Original Article

A Possible Association Between Aprotinin and Improved Survival After Radical Surgery for Mesothelioma

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BACKGROUND: Aprotinin has been used to decrease blood loss with complicated cardiac surgery but has not been investigated in extrapleural pneumonectomy, an operation that does not use cardiopulmonary bypass. In this prospective, randomized, placebo-controlled, double-blind trial, the authors investigated whether aprotinin decreased blood loss in patients who underwent this operation. **METHODS:** After appropriate statistical design and institutional review board approval, eligible patients who were scheduled for extrapleural pneumonectomy were randomized to receive either aprotinin or placebo during the operation. Blood loss and survival data were obtained from electronic medical records and surgical databases. **RESULTS:** Of 20 patients who were enrolled, 16 patients met criteria for blood loss analysis. Four patients were excluded from the blood loss analysis: Three patients were inoperable because of tumor spread and underwent limited surgery, and 1 patient died intraoperatively because of acute, massive hemorrhage. The mean blood loss was 769 mL with aprotinin versus 1832 mL with placebo ($P = .05$; Wilcoxon test). All 20 patients were included in survival analyses. All 9 patients who received placebo died. In contrast, 7 of 11 patients who received aprotinin remained alive at the time of the current report. Kaplan-Meier survival curves differed significantly between the 2 groups ($P = .0004$). A Bayesian multivariate survival analysis of 18 patients who had complete data available on 8 prognostic variables indicated a posterior probability of .99 that aprotinin was beneficial. **CONCLUSIONS:** Aprotinin decreased blood loss. After accounting for covariate effects, there was a significant comparative benefit with aprotinin in postoperative survival. This finding was unexpected and could not be considered conclusive because of the small size of the current study. A confirmatory study may be warranted. **Cancer 2009;115:833–41. © 2009 American Cancer Society.**

KEY WORDS: Bayesian analysis, log-normal regression model, surgical blood loss, pneumonectomy, mesothelioma, serine protease inhibitor, aprotinin.

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Aprotinin (Trasylol; Bayer Corporation, West Haven, Conn) is a serine protease inhibitor that inhibits all serine proteases, including kallikrein and plasmin. Although it was investigated initially because of the possibility that its use would decrease the development of 'pump lung' or acute respiratory distress syndrome, it was discovered serendipitously that aprotinin significantly decreased blood loss during repeat cardiac surgery.[1] Because of this effect, it became a standard of care for complicated or repeat cardiac surgery.[2,3] Recently, its use was called into question by a controversial but influential study, which suggested that aprotinin used in the setting of coronary revascularization was associated with a doubling of the rate of renal failure requiring dialysis, a 55% increase in myocardial infarction or heart failure, and a 181% increase in stroke or encephalopathy.[4]

Studies also have demonstrated that aprotinin decreases blood loss during liver transplantation and major orthopedic surgery, although the mechanism of blood conservation in these models may differ from that in cardiac surgery, because cardiopulmonary bypass is not used for these surgeries.[5,6] It has been suggested that intraoperative fibrinolysis in patients who undergo these procedures, instead, is prevented by direct antiplasmin activity and through the inhibition of protein-C activity. Protease-activated receptors (PAR1-PAR4) on platelets are involved in platelet function and may account for some of the effects of aprotinin in these patients. Specifically, in preventing PAR1 receptor cleavage by thrombin, aprotinin prevents platelet activation by this mechanism without inhibiting the platelet response to endogenous collagen, epinephrine, and adenosine.[7] Nonetheless, despite uncertainty over the exact mechanism, aprotinin decreases hemorrhage in these widely disparate models.

