Edatrexate (10-Ethyl-Deaza-Aminopterin) (NSC #626715) with or without Leucovorin Rescue for Malignant Mesothelioma

Sequential Phase II Trials by the Cancer and Leukemia Group B

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BACKGROUND. The Cancer and Leukemia Group B (CALGB) conducted sequential Phase II multicenter trials to evaluate the activity of edatrexate alone (E) or with leucovorin rescue (EL) in patients with malignant pleural mesothelioma (CALGB Protocol 9131).

METHODS. Twenty patients were accrued to the E portion of the study and received edatrexate, 80 mg/m^2, intravenously over 20–30 minutes weekly. After a protocol amendment precipitated by excessive toxic events with E, 40 patients were enrolled in the EL arm and received the same dose of edatrexate with leucovorin, 15 mg orally, every 6 hours for 4 doses beginning 24 hours after edatrexate. Eligibility criteria included a CALGB performance status of 0–2 and no prior chemotherapy. A central pathology review was performed. Of the 58 patients included in this analysis (20 receiving E and 38 receiving EL), 36 had epithelial cell type and 22 had mixed or sarcomatous cell types. There were 31 patients with measurable disease and 27 with evaluable disease.

RESULTS. The overall response rate was 25% for E (95% confidence interval [95% CI], 9–49%) and 16% for EL (95% CI, 6–31%). There was a 5% complete response [CR] rate, a 10% partial response [PR] rate, and a 10% regression [R] rate for E and a 0% CR rate, a 3% PR rate, and a 13% R rate for EL. The median survival duration from study entry was 9.6 months and 6.6 months, respectively, for E and EL; 1-year survival was 50% and 32%, respectively, for E and EL. There were four early deaths with the E regimen (including two from neutropenic sepsis) and one early death with the EL regimen (from progressive disease). Principal toxicities included mu-

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cositis, myelosuppression, and rash, which were less frequent with leucovorin rescue.

CONCLUSIONS. Moderate antitumor activity has been observed with both regimens. Leucovorin rescue ameliorated the mucosal, hematologic, and dermatologic toxicities of edatrexate, but also may have reduced its efficacy. *Cancer* 1999;86: 1985–91. © *1999 American Cancer Society.*

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The relationship between asbestos and malignant mesothelioma initially was recognized in 1960 when an unusually high incidence of this disease was observed in South African asbestos miners.[1] Significant industrial use of asbestos in the U.S. began in the 1930s and did not decline until the 1970s, when regulations were instituted to decrease workplace exposure. Due to the 20–40 year latency period between asbestos exposure and the development of mesothelioma, the incidence rate of this malignancy is expected to peak before the year 2000 and then decline over the following 5 decades.[2]

Current therapeutic interventions have not affected the natural history of malignant mesothelioma appreciably. Although nearly every class of cytotoxic drug has been tested, the most active are the anthracyclines, platinating agents, and alkylating agents, which yield response rates of 10–20%.[3] Among the antimetabolites, the folic acid antagonists may have the most activity against this disease.[3-5] In three small Phase II trials, high dose methotrexate produced response rates of 37–66%.[3,6,7] An increased dose of the methotrexate analogue trimetrexate led to an improved median survival in a Phase II trial by the Cancer and Leukemia Group B (CALGB).[8]

Edatrexate (10-ethyl, 10 deaza-aminopterin), a methotrexate analogue produced by alkylation and substitution of carbon for nitrogen at the 10 position of 4-aminofolate, has been reported to be more effective than methotrexate against a variety of cultured cell lines, murine solid and ascites tumors, and human tumor xenografts.[9-12] The superior therapeutic index of edatrexate is believed to result from more selective tumor cell uptake and prolonged intracellular retention due to increased polyglutamation within malignant cells.[13] Stomatitis has been dose-limiting in Phase I trials.[14] Other toxicities have included myelosuppression, diarrhea, rash, nausea, emesis, transient elevation of transaminases, and pneumonitis.[15] Antitumor activity has been observed in nonsmall cell lung carcinoma, head and neck carcinoma, breast carcinoma, and non-Hodgkin lymphoma.[13,15,16]

Because of their proximity to World War II shipyards and centers using asbestos in manufacturing, a number of CALGB institutions currently are treating large numbers of patients with malignant mesothelioma. The group has conducted a series of Phase II trials attempting to define active single agents or combinations for the treatment of this disease. The known activity of methotrexate in mesothelioma and the preclinical and clinical data that suggested a superior therapeutic index for edatrexate prompted the CALGB to initiate a Phase II study of edatrexate in the treatment of chemotherapy-naïve patients with malignant mesothelioma.

