

Dihydro-5-Azacytidine in Malignant Mesothelioma

A Phase II Trial Demonstrating Activity Accompanied by Cardiac Toxicity

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BACKGROUND. Malignant mesothelioma is a disease that is refractory to chemotherapy. Therefore, the objective of this multi-institutional, cooperative group Phase II trial was to determine the efficacy of dihydro-5-azacytidine (DHAC), a pyrimidine analogue, in the treatment of malignant mesothelioma.

METHODS. Forty-one patients with histologically confirmed malignant mesothelioma received 120-hour continuous infusions of DHAC (1,500 mg/m²/day every 21 days) until maximal response, intolerable toxicity, or disease progression.

RESULTS. One patient had a complete response, two had objective partial responses, and four had regression of evaluable disease. The overall response rate was 17%. The one complete responder remains without disease progression at 6 years. Chest pain and nausea were the most common toxicities. Supraventricular tachycardia and pericardial effusion occurred in 20% and 15% of patients, respectively. In most patients, gastrointestinal effects were manageable. There was no significant hematologic toxicity.

CONCLUSIONS. In malignant mesothelioma, a disease that is refractory to chemotherapy, dihydro-5-azacytidine has definite antitumor activity. Its modest hematologic toxicity profile favors its use in combination with other agents. Caution regarding cardiac arrhythmias and pericardial effusion is necessary. *Cancer* 1997;79:2237-42. © 1997 American Cancer Society.

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Malignant mesothelioma is a lethal disease with a median survival after diagnosis of only 6-15 months.¹ Patients with a good performance status, those able to tolerate radical surgery, and those with an epithelial histology survive longer.^{1,2} However, few, if any, patients

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with this disease can be cured, even with radical surgery and radiation. Responses to chemotherapy have been seen in only a minority of cases and have not been associated with prolonged survival. Most single agents and combinations, when tested in adequate numbers of patients, produce responses in less than 20% of cases.²⁻⁴ Doxorubicin, cisplatin, mitomycin, and high dose methotrexate⁵ are among the most useful compounds, but new agents are clearly needed.⁶⁻¹¹

Dihydro-5-azacytidine (DHAC), a pyrimidine nucleoside analog of cytidine, is incorporated into DNA and inhibits DNA methylation, an important step in gene expression. DHAC also competes with cytidine triphosphate for incorporation into RNA, leading to ribosomal degradation and defective protein synthesis.¹²⁻¹⁷ DHAC has activity against Friend leukemia, L1210 leukemia, human MX-1 mammary xenograft, murine CD8F mammary tumor, and implanted colon 38 tumor.¹⁷ Phase I studies showed activity in lymphoma and stable disease in two patients with mesothelioma^{12,17} as well as an unusual dose-limiting toxicity involving chest pain, apparently caused by chemical pleuritis and serositis. Cytotoxic activity against tumors on serosal surfaces was therefore hypothesized, and the Cancer and Leukemia Group B (CALGB) decided to test DHAC in mesothelioma, a tumor arising in serosal cavities. A preliminary report of these data have appeared previously in abstract form.¹⁸

METHODS

Patients

Eligibility criteria required that patients have histologically confirmed malignant mesothelioma that was unresectable and inappropriate for radiotherapy. Disease had to be measurable in two perpendicular dimensions or evaluable by one dimensional measure. Further criteria required were a CALGB performance score of 0-2 (less than 50% of waking hours in bed), life expectancy longer than 2 months, adequate nutrition, no prior chemotherapy, recovery of at least 2 weeks since surgery and 4 weeks since radiotherapy, granulocytes greater than 1800/mm³, hemoglobin more than 10 gm/dL, bilirubin less than 1.5 times normal, and serum creatinine less than 1.8 mg/dL. All patients provided written informed consent. Excluded were patients with prior malignancies other than curatively treated carcinoma in situ of the cervix or skin, any serious medical or psychiatric history preventing informed consent, or pregnancy. After cardiac complications were encountered early in the trial, cardiac disease designated Grade 3 or worse according to New York Heart Association criteria, arrhythmias requiring medication, unstable angina, or myocardial infarction in the previous 6 months were added as exclusion criteria.

Therapy

DHAC was given by continuous 120-hour infusion at 1500 mg/m²/day every 21 days. Chest pain was treated with oral or intravenous narcotics or in severe cases by cessation of chemotherapy. Patients were continued on therapy until disease progression or intolerable toxicity. Patients with rapid disease progression were removed from the study after one cycle, but otherwise at least two cycles of therapy were given.

