Cancer Chemother Pharmacol (2007) 60:61–67
DOI 10.1007/s00280-006-0348-9

ORIGINAL ARTICLE

Phase II trial of 10-EDAM in the treatment of metastatic breast cancer

Garth A. Beinart · Ana M. Gonzalez-Angulo · Kristine Broglio · Debbie Frye · Ronald Walters · Frankie Ann Holmes · Shivaji Gunale · Daniel Booser · Julian Rosenthal · Kapil Dhingra · James A. Young · G. N. Hortobagyi

Received: 5 July 2006 / Accepted: 4 September 2006 / Published online: 29 September 2006

Abstract
Introduction This phase II trial was conducted to assess the efficacy and safety of 10-Ethyl-10-Deaza-Aminopterin (10-EDAM), a folate antagonist, in metastatic breast cancer patients who had received no more than one prior chemotherapy regimen.
Methods Fifty-five patients were treated on an initial weekly dose 80 mg/m^2 of 10-EDAM. Patients who had received a prior chemotherapy regimen in the adjuvant setting (group 1) were considered separately from patients who had received a prior chemotherapy regimen in the metastatic setting (group 2).
Results The response rate for both groups combined was 18%, and median time to progression was 3 months. Median overall survival was 12 months. Treatment was associated with common chemotherapy-related toxicities, such as 25% grade three or four neutropenia and 20% grade three or four stomatitis.
Conclusion In patients with metastatic breast cancer who had received one prior chemotherapy regimen, 10-EDAM was well tolerated. In general, while definite antitumor activity was documented, time to progression was brief.

Funding: supported by grants UO1 CA70172 and 2P30 CA016672 of the National Cancer Institute and by the Nellie B. Connally Breast Cancer Research. All authors have read and approved the manuscript. All participants in the study signed an IRB-approved informed consent form, in keeping with institutional and federal regulations. There are no other conflicts-of-interest present.

G. A. Beinart · A. M. Gonzalez-Angulo · D. Frye · R. Walters · F. A. Holmes · D. Booser · G. N. Hortobagyi
Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
e-mail: agonzalez@mdanderson.org

D. Frye
e-mail: dfrye@mdanderson.org

R. Walters
e-mail: rwalters@mdanderson.org

D. Booser
e-mail: dbooser@mdanderson.org

G. N. Hortobagyi
e-mail: ghortoba@mdanderson.org

K. Broglio
Department of Biostatistics and Applied Mathematics, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
e-mail: kbroglio@mdanderson.org

S. Gunale
Indiana Regional CCOP (Community Clinical Oncology Protocol), Indianapolis, IN, USA

J. Rosenthal
Kings County MB CCOP, Brooklyn, MI 49307, USA

K. Dhingra
Hoffman La Roche Inc, Nutley, NJ, USA

J. A. Young
Natalie W. Bryant CC and Colorado Cancer Research Program, Tulsa, OK, USA

G. A. Beinart (✉)
Department of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Unit 10, 1515 Holcombe Boulevard, Houston, TX 77030, USA
e-mail: gbeinart@mdanderson.org

Keywords Chemotherapy · Toxicity · Folic acid antagonist · Clinical trial

Introduction

Breast carcinoma is the most common malignancy in the United States among women, and accounts for the second most female cancer deaths [1]. Approximately one-third of all breast cancer patients will develop metastatic disease [2]. Significant improvements in survival from first relapse have occurred over the past two decades, coinciding with advances in breast cancer treatment [3, 4]. Single agent chemotherapy for metastatic breast cancer has produced response rates from 20 to 50%, with median duration of survival of 18–24 months [2, 5]. Although combination chemotherapy shows significant improved response rates and disease-free survival compared to single agent chemotherapy, there is only a modest improvement in overall survival and significantly worse toxicities for combination therapy [6].

Methotrexate has been used in the past as a single-agent chemotherapy in breast cancer, but it is more commonly administered in the adjuvant setting in the combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) [7]. 10-Ethyl-10-Deaza-Aminopterin (10-EDAM, also known as EDX or Edatrexate), is an analog of methotrexate (MTX) with improved pre-clinical activity, formed by the modification of the N10 position of the 4-aminofolate [8]. 10-EDAM has shown a 3.2-fold more potent inhibition of dihydrofolate reductase in breast cancer cell lines and an increased therapeutic index in animal models [9]. In phase I and II trials, 10-EDAM has demonstrated activity in head and neck, non-small cell lung cancer (NSCLC), and breast cancer patients [10, 11]. Two different phase II studies, each assessing 32 patients using 10-EDAM as first-line chemotherapy for metastatic breast cancer, yielded response rates of 34 and 41% [12, 13].

