Cancer Chemother Pharmacol (1986) 157–161

Cancer Chemotherapy and Pharmacology

A comparative study of bisantrene given by two dose schedules in patients with metastatic breast cancer*, **

Frankie A. Holmes, Laura Esparza, Hwee Y. Yap, Aman U. Buzdar, George R, Blumenschein, and Gabriel N. Hortobagyi

Department of Medical Oncology (Medical Breast Service), The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston, TX 77030, USA

Summary. Schedule dependency of bisantrene was evaluated in refractory metastatic breast cancer. Patients were randomly assigned to receive either a single (S) bolus injection of 300 mg/m^2 (37 patients) or an injection of 80 mg/m^2 daily for 5 days (Dx5) (35 patients) every 3–4 weeks after stratification by performance status, dominant disease site, and response to prior doxorubicin therapy. All but one patient had received prior doxorubicin. Partial remission (PR) was achieved by 5 of 35 patients (14%) in the S arm and 7 of 35 patients (20%) in the D × 5 arm (P= NS). There were 4 patients who had primary refractoriness to doxorubicin but responded to bisantrene. The median number of courses was two for both arms. The median time to progression was 5 months for the responders in each arm and 3 and 4 months, respectively, for patients who showed no change in the S and D × 5 arms. Myelosuppression was dose-limiting and greater for the D × 5 arm. Drug fever (34% versus 21% of courses; P=0.02) and myalgia (22% versus 10% of courses; P=0.02) were reported more often in the D × 5 arm; malaise was greater in the S arm. Grade 2–3 nausea and vomiting occurred more often in the S arm (40% versus 10% of courses; P<0.01). Significant hypotension that was not symptomatic occurred in 1 patient in the D × 5 arm. Phlebitis occurred in 3 patients without a central line. One patient who had previously received doxorubicin and mitomycin C developed heart failure, which was controlled with medication. Bisantrene is an effective drug for metastatic breast cancer that has incomplete cross resistance to doxorubicin, and there was no schedule dependency in this study.

Introduction

Bisantrene is a synthetic anthracene derivative formulated to be as efficacious as doxorubicin, but without cardiotoxicity [5, 23]. Preclinical studies in murine tumor systems and in vitro sensitivity testing against human tumor clonogenic cells demonstrated activity in many cancers, including breast cancer [7, 14, 25]. In comparative studies of equitoxic doses of doxorubicin or bisantrene administered to beagle dogs, cardiomyopathy developed in all dogs receiving doxorubicin, but in none receiving bisantrene [5]. While the exact mechanism of action of bisantrene is not known, its tricyclic, planar, electron-rich structure suggests it intercalates DNA. Bisantrene inhibits ^{3}H-uridine incorporation into RNA and ^{3}H-thymidine incorporation into DNA more effectively than doxorubicin. Cytotoxicity is not cell cycle phase specific [5]. Pharmacokinetic studies in patients given 260–300 mg/m^2 over 1–2 h showed triphasic plasma disappearance curves with a terminal half-life of 44 h. Less than 7% of the drug was excreted in the urine [1]. Greater than 60% of bisantrene was bound to plasma proteins, and biliary excretion was observed. Enterohepatic circulation was postulated [18].

Phase I trials explored three schedules: a single (S) i.v. injection on day 1 repeated every 21–28 days, a daily i.v. injection on days 1–5 (D × 5) repeated every 28 days, and a weekly i.v. injection in weeks 1–3, repeated every 5 weeks [1, 6, 23, 26, 29]. In five phase II studies in patients with metastatic breast cancer, bisantrene was given by an S schedule at a dose of 250–300 mg/m^2. Partial remission (PR) occurred in 4%–22% of patients. Granulocytopenia was the dose-limiting toxicity, but anaphylaxis and phlebitis caused termination of therapy in a minority. Drug fever and hypotension were infrequent [4, 9, 20, 21, 30]. In the phase II study using the D × 5 schedule bisantrene was given at a dose of 60 mg/m^2 per day for 5 days [6].

In the phase I trial the total dose of absantrene administered in each course with the D × 5 schedule was greater than that given by the S schedule. However, few patients received more than two courses [23]. Our experience with vinblastine suggested that dose and schedule were critical determinants of response and toxicity [10, 28, 31]. On the basis of these data and the information from the previously mentioned early trials, a comparative study of two schedules and doses was designed to determine which schedule was more effective and less toxic.