Mesothelioma has a very poor prognosis with survival unlikely beyond 3 years. Extrapleural pneumonectomy (EPP) has been used in an attempt to provide local control of this invasive tumor. The efficacy of the surgery itself has been questioned.[8] EPP is associated with the potential for significant blood loss because of the large, raw surface of the hemithorax left behind after resection of the parietal pleura. Because of the significant blood loss with EPP, we investigated methods to reduce blood loss. Because aprotinin was useful to decrease blood loss in cardiac surgery with cardiopulmonary bypass, its use was begun on an empirical basis for EPP approximately 7 years ago at The University of Texas M. D. Anderson Cancer Center. Because there was little experimental evidence that aprotinin would be helpful in the setting of EPP, which does not use cardiopulmonary bypass, we undertook an investigator-initiated, prospective, randomized, controlled, double-blind study of the estimated blood loss (EBL) in patients undergoing EPP who received aprotinin versus patients who received placebo. When designing this study, we were aware of a previous suggestion that malignancy may be susceptible to treatment by anticoagulants.[9] Thus, we examined the longer term survival of our study patients.

MATERIALS AND METHODS

Study Design

Historic data on 36 patients who received half-dose aprotinin for EPP at our center showed a mean EBL of 825 mL. This historic mean was targeted as a 50% drop from an assumed null blood loss of 1650 mL without aprotinin. Patients in the study were randomized in double-blind fashion between aprotinin and saline. The study design was based on a 2-sided, group-sequential procedure with 2 interim tests, after 10 patients and after 20 patients, using O'Brien-Fleming boundaries, with an overall type I error rate of 0.05 and a power of 0.90 to detect a 50% drop in blood loss.[10] This required a sample size of up to 30 patients. Survival after surgery was analyzed as a secondary outcome. An intention-to-treat analysis was planned. The study design was approved by the M. D. Anderson Clinical Research Committee. A randomization schedule based on study accession number was developed by our statistician (P.F.T.) and was provided to our pharmacy. The Institutional Data Monitoring Committee followed the interim results of this blinded study in case of unexpected toxicities.

Institutional review board approval was obtained. After they provided informed consent, eligible patients were assigned randomly in accordance with the previously determined randomization schedule to receive in double-blind fashion either aprotinin or saline (placebo) administered after a precautionary dose of 10,000 kallikrein inhibitor units (KIU) of aprotinin or of placebo for control patients. For the aprotinin group, a loading dose of 2 million KIU was infused over 1 hour followed by a

maintenance infusion of 500,000 KIU per hour that was continued throughout the surgery until the patient was admitted to the intensive care unit. This regimen is the 'High Hammersmith' dosage or 'Regimen A' in the US with omission of the 'pump-prime' loading dose used for cardiopulmonary bypass surgery. The placebo group received a continuous infusion of the same volume of saline placebo. Both drug and placebo were recorded as 'Aprotinin Study Solution' on the anesthetic record. Our standard anesthetic management for all patients included the use of thoracic epidural postoperative analgesia, the placement of double-lumen endotracheal tubes for the required 1-lung ventilation, and the infusion of diltiazem as prophylaxis for atrial fibrillation. A desflurane/air/oxygen anesthetic was used with infusions of sufentanil citrate for analgesia and rocuronium bromide for muscle relaxation. Blood loss was estimated by the attending anesthesiologist and was recorded on the electronic anesthetic record. Survival was recorded from the hospital electronic medical record database, which contains not only patient data but also the time of the last known contact. Progression-free survival data were obtained from the thoracic surgical database.

