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Pharmacokinetics and clinical impact of all-*trans* retinoic acid in metastatic breast cancer: a phase II trial

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Abstract *Purpose*: The purpose of this trial was to evaluate tumor cytoreduction by all-*trans* retinoic acid (ATRA) in patients with metastatic breast cancer and to characterize the initial pharmacokinetics of this agent. *Methods*: The study was a single institution, phase II study. The treatment regimen consisted of ATRA administered orally at a dose of 50 mg/m^2 three times a day for 14 consecutive days of a 21-day cycle. Cycles were repeated until disease progression, unacceptable toxicity or patient withdrawal. Plasma samples were obtained following the first dose of ATRA for pharmacokinetic analysis. *Results*: A total of 17 patients with metastatic breast cancer were enrolled in the study, and 14 completed at least one cycle of therapy and were evaluable for response. One patient achieved a partial response in soft tissue of 4 months duration. Three patients had stable disease for 4, 2, and 2 months duration. The remainder had progressive disease. ATRA was reasonably well tolerated. Pharmacokinetic analysis revealed a high degree of interpatient variability in systemic exposure following the initial dose of ATRA. *Conclusions*: We conclude, that in the dose and schedule tested, ATRA does not have significant activity in patients with hormone-refractory, metastatic breast cancer. Future studies should focus on more intensive investigation of those individuals with very high or low ATRA initial systemic exposure in the hope of expanding our understanding of ATRA's clinical pharmacology, ultimately leading to improved efficacy.

Key words Retinoids · All-*trans* retinoic acid Pharmacokinetics · Breast neoplasms

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Introduction

Breast cancer is a substantial public health problem with approximately 185 000 new cases and 45 000 deaths in the United States in 1996 [36]. While great strides have been made in the development of improved treatment modalities, metastatic breast cancer remains an incurable condition. Chemotherapy, hormonal therapy or radiation therapy used singly or in combination can provide effective palliation. However, new therapeutic agents and treatment strategies are needed.

The retinoids are a class of pharmacologic agents consisting of vitamin A (retinol) and its derivatives. They have long been known to play a pivotal role in the development and maintenance of normal epithelial tissues as well as in growth, reproduction, immune function, and vision. All-*trans* retinoic acid (ATRA) is a natural retinol metabolite formed by intestinal cells from dietary beta carotene and from the tissue metabolism of retinol. ATRA can substitute for many of the functions of retinol except its role in reproduction and vision [40]. It is likely that many of the effects of vitamin A are mediated via its conversion to ATRA.

The antiproliferative and differentiating effects of retinoids have been well documented. Cell lines of diverse histologic origin have diminished in vitro proliferation in the presence of retinoids [23, 24]. The response demonstrated by leukemic cells in vitro has translated into effective therapy of acute promyelocytic leukemia with ATRA [7, 9, 17, 43]. Preclinical studies, both in vitro and in vivo, suggest that retinoids may be effective in the prevention and treatment of breast cancer. Indeed, growth of well-established breast cancer-derived cell lines can be inhibited by retinoid exposure [19, 25, 26]. Retinoids such as fenretinide (4-hydroxyphenyl retinamide, 4-HPR) have been shown to inhibit carcinogen-induced malignant transformation of mammary cells in organ culture [8]. In rat models, dietary supplementation with retinyl acetate inhibits chemically induced mammary carcinogenesis, while ATRA

supplementation slows progression of established nitrosourea- induced tumors [13, 20, 28, 31]. In addition, retinol and ATRA have been shown to diminish proliferation of a human breast cancer cell line, both in vitro and after xenotransplantation into athymic mice. Notably, 13-*cis*-retinoic acid (isotretinoin) was unable to inhibit the growth of the xenotransplanted carcinoma cells despite in vitro inhibition [11, 14].

The ability of retinoids to inhibit malignant transformation and restore normal morphology to metaplastic tissues has provided the impetus for clinical trials using retinoids as chemopreventive agents. The retinoids have demonstrated the ability to subvert the malignant potential of oral leukoplakia and to prevent second primary tumor development in patients with head and neck squamous cell carcinoma [15, 16]. An Italian study is examining the role of fenretinide in preventing contralateral breast cancer in approximately 3500 women with personal histories of breast cancer. Data from this study are not yet mature. In the United States, the National Cancer Institute is sponsoring a randomized trial comparing tamoxifen with tamoxifen plus fenretinide in postmenopausal women with stage II breast cancer.