Material and methods

Between June 1982 and February 1983, 76 patients with refractory metastatic breast cancer were entered in this study. Patients had a Zubrod performance status ≤3; a life expectancy of 8 weeks or greater; and had not received chemotherapy, hormonal therapy or radiotherapy for at

* Presented, in part, at the 8th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, November 7–8, 1985

** This study was supported by a grant from American Cyanamid Company, Medical Research Division, Lederle Laboratories

Offprint requests to: Frankie Ann Holmes, Department of Medical Oncology, Box 78, U. T. M. D. Anderson Hospital, 6723 Bertner Avenue, Houston, TX 77030, USA

least 3 weeks. Patients were required to have measurable lesions which could be evaluated for antitumor effect, adequate bone marrow function (defined as a peripheral absolute granulocyte count of $\geq 2000/mm^3$ and a platelet count of $\geq 100000/mm^3$) unless cytopenias were caused by tumor, adequate renal function (defined as a serum creatinine of <2.5 mg/dl), and adequate hepatic function (defined as a bilirubin of ≤ 2 mg/dl) unless hepatic dysfunction was caused by tumor, in which case a bilirubin of ≤ 5 mg/dl was acceptable. Patients who had received cumulative doses of ≥ 350 mg/m^2 doxorubicin were required to have a left ventricular ejection fraction (EF) ≥ 0.50 as measured by echocardiography or gated radionuclide cardiac scan. If there was a history of congestive heart failure at any time during the administration of prior chemotherapy, despite an adequate EF, an endomyocardial biopsy was performed. Biopsies were graded on a modified Billingham scale [15]. A biopsy score <1.5, signifying the absence of myofibrillar necrosis, was required for entry. Pretreatment evaluation included a complete history, physical examination, complete blood count with differential count, chemistry profile, serum carcinoembryonic antigen assay, and documentation of all measurable disease with chest X-ray, bone X-rays and scans, and liver scans, ultrasound, or computed tomography as appropriate. Physical examination and review of blood work was done every 3–4 weeks. Selective X-rays and scans were performed after every two to three courses, to evaluate tumor response. Evaluation of left ventricular function was repeated after every four courses of therapy. Written informed consent approved by the Institutional Review Board was obtained from all patients.

All patients were stratified by performance status, number of organ sites involved, dominant disease site, prior response to doxorubicin combination chemotherapy (responders or nonresponders), and menopausal status. Matching patients were randomly allocated to receive either the S schedule or the D × 5 schedule. Treatments were repeated every 21 days or whenever the absolute granulocyte count was $1500/mm^3$ or more and the platelet count was $\geq 100-000/mm^3$ or more. The S treatment consisted of 300 mg/m^2 bisantrene in 1000 ml D5W administered over 2 h. Patients with bilirubin ≥ 2 but ≤ 5 mg/dl, and patients with poor bone marrow reserve caused by prior therapy (poor risk), were given 250 mg/m^2. The D × 5 treatment consisted of 80 mg/m^2 bisantrene in 500 ml D5W over 2 h on days 1–5 of each treatment cycle. Poor-risk patients received 60 mg/m^2 bisantrene daily. Doses in subsequent courses were modified by 20% to maintain a lowest recorded granulocyte count of ≥ 500 and $\leq 1000/mm^3$ and a platelet count of ≥ 50000 and $\leq 100000/mm^3$. The occurrence of infection or hemorrhage during a period of cytopenia required a 20% dose reduction. Toxicities were graded according to standard WHO criteria [17]. Blood pressure and pulse were monitored immediately before treatment, at 5 min after the start of the infusion, then every 15 min during infusion and at 30 and 60 min after completion of the infusion.

Standard UICC definitions of response categories were used [11]. Time to response (TTR) was defined as the interval from initiation of therapy until first evidence of response. Time to progression (TTP) was defined as the interval from the start of therapy until the first evidence of progressive disease. Statistical analyses of the results in each group were performed by chi-square tests or Mann-Whitney tests, as appropriate, for categorical or continuous variables, respectively.

