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Amonafide as First-line Chemotherapy for Metastatic Breast Cancer

G. Kornek, M. Raderer, D. Depisch, K. Haider, B. Fazeny, C. Dittrich and W. Scheithauer

In a phase II study, 32 patients with advanced breast cancer previously unexposed to palliative cytotoxic chemotherapy were treated with amonafide, 800–900 mg intravenously over 3 h repeated every 4 weeks. Objective response was seen in 8 patients including 1 complete response, 10 patients had stable disease and 14 patients progressed so the overall response was 25% (95% confidence interval, 11–43%). The most frequently encountered side-effects were haematological (granulocytopenia ≥ WHO grade 3 was encountered in 7/24 patients at 800 mg/m² and in 3/8 patients at 900 mg/m² amonafide) and nausea/vomiting (62%), despite prophylactic use of ondansetron. Non-haematological severe adverse reactions included neurotoxicity WHO grade 3 in 1 patient and orthostatic hypotension WHO grade 4 in another. In summary, the results of this trial suggest a limited therapeutic index of amonafide if used at this dose with this administration schedule.
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INTRODUCTION

AMONAFIDE, A new synthetic imide derivate of naphtalic acid with both DNA intercalative properties and effects on macromolecular synthesis [1], has shown significant activity against intraperitoneally implanted murine leukaemias and solid tumour models [2]. Fairly good tolerance of the compound with myelosuppression as the dose-limiting toxicity has been reported in phase I/II trials [3–8], but whereas only modest antitumour activity has been noted in several different solid tumour types [4–8], encouraging therapeutic results were recently reported in metastatic breast cancer [9,10]. The preliminary findings of the Cancer and Leukemia Group B (CALGB) in previously untreated patients [9], and our own data yielding an 18% overall response rate in patients with advanced refractory disease [10], along with the predictable and reversible toxicity profile of the compound, encouraged us to initiate the present phase II trial of amonafide as first-line therapy in patients with metastatic breast cancer.

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PATIENTS AND METHODS

Patients were eligible for this study if they had progressive, histologically confirmed, metastatic breast cancer. Additional criteria included: bidimensionally measurable disease, age ≤ 72 years, World Health Organization (WHO) performance status ≤ 1, leucocyte count ≥ 4000/μl, platelet count ≥ 100 000/μl,

serum creatinine level ≤ 1.5 mg/dl, serum bilirubin level ≤ 1.5 mg/dl, a life expectancy of 12 weeks or more, and informed consent according to institutional regulations. In case of prior palliative hormonal therapy, patients had to be off treatment for at least 4 weeks. Patients who had received prior cytotoxic chemotherapy (except as part of adjuvant therapy, which must have been completed at least 6 months prior to study entry) and those who had received more than one endocrine regimen were excluded from the study, as were patients with central nervous system (CNS) involvement or osteoblastic bone lesions as the only manifestation of disease.

Amonafide (supplied by Knoll AG, Ludwigshafen, Germany) was given at a starting dose of 800 mg/m^2 body surface by intravenous infusion over 3 h, repeated every 4 weeks. A 100 mg/m^2 dose escalation was allowed at the investigator's discretion when systemic toxicity was absent or minimal. Treatment could be delayed for up to 2 weeks if the white blood cell (WBC) count was lower than 3000/μl and/or the platelet count was lower than 75 000/μl; any patient who required more than 2 weeks for haematological recovery was taken off the study.

A 25% dose reduction of amonafide for subsequent cycles was indicated if the lowest WBC count was less than 1000/μl, or the lowest platelet count was less than 50 000/μl in the previous cycle. The patients were evaluated with biweekly complete blood counts, histories and physical examinations, and monthly chemical tests of hepatic and renal function. Objective tumour measurements were re-evaluated every two cycles. WHO standard criteria [11] were used for response and toxicity (which was recorded by worst degree of treatment complication).

RESULTS

From March 1990 to May 1992, 32 patients were entered. All patients were considered evaluable for response and toxicity assessment, although treatment was discontinued early in 2 cases because of protracted myelosuppression (incomplete haematological recovery within 6 weeks) and reproducible acute epigastric pain during amonafide infusion. The pretreatment characteristics of the patients are presented in Table 1. The median number of treatment courses was three (range one to 19). There were eight objective responses, including one complete response (CR), 10 patients had stable disease, and 14 progressed, so the overall response was 25% (95% confidence interval 11.5–43.4%). Median duration of response was 7.5 months (range 3–33). The complete remission occurred in a premenopausal oestrogen receptor-negative patient with soft tissue metastases, and currently has lasted for 25 months. Median time to progression was 7 months (range 3–35), and median survival for all patients was 11 months (range 2–36).

