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# Factors Predictive of Survival Among 337 Patients With Mesothelioma Treated Between 1984 and 1994 by the Cancer and Leukemia Group B*

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*Purpose:* To examine the individual and joint effect of various pretreatment clinical characteristics on the survival of patients with mesothelioma treated by the Cancer and Leukemia Group B (CALGB).

*Patients and methods:* Between June 1984 and September 1994, 337 patients with malignant mesothelioma and no prior chemotherapy were accrued to seven phase II studies conducted by the CALGB which screened the efficacy of 10 treatment regimens or dose levels. The eligibility criteria for all studies were virtually identical. Patient characteristics include the following: age older than 60 years (63%); male (83%); performance status (PS) of 0 or 1 (81%); chest pain (60%); definite asbestos exposure (62%); >5% weight loss (41%); and pleural involvement (94%). Median survival time (MST) for the 10 treatment regimens ranged from 3.9 to 9.8 months (overall=7.2; 95% confidence interval [CI], 6.5 to 8.3), with 1-year survival between 14% and 50% (overall=27%; 95% CI, 23 to 33%).

*Results:* Cox survival models and exponential regression trees were used to examine the prognostic importance of pretreatment patient characteristics. Univariate analyses show that patients with poor Eastern Cooperative Oncology Group PS, chest pain, dyspnea, platelet count (PLT) >400,000/μL, weight loss, serum lactate dehydrogenase (LDH) level >500 IU/L, pleural involvement, low hemoglobin (HGB) level, high WBC count, and increasing age over 75 years have a worse prognosis. With decreasing risk ratio, multivariate Cox analyses showed that pleural involvement, LDH >500 IU/L, poor PS, chest pain, PLT >400,000/μL, nonepithelial histology, and increasing age older than 75 years jointly predict poor survival. PS was the most important prognostic split in the regression tree. Terminal nodes were amalgamated to form six distinct prognostic subgroups with MST (2-year survival) of 13.9 (38%) in 36 patients, 9.5 (21%) in 36 patients, 9.2 (10%) in 146 patients, 6.5 (3%) in 33 patients, 4.4 (0%) in 73 patients, and 1.4 (0%) in 13 patients ($p<0.0001$).

*Conclusions:* The subgroup with the best survival (MST=13.9 months) included patients with PS=0 and age younger than 49 years, and patients with PS=0, age of 49 years or older, and HGB ≥14.6. The worst survival (MST=1.4 months) occurred for patients with PS=1/2 and WBC ≥15.6/μL.

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Key words: mesothelioma; prognostic factor; survival

Abbreviations: CALGB=Cancer and Leukemia Group B; DHAC=dihydro-5-azacytidine; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; MST=median survival time; PS=performance status

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Malignant mesothelioma is a rare, seldom curable disease that has a median survival of 6 to 12 months.[1-4] The use of single-agent and combination chemotherapy for the treatment of this disease has been studied in numerous clinical trials without significantly affecting the prognosis of the disease.[1,2,5] The Cancer and Leukemia Group B (CALGB) has been part of that effort to investigate new chemotherapy regimens for the treatment of malignant mesothelioma. Between 1984 and 1994, CALGB conducted seven multi-institutional phase II studies that screened the efficacy of 10 treatment regimens or dose levels.[6-14]

The purpose of this article is to examine the

individual and joint effect of various pretreatment clinical characteristics on the survival of patients with mesothelioma treated on CALGB studies. By means of this analysis, future CALGB mesothelioma studies may be able to more precisely identify patient subgroups that are unlikely to benefit from chemotherapy; such patients may be candidates for more creative, innovative therapies.

## Materials and Methods

### *Study Design and Eligibility Criteria*

Table 1 summarizes the seven phase II studies for the treatment of mesothelioma that have been conducted by the CALGB between 1984 and 1994. The eligibility criteria for all studies were almost identical and included the following requirements: histologically confirmed malignant mesothelioma with measurable or evaluable disease; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2 (<50% of waking hours in bed); expected survival >2 months; adequate nutrition; no prior chemotherapy; >2 weeks since surgery and >4 weeks since prior radiotherapy; adequate hematologic, renal, and hepatic function; adequate cardiac function (*eg*, no arrhythmia requiring medications, no myocardial infarction in past 6 months); no other serious medical or psychiatric problems; and informed consent.