Because of promising preclinical and clinical data, a phase II trial was initiated at MD Anderson Cancer Center in Houston, TX, enrolling patients from April 1991 to February 1992 to assess to the toxicity and response rates of 10-EDAM in metastatic breast cancer patients who had received no more than one prior chemotherapy regimen.

Patients and methods

Inclusion criteria

Between April 1991 and February 1992, 55 patients with documented and measurable metastatic breast cancer were enrolled in Protocol DM90-086 at MD Anderson Cancer Center and associated CCOP (Community Clinical Oncology Protocol) sites. Patients had received no more than one previous chemotherapy regimen, not including MTX, and then relapsed. Patients who received a prior chemotherapy regimen in the adjuvant setting (group 1) were considered separately from patients who received a prior chemotherapy regimen in the metastatic setting (group 2). For adjuvant patients at least 12 months must have elapsed since previous chemotherapy. For non-adjuvant patients, at least 3 weeks must have elapsed since prior chemotherapy before enrollment on the trial. No hormonal, radiation, nor other investigational therapy was permitted concurrently nor within 3 weeks of entrance into the study. Other eligibility criteria included a life-expectancy of >12 weeks, a Zubrod scale performance status ≥ 2, a white count of at least 4,000 mm^{-3}, an absolute granulocyte count of at least 1,500 mm^{-3}, and a platelet count of at least 100,000 mm^{-3}. In addition, patients required a bilirubin of no greater than 1.5 mg/dL, a SGPT of no more than 1.5× the upper limit of normal, and a serum creatinine of no greater than 1.5 mg/dL. Patients with brain metastases were eligible, providing other measurable disease existed. All participants signed an IRB-approved informed consent form, in keeping with institutional and federal regulations.

Exclusion criteria

Patients were excluded if they were pregnant, had clinically significant third-space fluid collections, or had a history of a prior malignancy, unless there was no recurrence for at least 5 years. Patients with unstable angina, congestive heart failure, serious concomitant infection, or inability to participate as an outpatient weekly were not permitted in the study.

Evaluation before and during treatment

The pretreatment evaluation included a complete medical history and physical, laboratory studies, documentation of all measurable disease, and radiographic studies including chest X-ray, CT scan of the abdomen, and radionucleotide bone scan. While on treatment, a weekly history and physical, CBC, serum creatinine and SGPT were performed. SMA-12 electrolyte panel was performed at least every 5 weeks. Appropriate radiographic studies were repeated once every 5 weeks. All relevant information regarding drug dosage, tumor response, laboratory evaluation, and treatment-related toxicities were recorded prior administration of each treatment.

Treatment plan

The starting dose (level 0) of 10-EDAM was 80 mg/(m^2 week) for all 5 weeks given on days 1, 8, 15, 22, and 29. Subsequent courses of weekly 10-EDAM were started on day 36 if therapeutic effects were evident and toxicity permitted. The concentration of 10-EDAM was 12.5 mg/mL diluted into 50 mL normal saline and administered as an intravenous infusion over 20–30 min. Dosages were adjusted according to the development of toxicities. All toxicities encountered during the study were evaluated by the common toxicity criteria, grades 0–4. There was no dose reduction for grade 1 hematologic toxicity. Weekly doses of 10-EDAM were withheld in patients with grade 2 or greater mucositis or other major organ toxicity until the toxicity resolved. Subsequent doses were administered at the original level for grade 2 toxicities and at 50% of the original level for grade 3 or 4 toxicities. Patients showing no toxicity after 5 weekly doses had their weekly dose increased to the next dose level. Dose levels were as follows: dose level −2: 40 mg/(m^2 week), dose level −1: 60 mg/(m^2 week), dose level 0: 80 mg/(m^2 week) (starting dose), dose level +1: 100 mg/(m^2 week), and dose level +2: 120 mg/(m^2 week). Leucovorin 15 mg orally every 6 h for 8 doses was given to patients who developed mucositis within 24 h after 10-EDAM dose. Patients who developed progression of disease after a minimum of 3 weekly doses of 10-EDAM had protocol treatment discontinued. Patients with stable disease or objective responses remained on treatment until evidence of disease progression or unacceptable toxicity occurred. Complete response (CR) was defined as disappearance of all clinical evidence of tumor, persisting for 4 weeks. Partial response (PR) was defined as 50% or greater reduction in the sum of the products of the longest perpendicular diameters of all measured lesions persisting for a minimum of 4 weeks. Progressive disease (PD) was any increase in >25% of the sum of the products of diameters of any measurable disease or unequivocal new lesions. No change or stable disease (SD) was any regression not meeting CR/PR criteria and no evidence of progression as defined by PD above.