Statistical Methods

Unadjusted survival probabilities were estimated using the method of Kaplan and Meier,[11] and between-group survival comparisons were done using the log-rank test.[12] Blood loss was compared between treatment groups using the Wilcoxon-Mann-Whitney *U* test,[13] and proportions were compared between groups using the Fisher exact test.[13] Because of the small sample size, the use of a Cox model[14] to assess the joint effects of patient covariates and treatment on survival would have been invalid, because the established partial likelihood distribution theory for the Cox model relies on large sample approximations. This problem also would be the case if maximum likelihood estimation (MLE) were used assuming a frequentist time-to-event regression model, because the standard distribution theory for MLEs also relies on large sample approximations. Consequently, a Bayesian log-normal regression model[15] was used to assess the joint effects of patient covariates and treatment (aprotinin vs placebo) on overall survival, because this methodology is valid for samples of any size. The log-normal distribution was chosen based on preliminary goodness-of-fit assessments of several possible distributional forms, including exponential, Weibull, gamma, log-logistic, and log-normal. This was done using the Bayes Information Criterion (BIC) = $-2\log(\text{likelihood}) + p\log(n)$, in which *log* denotes natural logarithm, *likelihood* denotes the fitted likelihood under the assumed model, n = sample size, and p = the number of model parameters. Smaller BIC values correspond to a better model fit, with 'p log(n)' a term that penalizes models with more parameters. The log-normal model assumes a normal distribution for the log-transformed survival time (T) denoted $\log(T) \sim N(m,v)$, in which $m = \beta_0 + \beta_1$ (age) $+ \beta_2$ (EPP) $+ \beta_3$ (postsurgical chemotherapy) $+ \beta_4$ (intensity-modulated radiotherapy) $+ \beta_5$ (man) $+ \beta_6$ (histology = biphasic) $+ \beta_7$ (disease stage 4) $+ \beta_8$ (lymph node involvement) $+ \beta_9$ (aprotinin) is a linear combination of 8 covariate effects and the treatment effect; and v is the variance of log(T). In particular, β_9 is the aprotinin-versus-placebo effect after adjusting for the 8 patient covariates. Because m is the mean of log(T), a positive (negative) value of a given parameter corresponds to a beneficial (deleterious) effect of the corresponding covariate. For the Bayesian model fit, we assumed that each of the parameters β_0 through β_9 in m followed a noninformative normal prior with mean 0 and variance 1000 and assumed a noninformative inverse gamma prior for v with mean 1 and variance of 1000. Statistical analyses were performed using Splus software,[16] or, for the Bayesian model fits, posterior quantities were computed using Markov chain Monte Carlo (MCMC) in WinBugs1.4.[17] The covariates included in the fitted log-normal model were age, EPP, whether the patient received chemotherapy postsurgery, intensity-modulated radiotherapy, sex, histology, disease state, and lymph node involvement.

Role of the Funding Source

After initial design of this protocol, we were able to secure partial funding from Bayer Pharmaceuticals Corporation. The only change they requested to the protocol as written was that they preferred that we use the High Hammersmith dosage schedule rather than the half-dose regimen we had been using before this study was initiated. The originators of the study (P.H.N., W.R.S.) agreed to this suggestion.

Table 1. Demographics, Therapy, and Outcome

Patient No.	Sex	Age, Years	Group	EBL, mL	Surgery	Stage	Type	Survival, Months	Status	Cause of Death
1	Man	57	Aprotinin	220	P/D	T4Nx	E	16	D	Mesothelioma
3	Woman	56	Aprotinin	500	EPP	T1bN0	E	33	D	Mesothelioma
5	Man	77	Aprotinin	800	EPP	T3N2	E	1	D	Medical (CVA, hemiparesis)
6	Man	63	Aprotinin	2000	EPP	T2N1	E	10	D	Mesothelioma
10	Man	65	Aprotinin	250	EPP	T3N0	E	26	AWD	
12	Man	60	Aprotinin	100	ExThor	T4Nx	E	22	AWD	
14	Man	71	Aprotinin	1500	P/D	T4N0	E	21	AWD	
15	Man	61	Aprotinin	350	EPP	T3N0	E	19	NED	
16	Woman	66	Aprotinin	400	EPP	T2N0	E	16	NED	
18	Woman	60	Aprotinin	400	EPP	T4N0	E	8	NED	
19	Man	62	Aprotinin	1450	EPP	T2N2	B	9	AWD	
2	Man	56	Placebo	800	EPP	T2N0	E	6	D	Unknown
4	Man	58	Placebo	750	EPP	T3N2	E	6	D	Medical (pneumonia)
7	Man	66	Placebo	2500	EPP	T3N0	E	3	D	Medical (arrhythmia)
8	Man	59	Placebo	10400	EPP	T4N0	S	0	D	Surgical (hemorrhage)
9	Man	48	Placebo	1350	EPP	T3N1	E	23	D	Medical (respiratory arrest)
11	Man	69	Placebo	700	EPP	T3N2	B	1	D	Medical (PE±recurrence)
13	Man	73	Placebo	2050	EPP	T4N2	E	4	D	Mesothelioma
17	Man	67	Placebo	1500	EPP	T3N0	S	8	D	Mesothelioma
20	Man	62	Placebo	5000	EPP	T4N1	B	3	D	Mesothelioma