The study 8435 was conducted as a randomized phase II study; whereas 8638, 8833, 9031, and 9234 were conducted as single-arm studies. Both 8933 and 9131 were originally designed as single-arm studies; however, a second arm replaced the original arm in each study when the experimental regimen was modified by amendment. The dose of trimetrexate in 8933 was increased to 10 mg/m$^2$/d due to the lack of toxicity observed at the lower dose of 6 mg/m$^2$/d. In 9234, the treatment regimen was amended by the addition of leucovorin and acyclovir after significant toxic reactions were observed with edatrexate, 80 mg/m$^2$/wk, administered alone.

### *Pretreatment Patient Characteristics*

A total of 347 patients were registered to these seven studies between June 1984 and September 1994. Of these patients, three had their registration canceled prior to treatment, one provided no data, and six patients were ineligible upon retrospective review of institutional records. Reasons for ineligibility included the following: one patient with adenocarcinoma had been incorrectly diagnosed as having mesothelioma; three patients had preexisting medical conditions (history of myocardial infarction, arrhythmia, and pericarditis); and two patients had been treated previously with intrapleural bleomycin. Analyses presented below include only the 337 eligible patients who were treated and provided follow-up data.

Central pathologic review was completed by at least one reviewing pathologist (Y.S. or J.M.C.) in 78% of cases. Probable or definite mesothelioma was confirmed in >90% of all reviewed cases. An analysis limited to patients with mesothelioma confirmed by central pathology review is planned in a future article.

The following pretreatment characteristics were available on computer files for virtually all patients: age, gender, ECOG PS; histology as determined by the treating institution, asbestos exposure, platelet count, hemoglobin, WBC count, serum lactate dehydrogenase (LDH), disease involvement (pleural, pericardial, peritoneal), and extent of disease (local, regional/distant). In studies conducted since 1988 (8833, 8933, 9031, 9131, and 9234),

**Table 1—*Mesothelioma Studies Conducted by CALGB Between 1984 and 1994***

| Study Number | Reference No. | Accrual Period | Treatment Regimens | No. of Eligible Patients | Response Rate, % | Median Survival, mo (95% CI)[¶] |
|---|---|---|---|---|---|---|
| 8435 | 6 | 6/84-10/86 | Mitomycin, 10 mg/m$^2$ and cisplatin, 75 mg/m$^2$ q28d | 37 | 26 | 8.1 (6.1, 11.2) |
| | | | Doxorubicin (Adriamycin), 60 mg/m$^2$ and cisplatin, 75 mg/m$^2$ q28d | 39 | 14 | 8.8 (6.1, 11.1) |
| 8638 | 7 | 2/87-2/88 | Carboplatin, 400 mg/m$^2$ IV bolus q28d | 41 | 7 | 7.1 (6.1, 9.0) |
| 8833 | 8 | 6/88-6/89 | DHAC, 1,500 mg/m$^2$/d × 5 d q21d | 41 | 17 | 6.7 (5.0, 9.6) |
| 8933 | 9 | 7/89-8/91 | Trimetrexate, 6 mg/m$^2$/d bolus × 5 d q21d | 18 | 12 | 3.9 (1.9, 9.6) |
| | | | Trimetrexate, 10 mg/m$^2$/d bolus × 5 d q21d | 33 | 12 | 9.8 (7.1, 13.8) |
| 9031 | 10, 11 | 7/90-7/93* | DHAC, 1,500 mg/m$^2$/d continuous IV and cisplatin, 20 mg/m$^2$/d IV over 1 h on days 1-5 q21d | 35 | 14 | 6.4 (4.8, 10.1) |
| 9131 | 12, 13 | 5/92-9/94 | Edatrexate, 80 mg/m$^2$/wk | 20 | 25 | 9.6 (5.8, 15.5) |
| | | | Edatrexate, 80 mg/m$^2$/wk with leucovorin, 15 mg po × 4, acyclovir 80 mg po bid | 38 | 18[†] | 6.9 (5.5, 12.4) |
| 9234 | 14 | 3/93-9/94 | Paclitaxel, 250 mg/m$^2$ IV infusion over 24 h q21d with G-CSF,[‡] 300 μg/d d3-18 | 35 | 9 | 5.0 (4.1, 6.8) |

