Phase II Trial of a Single Weekly Intravenous Dose of Ranpirnase in Patients With Unresectable Malignant Mesothelioma

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Purpose: A multicenter phase II trial of ranpirnase (Onconase; Alfacell Corp, Bloomfield, NJ) as a single agent was conducted to further assess the safety and clinical efficacy of this novel antitumor ribonuclease. Patients with unresectable and histologically confirmed malignant mesothelioma (MM) were eligible.

Patients and Methods: One hundred five patients with Eastern Cooperative Oncology Group performance status 0 to 2 were enrolled onto the study. Thirty-seven percent of patients had not responded to prior chemotherapy. The primary end point of the study was survival. Tumor responses and time to progression were also assessed. The Cancer and Leukemia Group B (CALGB) prognostic group criteria were used to define a treatment target group (TTG). Both the intent-to-treat (ITT) and the TTG populations were analyzed for survival.

Results: Median survival times of 6 months for the ITT and 8.3 months for the TTG populations were observed. The 1- and 2-year survival rates were 34.3% and 21.6% for ITT, respectively, and 42% and 26.8% for TTG, respectively. Among the 81 patients assessable for tumor response, four had partial responses, two had minor regressions, and thirty-five experienced stabilization of previously progressive disease. Patients with responses and stable disease demonstrated markedly prolonged survival. Ranpirnase was well tolerated in the majority of patients, and there were no drug-related deaths.

Conclusion: Ranpirnase demonstrated activity and a tolerable toxicity profile in patients with unresectable MM. The prognostic value of the CALGB groups was confirmed.

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MALIGNANT MESOTHELIOMA (MM) remains a major therapeutic challenge. Despite decades of intensive efforts to control its clinical course, unresectable disease has evaded most of the known systemic treatments. The majority of patients with pleural involvement and essentially all patients with abdominal involvement have unresectable disease. The dismal therapeutic outcome in this disease has led many physicians to recommend only supportive care to their patients as the standard of treatment. Given the ambiguity and uncertainty as to the standard of treatment for MM, any agent that has even minimal activity in this disease is of considerable interest to physicians treating this disease but is even more so to patients and their families. Although no drug, thus far, seems to have a meaningful impact on the survival of these patients, no randomized trials of drug versus only supportive care have been completed.

The accurate assessment of therapy in MM has been complicated by its variable natural history and by significant difficulties in staging the extent of the disease in inoperable or unresectable cases. Several extensive reviews regarding these problems have recently been published.[1-3]

The published literature on the systemic therapy of MM has been biased by reports of small series of patients with relatively successful outcomes. The median survival times (6 to 7 months) of patients with unresectable MM are far inferior to those from some surgical series that reported median survival times in excess of 20 months.[4-7]

On the basis of a surgical series that involved 131 thoracotomies, Rusch and Venkatraman[8] concluded that more than 50% of MM cases were clinically understaged relative to their true pathologic nodal status. They also concluded that survival correlated with stage, type of surgical resection, and histologic type of the tumor. Even in this surgical series, the median survival time of clinically operable patients with the most advanced disease was 5.9 months. In all published series, survivals seemed to depend on the distribution of significant prognostic variables at the outset of the clinical trial. Many of the published studies suggest that survival is related to performance status (PS) and histology.[1,2]

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Ranpirnase (Onconase for Injection; Alfacell Corp, Bloomfield, NJ) is a nonmyelosuppressive agent with no apparent toxicity to vital organs. It is a single-chain, 104-amino-acid-residues protein with M_r of approximately 12,000 whose enzymatic activity is required for all its biologic activities demonstrated to date.[9] It binds to the cell surface and penetrates the cell's interior through the energy-dependent endocytotic process.[10] On reaching the cytosol, it preferentially degrades tRNA.[11] This irreparable RNA damage may constitute a death signal for apoptosis and also contributes to the inhibition of the cell growth and proliferation through the protein-synthesis inhibition–dependent and protein-synthesis inhibition–independent mechanisms.[11,12] The previously observed decreased RNA content in G1-phase HL-60 leukemia cells treated with ranpirnase suggests that these cells may have been induced to transition from the cell cycle to quiescence.[13] In contrast to normal cells, which can remain in quiescence and are characterized by low RNA content for an extended period of time, quiescence of tumor cells is short lived and results in a loss of cell viability.[14,15] These findings suggest that, overall, malignant phenotype cells may be more susceptible to ranpirnase than normal cells. In in vitro primary cell cultures, ranpirnase induced significant inhibition of malignant mesothelioma cell growth at nanomolar concentrations.[16]