The role of retinoids in advanced breast cancer is not well established. Phase II trials of retinoids in patients with metastatic disease have been disappointing. Neither isotretinoin nor fenretinide have demonstrated significant activity in metastatic breast cancer [6, 30]. However, the preclinical data suggest that ATRA may be effective where other retinoids are not. A phase I study of ATRA in adults with various solid tumors (mostly lung cancers) concluded that a dose of 150 mg/m^2 per day be used for subsequent studies [21]. Of note, no major objective response was observed among those patients. To date there have been no published clinical trials evaluating the efficacy of ATRA in the treatment of advanced breast cancer.

The purpose of this trial was to evaluate tumor cytoreduction by ATRA in patients with metastatic breast cancer and to characterize the initial pharmacokinetics of this agent in our patient population.

Material and methods

The study was a single institution, phase II study. Eligibility for the study required a histological diagnosis of metastatic breast cancer. Patients could have received no more than two prior chemotherapy regimens for metastatic breast cancer in addition to adjuvant chemotherapy. Any number of prior hormonal therapies was acceptable. All prior chemotherapy and hormonal therapy must have been completed more than 4 weeks prior to entry into the protocol. In the event of clear progression while on prior hormonal treatment, a 2-week interval between completion of hormonal therapy and entry into protocol was considered sufficient. Prior radiation therapy was allowed when completed more than 2 weeks prior to study entry. All toxicity attributable to previous chemotherapy, hormonal or radiation therapy must have resolved by the time of entry. No concurrent chemotherapy, hormonal or radiation therapy was allowed. Eligible patients were required to have a performance status of 2 or better and an expected survival of at least 8 weeks. Written, informed consent was obtained from all patients. Enrollment into the study began following approval of the protocol and consent form by the Institutional Review Board of Duke University Medical Center.

The treatment regimen consisted of ATRA administered orally at a dose of 50 mg/m^2 three times a day with meals for 14 consecutive days of a 21-day cycle. Cycles were repeated until disease progression, unacceptable toxicity or patient withdrawal. All patients who received any doses of ATRA were evaluable for toxicity and pharmacokinetic analysis, but only those patients who had received 14 days of continuous therapy were evaluable for response.

A two-stage design was employed such that if fewer than 3 of the first 15 evaluable patients had objective responses, then the study would be terminated. If 3 or more responses were seen in the first 15 patients then an additional 22 patients would be entered (total 37). With this design there is a less than 10% probability of erroneously concluding that the response rate was less than or equal to 15% when in fact it was actually higher.

Dose reductions were planned for patients experiencing visual, dermatologic, hepatic, or neurologic toxicity of grade 2 or greater according to the common toxicity criteria of the National Cancer Institute. Planned dose reductions were made for platelet counts below 100 000/dl and granulocyte counts less than 1500/dl.

Heparinized plasma samples were obtained in foil-protected tubes from all patients at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 6 h following the first dose of ATRA. Specimens were immediately centrifuged and stored in the dark at −70 °C until analysis. ATRA and isotretinoin concentrations were determined by a liquid extraction/HPLC technique [27]. All sample extraction steps were conducted in amber-colored apparatus and under yellow light to avoid sample decomposition. The HPLC system (Waters, Milford, Mass.) consisted of a Model 715 Ultra Wisp autosampler, a Model 490E variable wavelength detector and baseline chromatographic integration software. ATRA and isotretinoin concentrations in patient samples were simultaneously determined by comparing the ratios of their absorbances divided by that of the internal standard (retinyl acetate) with those of known concentrations of each analyte. The standard curves were determined on each run and were linear over the concentration range 0 to 2000 ng/ml. Results were considered acceptable if both high and low spiked controls of both analytes were within 10% of expected values and the sample concentrations were within the standard curve range. The lower limits of quantitation were 10 ng/ml for each analyte.