EBL indicates estimated blood loss; P/D, pleurectomy/decortication; T, tumor classification; N, lymph node status; E, epithelioid; D, dead; EPP, extrapleural pneumonectomy; CVA, cerebrovascular accident; AWD, alive with disease; ExThor, exploratory thoracotomy; NED, no evidence of disease; B, biphasic; S, sarcomatoid; PE, pulmonary embolism; ±, with or without.

RESULTS

Only 20 of the planned maximum of 30 patients were enrolled in this study because of a change in aprotinin labeling mandated by the US Food and Drug Administration (FDA).[18] This change was made because the retrospective analysis of aprotinin noted above suggested a higher death rate from allergic reactions in cardiac surgery patients who were given aprotin.[4] After this, the FDA required the immediate availability of cardiopulmonary bypass when aprotinin is used in case of an allergic reaction. Our institution does not routinely have cardiopulmonary bypass available, and we believed that it was unethical to require patients or insurers to pay for this service. Consequently, the trial was closed to further enrollment.

Of the 20 patients enrolled in the study, 11 were randomized to aprotinin, and 9 were randomized to placebo. The data on 4 patients were excluded from the EBL analysis: Three patients, all in the aprotinin group, did not undergo EPP because they were diagnosed with advanced/locally invasive disease at the time of surgery, they did not meet surgical criteria for EPP, and, thus, they underwent either pleurectomy/decortication or exploratory thoracotomy only; the fourth excluded patient, who was assigned to the placebo group, died intraoperatively from acute hemorrhage after disruption of the superior vena cava, which was involved by tumor. Another patient had the planned study EPP cancelled after line trauma forced arterial repair and a delay in surgery. Because unblinding had not been performed at this early stage, this patient underwent EPP 1 month later with the then institutional standard half-dose aprotinin therapy. We believed that it was unethical to submit the patient to a blinded drug because of uncertainty regarding whether the test dose had been administered before the trauma from line insertion. The patient was included in the aprotinin group for EBL analysis under the intention-to-treat design. All 20 patients were analyzed for survival comparison on an intention-to-treat basis.

There were no significant differences in disease status according to American Joint Committee on Cancer stage between the aprotinin group and the placebo group. However, among the patients who underwent EPP, 5 of 9 patients (56%) in the placebo group had lymph node metastases compared with 3 of 8 patients (38%) in the aprotinin group ($P = .64$). There was a trend for nonepithelioid histology (44%) in the placebo group compared with the aprotinin group (9%; $P = .20$). Details of patient demographics, surgery, and outcomes are shown in Table 1, and patient characteristics are summarized in Table 2.

Table 2. Patient Characteristics Stratified by Treatment

Characteristic	No. of Patients (%)		
	Saline Placebo	Aprotinin	*P**
No. of patients	9	11	
Age, y: Mean±SD	62±7.6	63.5±6.2	.85
EBL, mL: Mean±SD	1831.3±1433.8	768.8±629	.05
EPP			
No	0 (0)	3 (27.3)	
Yes	9 (100)	8 (72.7)	.22
Chemotherapy			
No	5 (55.6)	5 (45.5)	
Yes	4 (44.4)	6 (54.5)	1.0
AIMRT			
No	5 (55.6)	5 (45.5)	
Yes	4 (44.4)	6 (54.5)	1.0
Lymph node involvement			
No	4 (44.4)	6 (66.7)†	
Yes	5 (55.6)	3 (33.3)	.64
Sex			
Women	0 (0)	3 (27.3)	
Men	9 (100)	8 (72.7)	.22
Histology			
Epitheloid	5 (55.6)	10 (90.9)	
Biphasic	2 (22.2)	1 (9.1)	
Sarcomatoid	2 (22.2)	0 (0)	.20
Stage			
I	0 (0)	1 (9.1)	
II	1 (11.1)	1 (9.1)	
III	5 (55.6)	5 (45.4)	
IV	3 (33.3)	4 (36.4)	1.0