Results

In all, 39 patients were entered in the S and 37 in the D × 5 arms. Two patients in each arm were not evaluable for response. One patient failed to return after the second course of therapy. One patient did not receive the drug. One patient developed aspiration pneumonia on day 9 of the first course of treatment and died on day 16. One patient received concomitant treatment with prednisone and megestrol acetate. Patient characteristics are noted in Table 1. The two arms were statistically similar with respect to age, disease-free interval, menopausal status, estrogen receptor status, median number of prior chemotherapy treatments, response to prior doxorubicin therapy, cumulative dose of prior doxorubicin, number of disease sites, dominant sites of disease, and performance status. The median number of courses for each arm was two. No patient attained CR. There were 5 (14%) patients in the S arm and 7 (20%) patients in the D × 5 arm for whom PR was recorded. No change was seen in 8 (22%) and 5 (14%) patients in the S

Table 1. Patient characteristics

	Single	Daily × 5
Number entered	39	37
Number evaluable for response	37	35
Median age (year)	50	51
Range	28–70	36–68
Median time disease-free (mo)	23	14
Range	0–101	0–94
Percent premenopausal	32	29
ER status (%)		
Positive	30	23
Unknown	27	31
Median no. of prior chemotherapies	3	3
Range	1–6	1–6
No. of pts treated with hormones	23	25
Median no. of prior hormone therapies	1	2
Range	1–3	1–4
% of pts with prior doxorubicin (Dox)	97	100
% OR with Dox	36	50
% NC with Dox	39	31
% PD with Dox	11	11
% with Dox as adjuvant only	14	11
Median dose of prior Dox (mg/m^2)	370	440
Range	100–857	90–750
Median no of disease sites	2	2
Range	1–5	1–5
% Pts with dominant disease		
Visceral	67	54
Osseous	22	31
Soft tissue	11	20
Median Zubrod performance status	2	1
Range	0–3	0–3

Both arms statistically comparable (Mann-Whitney or chi-square tests as appropriate)
OR, objective response: NC, no change; PD, progressive disease

Table 2. Non-hematologic toxicity

	Single	Daily × 5	*P*
Nausea/vomiting			
% Grade 0–1	60	90	<0.01
% Grade 2–3	40	10	
Stomatitis grade 2+ (%)	6	2	
Diarrhea (%)	2	10	
Hemorrhage (%)	1	0	
Drug fever			
% Grade 1	5	18	0.02
% Grade 2–3	16	16	
Malaise grade 2–3 (%)	37	15	<0.01
Myalgia grade 2–3 (%)	10	22	0.02
Phlebitis (No. of pts)[a]	1	2	
% Courses with neutropenia and			
Fever	2	6	
Infection	2	3	
% Courses without neutropenia			
With fever	2	0.7	
With infection	5	6	

[a] Did not have central venous catheter

Table 3. Hematologic toxicity

Lowest recorded granulocyte count ($/mm^3 \times 10^3$)	Course number 1	2	3	6
Single	600	601	728	288
range	33–1736	3–3355	320–1372	64–855
Daily × 5	168	233	321	287
range	0–1125	0–1428	5–980	94–308
Platelet count ($/mm^3 \times 10^3$)				
Single	146	189	188	112
range	18–399	19–375	91–284	70–240
Daily × 5	159	138	157	120
range	12–324	39–357	84–354	86–258
Number of pts w/ data				
Single	33	24	12	5
Daily × 5	31	26	10	3
Median dose bisantrene				
Single	300	300	376	384
Daily × 5	400	340	300	324

* $P<0.01$; ** $P=0.01$

and D × 5 arms, respectively. These results were not significantly different. The median TTP was 5 months for the responders in each arm and 3 and 4 months, respectively, for patients who showed no change in the S and D × 5 arms. The median TTR was 2 and 3½ months for the S and D × 5 arms. Objective responses to bisantrene were seen in 4 patients who had shown primary refractoriness to prior doxorubicin and in 5 patients who had developed secondary resistance to doxorubicin.

Nonhematologic toxicity is shown in Table 2. Nausea and vomiting were the most common side effects and were more severe in the S arm, as was malaise. Drug fever and myalgia were more common in the D × 5 arm, but occurred in less than one-third of the courses. One patient discontinued therapy because of myalgias. Three patients who did not have central venous catheters experienced serious phlebitis. Infectious complications were infrequent in either arm. Of 133 courses given according to the S schedule and 127 courses given according to the D × 5 schedule, only 2 and 4 courses, respectively, were complicated by documented infections during neutropenia and only 3 and 7 courses, respectively, resulted in a fever of unknown source during neutropenia. One patient experienced fatal hemorrhage from a known peptic ulcer when the platelet count was 27000/mm³.