A variety of pharmacokinetic models were evaluated to describe each patient's ATRA concentration-time profile using a weighted nonlinear least squares regression technique (PCNONLIN V 4.2, Scientific Consulting, Apex, N.C.). Concentrations were weighted by the inverse of the variance for the predicted values. Model selection was based on the Akaike Information Criterion in addition to examination of the differences between measured and estimated concentrations [42]. Estimates of the AUC were determined by both model and trapezoidal techniques. Patient characteristics including age, race, body surface area, menopausal status and concurrent medications were analyzed in relation to the AUC.

Results

A total of 17 patients with metastatic breast cancer were enrolled in the study. Patient characteristics are presented in Table 1. The median age was 55 years with a range of 41 to 73 years. Six patients had not received prior chemotherapy for metastatic breast cancer. Six patients had received one previous chemotherapy and five had received two previous chemotherapies for metastatic disease. Nine patients had tumors that were estrogen receptor (ER) and/or progesterone receptor (PR) positive, six were negative and two unknown. All nine

Table 1 Patient characteristics

Characteristic	No. (n = 17)	%
Age (years)		
Median	55	
Range	41–73	
Prior chemotherapy		
None	6	35
1 regimen	6	35
2 regimen	5	29
Prior hormonal therapy for metastatic disease		
None	8	47
Prior therapy	9	53
Hormonal receptors		
ER and/or PR positive	9	53
ER/PR negative	6	35
Unknown	2	12
Performance status		
0	6	35
1	11	65
Sites of disease		
Soft tissue and/or bone only	5	29
Visceral ± other sites	11	65

patients who were ER and/or PR positive had failed prior hormonal therapy.

Of the 17 patients, 14 completed at least one course of therapy (14 days) and were evaluable for response. Of the three patients who were not evaluable for response, two did not complete the first cycle because of toxicity and the third patient had rapid progression of her disease prior to completion of the first cycle of therapy. Of the 14 patients assessable for response, one achieved a partial response in soft tissue of 4 months duration. Therefore, the overall response rate was 7% (95% confidence interval 0–21%). Three patients had stable disease for 4, 2, and 2 months. Median time to progression was 6 weeks for these 14 patients. The study was terminated after the initial cohort of patients were treated because of failure to observe three or more responses in the first 15 evaluable patients.

All 17 patients were evaluable for toxicity. ATRA was reasonably well tolerated. No hematologic toxicity was observed. Nine patients experienced grade 2 skin toxicity. Two patients experienced grade 3 nausea and vomiting. Two patients experienced grade 3 headache and discontinued therapy during the first cycle which resulted in resolution of their symptom. The severe headache recurred in both patients upon rechallenge. Grade 2 headache was present in an additional six patients.

Approximately 180 samples were analyzed from the first dose of the first cycle of therapy in 17 patients for both ATRA and isotretinoin concentrations. ATRA was the primary analyte detected, while small quantities were isomerized to isotretinoin in some patients. Neither compound was found in any of the samples taken immediately prior to drug administration. Patients 8 and 11 displayed the highest isotretinoin concentrations; however, these were only in the range 10–15 ng/ml

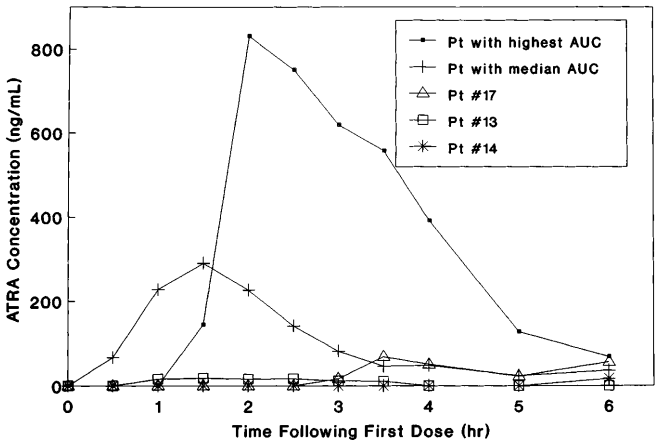

Fig. 1 Examples of ATRA plasma disposition. ATRA concentration vs time data are displayed for the patient with the highest AUC, the patient with the median AUC, and the three patients with extraordinarily low exposures

(roughly 50-fold below the maximal ATRA concentrations). Interestingly, three patients (numbers 13, 14 and 17) exhibited very low concentrations of ATRA during all sample times as displayed in Fig. 1.