SD indicates standard deviation; EBL, estimated blood loss; EPP, extrapleural pneumonectomy; AIMRT, adjuvant intensity-modulated radiotherapy.
* Wilcoxon test for continuous variables or Fisher exact test for categoric variables.
† One inoperable patient in the aprotinin group did not have mediastinal lymph nodes excised.

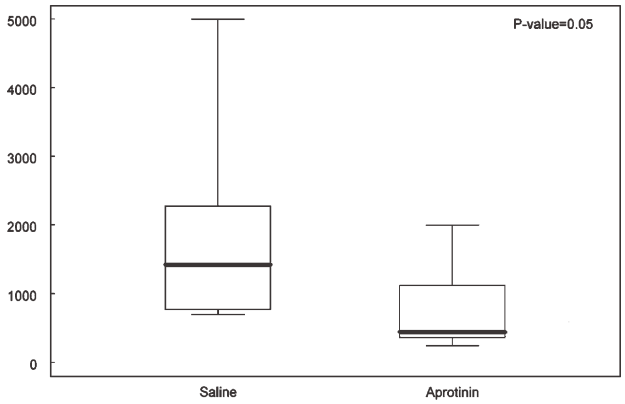

FIGURE 1. This box-and-whiskers plot depicts the median, interquartile range, and range for estimated blood loss in patients who received either aprotinin or placebo during extrapleural pneumonectomy (N = 16 patients).

The plot in Figure 1 indicates that aprotinin was associated with a decrease in blood loss ($P = .05$, Wilcoxon test), with mean loss of 769 mL (95% confidence interval [95% CI], 243-1295 mL) in the aprotinin group (3 inoperable patients were excluded) and a mean loss of 1832 mL (95% CI, 633-3030 mL) in the placebo group (1 intraoperative death was excluded). The frequency of transfusion of blood products also was significantly lower ($P < .001$; 2-tailed Fisher exact test) in the aprotinin group, in which 2 of 8 patients received transfusions (3 inoperable patients were excluded) compared with 8 of 8 patients in the placebo group (1 intraoperative death was excluded).

All 9 patients who received saline as placebo died, and 7 of 11 patients who received aprotinin remained alive at the time of this report, including 2 patients who did not undergo EPP. Of the 7 aprotinin patients who remained alive, 3 were without evidence of disease recurrence. Excluding the 3 aprotinin patients who underwent a lesser resection or no resection and who, by definition, had persistent disease, recurrent mesothelioma occurred in 4 of 8 patients in the aprotinin group and in 3 of 8 patients in the placebo group. All recurrences were distant (contralateral lung or abdomen) with the exception of 1 patient in the aprotinin group who developed a local chest wall recurrence 20 months after EPP. This patient did not receive adjuvant radiation treatment.

The unadjusted survival difference between the aprotinin and placebo groups was highly significant ($P = .0004$; log-rank test), as demonstrated by the striking difference between the Kaplan-Meier estimates of survival for the 2 treatment arms in Figure 2. Although this comparison indicates an apparent beneficial effect of aprotinin, and none of the patient covariates summarized in Table 2 revealed a significant imbalance between the 2 treatment arms, there remains the possibility that the collective effects of these covariates may explain the difference in survival. This issue is especially important because of the small sample size of the study. For example, there were more noncancer deaths in the placebo group than in the aprotinin group (6 vs 1, respectively; $P = .05$). In addition, unfavorable histology or tumor stage,

