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Amonafide: An Active Agent in the Treatment of Previously Untreated Advanced Breast Cancer—A Cancer and Leukemia Group B Study (CALGB 8642)¹

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ABSTRACT

Amonafide is a new imide derivative of naphthalic acid. The drug had demonstrated significant activity in preclinical studies and some activity in Phase I trials. The drug is extensively metabolized and detected in plasma and urine. Its toxicity has previously been correlated to the formation of an active metabolite, *N*-acetyl-amonafide. Amonafide was chosen for inclusion in the Cancer and Leukemia Group B (CALGB) master metastatic breast cancer protocol. CALGB 8642 randomizes previously untreated metastatic breast cancer patients either to one of several Phase II agents given for up to four cycles and then followed by standard cyclophosphamide-doxorubicin-5-fluorouracil, or to immediate treatment with standard cyclophosphamide-doxorubicin-5-fluorouracil. The end point of CALGB 8642 is to assess the difference in survival, toxicity, and overall response when limited exposure to Phase II agents precedes standard chemotherapy. This report deals only with amonafide as a Phase II agent. Comparisons with the cyclophosphamide-doxorubicin-5-fluorouracil arm will not be addressed. Patients had to have histologically documented measurable breast cancer and a performance status of 0-1. Patients could not have had prior chemotherapy for meta-

static disease. Prior adjuvant chemotherapy was permitted. Patients could not have visceral crisis. Amonafide was given at 300 mg/m²/day i.v. for 5 days, and repeated at 21-day intervals for a maximum of four cycles. Escalation and reduction in dose was mandated dependent on hematotoxicity or lack thereof. Toxicity was primarily hematological and bimodal: 32% had grade 3 or 4 leukopenia and 24% had grade 3 or 4 thrombocytopenia; 22% had no leukopenia and 44% had no thrombocytopenia. The response rate was 18%, including one complete response. When response was analyzed by hematological toxicity, there was a 35.7% response if patients had leukopenia grade 3/4 (versus 8.3%, $P = 0.08$). There was a 50% response if patients had thrombocytopenia grade 3/4 (versus 7.1%, $P = <0.01$). We conclude that amonafide is somewhat active in previously untreated breast cancer patients. There may be a steep dose-response curve, based on the significant correlation between myelosuppression and response. Rates of responses in patients adequately dosed (*i.e.*, with significant hematotoxicity) with amonafide ranged from 35 to 50%. Further studies will incorporate individualized dosing based on pretreatment acetylator phenotyping.

INTRODUCTION

Traditionally the use of Phase II agents in breast cancer patients has been limited to heavily pretreated patients. The performance of active Phase II agents will almost certainly be inferior to that which might have been observed in previously untreated patients. The most striking example of this is the poor response rate of doxorubicin (Adriamycin) when used as a Phase II agent in the traditional setting (1). Since there is widespread acknowledgment of the pressing need to discover new and active agents for this disease, some centers are beginning to use Phase II agents in previously untreated breast cancer patients, although this practice has not been demonstrated to be safe to the patient (2, 3). In order to address the safety as well as the benefit of using Phase II agents in previously untreated patients, the CALGB³ has developed a master protocol (CALGB 8642) that compares survival, toxicity, and cumulative response rate in previously untreated patients randomized either to Phase II agents for up to four cycles followed by standard CAF regimen or to the CAF arm alone. Five single agents will be tested sequentially before the trial closes (4, 5). This is a report of the Phase II evaluation of amonafide as a part of protocol 8642.

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³ The abbreviations used are: CALGB, Cancer and Leukemia Group B; CAF, cyclophosphamide-doxorubicin-5-fluorouracil; UTSA, University of Texas at San Antonio; OSU, Ohio State University; MDA, M. D. Anderson; MTD, maximum tolerated dose.

Preclinical Studies. Amonafide (benzisoquinolinedione, BIDA, NSC308847) is a new imide derivative of naphthalic acid (6). When the naphthalic acid side chain has two methylene groups with a terminal nitrogen, as amonafide has, cytotoxic activity is maximum. Amonafide has demonstrated significant activity against P388 leukemia and L1210 cell lines as well as B16 melanoma and M5076 sarcoma cell lines (7). Amonafide is a site-specific intercalating agent and a topoisomerase II inhibitor (8, 9). Preliminary human pharmacology shows that amonafide is extensively metabolized, and the metabolites have been detected in both plasma and urine. The principal metabolite, *N*-acetyl-amonafide is cytotoxic (10).