In more than 700 patients treated to date, ranpirnase has not been associated with any drug-related deaths. The phase I study of ranpirnase as a single agent administered intravenously on a weekly schedule revealed that the maximum-tolerated dose (MTD) was 960 $\mu g/m^2$ (range, 60 $\mu g/m^2$ to 960 $\mu g/m^2$). The dose-limiting toxicity was renal as manifested by proteinuria with or without azotemia, peripheral edema, and fatigue. Other toxicities included flushing, myalgias, dizziness, and decreased appetite. Two of the 28 patients developed transient hypotensive reactions preceded by flushing that promptly responded to volume expansion. Ranpirnase was well tolerated by the majority of patients and demonstrated consistent and reversible clinical toxicity patterns.[17]

On the basis of the preclinical findings delineated above, a single-arm, open-label, multicenter phase II trial of ranpirnase as a single agent was initiated. The objective of this trial was to evaluate the potential clinical efficacy of ranpirnase as a single agent in unresectable MM patients and to further assess its safety. Survival was the primary end point in this trial. Secondary end points were tumor responses and time to progression.

PATIENTS AND METHODS

Patients who had a diagnosis of unresectable malignant mesothelioma, had clinically progressive disease (PD), had not received prior therapy for at least 4 weeks, and had recovered from all toxic effects of those treatments were eligible. A tumor was deemed unresectable when it could not be resected because of either mediastinal, chest wall, diaphragmatic, bilateral pleural/pulmonary, or abdominal involvement, or distal metastatic disease. The status of unresectability was only determined by the principal investigator. Patients were also required to have blood cell counts, blood chemistry values, and urinalyses within normal ranges, have an Eastern Cooperative Oncology Group PS of 0 to 2, and a minimal life expectancy of 3 months. Patients with abnormal creatinine clearance (< 50 mL/min) or proteinuria (> 500 mg/d) were excluded. Patients were excluded if there was clinical or laboratory evidence of cardiovascular disease, infection, psychiatric disorders or neurologic disease, uncontrollable diabetes mellitus, impairment of hemostasis, metabolic disorders, severe anorexia, nausea or vomiting, prior organ allograft, systemic corticosteroid use, pregnancy or lactation, or hepatitis B surface antigen–positivity. Also excluded were patients who were senile, emotionally unstable, or not capable of providing informed consent. Patients were excluded if they had received any prior therapy with biologic response modifiers. Four clinical centers participated in this trial: Thompson Cancer Survival Center, Knoxville, TN; New York Medical College, Valhalla, NY; Lone Star Oncology Consultants, Austin, TX; and Columbia-Presbyterian Medical Center, New York, NY. These centers enrolled 35, 15, 32, and 23 patients onto the study, respectively. Thus, a total of 105 patients were entered onto this study.

Tumors were assessed every 6 to 8 weeks using computed tomography scans and chest x-rays. The assessments were required to be performed using the same imaging technique as the baseline evaluations. There was no formal outside radiology review nor central pathology review required by the protocol.

Treatment Regimen

Ranpirnase was supplied for each patient in 2-mL vials, each of which contained 1 mg of ranpirnase and 40 mg of mannitol, and was stored in a frozen state.