In the initial phase of this study, edatrexate demonstrated promising activity but intolerable toxicity. Because of in vitro[17] and clinical evidence[18] that edatrexate toxicity may be ameliorated by leucovorin rescue without compromising efficacy, the study was subsequently amended to include leucovorin rescue.

MATERIALS AND METHODS

Patient Selection

Eligibility required histologically confirmed malignant mesothelioma (epithelial, sarcomatoid, or mixed); unresectable disease not amenable to treatment with radiation therapy; measurable or evaluable disease; a performance status of 0–2 by CALGB criteria; a life expectancy $>$ 2 months; adequate nutrition ($>$ 1000 calories orally per day); age $>$ 15 years; women were required to be nonpregnant, nonlactating, and using adequate contraception; $>$ 2 weeks since major surgery and $>$ 4 weeks since prior radiotherapy; no prior chemotherapy; granulocyte count $>$ 1800/μL, platelet count $>$ 100,000/μL, hemoglobin $>$ 10 gm/dL, bilirubin $\leq$ 1.5 times normal, creatinine $\leq$ 1.5 mg/dL; no previous or concomitant malignancy; no serious medical or psychiatric illness; adequate cardiac function (New York Heart Association Criteria $>$ Grade 3, no arrhythmia requiring medication, no unstable angina, and no myocardial infarction in the past 6 months); and obtainment of written informed consent.

Required Data

Baseline evaluation included history and physical examination; nutritional assessment; complete blood cell counts; chemistries, including tests of renal and hepatic function; chest X-ray; and an electrocardiogram. A baseline carcinoembryonic antigen (CEA)

level was required for quality control because mesotheliomas do not produce CEA. Complete blood counts were repeated weekly while the patients were on study; chemistries were obtained every other week. Chest X-rays were repeated monthly while the patients were on study, every 2 months after treatment ended, and at the time of suspected response or disease progression. Computed tomography (CT) scans of the chest or abdomen, depending on areas of involvement, were required before treatment and were repeated at the time of best response or disease progression. CT scans were obtained after 8 weeks of treatment and subsequently every 8 weeks if this was the only technique that established measurable disease.

As part of the quality assurance program of the CALGB, members of the Data Audit Committee visit all participating institutions at least once every 3 years. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, toxic effects, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a randomly selected subgroup of 22 of the 60 patients treated in this study (37%).

Central pathology review by two members of the CALGB Pathology Committee was required. This review included representative original pathology slides as well as paraffin blocks to perform special stains (hematoxylin and eosin, periodic acid–Schiff with and without diastase, colloidal iron or alcian blue with and without hyaluronidase, keratin, CEA immunoperoxidase, and LeuM1 immunoperoxidase). Electron microscopy was performed if appropriately fixed tissue was available. Both pathologists were aware of the institutional diagnosis, but each was unaware of the other's opinion.

Study Design and Treatment

Between June 1992 and February 1993, patients received single-agent edatrexate at a dose of 80 mg/m^2 as an intravenous bolus over 20–30 minutes weekly for 8 weeks per cycle (E regimen). Due to promising response rates but significant toxicity, the protocol treatment regimen was modified. Between September 1993 and September 1994, patients were given edatrexate at a dose of 80 mg/m^2/week with leucovorin, 15 mg orally, every 6 hours for 4 doses, beginning 24 hours after edatrexate (EL regimen). Acyclovir, 800 mg orally twice daily, was administered if the patient experienced any grade of mucositis and was continued until negative viral cultures were obtained. Between January and May of 1994, accrual to the second stage (EL) of the protocol was suspended while results of the first stage of the two-stage study were reviewed.

Dose Adjustments

Dose reduction was based on hematologic, hepatic, mucosal, and renal toxicity on the day of treatment. Side effects were graded from 0 (no toxicity) to 5 (lethal toxicity) according to CALGB expanded common toxicity criteria. If the granulocyte count was between 1200–1799/μL on the day of treatment, the dose of edatrexate was reduced by 50%. The dose was held for granulocyte counts $< 1200/\mu$L or platelet counts $< 50{,}000/\mu$L. A 50% dose reduction was made for a bilirubin level of 2.0–2.5; it was held for a bilirubin level > 2.5. There was a 50% dose reduction for Grade 1 mucositis; the dose was held for mucositis of $\geq$ Grade 2.