Phase I Studies. Phase I studies were performed at the UTSA (11), OSU (12), and MDA (13). When given as a single bolus, the MTD was 800 mg/m². The dose-limiting toxicity was myelosuppression (UTSA). When a daily times five dose was given every 21 days, the MTD was 400 mg/m² (MDA) or 250 mg/m² (OSU). Again, myelosuppression was the dose-limiting toxicity. Other reported toxicities were mild to moderate nausea, vomiting, and alopecia. All three centers reported acute toxicity with rapid amonafide infusion. This consisted of local inflammatory reactions, diaphoresis, flushing, tinnitus, headache, and/or dizziness. Increasing the duration of the infusion to 1 h minimized these effects. One complete response was noted at UTSA in lung cancer.

Regarding the different regimens, no schedule dependency was noted. The bolus dose MTD was different in two studies. The UTSA investigators (11) showed a highly variable and individualized hematotoxicity at sub-MTD doses, although they did reach a MTD of 800 mg/m². The OSU study (12) reported an MTD of 1125 mg/m² but noted considerable and variable toxicity.

One group (12) compared bolus doses (1125 mg/m²) to a 5-day schedule (at 288 mg/m²) and concluded that the 5-day schedule was preferred since more drug could be given. In another 5-day schedule, the MDA study (13) found a higher MTD of 400 mg/m².

We chose to use the 5-day schedule so that more drug could be given. We chose to begin with 300 mg/m² as a compromise between the recommended start dose of 220 mg/m² (12) and 400 mg/m² (13). Because of the variability in dose-limiting hematotoxicity seen in the three Phase I trials, an escalation dose of 100 mg/m²/cycle was mandated. Because amonafide demonstrated significant activity in tumor cell lines and because it was a new agent of interest, it was chosen for testing in CALGB 8642, the metastatic breast cancer master protocol.

Phase II Studies. Subsequent to our initiation of this trial, a report (14) was published indicating that amonafide had activity in metastatic breast cancer. In that study, a single 3-h infusion dose of 800 mg/m² every 28 days was used. Three responses were noted in eight patients who had not received prior chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria. Eligible patients had to have histologically documented measurable breast carcinoma (either stage IV or inoperable disease), performance status of 0–1 (Eastern

Cooperative Oncology Group scale), life expectancy of greater than 4 months, age greater than 16 years and physiological age of less than 70, and adequate function of bone marrow, kidney, and liver. Patients could not have had prior chemotherapy treatment for metastatic disease. Adjuvant chemotherapy for breast cancer was permitted if more than 12 months had intervened since the completion of therapy. Doxorubicin could have been used as an adjuvant agent but the cumulative dose could not exceed 250 mg/m². Hormone therapy was permissible but 4 weeks had to intervene between cessation and entry on this protocol. In addition, patients could not have had visceral crisis, defined as lymphangitic spread of the disease to lungs, bone marrow replacement, carcinomatous meningitis, or significant liver disease. All patients were required to sign an informed consent document.

Treatment and Dose Modifications. Amonafide was supplied by the Division of Cancer Treatment at the National Cancer Institute as a lyophilized powder. The drug was reconstituted in 4 ml sterile water of 0.9% sodium chloride with a concentration of 26 mg/ml with a pH of 5–7. After reconstitution and dilution, amonafide was infused over 1 h through an established free-flowing i.v. line. The schedule of drug administration was 300 mg/m²/day i.v. for 5 days, repeated at 21-day intervals. Escalation was required for Day 15 granulocytes of 1,000 or greater and platelet count of 75,000 or greater. The daily dose of amonafide was to be increased by 100 mg/m²/day/cycle. Doses were reduced by 50% if on the day of treatment (Day 1), granulocyte and platelet counts were below 1,800 or 100,000 respectively. No therapy was given if Day 1 granulocytes and platelet counts were below 1,000 and 75,000. After two cycles of amonafide, response was to be evaluated. If progressive disease was noted, patients did not receive more amonafide and began standard CAF therapy. Patients were to begin standard CAF therapy after a maximum of four cycles of amonafide, even if responding to amonafide.

Pretreatment Evaluation. Pretreatment evaluation included complete history and physical examination including blood pressure, pulse, height, weight, surface area, performance status, tumor measurements, laboratory tests consisting of WBC count, platelet count, differential, blood urea nitrogen, creatinine, creatinine clearance, electrolytes, calcium, serum transaminase, alkaline phosphatase, bilirubin, uric acid, phosphate, glucose, total protein, albumin, urine analysis, electrocardiogram, chest X-ray, and bone scan. A liver scan was required only if enlarged liver or abnormal liver function studies were documented. Computerized tomography of the abdomen and liver, bone marrow aspiration, and biopsy were not required unless they were clinically appropriate. Disease was categorized by the site of metastases: viscera, bones, or soft tissue. Evaluation during treatment included a complete history and physical examination, tumor measurement, WBC count and platelets, blood chemistries, and urinalysis on Day 1 of each of the cycles. Weekly WBC count, differential, and platelet count were also required. Formal evaluation of drug toxicity was to be done on Day 1 of each cycle.