Weekly intravenous (IV) infusions of ranpirnase at an initial dose of 480 $\mu g/m^2$ for 30 minutes were administered on an outpatient basis. All patients originally received an IV test dose of ranpirnase (equal to 1% of the full dose of ranpirnase) followed by 15 minutes of observation. If no evidence of hypersensitivity was observed, the full dose of ranpirnase was administered. After each dose had been administered, each patient was monitored every 15 minutes for a minimum of four periods (ie, 1 hour) for temperature, respiratory rate, heart rate, and blood pressure. Because the test dose was not predictive of the development of hypersensitivity reactions, the protocol was amended on July 18, 1996, to eliminate the test dose.

If there was any evidence of a hypersensitivity reaction, the infusion of ranpirnase was stopped. If the patient experienced a grade 1 or 2 hypersensitivity reaction, the patient was premedicated with IV diphenhydramine (Benadryl; Parke-Davis, Morris Plains, NJ) 50 mg for all subsequent doses. Thereafter, if the patient developed a ≥ grade 3 hypersensitivity reaction, the patient was removed from the study. Patients who developed renal toxicity, graded by changes in either serum creatinine or proteinuria, had their subsequent full doses of ranpirnase modified (75% of full dose for grade 2, 50% for grade 3, and temporary cessation of treatment for grade 4 toxicity). Renal toxicity grades were defined as follows: for serum creatinine, grade 1 = below 1.5 times, grade 2 = 1.5 to 3 times, grade 3 = 3.1 to 6 times, and grade 4 = over 6 times baseline value; for proteinuria, grade 1 if 1+ protein, grade 2 if 2+ to 3+ protein, grade 3 if 4+ protein, and grade 4 if nephrotic syndrome defined as over 3 grams 24 hours urine protein with hypoalbuminemia.

For nonrenal grade 1 and 2 toxicities, graded according to the National Cancer Institute common toxicity criteria, there was no dose modification and no delay of dosing. A 50% dose reduction was used for grade 3 toxicity. For grade 4, the dose was delayed until toxicity subsided, and subsequent doses were administered at the 75% dose level thereafter. If grade 4 toxicity recurred, the patient was terminated from the study.

Response and Toxicity Evaluation

All patients with measurable and/or assessable disease were assessed for tumor responses. All tumor measurements were recorded in centimeters and consisted of the longest diameter and the perpendicular diameter at the widest portion of the tumor. The tumor responses and changes in objective assessable disease were assessed by the principal investigator.

Tumor response (complete and partial response [PR]), stable disease (SD), and PD were defined as recommended by the World Health Organization,[18] except that minor regression (MR) was additionally defined as less than 50% but more than 25% decrease in the sum of the products of the perpendicular diameters of measurable disease with no appearance of new lesions. Time to progression was calculated from the date of the first dose of rampirnase to the earliest date of progression or to the date of termination from treatment, whichever occurred first.

Toxicity Assessments

The National Cancer Institute common toxicity criteria scale was used to record and grade toxicities. Toxicity was assessed before each cycle of treatment, and the most severe grade of toxicity for each patient in all cycles of treatment was used.

Safety was evaluated based on the frequency of adverse events, physical examination, vital signs, and laboratory evaluations. All patients who received at least one dose of rampirnase were assessable for safety (N = 105). Adverse events were coded using the COSTART dictionary (Food and Drug Administration, Rockville, MD).

Study Design, Data Management, and Statistical Methods

Study design. This phase II trial was an open-label, multicenter, single-agent, multiple dose study.

Data management. Data management was performed using a statistically validated ClinPro data management system (ClinPro International Co LLC, Union City, CA), which uses Statistical Analysis System (SAS; SAS Institute, Cary, NC) files. The computer-generated case report forms were 100% validated against the final database. The application included audit trails of all data changes. Adverse events were standardized for terminology and classification using the COSTART dictionary.