If the dose of edatrexate was held at any time due to one or more of the above-mentioned toxicities, subsequent doses of edatrexate were held until the toxicity resolved completely. Chemotherapy then was restarted at the next scheduled visit at a dose of 40 mg/m^2/week. If only Grade 1 toxicity was observed, edatrexate was given at a dose of 40 mg/m^2 until the toxicity resolved, and the dose then was increased to 80 mg/m^2. If Grade 2 mucositis occurred, edatrexate was withdrawn until the next visit. Chemotherapy resumed at the following regularly scheduled visit, when toxicity from mucositis completely resolved, at a dose of 40 mg/m^2, increasing by 20 mg/m^2 per treatment until toxicity recurred or until a dose level of 80 mg/m^2 was reached.

A 50% dose reduction was made for serum creatinine levels between 1.6–2.0 mg/dL; the dose was held for creatinine levels > 2.0 mg/dL and was resumed when the creatinine fell below 2.0 mg/dL. The dose of acyclovir was modified based on renal function and hydration status at the discretion of the treating physician.

Response Criteria

The previously published CALGB response criteria for chemotherapy trials in patients with malignant mesothelioma[8,19,20] were used for this study.

All patients considered to have an objective response had that response status confirmed by independent review of the pretreatment and posttreatment radiographs used to assign response category. An ad hoc review committee comprised of the protocol chair, appropriate diagnostic radiologists, and one or two respiratory core members with a particular interest in malignant mesothelioma met at selected CALGB Group meetings for the purpose of radiographic review.

Statistical Methods

For each treatment regimen, an optimal 2-stage Phase II design was initiated to differentiate between a response rate of 10% and 30% assuming Type I and Type II error rates of 0.05 and 0.10, respectively.[21] Eighteen patients were scheduled to be enrolled in the first stage. If at least 3 of these 18 patients showed evidence of response, an additional 17 patients then were to be entered onto the study.

Survival time was defined as the time between registration and death. Failure free survival was defined as the time between registration and disease progression or death. Kaplan–Meier curves were used to describe survival and time to clinical failure.[22] Exact chi-square tests were used to compare the toxicity profiles of the two regimens, and the Wilcoxon signed rank test was used to compare the length of treatment.

RESULTS

Patient Accrual and Characteristics

A total of 20 patients were entered onto the E portion of the study and 40 patients were enrolled in the EL arm. Two of the 40 patients on the EL arm were excluded from analysis because they previously had been treated with intrapleural bleomycin and thus were ineligible for the study.

The 2 CALGB expert pathology reviewers evaluated specimens from 45 of the 60 patients enrolled on this study. Given that central pathologic review was not feasible for all patients, the results of this review were not used as the basis for including or excluding patients from analysis. On central review, the diagnosis of mesothelioma was questionable in only one specimen, which Reviewer 1 diagnosed as an adenocarcinoma and Reviewer 2 considered as a possible epithelial mesothelioma.

The prestudy characteristics of the 58 patients included in the analysis are listed by treatment arm in Table 1. The distribution of patient characteristics in the two treatment arms was similar. A positive history of asbestos exposure was found in 67% of patients. The majority of patients (62%) had epithelial histology.

TABLE 1
Patient Characteristics

Variable	No. of patients (%)	
	Edatrexate without leucovorin	Edatrexate with leucovorin
Total	20	38[a]
Gender		
Male	19 (95%)	32 (84%)
Female	1 (5%)	6 (16%)
Performance status		
0	4 (20%)	13 (34%)
1	12 (60%)	19 (50%)
2	4 (20%)	6 (16%)
Age (yrs)		
<60	4 (20%)	11 (29%)
>60	16 (80%)	27 (71%)
Mean (SD)	66.7 (7.6)	62.9 (9.1)
Range	53–77	43–81
Institutional histology		
Epithelial	13 (65%)	23 (61%)
Mixed	5 (25%)	8 (21%)
Sarcomatoid	2 (10%)	7 (18%)
Chest pain		
No	7 (35%)	16 (42%)
Yes	13 (65%)	22 (58%)
Duration of symptoms (mos)		
<6	14 (70%)	31 (82%)
>6	6 (30%)	7 (18%)
Weight loss		
None	12 (60%)	19 (50%)
>5%	8 (40%)	15 (39%)
Unknown	0	4 (11%)
Disease assessment		
Measurable	12 (60%)	19 (50%)
Evaluable	8 (40%)	19 (50%)
Asbestos exposure		
No	5 (25%)	10 (26%)
Yes	14 (70%)	25 (66%)
Unknown	1 (5%)	3 (8%)
Prior radiotherapy		
No	18 (90%)	37 (97%)
Yes	2 (10%)	1 (3%)
Prior surgery		
No	3 (15%)	10 (26%)
Yes	17 (85%)	28 (74%)
Platelet count >400,000		
No	13 (65%)	17 (45%)
Yes	7 (35%)	21 (55%)
Hemoglobin, median (Range)	12.9 (10.1–15.6)	13.1 (9.4–15.4)
Leukocyte median (Range)	10.9 (7.3–23.0)	9.2 (4.8–21)

SD: standard deviation.
[a] Excludes two patients who previously were treated with intrapleural bleomycin.