*Trial restricted to selected institutions.
[†]Interim analysis reported in reference 13.
[‡]G-CSF=granulocyte colony-stimulating factor.
[¶]CI=confidence interval.

Table 2—*Patient Characteristics and Univariate Survival Analyses*

| Variable | No. (%)* |
|---|---|
| Overall | 337 |
| Age, yr | |
| <50 | 47 (14) |
| 50-59 | 79 (23) |
| 60-69 | 137 (41) |
| 70+ | 74 (22) |
| Median | 62 |
| Minimum, maximum | 23, 83 |
| Sex | |
| Male | 279 (83) |
| Female | 58 (17) |
| PS | |
| 0 | 99 (29) |
| 1 | 176 (52) |
| 2 | 62 (18) |
| Epithelial histology† | |
| No | 107 (33) |
| Yes | 221 (67) |
| Presence of chest pain† | |
| No | 88 (40) |
| Yes | 131 (60) |
| Presence of dyspnea† | |
| No | 65 (30) |
| Yes | 151 (70) |
| Duration of symptoms,† mo | |
| <3 | 100 (46) |
| 3-6 | 67 (31) |
| >6 | 51 (23) |
| Weight loss† | |
| None | 126 (59) |
| >5% | 86 (41) |
| Asbestos exposure | |
| No | 89 (26) |
| Yes | 209 (62) |
| Unknown | 39 (12) |
| Smoking† | |
| No | 59 (27) |
| Yes | 158 (73) |
| Platelet count >400,000/μL | |
| No | 152 (45) |
| Yes | 184 (55) |
| LDH level >500 IU/L | |
| No | 298 (93) |
| Yes | 21 (7) |
| Hemoglobin, /μL | |
| <14.6 | 287 (86) |
| ≥14.6 | 48 (14) |
| WBC count, /μL | |
| <8.7 | 156 (46) |
| ≥8.7 | 180 (54) |
| Pleural involvement | |
| No | 19 (6) |
| Yes | 318 (94) |
| Peritoneal involvement | |
| No | 301 (89) |
| Yes | 36 (11) |
| Pericardial involvement | |
| No | 318 (94) |
| Yes | 19 (6) |
| Extent of disease | |
| Local | 163 (48) |
| Regional/distant | 174 (52) |
| Study arm | |
| 8435/Cisplatin + mitomycin | 37 (11) |
| 8435/Cisplatin + doxorubicin (Adriamycin) | 39 (12) |
| 8638/Carboplatin | 41 (12) |
| 8833/DHAC | 41 (12) |
| 8933/Low-dose trimetrexate | 18 (5) |
| 8933/High-dose trimetrexate | 33 (10) |
| 9031/Cisplatin + DHAC | 35 (10) |
| 9131/Edatrexate without leucovorin | 20 (6) |
| 9131/Edatrexate with leucovorin | 38 (11) |
| 9234/Paclitaxel | 35 (10) |

*Due to missing data, the total number of patients may not sum to 337.

†For all studies except 9234, histology was assessed by the institution treating the patient. For 9234, the protocol accidentally omitted the requirement that information about the institution's assessment of histology be submitted. Hence, such information is not available for all patients treated on 9234. For patients treated on 9234 who are missing the institutional assessment, the histology as determined by central review was used if such information was available.

‡Data were not collected in 8435 and 8638.

the following data were also available: presence of chest pain, presence of dyspnea, symptom duration, weight loss, and smoking history.