Criteria for Evaluation. Patients were stratified by estrogen receptor protein status, dominant site of metastatic disease, and menopausal status. The definitions of response were: complete response was defined as the disappearance of signs

and symptoms related to measurable disease without the appearance of new lesions for a period of at least 4 weeks. Lytic lesions had to recalcify to be scored as a complete response. Partial response was defined as a reduction of 50% or greater in the sum of the products of the perpendicular diameters of all measurable lesions without the appearance of new lesions or an increase in the size of existing lesions for 4 or more weeks. Stable disease was defined as <50% reduction or <25% increase in the sum of the products of the two perpendicular diameters of all measured lesions without the appearance of new lesions for a period greater than 8 weeks. Progressive disease was defined as an increase in the product of two perpendicular diameters of any measured lesion by 25% or more of the size present at entry on study or for patients who responded to therapy, or the appearance of new areas of malignant disease. The toxicity criteria used were those of the National Cancer Institute.

Pharmacological Studies. An optional companion pharmacological study was conducted in conjunction with this and other Phase II trials of amonafide. The complete results were reported separately (15). Plasma concentrations of amonafide and its active metabolite *N*-acetyl-amonafide were determined by HPLC analysis as described previously (16, 17). Slow acetylators were defined as having 24-h *N*-acetyl-amonafide concentrations of <80 ng/ml and fast acetylators had >100 ng/ml (13, 17).

RESULTS

Between April 1988 and February 1990, 52 patients were randomized to the amonafide arm. Six patients were ineligible. Of the remaining 46 patients, 7 were inevaluable for response although they were evaluable for toxicity. Of the seven inevaluable patients, one died from breast cancer within 10 days of entering the study, one patient withdrew consent, two patients refused further therapy after one cycle, and three patients were on treatment less than two full cycles of treatment due to excessive toxicity. Table 1 gives the characteristics at entry for the 46 eligible patients. The majority of patients were postmenopausal. Thirty-seven percent were estrogen receptor negative. The dominant site of disease was visceral in 78% of the cases. Thirty-nine percent of patients had received adjuvant chemotherapy.

Toxicity

Hematological Toxicity. Twenty-four percent of patients had severe (grade 3) leukopenia and 9% experienced life-threatening (grade 4) toxicity. Eleven percent of patients had severe (grade 3) thrombocytopenia and 13% experienced life-threatening (grade 4) thrombocytopenia (Table 2).

Gastrointestinal Toxicity. Grade 3 nausea and vomiting was noted in 16% of patients and 4% had life-threatening nausea and vomiting (Table 2).

Other Toxicity. Of the nonhematological and nongastrointestinal toxic effects, the most common and troublesome one was local toxicity consisting of phlebitis and/or local swelling with erythema. Systemic allergic reactions occurred in seven patients and consisted of one or more of the following: fever to >103°F, rash, hives, and/or burning sensation of the scalp. One patient developed the Stevens-Johnson syndrome. None of the

Table 1 Patient characteristics

Age (yr)	No. of patients (n = 46)
<40	3 (7%)
40-49	10 (22%)
50-59	20 (44%)
60-69	12 (26%)
70+	1 (2%)
Performance status	
0	30 (65%)
1	16 (35%)
Menopausal status	
Premenopausal	7 (15%)
Peri/postmenopause	28 (61%)
Surgical menopause	11 (24%)
Estrogen receptor status	
Positive	19 (41%)
Negative	17 (37%)
Unknown	7 (15%)
Borderline	3 (7%)
Site of metastasis	
Soft tissue ^a	27 (59%)
Visceral ^b	36 (78%)
Bone	22 (48%)
Principal prior therapies	
Hormonal therapies	19 (41%)
Adjuvant chemotherapy	18 (39%)
Radiotherapy	15 (33%)

^a Includes recurrent primary, inoperable primary chest wall, nodes, and skin.

^b Includes lung, pleura, liver, brain, and bone marrow.

patients received a rapid infusion of drug. Most of the systemic allergic reactions occurred during the second cycle of drug administration (Table 2).