Statistical methods. Survival was the primary end point of the study. Survival rates were calculated from the time of the first dose of rampirnase using the Kaplan-Meier survival function estimates (log-rank and Wilcoxon analyses were used to compare the survival estimates of specific background variable levels). In 1996, the Cancer and Leukemia Group B (CALGB) first reported that a set of criteria that defined six prognostic groups[19] and was derived using Cox survival models and exponential regression trees could predict survival in MM. The two most prognostically unfavorable groups (groups 5 and 6) were considered to be probably unsuitable for currently available systemic chemotherapy.[20] Thus, this study prospectively used an intent-to-treat (ITT) analysis that included all patients (N = 105) enrolled onto the study, and retrospectively used a treatment target group (TTG) analysis that included only those patients who met the predefined criteria for groups 1 to 4 combined (n = 81) (Table 1). The survival variables for both the ITT and TTG populations included median survival time (MST) and survival rates at 1 and 2 years. Separate survival analyses were conducted for the subsets of patients according to histologic type of the tumor and PS.

Table 1. Distribution of Patients According to CALGB Prognostic Groups in a Phase II Study of Rampirnase

CALGB Prognostic Groups	ITT	TTG
Group 1	10	10
PS, 0; age < 49 years		
PS, 0; age ≥ 49 years; HGB ≥ 14.6		
Group 2 PS, 1 or 2; WBC < 8.7; no chest pain	14	14
Group 3	45	45
PS, 0; age > 49 years; HGB < 14.6		
PS, 1 or 2; WBC < 15.6; chest pain; no weight loss; HGB ≥ 12.3		
PS, 1 or 2; 9.8 ≤ WBC < 15.6; chest pain; weight loss; HGB ≥ 11.2		
Group 4 PS, 1 or 2; 8.7 ≤ WBC < 15.6; no chest pain	12	12
Group 5	18	0
PS, 1 or 2; WBC < 15.6; chest pain; no weight loss; HGB < 12.3		
PS, 1 or 2; 9.8 ≤ WBC < 15.6; chest pain; weight loss; HGB < 11.2		
PS, 1 or 2; WBC < 9.8; chest pain; weight loss		
Group 6 PS, 1 or 2; WBC ≥ 15.6	6	0
TOTAL	105	81

NOTE. HGB is given in g/%; WBC, × 1,000/μL.
Abbreviation: HGB, hemoglobin.

Stepwise Cox proportional hazards regression multivariate analyses were performed to determine the significant clinical prognostic predictors associated with patient survival. The secondary end points of the study were objective tumor response rate and time to disease progression.

Study Flow

This study was initiated on October 12, 1992, and was closed to patient enrollment on June 15, 1997. Among the first 25 patients treated, there were three PRs (mean duration, 4.3 months) and 10 stabilizations of previously PD observed at that time. These early encouraging results were presented at the 1996 Annual Meeting of the American Society of Clinical Oncology in Philadelphia, PA.[16] On the basis of these results, the phase III randomized trial of rampirnase versus doxorubicin as single agents was launched.[21] The accrual onto the phase II trial was continued to allow patient access to rampirnase until the phase III trial was initiated. A total of 105 patients were enrolled. One hundred four patients have had treatment discontinued, and one patient continues on the study. Two patients completed the treatment and had their residual tumor resected. These two patients remain alive and tumor-free.

RESULTS

Demographics

The demographic characteristics are listed in Table 2. The majority of patients were male (male, 85; female, 20) who

Table 2. Demographic Data at Entry

Parameter	No. of Patients	%
Total	105	
Age	17	16.2
50-59 years	30	28.6
60-69 years	32	30.4
> 70 years	26	24.8
Sex		
Male	85	81.0
Female	20	19.0
PS		
0	29	27.6
1	64	61.0
2	12	11.4
Histology		
Epithelioid	50	47.6
Nonepithelioid	16	15.2
Undetermined	39	37.2
Epithelioid + undetermined	89	84.7
Tumor involvement		
Thoracic, overall	97	92.4
Thoracic only	80	76.2
Abdominal only	8	7.6
Abdominal + thoracic	17	16.2
Lymph node involvement		
No	61	58.1
Yes	38	36.2
N/A	6	5.7
Distant metastases		
No	71	67.6
Yes	34	32.4
Resected		
No	93	88.6
Yes	11	10.4
N/A	1	1.0
Prior treatment		
Chemo ± radiation	39	37.1
Radiation only	4	3.8

ranged in age from 28 to 82 years (median, 62 years). All patients had advanced disease, and eleven patients had prior surgery, but no patient received adjuvant ranpirnase. Thirty-nine patients (37%) had been treated with prior chemotherapy (Table 3). A retrospective classification of all patients enrolled onto this trial by the CALGB prognostic groups revealed a large number of patients (24 of 105) in the prognostically poor groups 5 and 6 (Table 1).