Information concerning the primary site of the mesothelioma was not available from computer files for this retrospective analysis; rather information about anatomic sites of disease involvement was available. Hence, the variable describing pleural disease involvement is an indicator of whether mesothelioma involved the pleura.

Institutional normal ranges were not available for LDH. Hence, for convenience, a high LDH level was defined in statistical analyses as an LDH level >500 IU/L.

At the time CALGB conducted its phase II studies, staging information and detailed information on which a determination of stage could be made according to the criteria of Butchart et al[15] or Rusch[16] were not collected. Given the importance of stage reported in previous studies, an attempt was made by one of us (N.J.V.) to categorize patients as having local or regional/distant disease based on computerized information about sites of involvement at registration, and on review of copies of the baseline radiograph report when available. Regional/distant disease was considered present when there were direct extensions of the disease into local organs (eg, chest, liver, or transdiaphragmatic extension) and/or metastatic disease.

### *Statistical Methods*

Survival time was defined as the period between the date of study registration and the date of death or last contact if the patient had not died at the time of analysis. All survival data are updated through September 1995. Analyses examined the prognostic importance of the following factors measured at study entry: age, gender, ECOG PS, epithelial histology, presence of chest pain, presence of dyspnea, duration of symptoms (<3 months/3 to 6 months/>6 months), weight loss in past 6 months (>5% loss of body weight/none or <5%), asbestos exposure (no/yes/unknown), smoking history, LDH level (>500/≤500 IU/L), platelet count (>400,000/≤400,000/μL), hemoglobin, WBC count, location of disease involvement (pleural/peritoneal/

Table 3—*Multivariate Stepwise Model*

| Variable | Model With Variables Collected in All Studies (N=309)* Parameter Estimate | SE | p Value | Risk Ratio (95% Confidence Interval) | Model With All Variables (N=195)† Parameter Estimate | SE | p Value | Risk Ratio (95% Confidence Interval) |
|---|---|---|---|---|---|---|---|---|
| (Age −75) * (age >75) | 0.29 | 0.06 | <0.001 | 1.34 (1.18, 1.52) | 0.26 | 0.07 | <0.001 | 1.29 (1.13, 2.47) |
| PS | 0.50 | 0.09 | <0.001 | 1.65 (1.37, 1.97) | 0.58 | 0.12 | <0.001 | 1.79 (1.13, 1.47) |
| Epithelial histology | −0.28 | 0.13 | 0.032 | 0.75 (0.58, 0.98) | | | | |
| Platelet count >400,000/μL | 0.45 | 0.12 | <0.001 | 1.57 (1.23, 2.00) | 0.36 | 0.16 | 0.024 | 1.44 (1.05, 1.96) |
| Pleural involvement | 0.97 | 0.29 | 0.001 | 2.64 (1.48, 4.69) | | | | |
| LDH >500 IU/L | 0.65 | 0.25 | 0.009 | 1.91 (1.18, 3.11) | 0.69 | 0.33 | 0.036 | 1.99 (1.05, 3.78) |
| Presence of chest pain | | | | | 0.50 | 0.16 | 0.002 | 1.65 (1.19, 2.27) |

*Not all data were available on all 337 eligible patients.
†Information about the presence of chest pain or dyspnea at presentation, duration of symptoms, weight loss, and cigarette exposure was not collected in 8435 and 8638. Hence, data from these studies are not included in the "Model With All Variables."

pericardial), extent of disease (local/regional or distant), and study arm. Survival curves were generated using the product limit estimator[17] for subgroups defined by these factors; survival comparisons were made using two-tailed log-rank tests.[18] The Cox proportional hazards model was used to examine the linear and nonlinear effect of continuous variables on survival.[19] Martingale and Schoenfeld residuals were used to assess the adequacy of linearity and proportional hazards assumptions.[20,21] The proportional hazards model was used in a stepwise manner to assess the joint effect of predictors on survival. Exponential regression trees with cross-validation were used to define prognostic subgroups with similar survival.[21-24] This recursive partitioning algorithm defined patient subgroups by maximizing differences in the survival distribution as measured by the log rank test. Beginning with all patients, the algorithm found the best split that maximized subgroup differences. Each of these subgroups was then successively split in a similar manner until a minimum subgroup (or node) size was reached.