Dose Modifications

One hundred thirteen courses of amonafide were given to 39 patients (average, 3.0 courses). Dose escalations were carried out in 30% of the courses, and dose reductions were implemented in 30% (see Table 3).

Responses

Responses are shown in Table 4. The complete remission rate was 2.2% and the partial remission rate was 15.4%. The overall response rate was 17.6%. Of the seven responders, three patients had adjuvant chemotherapy. Four responders had received prior endocrine therapy.

Duration of Response. Duration of response is not evaluable in this study since at the end of four cycles, all patients, whether responding or not, began standard CAF therapy. Of the seven responding patients, all were still responding at the time of initiation of standard CAF therapy.

Response Rate and Hematopoietic Toxicity. Table 5 shows the relationship between significant granulocytic and/or platelet toxicity and response status. Those patients who experienced grade 3 or 4 toxicity for either granulocytes or platelets had a greater response rate than those who did not. The relationship was significant with respect to platelet toxicity.

Response Rate and Acetylation Status. Of the 18 patients who had plasma drug and metabolite concentrations de-

Table 2 Patient toxicity

	Maximum toxicity (n = 46)				
	0 (none)	1 (mild)	2 (moderate)	3 (severe)	4 (life-threatening)
Hematopoietic					
Leukopenia	10 (22%)	10 (22%)	10 (22%)	11 (24%)	4 (9%)
Thrombocytopenia	20 (44%)	10 (22%)	4 (9%)	5 (11%)	6 (13%)
Anemia	22 (49%)	7 (16%)	13 (29%)	2 (4%)	1 (2%)
Nonhematopoietic					
Nausea and vomiting	15 (33%)	10 (22%)	11 (24%)	7 (16%)	2 (4%)
Hepatic	41 (93%)	1 (2%)	2 (5%)	0 (0%)	0 (0%)
Renal	42 (93%)	2 (4%)	1 (2%)	0 (0%)	0 (0%)
Infection	37 (82%)	2 (4%)	2 (4%)	3 (7%)	1 (2%)
Local toxicity	28 (62%)	7 (16%)	5 (11%)	4 (9%)	1 (2%)
Systemic allergic reaction	39 (85%)	2 (4%)	3 (7%)	1 (2%)	1 (2%)

Table 3 Dose modifications

Dose change	Cycle 1 → 2	Cycle 2 → 3	Cycle 3 → 4	
Escalation	11	7	5	23 (29.9%)
Reduction	15	4	4	23 (29.9%)
None (same dose)	13	8	10	31 (40.3%)
	39	19	19	77

Table 4 Response rate (n = 39)

Complete response	1 (2.2%)
Partial response	6 (15.4%)
Stable disease	16 (41%)
Progressive	16 (41%)

terminated, 4 could not be evaluated for response and 4 could not be evaluated for acetylation status. There were 10 patients evaluable by acetylator status and by response. By acetylator status, the response rates were 17% (1/6) in the slow group and 25% (1/4) in the fast group.

Response Rate and Prior Adjuvant Chemotherapy.

Of the 39 patients evaluable for response, 6 had prior adjuvant doxorubicin. No response in these patients was noted. Of the 33 patients who had not received adjuvant doxorubicin, 10 received other adjuvant chemotherapy. Response rate in these 10 patients was 30%. These results are not significant because the numbers are small.

Response Rate and Systemic Allergic Reactions. Of the 39 patients evaluable for response, 30 did not receive steroids as part of their antiemetic regimen and were thus "unprotected" for allergic reactions. Three of 4 patients having significant allergic reactions had a response, whereas only 1 of 26 patients without an allergic reaction had a response ($P < 0.01$). Three additional patients who had systemic allergic reactions could not be evaluated for response. The reactions included hives, burning and darkened face, and rashes of grade 2–4 intensity. These occurred typically on the second or third day of the second cycle.

Table 5 Response by hematopoietic toxicity

	Total no. of patients (n = 38) ^a	Response		Response rate
		Complete	Partial	
WBC				
Grade 0, 1, 2	24	1	1	8.3%
Grade 3, 4	14	0	5	35.7%
				$p = 0.08$
Platelets				
Grade 0, 1, 2	28	1	1	7.1%
Grade 3, 4	10	0	5	50%
				$p < 0.01$

^a Of 39 patients evaluable for response, 1 had no nadir counts available for review.