While most patients experienced an increase in pulse rate and a decrease in blood pressure, this was rarely symptomatic or serious. There was no evidence of a daily cumulative decrease in blood pressure in the D × 5 arm. In one patient in the D × 5 arm, bisantrene was discontinued when the blood pressure decreased from 100/70 to 80/46 mm Hg at 45 min after initiation of the infusion. Fluids were given i.v. and the blood pressure returned to the baseline within 5 min. The patient had no other symptoms and bisantrene was infused on the following day.

Congestive heart failure occurred in two patients in the S arm. However, direct bisantrene cardiotoxicity was plausible only in one patient. The other patient experienced a subendocardial myocardial infarction resulting from hypotension caused by sepsis. She had received only 700 mg/m² bisantrene. The first patient had previously received 750 mg/m² doxorubicin, 300 mg/m² of which was administered by continuous infusion with 13 mg/m² mitomycin C. One year before treatment with bisantrene, she had developed congestive heart failure and been given digoxin. Before treatment with bisantrene, the EF was 0.65 and a transvenous endomyocardial biopsy of the septum showed grade 0.5 changes [28]. After six courses (2400 mg/m²) of bisantrene, the patient developed shortness of breath. The EF was 0.46 at rest and 0.47 with exercise. No further bisantrene was given and the EF was 0.60 when measured 5 months later.

Granulocytopenia was dose-limiting and more severe for the D × 5 arm, which received 33% more drug (Table 3). More than half the patients on the D × 5 arm experienced grade 4 leukopenia, as against a median of grade 3 leukopenia on the S arm. Dose reduction was required in the D × 5 arm while doses were increased in some patients in the S arm.

Discussion

These data confirm our previous results that bisantrene is an active drug in metastatic breast cancer and show that activity is identical whether it is given by the S or the D × 5 schedule. Pharmacokinetic data have shown the drug has a 44-h terminal half-life. The long half-life and the absence of proven cardiotoxicity do not provide a rational basis for prolonged infusions [5, 18]. Although the initial studies suggested that patients were able to tolerate greater total doses of bisantrene when it was given in small amounts on a D × 5 schedule, this study showed that most patients required a subsequent reduction in dose because of severe granulocytopenia [23]. Conversely, most patients tolerated

mild dose escalation to 340 mg/m^2 when bisantrene was given by the S schedule. While a few patients in each arm received 13 courses, most patients received 2 or fewer courses, so they could not be evaluated for cumulative toxicity.

Of the 12 responding patients in this study, 4 had shown primary refractoriness and 5 had shown secondary resistance to doxorubicin. This was also noted by other investigators and suggests incomplete cross resistance to doxorubicin [20].

Subjective toxicities were minimal, although the severity of nausea and vomiting was somewhat greater in the S schedule. This was similar to our previous experience with doxorubicin given by a continuous infusion schedule, which produced significantly less nausea and vomiting than the bolus injection schedule [16]. More patients in the S arm experienced myalgias. Since the total dose of bisantrene was greater in the D × 5 arm, this may reflect schedule differences. Whether the incidence of grade 2–3 drug fever and myalgia reflects a schedule or a dose effect is impossible to determine. These effects occurred more often in the D × 5 arm, in which patients received a higher total dose per courses initially. Drug fever was observed in a minority of courses, but it was not dose- or schedule-dependent. A decrease in the blood pressure and an increase in the pulse rate occurred regularly, but these were not hemodynamically significant. No episodes of anaphylaxis occurred in this study – although that is a recognized, though infrequent, complication of bisantrene which occurs after multiple exposures without any other known predisposing factors [19]. The incidence of anaphylaxis is probably no higher than with other commonly used agents, particularly cisplatin [27]. With the current formulation of bisantrene, chemical phlebitis is a serious problem unless the drug is administered through a central venous catheter. Recently, some investigators have sought to exploit this as an advantage in regional therapy [13].