Statistical considerations

The primary objective of this study was to determine the efficacy, as measured by response rate, of 10-EDAM. In each group, response was to be assessed in the first 14 patients. If no responses were observed, further recruitment to that group was to be terminated. If one or more responses were observed, the group was to enroll an additional 16 patients in order to estimate the response rate with a standard error no greater than 10%.

Patient characteristics were tabulated. Response rates were estimated and presented with their exact binomial 95% confidence intervals. Patients not evaluable for response were considered non-responders. Overall survival was measured from the start of treatment to the date of death from any cause or last follow-up. Progression-free survival was measured from the date of treatment start to the date of disease progression or last follow-up. Patients who died before experiencing disease progression were considered censored in the analysis of progression-free survival. Survival outcomes were estimated by the Kaplan–Meier method. Median follow-up was calculated as the median observation time among all patients.

Results

Patient demographics

This study enrolled a total of 55 patients, 21 in group 1 and 34 in group 2, from April 1991 to February 1992. Table 1 shows the tabulation of patient characteristics. Among patients in group 1, median age was 59, 86% were white, 95% had received prior chemotherapy, 57% had received prior hormonal therapy, 62% had received prior radiotherapy, the median number of metastatic sites was 2, and 67% had visceral metastasis. Among patients in group 2, the median age was 56.5, 68% were white, all patients had received prior chemotherapy, 59% received prior hormonal therapy, 47% received prior radiotherapy, the median number of metastatic sites was 2, and 62% had visceral metastasis. Menopause status, nuclear grade, and hormonal receptor status were unknown for most patients.

Efficacy

Table 2 shows the tabulation of responses by group. In group 1, 5 patients achieved a PR (23.8%, 95% CI = 8.2%, 47.2%) and 9 patients achieved stable disease or better (SD + PR) (42.9%, 95% CI = 21.8%, 66.0%). In group 2, 5 patients achieved a PR (14.7%, 95% CI = 5.0%, 31.1%) and 15 patients achieved stable disease or better (44.1%, 95% CI = 27.2%, 62.1%). Combining both groups, 10 patients achieved a PR (18.2%, 95% CI = 9.1%, 30.9%) and 24 patients achieved stable disease or better (43.6%, 95% CI = 30.3%, 57.7%).

Table 1 Patient characteristics

	N	Percent	*N*	Percent
N	21	–	34	–
Median age, years (range)	59 (37,76)	–	56 (38,75)	
Race				
Black	2	9.5	5	14.7
Hispanic	1	4.8	5	14.7
Other	0	0.0	1	2.9
White	18	85.7	23	67.6
Menopause status				
Post-surgical	1	20.0	3	20.0
Post-Natural	2	40.0	6	40.0
Pre	2	40.0	6	40.0
Prior CT				
Yes	20	95.2	34	100
No	1	4.8	0	0.0
Prior HT				
Yes	12	57.1	20	58.8
No	9	42.9	14	41.2
Prior XRT				
Yes	13	61.9	16	47.1
No	8	38.1	18	52.9
Number of metastasis sites				
Minimum	1	–	1	–
Median	2	–	2	–
Maximum	5	–	7	–
Dominant metastasis site				
bone	3	14.3	7	20.6
Subcutaneous tissue	4	19.0	6	17.6
Visceral	14	66.7	21	61.8

Table 2 Response to treatment

	Group1		Group 2	
	N	Percent	*N*	Percent
Non-evaluable	1	4.8	1	2.9
SD	4	19.0	10	29.4
PD	11	52.4	18	52.9
PR	5	23.8	5	14.7

Tables 3 and 4 show the estimates of overall survival and progression-free survival, respectively. Median follow-up was 11.8 months (range 2.5–150.0 months). In group 1, all 21 patients died and median overall survival was 12.8 months (range 2.5–64.5 months). In group 2, 33 out of 34 patients have died and median overall survival was 11.6 months (range 3.8–69.5 months). In both groups combined, median overall survival was 11.8 months (Fig. 1).