The individual ATRA concentration-time profiles were best described by a one-compartment model with first-order input, an oral absorption lag time and first-order elimination. The pharmacokinetic parameter estimates for each individual as well as the statistical summary for the group are displayed in Table 2. The median values for the elimination half-life (36.6 min) and apparent clearance (74 l/h per m^2) are similar to those reported by others [12]. Maximal plasma concentrations (Cmax) were generally observed within 2–3 h of drug ingestion. Systemic exposure to ATRA as measured by either the Cmax or AUC, was extremely variable as reflected in the 50-fold difference from highest to lowest observations. AUCs calculated by the pharmacokinetic model were not significantly different from those determined by the trapezoidal method. Approximately 7% of the AUC was extrapolated by using the terminal elimination rate for the latter calculation; however, patients 3 and 6 appeared to have a delayed absorption pattern and thus the AUC was potentially underestimated. In contrast to the three patients with very low systemic exposures mentioned above, one patient (number 11) exhibited an AUC which was much higher than that of others. Frequency distributions of the systemic exposure parameters are shown in Fig. 2.

Discussion

In vitro and animal studies have suggested that the retinoids are active in breast cancer. Unfortunately, the preclinical data have not translated into meaningful clinical results. Phase II studies of the retinoids, isotretinoin and fenretinide, have not demonstrated significant activity in patients with metastatic breast cancer

Table 2 Pharmacokinetic parameters of ATRA. Cmax and Tmax are observed values. The AUC and associated clearance parameters were estimated from trapezoidal calculations

Patient number	BSA (m^2)	Actual dose (mg/m^2)	Cmax (ng/ml)	Tmax (h)	$t1/2_{abs}$ (min)	$t1/2_{el}$ (min)	Vd/F (l/m^2)	AUC (μg/lh)	Cl/F ($l/h/m^2$)
1	1.80	50	266	2.3	16.3	19.3	60.6	448	112
2	1.64	49	136	2.0	na	na	na	475	103
3	1.73	52	260	6.0	na	na	na	1055+	49
4	1.82	50	276	3.0	39.8	46.3	72.0	779	63
5	1.64	49	291	1.5	49.5	30.5	68.3	646	76
6	1.67	48	184	5.0	na	na	na	451+	106
7	1.94	52	243	2.0	27.7	26.9	80.9	409	126
8	1.55	52	565	1.5	27.1	27.7	28.0	1266	41
9	1.67	48	464	2.0	12.2	42.8	61.7	807	59
10	1.49	47	321	1.5	31.2	46.4	87.2	646	73
11	1.58	51	831	2.0	26.4	45.5	28.4	1981	26
12	1.88	48	274	2.0	39.1	17.2	45.2	454	106
13	1.59	50	18	1.5	na	na	na	44	1133
14	1.87	48	17	6.0	na	na	na	na	na
15	1.66	48	470	1.5	18.0	56.1	65.1	1031	47
16	1.71	47	350	3.5	na	na	na	876	53
17	1.56	51	69	3.5	na	na	na	180	285
Mean	1.69	49	296	2.8	28.7	35.9	59.7	722	154
Median	1.67	49	274	2.0	27.4	36.6	63.4	646	74
SD	0.13	1.7	205	1.5	11.6	13.2	20.2	467	268
CV (%)	8	3	69	56	40	37	34	65	174

[6, 30]. Our data confirm the lack of activity for ATRA, as well. Among our patients we observed only one partial response and three patients with stable disease of brief duration. Even though only 14 patients were evaluable for response, the chance of missing a significantly higher response rate was low. If the true response rate was actually 25%, then the probability of seeing only one response out of the 14 patients was 10%. More significantly, if the true response rate was 35%, then the probability was only 2% of observing one or fewer responses.