nonepithelioid histology, and lymph node metastases were observed more frequently in the placebo group than in the aprotinin group. It has been established that both of these factors have a negative impact on survival and could have contributed to the poorer outcome of patients in the placebo group. These considerations motivated a multivariate survival regression analysis, which was done on the 18 patients who had complete data available on all 8 prognostic variables. The preliminary model fits yielded BIC values of 91.04 for the exponential regression model, 84.86 for the Weibull model, 84.97 for the gamma model, 83.77 for the log-logistic model, and 83.31 for the log-normal model. Thus, the log-normal regression model was chosen for the analyses reported here. The fitted Bayesian log-normal regression model for predicting survival is summarized in Table 3. To interpret the table, note that, in the Bayesian paradigm, all parameters are considered random quantities. The fitted model is obtained by computing the posterior distributions of the parameters given the observed data. For example, the coefficient β_1 for patient age in the model has a posterior mean of -0.21 and a standard deviation of 0.07; consequently, on average, older age is predictive of shorter survival. Thus, the posterior probability that older age is beneficial (see the last column of Table 3) equals $Pr(\beta_1>0|\text{data})$, which is computed as .001. Equivalently, the posterior probability that older age is deleterious equals $Pr(\beta_1<0|\text{data}) = 1 - .001 = .999$. The main objective of this analysis is to assess the treatment effect (aprotinin vs saline) on survival time, which is quantified by the parameter β_9 in the linear term described above (see Statistical Methods), while accounting for the effects of the 8 patient covariates. A Bayesian analysis was performed, as noted above, because the more conventional

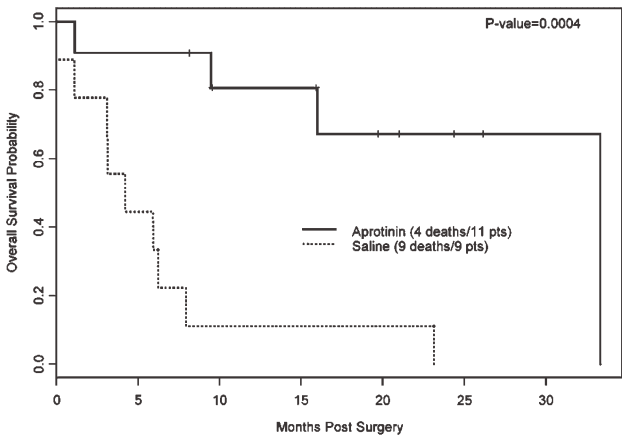

FIGURE 2. Kaplan-Meier curves of survival probability for the aprotinin group (N = 11 patients, including 3 who were inoperable) and the placebo group (N = 9 patient, including 1 operative death). Survival length differed significantly (P = .0004; log-rank test) between the 2 treatment groups.

Table 3. Summary of the Fitted Bayesian Log-normal Regression Model for Predicting Survival Time as a Function of Patient Covariates and Treatment

Variable	Posterior Quantities		
	Mean±SD*	95% Credible Interval†	Probability of a Beneficial Effect‡
Age	−0.21±0.07	−0.38, −0.09	.001
EPP (yes vs no)	−34.88±27.12	−90.56, 1.80	.05
Chemo (yes vs no)	6.06±1.53	3.68, 9.80	.99
IMRT (yes vs no)	0.57±0.75	−1.07, 2.0	.84
Sex (men vs women	2.56±2.08	−0.65, 7.26	.95
Histology (biphasic/ sarcomatoid vs epitheloid)	−4.25±1.10	−6.6, −2.27	.002
Stage (IV vs I-III)	−1.80±0.93	−3.63, 0.13	.03
Lymph node involvement (yes vs no)	−1.20±0.95	−3.43, 0.28	.05
Treatment (aprotinin vs saline)	3.15±1.46	1.11, 6.71	.99

SD indicates standard deviation; EPP, extrapleural pneumonectomy; IMRT, intensity-modulated radiotherapy.

* A positive (negative) parameter value corresponds to a beneficial (deleterious) effect on survival time.