In group 1, all 21 patients experienced disease progression and median time to progression was 3.1 months (range 1–18.1 months). In group 2, 31 out of 34 patients have experienced disease progression and median time to progression was 2.6 months (range 0.4–31.5 months). In both groups combined, median time to progression was 3.0 months (Fig. 2).

Most patients were taken off the study due to disease progression. In group 1, 16 patients (76%) were removed because of disease progression. Among the rest of this group, 1 patient (5%) refused and 4 patients (19%) had treatment discontinued due to toxicity. In group 2, 28 patients (82%) had disease progression while 3 patients (9%) were removed secondary to toxicity. Three individual patients had discontinuation for treatment due to non-response, noncompliance, and refusal, respectively.

Safety

All patients enrolled in the study were included in the safety analysis. Table 5 reports the toxicities of patients while receiving 10-EDAM. The majority of adverse events were mild to moderate in severity.

Common nonhematologic events were typical of chemotherapy-related toxicities, including fatigue, nausea, alopecia, anorexia, and diarrhea. Skin reactions were observed in 35% of patients, with 9% having grade three or four skin toxicity. Stomatitis was present in 67% of patients, with 20% representing grade three or four reactions. Transaminases increased in 55% of patients, and 15% experienced grade three or four transaminase increases.

Hematologic toxicity was relatively common. Grade three or four leukopenia and granulocytopenia were 11 and 25%, respectively. Fourty-four percent of patients suffered from anemia, with only 4% being grade three or four. Thrombocytopenia was noted in 27% of patients, with 11% of those having grade three or four.

Discussion

This open-label phase II trial evaluated the efficacy and safety of 10-EDAM on metastatic breast cancer patients who had received no more than one prior chemotherapy regimen. The trial was designed to estimate response rates in two separate groups, one with prior chemotherapy in the adjuvant setting and the other with prior chemotherapy in the metastatic setting. Over half of the patients on 10-EDAM achieved stable disease or better.

Overall survival of patients on the trial was approximately 12 months. Though no other single-agent chemotherapy shows significant improvement in overall survival, 10-EDAM does not measure up to currently

Table 3 Overall survival estimates

	N	No events	Median (months)	1 Year estimate (%)	95% Confidence interval	3 Year estimate (%)	95% Confidence interval	5 Year estimate (%)	95% Confidence interval
Group 1	21	21	12.8	52.4	(34.8%, 78.8%)	14.3	(5%, 40.7%)	4.8	(0.7%, 32.2%)
Group 2	34	33	11.6	44.1	(30.2%, 64.4%)	11.8	(4.7%, 29.5%)	5.9	(1.5%, 22.6%)
Combined	55	54	11.8	47.3	(35.8%, 62.5%)	12.7	(6.4%, 25.4%)	5.5	(1.8%, 16.4%)

Table 4 Progression-free survival

	N	No events	Median (months)	6 Month estimate (%)	95% Confidence interval	12 Month estimate (%)	95% Confidence interval
Group 1	21	21	3.1	28.6	(14.5%, 56.2%)	4.8	(0.7%, 32.2%)
Group 2	34	31	2.6	32.4	(19.9%, 52.6%)	16.2%	(7.4%, 35.6%)
Combined	55	52	3.0	30.9	(20.8%, 45.9%)	11.3	(5.2%, 24.3%)