When amonafide was administered at a dose of 800 mg/m^2, 112 treatment cycles were assessable for haematological toxicity. Granulocytopenia with neutrophil counts below 1000/μl was observed in 7 patients. The median nadir granulocyte count was 2236/μl (range 12–7440). The median platelet count was 169 000/μl (range 7000–507 000). In 8 patients, the dose was escalated to 900 mg/m^2. 3 patients had WHO grade 3 granulocytopenia. The median nadir granulocyte and platelet counts at this dose level (14/14 assessable treatment cycles) were 1612/μl (range 574–3198) and 165 000/μl (range 53 000–292 000), respectively. Febrile episodes associated with neutropenia occurred in 2 patients, and were successfully treated with broad spectrum antibiotics. The most frequent non-haematological side-effects were nausea and vomiting (62%) usually of mild intensity, although occurring despite prophylactic use of ondansetron.

Table 1. Patients' characteristics

Number of evaluable patients	32
Age (years)	
Median	59
Range	40–72
Performance status	
WHO 0	9
WHO 1	23
Menopausal status	
Premenopause	5
Postmenopause	27
Dominant disease site	
Soft tissue	17
Viscera	14
Bone	1
Oestrogen-receptor status	
Positive	10
Negative	16
Unknown	6
Prior chemotherapy (adjuvant)	
Yes	15
No	17
Prior endocrine therapy (adjuvant)	
Yes	10
No	22
Prior endocrine therapy (advanced disease)	
Yes	6
No	26

Other minor adverse reactions included partial alopecia in 7 patients, local irritation at the injection site in 5 patients, and reversible acute toxicity during the drug infusion such as headache, dizziness and tinnitus in 9 patients. These symptoms were promptly ameliorated by an increase in the duration of infusion, and paracetamol in all patients except 1, who experienced protracted neurotoxicity with WHO grade 3 ataxia, vertigo and hearing loss lasting for 24 h. There was 1 other patient with severe orthostatic hypotension requiring hospitalisation.

DISCUSSION

In summary, 25% of the patients with advanced breast cancer showed an objective response to first-line chemotherapy with amonafide. Side-effects observed are in agreement with earlier data [3–10], though frequent occurrence of (ondansetron-refractory) gastrointestinal symptoms—1 case presenting with "non-rate-of-infusion-dependent" WHO grade 3 neurotoxic symptoms, and another case with orthostatic hypotension WHO grade IV, support the impression of a limited therapeutic index of amonafide in breast cancer if used at this dose and administration schedule.

Since both *in vitro* studies, showing that L1210 leukaemia cell killing is dependent on amonafide concentration and duration of exposure [12], and pharmacokinetic studies, showing a short half-life [2], suggest that administration by continuous infusion may be a more optimal method of drug delivery, alternative administration schedules should be investigated in future trials.

To allow administration of higher, potentially more effective initial doses, and in order to reduce the risk of adverse reactions to amonafide, which seem to be related to the extent of conversion to its active acetylated metabolite [13], prospective assessment of the individual acetylator phenotype may eventually be incorporated into these studies.

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Feature Articles

Immunomodulatory Agents: the Cytokines

R.C. Stein and A.G. Dalgleish

THE ACTION of several cytokines against tumour cell lines *in vitro* or certain animals *in vivo* is impressive enough to expect them to exhibit significant anti-cancer activity in man. Dramatic responses and rejection of some animal tumours to schedules involving interferon, interleukin (IL)-2 and tumour necrosis factor lead to high hopes that they might prove to be the elusive panaceas for cancer, a hope that was widely publicised by the media with both interferon and interleukin-2 appearing as 'cancer cure' cover stories in *TIME* magazine. The failure to fulfil the preclinical promise has mimicked the course of many conventional 'wonder' drugs, where early (unrealistic) expectations were soon disappointed, leading to a backlash ("it's far too toxic, I wouldn't give it to my dog") which over the months and years may lead to the drug finding a niche in the treatment of a particular disease condition for which it is well suited. (This scenario will be familiar to all those who have read Lawrence's "Clinical Pharmacology.") It should, therefore, not be surprising that the first anti-cancer cytokines are following a similar course. In the case of interferon-α, the initial hopes have been dashed, the toxicity has virtually prevented any further high dose trials, yet a number of 'niche' uses in the treatment of hairy cell leukaemia, chronic myeloid leukaemia, Kaposi's sarcoma and maintenance treatment for multiple myeloma has led to widespread acceptance that it has a role to play in treating cancer[1]. The learning curve has also led to the realisation that cytokines are not drugs and are not necessarily associated with a direct dose-effect which is the case for many conventional drugs. Indeed, the use of low dose interferon-α is not only much less toxic (and cheaper) but also more practical [as it may be given subcutaneously (s.c.) at home] and in many conditions is as effective. In addition, even though partial responses might not be achieved, prolonged periods of static disease with improved Karnofsky or ECOG scores may be of considerable clinical benefit. The low dose, low toxicity regimens have now led to a number of studies looking at the role of interferon-α in combination with chemotherapy and other cytokines. There are three main types of interferon: α, β and γ. The studies referred to so far involve interferon-α. Perhaps, surprisingly, β and γ have not been as effective as interferon-α and have even been detrimental in some conditions (e.g. β in Kaposi's sarcoma and γ in renal cell carcinoma). Nevertheless, it still remains possible that combinations of α and γ may be better than α alone.

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IL-2

IL-2, initially known as T-cell growth factor, was first used in the clinics in conjunction with lymphokine-activated killer