† For each variable, denoting its parameter in the log-normal model's linear term by β, the posterior 95% credible interval is the 2.5th and 97.5th percentile of the distribution of β (eg, for the effect β_1 of age, $Pr(-0.38<\beta_1<-0.09|\text{data})=.95$, in which Pr indicates probability, and "data" refers to the covariate, treatment, and survival time data on the 18 patients for whom all of these variables were available.

‡ For each variable with parameter β, the probability that the variable has a beneficial effect is $Pr(\beta>0|\text{data})$; eg, for the effect β_1 of age, $Pr(\beta_1>0|\text{data})=.001$.

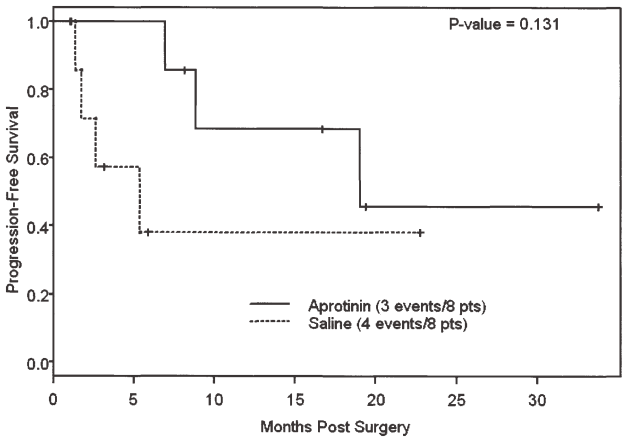

FIGURE 3. Kaplan-Meier curves of progression-free survival probability for the aprotinin group (N = 8 patients who were evaluable for disease progression) and the placebo group (N = 8 patients who were evaluable for disease progression). Progression-free survival did not differ significantly ($P = .131$; log-rank test) between the 2 treatment groups.

Cox model analyses, or a frequentist (non-Bayesian) analysis relying on MLEs, would necessarily rely on large sample approximations and, hence, would be invalid for this small study. All posterior quantities were computed using MCMC methods. On the basis of the observed data on the 18 patients who had covariates available and who were evaluable for overall survival, and accounting for the noted patient covariates with known significant effects on survival, the fitted Bayesian model indicated that the posterior probability that aprotinin was associated with longer survival was $Pr(\beta_9 > 0|\text{data}) = .99$.

Figure 3 provides Kaplan-Meier plots of progression-free survival for the 8 aprotinin patients and 8 placebo patients who were evaluable for disease progression (3 patients with inoperable disease and 1 immediate death were excluded). The improved progression-free survival of aprotinin-treated patients in this subgroup did not reach statistical significance ($P = .131$; log-rank test).

DISCUSSION

Despite early closure of the study to enrollment because of the FDA ruling, we observed that aprotinin had a statistically significant beneficial effect compared with placebo both in terms of decreasing blood loss and improving overall survival, the latter after accounting for prognostic covariate effects. It also is noteworthy that a recent retrospective analysis of the use of aprotinin for EPP conducted by thoracic surgeons at our institution[19] did not demonstrate an increased rate of the complications suggested by the recent aprotinin risk review.[4] Therefore, although our dataset was quite small, the magnitude of the beneficial effect associated with aprotinin use suggests that aprotinin still should be considered as a means of decreasing blood loss and lengthening survival in patients who undergo EPP.

The improvement in survival observed in the treatment group was an unexpected finding in this study. This is made more intriguing by the finding that traditional chemotherapy consisting of cisplatin and premetrexed (a multitargeted antifolate) reportedly improved survival in patients who had mesothelioma by an average of only 3 months compared with no chemotherapy.[20] Radiotherapy generally is not feasible because of the large target volume required and the associated risk of toxicity to intrathoracic organs. Although our study did not involve a search for the mechanism of survival improvement, it is reasonable to speculate that aprotinin may have improved survival either by preventing tumor progression, perhaps through an effect on the urokinase-type plasminogen activator (uPA), or by stimulating the immune system to oppose cancer progression. In support of the latter theory was the finding that all 3 patients who did not undergo EPP because of local invasion were in the aprotinin group and still had better than expected survival.