The absence of significant antitumor activity in this phase II study should not preclude future studies of ATRA and other retinoids. Preclinical studies have demonstrated the ability of retinoids to prevent carcinogen-induced malignancy and to diminish proliferation of breast cancer cell lines. Direct cytotoxic effects on human breast cancers have not been demonstrated and therefore traditional measures of tumor response, such as those used to evaluate other chemotherapeutic agents, may not be appropriate for the study of retinoids. Alternative endpoints such as reduction in the rate of growth of metastatic lesions could be considered in future trials. In the adjuvant setting, prevention of contralateral breast cancer or improved survival may be more appropriate measures of the efficacy of the retinoids. However, at the time of design of this trial we elected to use the standard, but imperfect, definitions of response. Interestingly, 3 of the 14 patients in this study had stable disease, but this was only of brief duration.

In general, patients who have had less extensive prior therapy are more likely to respond to subsequent therapy. Our patients had received a moderate amount of previous therapy. Approximately 65% had been treated with one or two previous chemotherapy regimens. All nine patients who were hormone receptor positive had failed previous hormonal therapy. The hormone receptor status of our patients may have been an important factor as evidenced by recent preclinical data. ER-positive breast cancer cell lines have been shown to be sensitive to the growth inhibitory effects of retinoids where ER-negative cell lines are resistant [5]. Synergism between tamoxifen and retinoids has also been shown [4]. It is therefore possible that our results might have been different had we not looked at a population of patients with hormone-refractory disease.

The high degree of interpatient variability in systemic exposure observed following the initial dose of ATRA in this study was not anticipated. The sensitivity of our analytic method was similar to that of other investigators (Table 3). However, two of our patients displayed ATRA concentrations which were only briefly above the detection limits of the assay. The minimal systemic exposures found in some patients on our study are among the lowest of any reported in the literature, as shown in Table 3.

The exact etiology for this extremely divergent systemic exposure cannot be discerned from our results or other published data; heterogeneity in either absorption or elimination could be implicated. The bioavailability of ATRA in normal volunteers is incomplete (approximately 50%) but relatively little is known about the variability in this parameter, particularly in patients with malignancies [2,12]. Some information on absorption could be gained by measurement of metabolite concentrations in situations where extensive metabolism is suspected. However, the main metabolite of ATRA (4-oxo derivative) is generally undetectable at the doses utilized on this study, and thus we did not attempt such analyses.

A number of investigators have shown that the apparent clearance of ATRA is reduced upon repeated

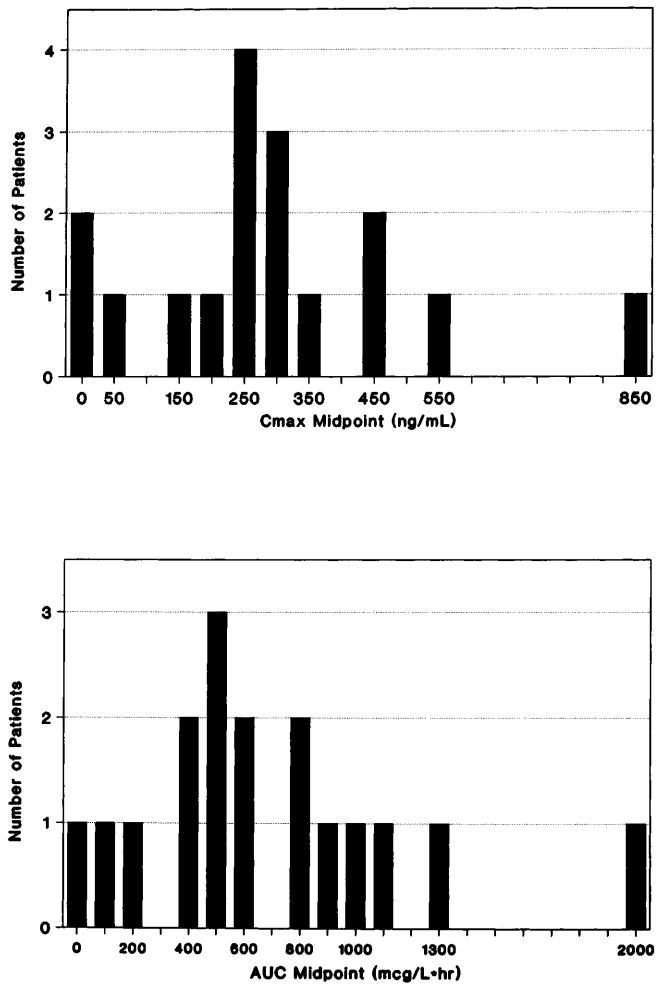

Fig. 2 Frequency distributions for maximal observed ATRA concentrations (Cmax) and area under the concentration-time curve (AUC). The values on the *x*-axis indicate the midpoint in the data distribution