Survival

November 1, 1999, was the cutoff date for updating survival. Using the Kaplan-Meier survival function estimates, the overall MST was 6 months (95% confidence interval, 4.7 to 10.0), and the 1-year and 2-year survival rates were 34.3% and 21.6%, respectively, with 10 patients (9.5%) alive at the time of analysis (censored with regard to survival analysis).

Table 3. Patients Who Had Prior Chemotherapy

Site No.	Patient No.	Group	Age (years)	Regimen
1	5	2	72	Mit C + CDDP
1	6	5	28	DOX + CDDP
1	7	3	42	DOX + CDDP; DOX + CBCDA
1	12	3	50	CDDP + TMX + IFN-alpha
1	13	2	53	Mit C + CDDP + VLB + IL-3; CBCDA + MTX + VLB
1	15	5	58	CTX + DOX + CDDP
1	18	2	47	MTX + VCR + leucovorin
1	20	4	69	CDDP + VLB + MTX
1	26	1	41	CDDP + TMX + IFN-alpha
1	28	3	61	CDDP + TMX + IFN-alpha
1	30	5	66	CDDP + MTX + VLB; CBCDA + Mit C
1	31	3	56	CTX + DOX + CDDP
2	1	5	78	Unknown
2	2	4	74	Unknown
2	3	2	68	Mit C + CBCDA
2	7	3	66	DOX + CDDP
2	9	2	67	DOX
2	12	3	52	CTX + DOX + CDDP
2	13	2	64	DOX
3	3	1	67	PTX
3	5	2	34	IUDR + folinic acid
3	6	1	43	DOX + CDDP + IFS + VP-16; PTX + MXN
3	9	2	76	BLM
3	12	6	48	DOX + CDDP; PTX + CBCDA; NVB
3	13	3	60	DOX + CDDP
3	14	3	49	Doxil; TMX + CDDP
3	16	2	51	Unknown
3	17	3	66	Mit C + VCR + 5-FU
3	18	3	58	DOX + CBCDA
3	22	6	57	CDDP + TMX
3	23	5	64	Mit C + CDDP; IFN-gamma + IFN-alpha + TNF-alpha
3	25	4	57	PTX + CBCDA
3	26	3	60	CDDP + VP-16
3	28	5	52	DOX + MTX + VLB + CDDP
3	31	4	66	DOX + CDDP + CTX; doxil
4	4	3	41	High-dose MTX + leucovorin
4	15	5	50	Mit C + CDDP
4	19	3	49	CTX + DOX + CDDP
4	23	3	50	CTX + DOX + CDDP

Abbreviations: Mit C, mitomycin; CDDP, cisplatin; DOX, doxorubicin; CBCDA, carboplatin; TMX, tamoxifen; IFN-alpha, interferon-alpha; VLB, vinblastine; IL-3, interleukin-3; MTX, methotrexate; CTX, cyclophosphamide; VCR, vincristine; PTX, paclitaxel; IUDR, 5-iododeoxyuridine; IFS, ifosfamide; VP-16, etoposide; MXN, mitoxantrone; BLM, bleomycin; NVB, navelbine; 5-FU, 5 fluorouracil; IFN-gamma, interferon-gamma; TNF-alpha, tumor necrosis factor alpha.

Analysis of survival by PS and histologic type (epithelioid *v* nonepithelioid) is presented in Table 4. Patients with better PS and epithelioid histology (the latter included epithelioid and undetermined types, n = 89) had, as expected, more favorable survival outcomes. For example, patients with PS of 0 had a median survival time of 18.5 months.