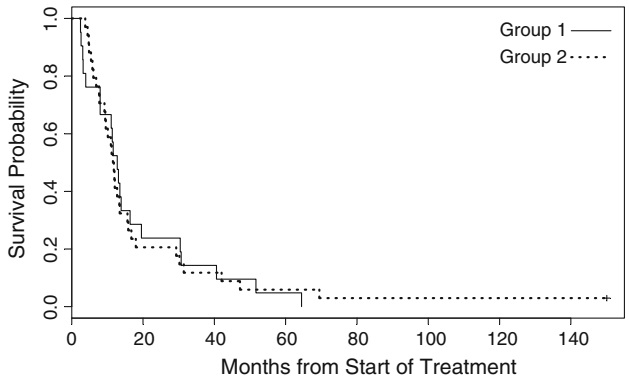

Fig. 1 Overall survival groups 1 and 2

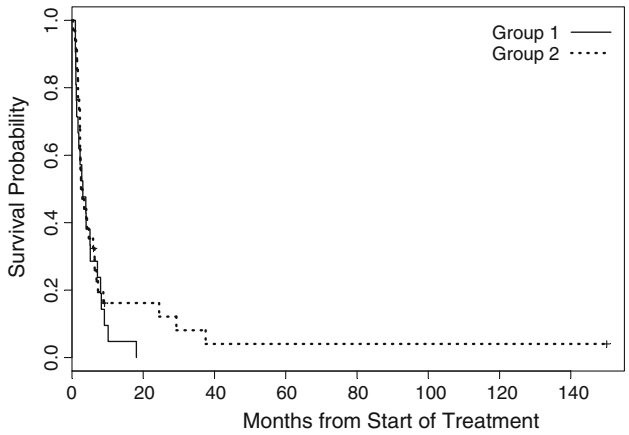

Fig. 2 Progression-free survival, groups 1 and 2

accepted regimens when comparing response rates and time to progression. [14–16] The response rate for 10-EDAM was 18%, and median time to progression was 3 months. Other single agents currently used in metastatic breast cancer, though, have response rates of 20–50%, with median time to progression of 4–8 months [2]. In the 10-EDAM study, however, patient characteristics, such as receipt of prior chemotherapy, may contribute to 10-EDAM's decreased activity.

Table 5 Incidence of adverse events (% of patients)

	Total	Grade three-fourth
Adverse event	(*n* = 55) (%)	(*n* = 55) (%)
Abdominal pain	2	0
Alkaline phosphatase increase	9	0
Alopecia	31	0
Anemia	44	4
Anorexia	27	2
Bilirubin increase	4	4
Cardiac function	2	2
Chills	2	0
Conjunctivitis	9	2
Constipation	9	0
Creatinine increase	2	0
Diarrhea	35	5
Drug fever	5	0
Dysgeusia	2	0
Edema peripheral	4	0
Fatigue	45	9
Granulocytopenia	56	25
Headache	11	0
Hyperglycemia	7	0
Hypocalcemia	2	0
Leukopenia	60	11
Mood	4	0
Myalgia	7	0
Nausea alone	47	0
Respiratory symptoms	2	2
Sensory	2	0
Skin reaction	35	9
Stomatitis	67	20
Thrombocytopenia	27	11
Transaminase increase	55	15
Vomiting	38	4
Weight loss	9	0

In other phase II trials of metastatic breast cancer patients, 10-EDAM had higher response rates of 34–41% versus 18% in this study. One explanation is that the more successful studies had a majority of chemotherapy-naïve patients, making comparisons with the current study difficult. 10-EDAM may have a role in the treatment of metastatic breast cancer as a frontline therapy in patients who are chemotherapy-naïve. In addition, a folate antagonist such as methotrexate has a stronger role in combination therapy with CMF, and 10-EDAM may have a greater impact in the combination chemotherapy setting. When administered in combination with platinum compounds, paclitaxel, and other agents in preclinical and clinical studies, 10-EDAM has shown a synergistic effect [17–20].

Over the past twenty years, numerous other folate antagonists have attempted to improve upon the efficacy of methotrexate. Despite extensive efforts in molecular modeling, synthesis, preclinical testing, and clinical trials, numerous drugs such as 10-EDAM, trimetrxate, piritrexim, and triazinate have been unsuccessful in improving the clinical standard [21]. One multitargeted folate antagonist, pemetrexed, however, has shown a minor benefit in the treatment of malignant mesothelioma and non-small cell lung cancer, with response rates of 9–14% [22, 23].