Although it has been postulated that aprotinin inhibits tumor growth,[21,22] this original claim was considered an overstatement, and the tumor-inhibiting potential of aprotinin was not studied further for many years. Recently, it has been suggested that tumor growth and/or metastasis may be affected by aprotinin.[23,24] In further support of the antineoplastic properties of aprotinin was the finding that mortality was decreased significantly in patients with liver metastases from colon carcinoma who received the agent in a study that investigated the potential for blood-sparing in liver resection.[25] Similarly, another study demonstrated improved survival in patients who received aprotinin during esophagectomy, although this finding came from a nonrandomized, nonblinded study that was reported only in a meeting abstract.[26] Three mechanisms may be postulated as the source of the apparent beneficial effects of aprotinin. The most obvious explanation is that the decreased hemorrhage and resultant

lower transfusion volume may decrease the degree of immune system down-regulation by heterologous blood. A second potential explanation is that the anti-inflammatory properties of aprotinin may inhibit leukocyte-induced vascular changes, which may promote tumor cell migration. A third possibility that aprotinin inhibits all serine proteases including, kallikrein and uPA. During surgery, activation of the intrinsic coagulation system causes kinins to be released from high-molecular-weight kininogen. These kinins, which include bradykinin and kallidin, may contribute to the growth of tumors by increasing vascular permeability, which would increase the nutrients available to the tumor. A fourth possibility is that aprotinin may have an antiangiogenesis effect. as suggested by the finding of a decrease in basic fibroblast growth factor levels in a mutant rat study model.[27] The cell-bound plasmin created by the uPA that tumor cells express also may facilitate the local invasion of uPA-expressing neoplasms through protein barriers.[28-31] Thus, any tumor that expresses uPA, including breast, colon, nonsmall cell lung, prostate, esophageal, pancreatic, and gastric cancers, may respond to aprotinin.

This is the fourth study to demonstrate an apparent survival advantage for patients who receive aprotinin during cancer surgery or therapy. It also was a prospective, randomized, controlled, double-blind study that had the specific aim of investigating postresection survival from its conception. However, because it was a very small study conducted in a very-high-risk population, the results indicating a large survival advantage in patients who received aprotinin cannot be considered confirmatory. In Figure 3, the progression-free survival of patients who were considered to have achieved a 'complete' resection suggests that, although there was an improvement in patients who received aprotinin, the effect did not reach conventional statistical significance. Regardless of whether the putative mechanism of action of aprotinin is a direct antineoplastic effect or is caused by a nonspecific anti-inflammatory effect, our results suggest that the apparent survival advantage associated with aprotinin use in patients undergoing EPP for mesothelioma should be investigated further in a larger prospective, randomized, blinded, multicenter trial. Such a study could be done in the setting of a simpler operation than EPP. The Mesothelioma and Radical Surgery (MARS) trial (European Organization for the Research and Treatment of Cancer trial 08031), which is examining whether a simple debulking surgery is as effective as EPP in improving the survival of patients with mesothelioma, may be an appropriate type of study in which to investigate aprotinin.[32] Regardless of whether the putative survival-prolonging effect in patients with mesothelioma is indirect or direct, our study suggests that anesthesia techniques and agents may affect longer term outcome more than is currently believed, and our results argue for the inclusion of anesthesiologists in trials such as MARS.

A recent editorial[33] praised the method used in the analysis of the large numbers of patients receiving aprotinin for rare side effects[4] that led the FDA to issue its warning regarding the use of aprotinin.[18] In fact, the author of that editorial suggested that the large review should be a model for future studies of drug safety and cited the admonition to 'first, do no harm' as the overriding consideration. However, the more practical admonition perhaps should be to 'do more good than harm,' especially for patients with a dire prognosis in whom the benefits of a drug outweigh the risks.

Conflict of Interest Disclosures

Honorarium was paid into general department funds for attendance at a seminar on aprotinin and micrometastases. The seminar led to the plan to include survival data in this proposed study on blood loss.

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