR or a PR in 10 patients; 11 additional patients had stable disease. The median duration of tamoxifen treatment was 25 months (range 10–43 months). At study entry, the most frequent dominant sites of disease were bone or single viscera, with the majority of patients having one or two metastatic sites involved.

**Table 1.** Patient characteristics ($n$=27)

| | | |
|---|---|---|
| Age (years) | | |
| Median | 67 | |
| range | 39–86 | |
| Performance status (ECOG) | | |
| 0 | 10 | (37%) |
| 1 | 12 | (44%) |
| 2 | 4 | (15%) |
| unknown | 1 | (4%) |
| Receptor status | | |
| ER+ and PgR+ or PgR unknown | 18 | (67%) |
| ER+ and PgR− | 4 | (15%) |
| ER and PgR unknown | 5 | (18%) |
| Disease-free interval (years between initial diagnosis and first recurrence) | | |
| median | 4.2 | |
| range | 0–19.0 | |
| Prior adjuvant therapy | | |
| tamoxifen | 2 | (7%) |
| chemotherapy | 5 | (18%) |
| tamoxifen+chemotherapy | 1 | (4%) |
| ovariectomy | 1 | (4%) |
| none | 18 | (67%) |
| Prior tamoxifen for metastatic disease | 25[a] | (93%) |
| median duration [months (range)] | 25 months | (10–43) |
| Dominant site of disease | | |
| soft tissue | 4 | (15%) |
| bone | 11 | (41%) |
| single visceral | 10 | (37%) |
| multiple visceral | 2 | (7%) |
| No. of disease sites | | |
| 1 | 9 | (33%) |
| 2 | 10 | (37%) |
| ⩾3 | 8 | (30%) |

[a] One patient received tamoxifen for adjuvant and for metastatic disease.

**Table 2.** Response and time to progression ($n$=27)

| Category of response | No. of patients (%) | Time to progression (days) | |
|---|---|---|---|
| | | Median | Range |
| CR | 2 (7) | – | 520–617 |
| PR | 6 (22) | 325 | 203–1217 |
| NC | 9 (33) | 238 | 111–1204 |
| PD | 10 (37) | 57 | 34–83 |
| All | 27 (100) | 177 | 34–1217 |

### Antitumor activity

All patients entered in the study were evaluable for response. The median time to progression among these 27 patients was 5.9 months (range 1.1–40.5). An objective response rate of 30% (8/27; 95% CI: 13–51%) was documented with two CR and six PR (Table 2). Sites of response were skin (three patients), lymph nodes (two patients), lung (two patients) and chest wall plus lymph nodes (one patient). The median duration of objective tumor regression was 15.2 months (range 6.8–40). Nine additional patients had stable disease for a median duration of 7.9 months (range 3.7–40.1). Progression within the first 3 months of therapy was documented in 10 patients. Characteristics of the patients in relation to their response to vorozole are described in Table 3. From this phase II series it seems that patients with predominant bone metastases or with multiple visceral involvement had lower response rates than those with small tumor burden and predominant soft tissue localizations. The response to vorozole as a function of the previous response to tamoxifen is further displayed in Table 3. As it is well known from the literature, a response under vorozole was most likely to be observed if a previous response to tamoxifen had been documented. Patients with tumors displaying the ER+ and PgR+ phenotype had a higher chance of getting a remission or a disease stabilization (11 of 13) than those having a PgR− or a receptor unknown status (six of 14). Finally, age, disease-free interval or performance status at onset therapy did not seem to influence the pattern of response to vorozole (data not shown).

### Toxicity

Tolerability of the drug was documented in all patients. No hematological or other laboratory toxicity was observed. All the non-hematological toxicities quoted as possibly, probably or definitely related to vorozole are reported in Table 4. Fifteen patients experienced a quoted 'drug-related' toxicity, which was usually mild or moderate. Hot flushes were seen in 15% of the patients and were mild or moderate. Anorexia was observed in 11% as well as fatigue/malaise. No patient discontinued therapy for adverse events. One patient withdrew consent after 182 days of drug intake while she was in PR.

## Discussion

The results of the present phase II trial clearly show that vorozole is an effective second-line endocrine treatment for patients with advanced breast cancer, previously treated with tamoxifen. The objective response rate of 30% observed here, together with 33% of disease stabilizations with an overall time to progression for the whole population of patients of 6

**Table 3.** Response to vorozole ($n$=27) accordings to pretreatment characteristics

| | No. of patients | | | |
|---|---|---|---|---|
| | CR (2) | PR (6) | NC (9) | PD (10) |
| Dominant site of disease | | | | |
| soft tissue | 2 | 1 | | 1 |
| bone | | 2 | 4 | 5 |
| single visceral | | 3 | 4 | 3 |
| multiple visceral | | | 1 | 1 |
| Hormonal receptor status of the primary tumor | | | | |
| ER+ and PgR+ | 2 | 4 | 5 | 2 |
| ER+ and PgR− | | | | 4 |
| ER+ and PgR? | | 2 | 1 | 2 |
| ER? and PgR? | | | 3 | 2 |
| Adjuvant therapy | | | | |
| no | 1 | 6 | 7 | 5 |
| yes | 1 | | 2 | 5 |
| with hormones | | | | 2 |
| with chemotherapy | 1 | | 2 | 2 |
| with hormones+chemotherapy | | | | 1 |
| Response to prior tamoxifen for metastatis disease ($n$=25) | | | | |
| CR | 2 | 1 | 1 | 1 |
| PR | | 1 | 3 | 1 |
| stable disease | | 3 | 4 | 4 |
| progression | | | | 1 |
| not evaluable | | 1 | 1 | 1 |