Analysis of Response

There was 1 complete response (CR) among 20 patients (5%) in the E arm. In addition, 2 partial responses (PRs) and 2 regressions were observed, for an overall objective response rate for E of 25% (95% confidence interval [95% CI], 9%–49%). For EL there were no CRs, 1 PR, and 5 regressions in 38 patients, for an overall objective response rate of 16% (95% CI, 6%–31%). All responding cases were reviewed by at least one independent pathologist and the diagnosis of malignant mesothelioma was confirmed.

Time to Treatment Failure and Survival

Patients on the E treatment arm received a median of 10 weeks of treatment (range, 1–107 weeks). Patients

TABLE 2
Toxicity, Grades 3 and 4 Combined

Toxicity	Percent of patients with Grade 3 or 4 toxicity	
	E (N = 20)	EL (N = 38)
Hematologic		
Leukocytes	25	3
Granulocytes	25	3
Lymphocytes	30	25
Hemoglobin	5	3
Platelets	15	0
Infection	45[a]	4
Nausea	10	0
Emesis	10	0
Mucositis	40	5
Esophagitis/dysphagia	20	3
Dermatologic	25	3
Anorexia	25	3
Malaise/fatigue	15	6
Cardiac	15	8
Pulmonary	45	16
Renal	10	0
Hepatic	5	3
Neurologic	20	3

E: edatrexate alone; EL: edatrexate with leucovorin rescue.
[a] Includes two Grade 5 toxicities.

on the BL arm received a median of 13 weeks of treatment (range, 2–88 weeks). A Wilcoxon signed rank test did not demonstrate a statistically significant difference in the duration of treatment among patients who received edatrexate with or without leucovorin ($P = 0.262$).

The median time to treatment failure was 5.2 months for the E arm and 3.4 months for the EL arm. The 1-year survival rate was 50% for E and 32% for EL. The median survival duration from study entry was 9.6 and 6.6 months, respectively, for E and EL.

Toxicity

The maximum toxicities (Grade 3 = severe; Grade 4 = life-threatening, and Grade 5 = lethal) experienced in each treatment arm are listed in Table 2.

Hematologic toxicity was mild. Twenty-five percent of patients on the E treatment arm experienced Grade 3 or 4 granulocytopenia or leukopenia; only 3% of the patients who received the BL regimen developed granulocytopenia or leukopenia of ≥ Grade 3 ($P = 0.028$). Anemia and thrombocytopenia were uncommon in both treatment arms. Grade 3 or higher infections developed in 45% of patients on the E treatment arm; this included 2 Grade 5 toxicities. Only 4% of patients who received leucovorin rescue developed Grade 3 or 4 infections ($P = 0.0058$).

Mucosal toxicity was the most significant side effect of edatrexate; it was ameliorated by the administration of leucovorin. Forty percent of the patients who received the E regimen experienced Grade 3 or 4 mucositis, compared with only 5% of the patients who were given the EL regimen. Seventy-nine percent of the patients receiving EL experienced Grade 0 or 1 mucositis, compared with 20% of the patients who received E. The difference in mucosal toxicity between the E and EL arms was statistically significant ($P < 0.0001$). Dermatologic toxicity also diminished with the administration of leucovorin. A Grade 3 macular rash developed in 25% of the patients on the E treatment arm, but was not observed when EL was administered ($P = 0.0025$).

Chronic interstitial pneumonitis developed in 2 patients: once after 86 weekly courses of EL and once after 7 weeks of treatment with E. The remaining pulmonary symptoms recorded as toxicities were deemed most likely to be related to disease progression.

Five patients died without documentation of progressive disease and before tumor response could be assessed; four received the E regimen and one was treated with the BL regimen. A 66-year-old man died of intractable diarrhea, *Clostridium difficile* colitis, and neutropenic sepsis 10 days after receiving his initial dose of edatrexate. A 77-year-old man died of neutropenic sepsis 9 days after receiving the initial dose of chemotherapy. A 61-year-old man who had a significant previous cardiac history died at home from an unwitnessed cardiac arrest on Day 17. The treating physician considered this possibly to be related to edatrexate. A 76-year-old man died on Day 20 due to respiratory failure from progressive mesothelioma. The 1 early death on the EL arm occurred on Day 29 in a 75-year-old woman who had progressive pericardial involvement from malignant mesothelioma confirmed at autopsy.