Despite the significant differences in the lowest recorded granulocyte counts between patients in each arm, there was no difference in the incidence of infectious complications during periods of neutropenia. This may be explained by the relatively rapid recovery of granulocyte counts, since the occurrence of infection has been shown to correlate with the duration of granulocytopenia [2, 8]. This suggests that bisantrene would be a useful drug in combination therapy.

The limited data in this study cannot illuminate the question of bisantrene cardiotoxicity. One patient with significant exposure to other cardiotoxic agents experienced congestive heart failure associated with a marked decrease in left ventricular EF that reversed with cessation of further bisantrene [3]. The initial experience with mitoxantrone, an anthraquinone that also appeared to have less potential for cardiotoxicity, has revealed potentiation of doxorubicin toxicity as wll as direct cardiotoxicity in previously untreated patients [3, 12, 22].

Bisantrene is an active drug in metastatic breast cancer, which has incomplete cross-resistance to doxorubicin; there was no schedule dependency in this study.

Acknowledgement. The authors would like to thank Vickie E. Richard for her help in the preparation of this manuscript.

References

1. Alberts DS, Mackel C, Pocelinko R, Salmon SE (1982) Phase I clinical investigation of 9,10-anthracenedicarboxaldehyde bis [4,5-dihydro-1*H*-imidazol-2-yl) hydrazone dichloride with correlative in vitro human tumor clonogenic assay. Cancer Res 42: 1170
2. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 61: 328
3. Buzdar AU, Legha SS, Tashima CK, Hortobagyi GN, Yap HY, Krutchik AN, Luna MA, Blumenschein GR (1978) Adriamycin and mitomycin C: Possible synergistic cardiotoxicity. Cancer Treat Rep 62: 1005
4. Cavalli F, Gerard B, ten Bokkel Huinink W, Clavel M, Rosencweig M (1985) Phase II evaluation of bisantrene in metastatic breast cancer. Cancer Treat Rep 69: 337
5. Citarella RV, Wallace RE, Murdock KC, Angier RB, Durr FE, Forbes M (1982) Activity of a novel anthracenyl bishydrazone, 9, 10-anthracenedicarboxaldehyde-bis [(4,5-dihydro--1*H*-imidazol-2-yl]hydrazone) dichloride, against experimental tumors in mice. Cancer Res 42: 440
6. Coltman CA Jr, Osborne KC (1984) Bisantrene, biological and clinical effects. Cancer Treat Rev 11: 285
7. Cowan JD, Osborne CK, Neidhart JA, Von Hoff DD, Constanzi JJ, Vaughn CB (1985) A randomized trial of doxorubicin, mitoxantrone and bisantrene in advanced breast cancer (A South West Oncology Group Study). Invest New Drugs 3: 149
8. Esparza L, Yap HY, Smith T, Blumenschein G, Bodey GP (1983) Quantitative relationships between degree of myelosuppression and infection in patients with metastatic breast cancer. Proc Am Soc Clin Oncol 2: 89 (Abstract C-348)
9. Forastiere AA, Perry MC, Hughes AK, Wood WC (1984) Bisantrene (NSC 337766) (CL 216,942) in advanced breast cancer. A Cancer and Leukemia Group B study. Cancer Chemother Pharmacol 13: 226
10. Fraschini G, Yap HY, Hortobagyi GN, Buzdar AU, Blumenschein GR (1985) Five-day continuous infusion vinblastine in the treatment of breast cancer. Cancer 56: 225
11. Hayward JL, Rubens RD, Carbone PP, Heuson JC, Kumaoka S, Segaloff A (1977) Assessment of response to therapy in advanced breast cancer. Br J Cancer 35: 292
12. Holmes F, Yap H, Buzdar A, Esparza L, Hortobagyi G, Blumenschein GR, Bodey G (1984) Sequential chemotherapy with mitoxantrone, cyclophosphamide, and fluorouracil followed by doxorubicin and vinblastine in hormone unresponsive advanced breast cancer. Br Cancer Res Treat 4: 354 (abstract 78)
13. Kovach JS, Buck M, Tsukamoto T, Odegaard A, Lieber MM (1985) Regional targeting of bisantrene by directed intravascular precipitation. Cancer Chemother Pharmacol 15: 192
14. Kuhn JG, Von Hoff DD, Myers W, Coltman CA Jr (1983) Phase I and II trials with bisantrene hydrochloride. In: Rosencweig M, Von Hoff DD, Staquet MJ (eds) New anticancer drugs: mitoxantrone and bisantrene. Raven, New York, p 143
15. Legha SS, Benjamin RS, MacKay B, Ewer M, Wallace S, Valdivieso M, Rasmussen SH, Blumenschein GR, Freireich EJ (1982a) Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann Intern Med 96: 133
16. Legha SS, Benjamin RS, Mackay B, Yap HY, Wallace S, Ewer M, Blumenschein GR, Freireich EJ (1982b) Adriamycin therapy by continuous intravenous infusion in patients with metastatic breast cancer. Cancer 49: 1762
17. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
18. Muggia FM, Spiegel RJ, Gams RA, Levin M, Cumps E, Ostroy F (1983) Clinical development of bisantrene: A novel anthracene derivative. In: Rosencweig M, Von Hoff DD, Staqu-