## Results

### *Patient Demographics*

The profile of patients with mesothelioma treated on CALGB protocols is summarized in Table 2. Patients were generally male (83%), had good PS (ECOG PS=0 or 1; 81%), presented with chest pain (60%) or dyspnea (70%) after experiencing symptoms for <3 months (46%), had a history of asbestos exposure (62%) or smoking (72%), and had disease involving the pleura (94%). Age ranged from 23 to 83 years, with an average of 61.3 years.

The overall response rate and median survival for each treatment regimen are presented in Table 1. Response rates range from 7% for carboplatin in 8638 to 26% for mitomycin/cisplatin in 8435. With 92% of all patients dead, the median survival for the 10 treatment regimens ranged from 3.9 to 9.8 months (overall=7.2 months; 95% confidence interval, 6.5 to 8.3). One-year survival ranged between 14% and 50% (overall=27%; 95% confidence interval, 23 to 33%).

### *Univariate Survival Analyses*

Univariate comparisons of subgroups using the log-rank test show that poor PS ($p<0.001$; median survival time [MST]=3.3, 7.6, and 10.9 months with PS=2, 1, and 0, respectively), presence of chest pain ($p<0.001$; MST=5.4 and 8.8 months with and without chest pain), presence of dyspnea ($p=0.033$; MST=6.3 and 8.3 months with and without dyspnea), platelet count >400,000/μL ($p<0.001$; MST=6.2 and 9.4 months with high and low platelet counts), weight loss ($p=0.004$; MST=5.1 and 7.9 months with and without weight loss), LDH >500 IU/L ($p<0.001$; MST=3.4 and 7.6 with high and low LDH), and pleural involvement ($p=0.003$; MST=7.1 and 12.3 months with and without pleural involvement) are individually associated with worse prognosis.

Though comparisons of the survival experience within defined categories of age, hemoglobin, and WBC count were conducted, the effect of these variables on survival without categorization was also assessed. For hemoglobin and WBC count, there was a statistically significant linear relationship with survival ($p<0.001$ in both cases). An elevated hemoglobin level and a low WBC count were associated with a better prognosis. Age had a statistically significant nonlinear relationship with survival ($p<0.001$), which could be modeled as a combination of a linear effect of age and a linear effect for the number of years older than 75 years of age. In essence, the hazard ratio associated with a 5-year increase of age for patients younger than 70 years was 1.10; whereas, for patients older than 75 years, the hazard ratio associated with a 5-year increase of age was 4.64.

### *Multivariate Analyses Without Adjustment for Study Arm*

Several important prognostic factors were not collected on patients from all studies. Hence, the