**Table 4.** Number of patients with possibly, probably or certainly treatment-related toxicities ($n$=27)

| Toxicity type | CTC grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Nausea | 2 | 1 | – | – |
| Constipation | 2 | 1 | – | – |
| Fatigue/malaise | 2 | 1 | – | – |
| Anorexia | 3 | – | – | – |
| Pruritus | 1 | – | – | – |
| Hot flushes | 2 | 2 | – | – |
| Weight change | 2 | – | – | – |
| Edema | 1 | 1 | – | – |
| Peripheral neuropathy | 1 | – | – | – |
| Mood disturbance | 1 | – | – | – |
| Pulmonary (dyspnea) | – | 1 | – | – |
| Pain | – | – | 1 | – |
| Dizziness | 1 | – | – | – |
| Somnolence | – | 1 | – | – |
| Gastric complaints[a] | 1 | – | – | – |
| Nose drip and sneezing[a] | 1 | – | – | – |
| Perspiration, headache[a] | 1 | – | – | – |

[a] Possibly related side effects, reported as mild by patient [assimilated to common toxicity criteria (CTC) grade 1].

months compares favorably with the results achieved with other standard modalities such as aminoglutethimide, medroxyprogesterone acetate or megestrol acetate. Our objective remission rate was comparable to that found by Johnston *et al.*[9] in a phase II setting, utilizing various dosages of vorozole ranging from 1 to 5 mg. In a recently published phase II trial utilizing the same dosage as in our study (i.e. 2.5 mg daily) a lower response of 11% (only three partial remissions among 29 patients) was found by Goss *et al.*[11] These rather disappointing results might be explained by chance or else by the selection of a group of patients displaying less favorable characteristics as, for example, the inclusion of more patients having not responded to tamoxifen. Indeed, the median duration of previous tamoxifen treatment (10 months) was shorter than in our series (23 months). Basal estradiol levels were also very low in the Canadian series.[11]

As will be shown in a separate publication of hormonal studies performed during this trial, a general lack of correlation between serum concentrations of vorozole and its effect on hormone serum levels or clinical response was observed. A significant suppression of estrone, estrone sulfate and to a lesser extent of estradiol was found in the present series, confirming previous endocrine studies with vorozole.[6-9] In most of our patients, previous hormonal treatment (tamoxifen) had been stopped 4 weeks before inclusion. It is therefore very unlikely that tamoxifen withdrawal could account for the objective response rate observed in the present trial. Such a withdrawal effect[12,13] results generally in very few objective regressions

(<5%) and is characterized by a short time to progression (usually several weeks), certainly shorter than the impressive median time to progression of 6 months recorded in our 27 patients. We found a trend towards a higher response rate associated with classical indicators of hormone responsiveness. Patients displaying the double-positive receptor phenotype (ER+ and PgR+) had higher response rates than patients displaying only one positive receptor or having an unknown receptor status. Similarly, objective remissions were mainly found in soft tissue and in lung nodular lesions while bone or multiple visceral localizations seemed to be less responsive.

Long-term treatment with vorozole was characterized by an excellent tolerance profile, with very few significant side effects. The latter might be comparable to what could be expected from a placebo treatment. None of the bothersome side effects related to aminogluthetimide[1-3] were observed (no lethargy, drowsiness, skin rash). No single patient displayed clinical signs suggesting adrenal insufficiency or hypothyroidism. No abnormal laboratory values were found and especially no single case of blood dyscrasia was reported.

In the present study, vorozole was tested as second-line therapy for advanced disease after progression under tamoxifen. Vorozole obviously deserves further randomized comparison with progestins (medroxyprogesterone acetate or megestrol acetate) or with aminogluthetimide. The results of these trials should be available in the near future. Other aromatase inhibitors belonging to the same class of non-steroidal triazolic compounds have been developed recently.[14] All showed similarly potent *in vitro* and *in vivo* inhibition of aromatase and clinical efficacy. It is unclear whether any of these compounds would be clinically superior to the others or whether their efficacy might differ. This seems very unlikely but deserves randomized comparison with a cross-over design eventually. Other aromatase inhibitors, displaying a steroidal structure analogous to androstenedione, the natural substrate of the enzyme, have also been developed over the last few years. They irreversibly bind to the enzyme leading to its definitive inactivation. Contrary to the triazolic compounds, they display a weak binding affinity to the androgen receptor and at the highest dosages they induce androgen-like side effects (hoarseness, mild hirsutism, acne). Formestane (4-hydroxyandrostenedione) is poorly absorbed when given by the oral route and must be administered intramuscularly while the more recently developed analog exemestane is available as an oral preparation. Remarkably, a lack of complete cross-resistance with aminogluthetimide and maybe with other triazolic compounds seems to exist[15,16] since, for example, exemestane is able to induce objective regressions after progression under aminogluthetimide. It is unknown whether the reverse sequence would lead to objective remissions.

## Conclusion

It is concluded that vorozole is an active second-line endocrine treatment for advanced breast cancer. Further randomized comparisons are required to define its exact place in the sequential use of the various endocrine modalities available, i.e. tamoxifen, progestins or steroidal and non-steroidal aromatase inhibitors, in advanced disease. Vorozole and possibly other new triazolic compounds will probably definitively replace aminogluthetimide in this setting, because of their excellent clinical tolerance. Possible use in the adjuvant setting will certainly be conditioned by the long-term effects of vorozole on lipids, bone mineralization and the endometrium. The latter should be subjected to further clinical investigation.

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