et MJ (eds) New anticancer drugs: mitoxantrone and bisantrene. Raven, New York p 175
19. Myers JW, Von Hoff DD, Kuhn JG, Osborne CK, Sandbach JF, Pocelinko R (1983) Anaphylactoid reactions associated with bisantrene infusions. Invest New Drugs 1: 85
20. Osborne CK, Von Hoff DD, Cowan JD, Sandbach J (1984) Bisantrene, an active drug in patients with advanced breast cancer. Cancer Treat Rep 68: 357
21. Pandya KJ, Muggia FM, Skeel RT, Falkson GF, Kaplan BM, Ettinger DS (1985) Phase II study of bisantrene in advanced refractory breast cancer: An Eastern Cooperative Oncology Pilot Study. Am J Clin Oncol 8: 353
22. Schell FC, Yap HY, Blumenschein G, Valdivieso M, Bodey G (1982) Potential cardiotoxicity with mitoxantrone. Cancer Treat Rep 66: 1641
23. Spiegel RJ, Blum RH, Levin M, Pinto CA, Wernz JC, Speyer JL, Hoffman KS, Muggia FM (1982) Phase I clinical trial of 9,10-anthracene dicarboxaldehyde (bisantrene) administered in a five-day schedule. Cancer Res 42: 352
24. Unverferth DV, Bashore TM, Magorien RD, Fetters JK, Neidhart JA (1984) Histologic and functional characteristics of human heart after mitoxantrone therapy. Cancer Treat Symp 3: 47
25. Von Hoff DD,Coltman Jr CA, Forseth B (1981a) Activity of 9-10 anthracenedicarboxaldehyde bis [(4,5-dihydro-1*H*-imidazol-2-yl(hydrazone) dihydrochloride (CL 216,942) in a human tumor cloning system. Leads for phase II trials in man. Cancer Chemother Pharmacol 6: 141
26. Von Hoff DD, Myers JW, Kuhn J, Sandbach JF, Pocelinko R, Clark G, Coltman CA Jr (1981) Phase I clinical investigation of 9,10-anthracenedicarboxaldehyde bis [(4,5-dihydro-1*H*-imidazol-2-yl) hydrazone] dihydrochloride (CL 216, 942). Cancer Res 41: 3118
27. Weiss RB (1982) Hypersensitivity reactions to cancer chemotherapy. Semin Oncol 9: 5
28. Yap HY, Blumenschein GR, Keating MJ, Hortobagyi GN, Tashima CK, Loo TL (1980) Vinblastine given as a continuous 5-day infusion in the treatment of refractory advanced breast cancer. Cancer Treat Rep 64: 279
29. Yap BS, Yap HY, Blumenschein GR, Bedikian A, Pocelinko R, Bodey GP (1982) Phase I clinical evaluation of 9,10-anthracendicarboxaldehyde [bis(4,5-dihydro-1*H*-imidazol-2-yl)-hydrazone) dihydrochloride (bisantrene). Cancer Treat Rep 66: 1517
30. Yap HY, Yap BS, Blumenschein GR, Barnes BC, Schell FC, Bodey GP (1983) Bisantrene, an active new drug in the treatment of metastatic breast cancer. Cancer Res 43: 1402
31. Yau JC, Yap YY, Buzdar AU, Hortobagyi GN, Bodey GP, Blumenschein GR (1985) A comparative randomized trial of vinca alkaloids in patients with metastatic breast carcinoma. Cancer 55: 337

Received February 11, 1986/Accepted May 27, 1986