Table 4. Kaplan-Meier Survival Function Estimates Histology, PS, and Survival Rates

Group	No. of Patients	MST (months)	Survival Rate 1-Year (%)	Survival Rate 2-Year (%)
PS 0	29	18.5	58.6	36.8
PS 1	64	5.8	28.1	17.2
PS 2	12	2.3	8.3	8.3
Epithelioid*	89	6.9	34.8	22.2
Nonepithelioid†	16	2.0	31.3	18.8

*Includes patients with epithelioid and undetermined histology.
†Includes patients with sarcomatoid and mixed (biphasic) histology.

Survival by CALGB groups 1 to 6 is shown in Fig 1. The MSTs for the CALGB groups 1 through 6 were 29.9, 6.6, 5.8, 10.7, 4.5, and 1.8 months, respectively. The survival of patients who had prior chemotherapy versus those who had not was not significantly different (MST, 7.3 *v* 5.7 months; 1-year survival rate, 33.3% *v* 34.9%; 2-year survival rate, 19.7% *v* 22.7%; log-rank $P = .971$).

The age, PS, histologic type (epithelioid plus undetermined *v* nonepithelioid), and the presence or absence of abdominal involvement were considered potential prognostic predictors. Using Cox proportional hazards regression analyses in the ITT population, PS as a stepwise linear variable and age as a continuous variable were chosen as significant (alpha $< .05$) prognostic variables. The age variable had a risk ratio of 1.02 ($P = .035$), although PS registered $P = .0013$, with a risk ratio of 1.78. The greater the patient's age and higher numerical performance status score, the greater the risk of death. Sex replaced age in the model and was associated with a risk ratio of 1.85 ($P = .028$), although PS registered $P < .0001$, with a risk ratio of 2.09.

Tumor Responses and Survival

Eighty-one of 105 patients who had both a baseline tumor assessment (computed tomography scan or chest x-ray) and at least one follow-up evaluation were assessed for tumor responses.

Four of the 81 patients assessable for tumor response had PRs. In addition, two MRs and 35 stabilizations of previously PD were observed (Table 5). Ten of 105 patients remained alive as of the time of analysis from 15.2+ to 54.8+ months. Among the 39 patients who had prior chemotherapy, one experienced PR, one experienced MR, and 11 experienced SD.

Time to Progression

The overall median time to PD among the 69 patients who experienced it was 102 days (95% confidence interval, 64 to 161). Thirty-six patients (34.3%) remained censored, ie, no evidence of progression was demonstrated at the time of analysis. One patient who originally achieved SD eventually achieved PR (October 1999), currently remains in PR, and continues on treatment more than 3 years after enrollment.

Treatment Compliance and Toxicity

One hundred five patients received a total of 1,397 doses of ranpirnase (range, one to > 109 doses per patient). Twenty-one patients developed grade 3 or 4 adverse events (33 total) that were considered related to treatment. Grade 3 events were reported in 18 patients, and grade 4 events were reported in four (one patient had both grade 3 and 4 toxicities) (Table 6).

Ranpirnase treatment was associated with asthenia, flu-like symptoms, arthralgia, fever, vasodilation (manifested