Pathology

Central pathology review was performed by two independent expert pathologists (J.M.C. and Y.S.) using previously published criteria.⁷ In addition to routine hematoxylin and eosin staining, studies of paraffin embedded tumor included periodic acid-Schiff with and without diastase, mucicarmine and colloidal iron or alcian blue with and without hyaluronidase. Immunohistochemistry for keratin, carcinoembryonic antigen (CEA), and Leu M1 was routinely performed, and in difficult cases immunostaining for S-100 and desmin was performed. Electron microscopy was available in some cases.

Response Evaluation

Complete response was defined as the disappearance of all measurable or evaluable disease, signs, symptoms, and biochemical changes related to tumor for more than 4 weeks, during which no new lesions appeared. Partial response was defined as a reduction of greater than 50% in the sum of the products of two perpendicular diameters of all measurable lesions lasting more than 4 weeks, during which no new lesions appeared or existing lesions became larger. Regression of evaluable disease was defined as a definite decrease in tumor size agreed on by two independent investigators, with no new lesion appearing for more than 8 weeks. Disease was considered stable if no new lesions appeared for more than 8 weeks, there was an increase of less than 25% in the sum of the products of diameters of measurable disease, and no clear change occurred in evaluable tumor. Progression was the designation if new disease appeared or if there was definite increase in evaluable disease or an increase of more than 25% in measurable disease. Chest radiographs and computed tomography scans of the chest were obtained at baseline and after every two cycles of therapy.

Data Audit

As part of the quality assurance program of the CALGB, members of the Data Audit Committee make site visits to all institutions at least once every 3 years. Committee members verify compliance with federal regulations and

TABLE 1
Characteristics of Mesothelioma Patients Who Responded to DHAC on CALGB Protocol 8833

Patient no.	Site of primary tumor	Age (yrs)	Duration (mos)	Central pathology review?
41940	Pleural	59	7.6	No
41953	Pleural	71	2.3	Yes: mesothelioma
42069	Pleural*	43	73+	No
42154	Pleural	68	7	Yes: mesothelioma
42458	Pleural	62	0.9	Yes: mesothelioma
42474	Pleural	68	25.4	No
43389	Pleural	50	5.1	Yes: mesothelioma

* This patient also had retroperitoneal and cervical lymph node involvement.

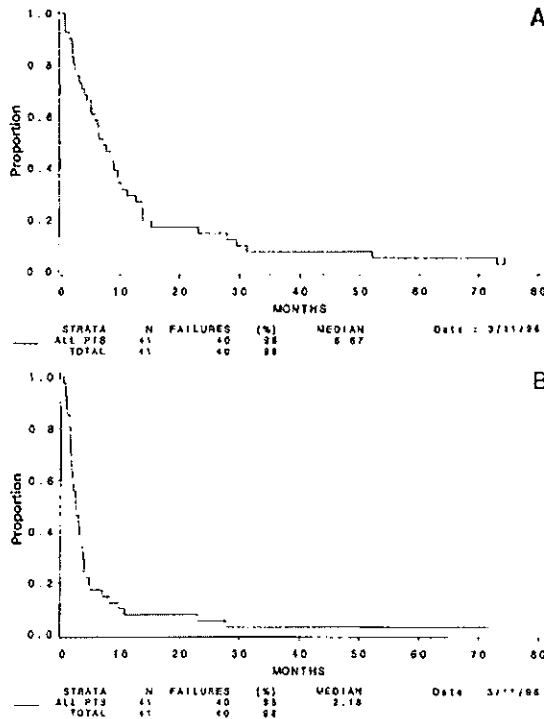


FIGURE 1. (A) Survival duration of patients with mesothelioma after treatment with dihydro-5-azacytidine is shown. (B) Time to clinical failure after treatment with dihydro-5-azacytidine is shown.

protocol requirements, including eligibility, treatment, tumor response, and follow-up, in a sample of protocols at each institution.¹⁹ The medical records and radiographs of a cohort of 9 patients (22%) enrolled in this study were subjected to such on-site review.

Statistical Analysis

The Kaplan-Meier product limit method was used to estimate survival duration and time-to-failure

distributions. Survival duration was measured from the date of study entry to the date of death or last follow-up. Time to failure was measured from the date of study entry to the date of disease progression or death, whichever occurred first. Patients who were alive and disease free were censored at the last time they were known to be disease free. The cutoff for updating information was March 1, 1996.

RESULTS

Patient Characteristics

Forty-three patients were treated with a median of 2 and a range of 1-10 cycles of DHAC. Two patients were determined to be ineligible on review. Ineligible Patient 43275 had received DHAC for only 4 days when the treating physicians realized that the patient had a preexisting atrial dysrhythmia and was receiving digoxin. The DHAC was stopped and the patient was withdrawn from the study. Maximal toxicity as a result of the 4 days of DHAC was Grade 2 diarrhea and anorexia. Ineligible Patient 43623 had a performance status of 3, had recently had a major surgical procedure, and had a pericardial effusion secondary to mesothelioma. After 1.5 days of DHAC, the patient's pericardial effusion worsened (to Grade 4). DHAC treatment was withdrawn, and 11 days later the patient began to receive cisplatin and interferon. This patient was considered ineligible and unevaluable for toxicity, although the worsening of the pericardial effusion may have been DHAC-related (see below). Excluding those 2 patients left 41 remaining for analysis of response, survival, and toxicity. One patient is still being followed and has not had disease progression.