DISCUSSION

Chemotherapy for malignant mesothelioma remains inadequate. Response duration is brief; the impact on survival is minimal. New agents clearly are needed. Although drugs such as doxorubicin, cyclophosphamide, dihydro-5-azacytidine, carboplatin, cisplatin, and mitomycin have some activity, response rates > 20% rarely are reproducible.[3-5,19,23,24] Combination chemotherapy has not proven to be more effective.[4,20] Median survival ranges from 6–18 months.[25] Prognostic factors predictive of poor survival in multivariate analysis include pleural involvement, elevated lactate dehydrogenase, poor performance status, chest pain, thrombocytosis, nonepithelial histology, and increasing age.[26]

The antifolates may prove to be the most active class of drugs for this disease.[3-5] Three small Phase II trials have reproducibly demonstrated the activity of high dose methotrexate.[3,6,7] Solheim observed a 37% response rate, a median survival of 11 months, and minimal toxicity in 60 assessable patients with malignant mesothelioma who received 3 g/m^2 of methotrexate with leucovorin rescue.[6] In a trial of 9 patients reported by Dimitrov et al., methotrexate at a dose of 1.5 g/m^2 with leucovorin rescue and vincristine produced 3 CRs and 3 PRs.[7] Djerassi reported a 44% response rate in 9 patients treated with high dose methotrexate.[3] Trimetrexate yielded identical response rates of 12% for 2 different dose levels in a CALGB trial; the median survival was 6 months on the lower dose arm and was prolonged to 10 months on the higher dose arm.[8] By contrast, the antifolate dideazafolic acid produced a response rate of only 6% in a small Phase II study.[3] Preliminary experience with the multitargeted antifolate MTA (LY231514) combined with cisplatin recently demonstrated substantial activity against malignant mesothelioma.[27]

The response rates observed in this study (25% for the E arm and 16% for the EL arm) clearly were within the range of other "active" agents for this disease. There appeared to be a trend toward a lower response rate (25% vs. 16%) and a shorter median survival (9.6 months vs. 6.6 months) on the EL arm of the study, which did not achieve statistical significance given the small sample size. However, because this was not designed as a randomized trial, it may not be valid to conclude that leucovorin rescue decreased the activity of edatrexate. In a study by Lee et al., the addition of leucovorin to the combination of edatrexate, cyclophosphamide, and cisplatin did not compromise the efficacy of the combination and permitted administration of a higher dose of edatrexate with less mucosal toxicity.[18]

If edatrexate were developed further for this disease, other doses and schedules might be considered. Perez et al. administered edatrexate on an every-other-week schedule and delivered doses up to 160 mg/m^2 with minimal mucosal toxicity.[28] Grunberg et al. escalated edatrexate to a dose of 2400 mg/m^2 every 2 weeks along with leucovorin rescue; this regimen was well tolerated.[29] Because there appears to be a dose-response curve for other antifolates in mesothelioma,[8] an evaluation of high dose EL would be of interest.

The 45% rate of infection, 25% incidence rate of Grade 3 and 4 neutropenia, 40% incidence rate of Grade 3 and 4 mucositis, and the 4 early deaths on the E arm prompted the CALGB to add leucovorin rescue to this otherwise active regimen. The reduction in these toxicities with the addition of leucovorin is impressive. The patients who received leucovorin rescue experienced statistically fewer hematologic, infectious, mucosal, and dermatologic Grade 3 and 4 toxicities than those patients who received edatrexate alone. Nausea, emesis, anorexia, malaise, and cardiac and renal toxicities also were reduced by leucovorin rescue, although these differences were not statistically significant, possibly due to the small sample size.

Third-space fluid collections can trap antifolates followed by prolonged low level drug release, resulting in increased toxicity.[30] This is problematic in patients with mesothelioma because fluid collection is part of the disease process. The Southwest Oncology Group noted severe myelosuppression including two deaths from neutropenic sepsis in patients with pleural effusions treated in a Phase II trial of edatrexate with carboplatin; they subsequently amended their protocol to exclude patients with pleural effusions.[31] The relative contribution of delayed drug excretion in fluid collections to the toxicities experienced in this study cannot be ascertained reliably because pharmacokinetic studies of the pleural fluid were not performed in this multicenter trial.

The activity exhibited by edatrexate in this study, the response rates of 37–66% reported for high dose methotrexate,[3,6,7] the 10-month median survival observed with trimetrexate in a CALGB trial,[8] and the early data reported with MTA[27] have demonstrated that antifolates clearly are active agents in the treatment of patients with malignant mesothelioma and warrant further studies.

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