DISCUSSION

Amonafide, a new imide derivative of naphthalic acid, shows minimal activity in breast cancer patients previously treated for metastatic disease. Phase I studies did not indicate major activity, although a single objective response (complete response) was noted in a patient with adenocarcinoma of the lung (UTSA). In one Phase II trial (14), objective responses were noted using a dose of 800 mg/m² every 4 weeks. Most patients in that study were considered refractory to prior treatment, and 20 of 28 had prior chemotherapy for their metastatic disease. In the 20 patients receiving prior chemotherapy, there were only 2 responses (10%). However, three responses were noted in the eight patients who had not received prior chemotherapy for metastatic disease.

Our Phase II study is of interest because all evaluable patients were previously untreated for metastatic breast cancer. In general, breast cancer patients without prior exposure to chemotherapy have a higher response to drug than patients with previous treatment. However, in our study this was not the case. The overall response rate in our study was 17.6%.

In this study we noted a negative relationship between adjuvant doxorubicin chemotherapy and response to amonafide. While this was not a significant result (due perhaps to small numbers), it is consistent with the observation that others have made (14). Possible mechanisms for cross-resistance might include p-glycoprotein-associated drug-resistance phenomenon (18). This resistance is inducible by *Vinca* alkaloids, anthracyclines, and podophyllotoxins derivatives. It is characterized by

the decreased intracellular accumulation of cytotoxic drugs. Another pathway might be the alteration of topoisomerases as is the case with anthracyclines and epipodophyllotoxins (19). These agents interfere with religation and stabilize the strand passage reaction by causing mutations in DNA topoisomerases. Again, prior exposure to doxorubicin may have resulted in topoisomerase II mutation.

An unexpected but significant finding was the association of amonafide response and the experience of systemic allergic reactions. A possible explanation of this association is that a drug-induced immune reaction somehow interacted with breast cancer cells, leading to their destruction. The result although technically significant may be spurious since the numbers of patients involved are small, and the observation is retrospective. On the other hand, the association was remarkable in several cases, prompting the retrospective analysis. The exact nature of the allergic reactions themselves is unclear. The drug was given slowly over at least 1 h. There was no sign of anaphylaxis, arthritis, glomerulonephritis serum, or vasculitis sickness. Allergic reactions consisted of hives, rashes, burning skin, fever to 103°C, and/or the Stevens-Johnson syndrome. Whatever the allergic responses induced by drug might be, it is less clear how such responses might trigger cancer cell cytotoxicity. Possible pathways might include antibody-dependent cell cytotoxicity: where drug and cancer cell share similar antigens (as in the penicillin involved hemolysis of RBCs), or where drug and antibody are passively absorbed onto a cancer cell, leading to complement-activated cytotoxicity (as in Sedormid-induced thrombocytopenia). Nonantibody pathways might include lymphocyte cell-mediated immune responses (as in natural killer-type-mediated cancer cell cytotoxicity). Natural killer activity might be triggered by cytokine release secondary to mast cell release of histamines (20).

Nonetheless, given the association of cancer responses with other immune-mediated reactions (21–23), this report of a possible association of allergic immune reactions and breast cancer response is worth pursuing in prospective studies.

The most important finding in our study is the relationship between myelosuppression, especially thrombocytopenia, and response. It has been previously demonstrated that the major determinant of myelosuppression is the genetically determined acetylator phenotype (15, 17, 24). Unfortunately, only two responding patients were accrued to the optional pharmacology study (15); thus, we cannot definitively state that response at this dose is determined primarily by acetylator phenotype.

Patients who are fast acetylators paradoxically have slower plasma clearance of amonafide and greater toxicity at a fixed dose (17). This appears to be due to the inhibition of the oxidation of amonafide (its major detoxification pathway) by *N*-acetyl-amonafide, resulting in higher concentrations of both amonafide and its active metabolite.⁴ From a clinical perspective, the dose of amonafide used in this study may be too low for slow acetylators (23), resulting in a decrease in both toxicity and response.

One way to deal with such variability in toxicity would be to treat all patients at the same high dose (a dose high enough to

cause most patients to become severely neutropenic) and simultaneously to try to protect them with granulocyte-colony-stimulating factors and an antibiotic. Whether such a strategy would be safe remains to be demonstrated. A more rational and safer strategy would be to dose patients initially according to their acetylator status. This would ensure that most patients get a biologically individualized and maximum dose. If necessary, escalations could then be made in subsequent cycles by using hematotoxicity as a criteria of adequate dosing. In the meanwhile, it should be noted that the maximum activity of amonafide has not been demonstrated in this study. The study did not seek MTD for each patient, and the length of treatment was limited by design to four cycles. What is shown is how variable hematotoxicity is and how it is related to response. Future studies should address the pharmacological principles of initial dosing based on acetylator status. Such a study is now under way (CALGB 9243).

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