The median age of patients was 62 years (range, 24-82 years), and 66% were male. Fifty-six percent of patients recalled definite exposure to asbestos, and 44% had symptoms for less than 3 months. The epithelial variant comprised 73% of cases. Thirty-nine pa-

TABLE 2
Toxicity of Dihydro-5-Azacytidine: Percentage of Patients Who Experienced Each Type and Grade

Type of toxicity	WHO grade of toxicity					
	0 None	1 Mild	2 Moderate	3 Severe	4 Life-threatening	5 Lethal
Chest pain	35	20	20	25	0	0
Nausea/vomiting	18	30	33	20	0	0
Hepatic	68	20	10	3	0	0
Diarrhea	70	25	5	0	0	0
Weight loss	44	36	21	0	0	0
Stomatitis	100	0	0	0	0	0
Dermatologic	90	10	0	0	0	0
Local	86	8	6	0	0	0
Alopecia	94	0	6	0	0	0
Genitourinary	80	13	8	0	0	0
Neurologic, CNS	90	8	3	0	0	0
Neurologic, peripheral	83	10	8	0	0	0
Allergy	100	0	0	0	0	0
Fever without infection	53	20	28	0	0	0
Infection	90	5	5	0	0	0
Leukopenia	83	13	5	0	0	0
Granulocytopenia	90	10	0	0	0	0
Thrombocytopenia	95	5	0	0	0	0
Anemia	35	8	43	15	0	0
Hemorrhage	100	0	0	0	0	0
Cardiac	45	15	15	13	10	3
Other	70	15	12	2 ^a	2 ^b	0

WHO: World Health Organization.

^aCardiac toxicity includes arrhythmia, Grade 3 (8%), Grade 4 (8%), and Grade 5 (3%), and Pericardial effusion, Grade 3 (8%) and Grade 4 (8%).

^bOther toxicity includes hypertension and low theophylline levels.⁸

tients presented with pleural involvement, whereas two had peritoneal primary tumors. Five patients had already received radiotherapy. Of the patients with radiographic TNM staging information available, two-thirds had T4 tumors, one-third had lymph node involvement,²⁰ and one-third had distant metastases. Radiologic assessment revealed that 18 patients had measurable disease and 23 had evaluable disease. Performance status was 0 for 13 patients, 1 for 22 patients, and 2 for 6 patients. The median platelet count at entry was 420,000/mm.³ CEA levels were measured in 16 patients, and the median value was 0.7ng/mL (range, 0.1–1.5 ng/mL), which was consistent with previous data indicating that the CEA is low or undetectable in mesothelioma patients.⁷

Central pathologic review was completed in three-quarters of cases. Probable or definite mesothelioma was confirmed in all but one case, in which mesothelioma was considered possible.

Response

There were 2 partial responses and 1 complete response among 18 patients with measurable disease

(16% objective response rate), whereas 4 of 23 patients with evaluable disease had regression. Table 1 describes the clinical characteristics of the seven responding patients. Thus, the overall response rate was 17% (7 of 41 patients, with a 95% confidence interval of 7–32%). The median duration of response was 7 months (range, 1–73+ months). Four of the seven responding patients underwent central pathologic review, during which mesothelioma was confirmed in all cases. Stable disease was observed in 13 patients, progressive disease was observed in 16, and 5 were unevaluable. Of the unevaluable patients, four experienced early death from disease (or possibly from drug in one case), whereas one was unable to complete a full cycle of treatment because of nausea.

The median survival for the entire cohort was 6.7 months (95% confidence interval, 5.0–9.6 months), and 6 patients lived at least 24 months past study entry. Figure 1A describes the overall survival experience. Median time to failure was 2.2 months (Fig. 1B), and one patient continued to have complete response 6 years after study entry.

Toxicity

Chest pain occurring during the infusion and ending with cessation of the infusion was the most frequent serious toxicity (Table 2). Twenty percent of patients had moderate pain, and 25% had severe pain that required parenteral morphine or cessation of therapy. Gastrointestinal toxicity with nausea and emesis was severe in 20% of patients, whereas mild-to-moderate diarrhea was experienced by 30%. No patient had stomatitis. Dermatologic, genitourinary, and neurologic toxicity of mild-to-moderate degree was reported in a few patients, as were rare elevations of blood pressure or glucose. An otherwise unexplained low theophylline level, causing severe exacerbation of asthma, occurred in one patient and was felt to be potentially life-threatening. There were no definite allergic reactions, although some moderate fevers not accompanied by obvious infection were reported. No Grade 3-4 hematologic, leukocyte, or platelet toxicity was documented, although most of the patients were anemic.