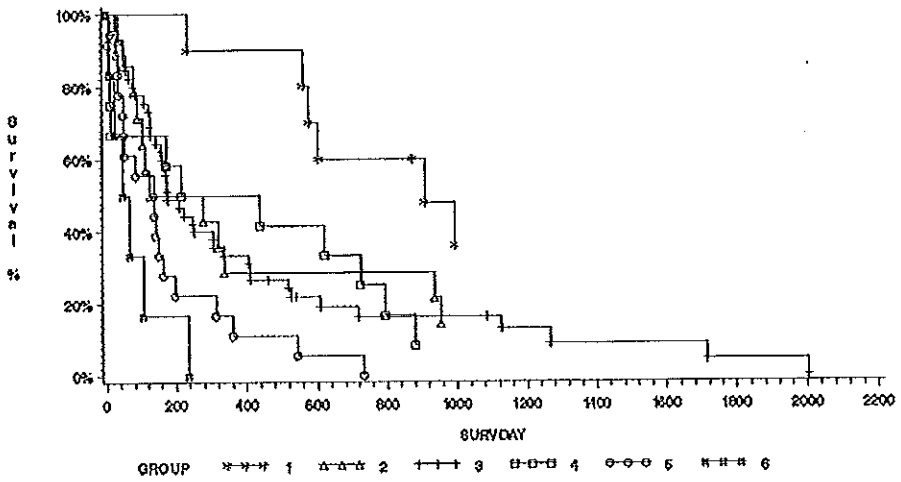

Fig 1. Survival profiles of the ITT population by the CALGB-defined prognostic groups 1 through 6 in days.

Table 5. Kaplan-Meier Survival Function Estimates of Patients Who Had PR, MR, and SD

Patients	No. of Patients	MST (months)	CEN (%)	95% CI	Survival (%) 1-Year	Survival (%) 2-Year
ALL	41	18.5	22.0	10.5-29.0	61.0	40.8
PR	4	61.1	50.0	56.3-65.9	100.0	100.0
MR	2	—	50.0	—	50.0	50.0
SD	35	17.1	17.1	10.0-23.6	57.1	33.3

Abbreviations: CEN, censored; CI, confidence interval.

primarily by flushing with occasional hypotensive and/or vasovagal reaction), paresthesias, peripheral edema, and allergic reactions. Sixteen (15.2%) of 105 patients were removed from the study because of adverse experiences (including renal insufficiency in four patients, allergic reaction in four, arthralgia in two, proteinuria in two, anaphylactoid reaction in one, hypotension in one, peripheral edema in one, and asthenia in one). Patients had received an average of 6.6 doses at the time of cessation of treatment. Nine (56.2%) of the 16 patients were receiving reduced doses of ranpirnase at the time of cessation. Five (4.8%) of the 105 patients were removed from the study for hypersensitivity reactions, and four (3.8%) were removed as a result of renal toxicity.

Ten deaths on study and 11 deaths within 30 days of the last dose of ranpirnase were reported to the Food and Drug Administration. None of the 41 patients who demonstrated evidence of clinical activity (including the 35 SD patients) died on study or within 30 days of the last dose of ranpirnase. There were no serious adverse events or deaths considered related to ranpirnase treatment.

Table 6. National Cancer Institute Grade 3 and 4 Adverse Events: Related (N = 105)

	Grade 3 (n = 18)		Grade 4 (n = 4)	
	No.	%	No.	%
Asthenia	6	5.7	0	0
Peripheral edema	4	3.8	0	0
Arthralgia	3	2.9	0	0
Pain	3	2.9	0	0
Anorexia	2	1.9	0	0
Nausea	2	1.9	0	0
Myalgia	2	1.9	0	0
Edema	1	1.0	0	0
Hypotension	1	1.0	1	1.0
Flu syndrome	1	1.0	0	0
Vasodilation	1	1.0	0	0
Gout	1	1.0	0	0
Neuropathy	1	1.0	0	0
Paresthesia	1	1.0	0	0
Anaphylactoid reaction	0	0	1	1.0
Worsening of lupus symptoms	0	0	1	1.0
Kidney function abnormal	0	0	1	1.0

NOTE. Each body system or preferred term relates to at least one event.

An analysis of the hematology parameters (hemoglobin, hematocrit, WBC, platelets, prothrombin time, and partial thromboplastin time) revealed essentially no clinically significant changes from baseline. An analysis of the clinically relevant serum chemistry parameters (total bilirubin, alkaline phosphatase, AST, serum creatinine, and glucose) revealed, again, few clinically significant changes from baseline.