administration over several days [33–35, 37, 39]. The likely etiology of this effect is an autoinduction of hepatic P450 enzymes which metabolize ATRA to its 4-hydroxy and subsequently, 4-oxo derivative. Attempts to modulate P450 function by the coadministration of metabolic inhibitors have resulted in a partial correction of the AUC deficit [38]. One study has suggested that the systemic clearance of ATRA cosegregates with that of the drug chlorzoxazone [41]. This relationship is interesting since chlorzoxazone is thought to be predominantly metabolized by the P450 isoenzyme CYP $2E_1$ and several restriction fragment length polymorphisms have been identified in the gene for that isoenzyme [10]. One would anticipate that drugs that are primarily metabolized by this pathway would display a high degree of interpatient variability. However, the biologic relevance of chlorzoxazone as a marker substrate is not yet fully established. At least one study has found no major relationships between the established genomic polymorphisms of CYP $2E_1$ and chlorzoxazone metabolism [18]. It remains intriguing that the data from two other groups, in addition to those presented here, suggest that the population systemic exposure to the initial dose of ATRA may be segregated into at least two unique groups of patients [22, 37]. An alternative explanation for a cohort of patients with relatively high systemic exposure can be found in a study conducted in monkeys which suggested that ATRA elimination could be saturable at the doses used in our trial [1]. The latter effect would result in potentially very high AUC values in a subset of individuals.

Recent work has correlated a high cellular content of physiologically generated lipid hydroperoxides with accelerated oxidative catabolism of ATRA [32]. Importantly, the regulation of these cofactors may be mediated by events that alter arachidonic acid metabolism and thus would not have to be related to previous exposure

Table 3 Comparison of ATRA systemic exposure on the first day of drug administration in the present study with that observed by other investigators with similar initial oral doses. Median values are in parentheses. *APML* acute promyelocytic leukemia, *NSCLC* non-small-cell lung cancer, HIV/KS human immunodeficiency virus positive/Kaposi's sarcoma

Diagnosis	Dosage (mg/m^2)	*N*	Cmax (ng/ml)	AUC (ng/ml h)	Comments	Reference
APML	45	15	30–2550 (380)	n/a	One patient with plasma concentrations < 3 ng/ml at all times	22
APML	45	13	95–948 (301)	247–1833 (523)		33
Solid tumors	60	2	742, 400	3800, n/a		21
NSCLC	45	31	n/a	40–2304 (319)	Only one patient with AUC < 250	36
APML	45	20	n/a	99–1894 (465)		36
Predominantly NSCLC	45	19	n/a	< 150–2400	At least five patients with AUC < 150	29
HIV/KS	40	8	151–725 (272)	378–1485 (629)		3
Breast cancer	50	17	17–831 (274)	44–1981 (646)	One patient was not evaluable for AUC because of low concentrations	Present study

to retinoids [35]. We could not find any predisposing factors which were unique to the patients with extraordinary disposition of ATRA in our study. It is unclear which of the factors mentioned above predominate in patients with very high or low ATRA systemic exposure or if others (e.g. retinoic acid-binding proteins) are important.

In conclusion, ATRA, in the dose and schedule employed in this study, was not effective in patients with hormone-refractory, metastatic breast cancer. Toxicity associated with ATRA administration was modest and would be acceptable for a chemotherapeutic agent. It would, however, be too toxic at this dose for use as a chemopreventive agent. Future studies should focus on a more intense investigation of those individuals with very high or low ATRA initial systemic exposure in the hope of expanding our understanding of ATRA's clinical pharmacology, ultimately leading to improved efficacy.

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