Cardiac toxicities were observed in 56% of patients, including 5 severe episodes (13%), 4 life-threatening episodes (10%), and 1 lethal episode (3%). These toxicities did not clinically correlate with the severity of chest pain or with the number of treatment cycles. Supraventricular tachycardias occurred in 8 patients (20%). All episodes rapidly converted to normal sinus rhythm when standard therapies (including digoxin, verapamil, quinidine, propranolol, or combinations) were given. Three of the eight patients resumed DHAC treatment without recurrence of the arrhythmia. In three patients, hypotension or congestive failure was considered life-threatening. In an otherwise unexplained episode, a patient died at home; this patient had an 8-year history of "palpitations" but was not diagnosed with or treated for arrhythmias. During the first cycle of DHAC, the patient experienced paroxysmal atrial fibrillation (PAT) and was treated with digoxin. The patient received two additional cycles of DHAC uneventfully, but suddenly died while at home one day after completing the third cycle. This patient was eligible for the study, but the episode of PAT perhaps should have led to further cardiac evaluation. Cardiac toxicity had not been reported previously with this agent. After the first few cases were reported, investigators were alerted to the danger of arrhythmias, and the eligibility criteria were changed to exclude patients with cardiac arrhythmia requiring medication, unstable angina, or prior myocardial infarction within 6 months.

Clinically important pericardial effusions developed in 6 patients (15%) after 1-3 cycles of treatment. In two cases, tamponade physiology developed, responding to pericardiocentesis in one and to pericar-

dial window in the other. Pericardial fluid cytology was negative in both cases. However, in these two cases and in the others with effusions, there was radiologic evidence of malignant disease in or adjacent to the pericardium. Tachyarrhythmias complicated the more severe episodes. Subsequent to these cases early in the trial, all patients were required to have echocardiograms at baseline, and no additional cases of tamponade occurred.

Perforation of the myocardium at a site involved by mesothelioma led to an early death for one patient. Prior to death and autopsy, this patient had been responding at other sites of disease, but not for long enough to have been considered a responder.

DISCUSSION

Objective documentation of response in the treatment of mesothelioma patients is often difficult, and the response rates to single agent chemotherapy are low. Although Dhingra et al. observed no responses to DHAC among 14 patients,²¹ the 17% response rate observed in this series suggests that DHAC is active against malignant mesothelioma. One complete response has been surprisingly durable. Vogler et al. also reported that two patients with mesothelioma responded to the parent drug, 5-azacytidine.²²

The toxicity profile of DHAC is problematic and yet potentially exploitable. Problems that arose in the management of unexpected cardiac toxicities cut short the treatment of some responding patients and may have contributed to some early deaths. Learning how to manage such toxicities might therefore improve the response rate and median survival, which in this study were consistent with previous CALGB experience.^{2,4,7} The previously unreported cardiac and pericardial toxicities might have resulted from chemical irritation of serosal surfaces, as is hypothesized for the origin of chest pain. Malignant involvement of serosal surfaces may also have contributed to these cardiac events, considering that arrhythmias and pericardial effusions have not been reported for patients with other malignancies treated with DHAC. We could speculate that a deaminase present in the blood and important for clearing DHAC is decreased in serosal fluids by the presence of malignancy, thus making it more difficult to clear DHAC from the pericardial sac and thereby resulting in more toxicity. Given that some responding patients experienced cardiac toxicities, tumor necrosis induced by DHAC could have caused irritation of the epicardial serosa. There was no convincing evidence that myocardial ischemia was a cause of chest pain in any patient or a cause of the deep T wave inversions experienced by one patient.

Myelosuppression was not a dose-limiting toxicity

in this protocol. Except in a few cases, nausea was also tolerable. The minimal hematologic toxicity pattern of DHAC, in addition to its demonstrated activity, make it a reasonable agent for combination with myelosuppressive drugs that have activity against mesothelioma. The CALGB therefore completed a Phase II trial of DHAC plus cisplatin in the treatment of malignant mesothelioma.²³ The response rate of the combination appeared similar to that induced by DHAC alone. Further studies of DHAC in combination with myelosuppressive agents could be conducted. Chahinian et al.²⁴ studied 5-azacytidine, the parent drug of DHAC, combined with doxorubicin, and reported a response rate of 22%. No other studies have examined DHAC or 5-azacytidine in combination.

The CALGB intends to continue exploring the use of single agents in the treatment of mesothelioma because there is still no agent with activity sufficient to warrant use as a standard therapy.

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