DISCUSSION

This large, phase II trial demonstrated that four of the 81 patients assessable for tumor response demonstrated evidence of objective PRs. In addition, two MRs and 35 cases of SD in patients with previously PD were identified. Among patients with objective clinical activity such as PR plus those with MR and SD, the Kaplan-Meier estimate of MST was 18.5 months, and the 1-year and 2-year survival rates were 61.0% and 40.8%, respectively.

The 1-year survival rate of 34.3% observed in this trial for the ITT population compares favorably with the previously published results. For example, Chahinian et al[22] reported 1-year survival rates for the combinations of doxorubicin plus cisplatin and mitomycin C plus cisplatin of 23% and 29%, respectively. The overall 1-year survival rate in the 337 patients treated with a variety of chemotherapy regimens between 1984 and 1994 and analyzed by the CALGB was 27%.[20] The 2-year survival rate was 12% (compared with 21.6% in this phase II trial).

Whether the SD rate reflects the benefit of ranpirnase or an intrinsic difference in tumor biology cannot be determined from a phase II design such as this. A randomized discontinuation trial design could be used to clarify this question.

As of the time of analysis, 10 patients remained alive 15.2+ to 54.8+ months from treatment. One of the 10 living patients has continued on treatment for more than 3 years since enrollment and has been in continued remission since October 1999. The prolonged survival in some patients, the objective responses, and the large number of patients with SD was encouraging and led to the design and conduct of the phase III program. These results also

confirmed that performance status, as previously reported, is a key prognostic factor in predicting survival outcome, regardless of histology.

In the CALGB report, groups 5 and 6 had short MSTs of 4.4 and 1.4 months, respectively.[19,20] These two prognostically unfavorable groups were considered to be less suitable for systemic chemotherapy. Our phase II trial analyses confirmed these findings, with MSTs of 4.5 and 1.8 months for groups 5 and 6, respectively (Fig 1). Thus, we believe that CALGB groups 5 and 6 do indeed have such a poor prognosis that they, perhaps, should be omitted from future trials. The TTG group (CALGB groups 1 through 4 combined) is suggested for future trials. Using the TTG concept allows for a larger number of patients to be compared rather than relatively small numbers per each group, therefore providing a more meaningful statistical analysis.

The MST and 1-year and 2-year survival rates for the TTG population were 8.3 months, 42%, and 26.8%, respectively, which, as expected, compared favorably with those of the respective values for the ITT population of 6 months, 34.3%, and 21.6%. The analysis of the TTG population confirms the importance of the CALGB prognostic groups and its utility as a meaningful tool for comparing systemic therapies in patients with unresectable malignant mesothelioma. Such analyses could enhance the ability of physicians to assess any claimed treatment-related clinical benefit. However, the overlapping survival times of groups 2, 3, and 4 (MSTs of 6.6, 5.8, and 10.7 months, respectively) (Fig 1) suggest the need for further refinement of the prognostic groupings.

The overall safety profile of ranpirnase suggests that it could be an alternative systemic treatment for those patients who have not responded to prior cytotoxic therapy (particularly with anthracyclines or patients with myocardial disease that precludes treatment with anthracyclines) or a valuable addition to the existing agents, particularly those that demonstrate synergistic interactions with ranpirnase, such as doxorubicin[23] and cisplatin.[24]

This phase II trial suggests the clinical activity of ranpirnase in patients with unresectable malignant mesothelioma, including those pretreated with one or more chemotherapy regimens. These results were the basis for the initiation of the randomized phase III trial and for focusing on the TTG as a population of patients who may benefit especially from ranpirnase treatment. The preliminary survival results of this phase III trial were presented at the Thirty-Sixth Annual Meeting of the American Society of Clinical Oncology, May 12-15, 2000, New Orleans, LA, and showed that ranpirnase is active in unresectable malignant mesothelioma and may be superior to doxorubicin in certain subsets of patients such as the TTG population. The respective MSTs and 1-year and 2-year survival rates of ranpirnase are 11.3 months, 46.2%, and 34.3%. The respective MSTs and 1-year and 2-year survival rates of doxorubicin are 9.1 months, 34.5%, and 10.7%[21]

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