Conclusion

Treatment with 10-EDAM is generally well tolerated, and monitoring of blood counts, mucositis, and liver function tests is required. Though minimal benefit was demonstrated in this Phase II trial, further studies are necessary to determine the role for 10-EDAM in the management of metastatic breast cancer. Regardless of this drug's future, continued investigation is warranted with experimental agents in breast cancer to establish effective treatments with minimal side effects.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ (2006) Cancer statistics. CA Cancer J Clin 2006 56(2):106–130
2. O'Shaughnessy J (2005) Extending survival with chemotherapy in metastatic breast cancer. Oncologist 10(Suppl 3):20–29
3. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN (2004) Is breast cancer survival improving? Cancer 100(1):44–52
4. Gennari A, Conte P, Rosso R, Orlandini C, Bruzzi P (2005) Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. Cancer 104(8):1742–1750
5. Vogel CL, Azevedo S, Hilsenbeck S, East DR, Ayub J (1992) Survival after first recurrence of breast cancer. The Miami experience. Cancer 70(1):129–135
6. Carrick S, Parker S, Wilcken N, Ghersi D, Marzo M, Simes J (2005) Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev (2):CD003372
7. Goldhirsch A, Colleoni M, Coates AS, Castiglione-Gertsch M, Gelber RD (1998) Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). Ann Oncol 9(5):489–493
8. Kuriakose P, Gandara DR, Perez EA (2002) Phase I trial of edatrexate in advanced breast and other cancers. Cancer Invest 20(4):473–479
9. Schmid FA, Sirotnak FM, Otter GM, DeGraw JI (1985) New folate analogs of the 10-deaza-aminopterin series: markedly increased antitumor activity of the 10-ethyl analog compared to the parent compound and methotrexate against some human tumor xenografts in nude mice. Cancer Treat Rep 69(5):551–553
10. Shum KY, Kris MG, Gralla RJ, Burke MT, Marks LD, Heelan RT (1988) Phase II study of 10-ethyl-10-deaza-aminopterin in patients with stage III and IV non-small-cell lung cancer. J Clin Oncol 6(3):446–450
11. Souhami RL, Rudd RM, Spiro SG, Allen R, Lamond P, Harper PG (1992) Phase II study of Edatrexate in stage III and IV non-small-cell lung cancer. Cancer Chemother Pharmacol 30(6):465–468
12. Schornagel JH, van der Vegt S, Verweij J, de Graeff A, Dullemond-Westland A, van Deijk WA, ten Bokkel Huinink WW (1992) Phase II study of edatrexate in chemotherapy-naive patients with metastatic breast cancer. Ann Oncol 3(7):549–552
13. Vandenberg TA, Pritchard KI, Eisenhauer EA, Trudeau ME, Norris BD, Lopez P, Verma SS, Buckman RA, Muldal A (1993) Phase II study of weekly edatrexate as first-line chemotherapy for metastatic breast cancer: a National Cancer Institute of Canada Clinical Trials Group study. J Clin Oncol 11(7):1241–1244
14. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, Catane R, Kieback DG, Tomczak P, Ackland SP, et al (2004) Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 15(3):440–449
15. Seidman AD, Tiersten A, Hudis C, Gollub M, Barrett S, Yao TJ, Lepore J, Gilewski T, Currie V, Crown J et al (1995) Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol 13(10):2575–2581
16. Valero V (1997) Docetaxel as single-agent therapy in metastatic breast cancer: clinical efficacy. Semin Oncol 24(4 Suppl 13):S13-11–S13–18
17. Laurie SA, Pfister DG, Kris MG, Tong WP, Chronowski G, Pisters KM, Heelan RT, Sirotnak FM (2001) Phase I and pharmacological study of two schedules of the antifolate edatrexate in combination with cisplatin. Clin Cancer Res 7(3):501–509
18. D'Andrea G, Fennelly D, Norton L, Baselga J, Gilewski T, Hudis C, Moynahan ME, Raptis G, Sklarin N, Surbone A, et al (1999) Phase I study of escalating doses of edatrexate in combination with paclitaxel in patients with metastatic breast cancer. Clin Cancer Res 5(2):275–279
19. Gandara DR, Edelman MJ, Crowley JJ, Lau DH, Livingston RB (1997) Phase II trial of edatrexate plus carboplatin in

metastatic non-small-cell lung cancer: a Southwest Oncology Group study. Cancer Chemother Pharmacol 41(1):75–78
20. Rigas JR, Kris MG, Miller VA, Pisters KM, Heelan RT, Grant SC, Fennelly DW, Chou TC, Sirotnak FM (1999) Phase I study of the sequential administration of edatrexate and paclitaxel in patients with advanced solid tumors. Ann Oncol 10(5):601–603
21. McGuire JJ (2003) Anticancer antifolates: current status and future directions. Curr Pharm Des 9(31):2593–2613
22. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, Gatzemeier U, Tsao TC, Pless M, Muller T et al (2004) Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22(9):1589–1597
23. Scagliotti GV, Shin DM, Kindler HL, Vasconcelles MJ, Keppler U, Manegold C, Burris H, Gatzemeier U, Blatter J, Symanowski JT et al (2003) Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. J Clin Oncol 21(8):1556–1561