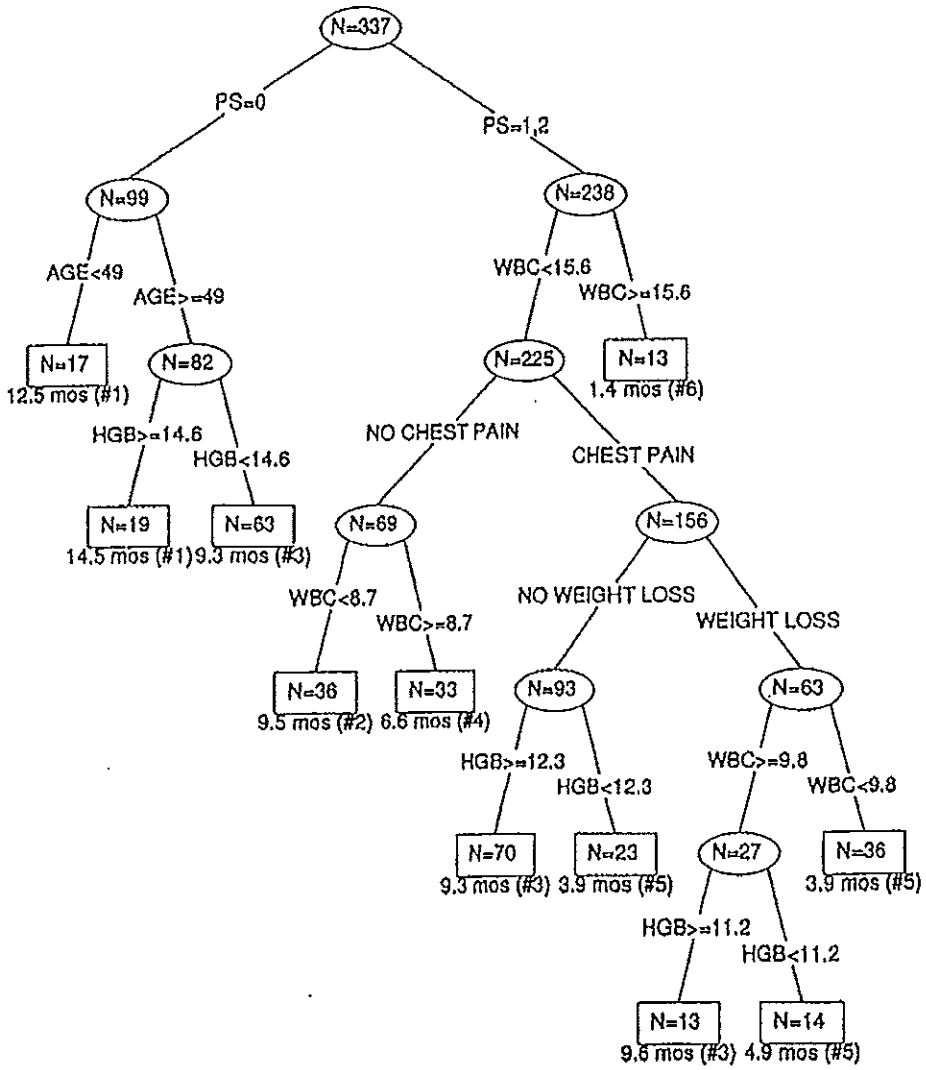


FIGURE 1. Regression tree. The sample size associated with a node is presented inside the node's circle or rectangular box. The median survival is noted below terminal node's rectangular box. The prognostic group to which the node belongs after amalgamation is also presented below the terminal nodes. Prognostic groups are further defined in Table 4. HGB=hemoglobin.

multivariate Cox regression analyses considered two sets of analyses: (1) an analysis limited to variables collected on all studies, and (2) an analysis limited to studies (8833, 8933, 9031, 9131, and 9234) on which information on all variables was available. Table 3 summarizes these analyses.

Owing to isolated randomly missing data items, only 309 patients have a complete set of data and are included in the analysis limited to variables collected in all studies. With decreasing risk ratio, the stepwise analysis shows that the following factors jointly predict poor survival: pleural disease involvement, LDH >500 IU/L, poor PS, platelet count >400,000/μL, nonepithelial histology, and increasing age >75 years. The hazard or risk of death among patients with pleural disease involvement is 2.64 times that of patients without pleural involvement. The risk for patients with a PS of 1 or 2 was 1.65 and 2.71 times greater, respectively, than that for patients with a PS of 0. Patients with nonepithelial histology, platelet count >400,000/μL, or LDH >500 IU/L were at 1.33, 1.57, and 1.91 times greater risk of dying early than patients without such characteristics. For patients older than 75 years of age, each additional year over 75 years was associated with an increase of the hazard by a factor of 1.34.

One hundred ninety-five patients are included in the analysis that is limited to studies in which all factors have been measured. This analysis showed that LDH >500 IU/L, poor PS, presence of chest

pain, platelet count >400,000/μL, and increasing age >75 years are predictive of a greater risk of dying early.

Exponential survival trees were used in an effort to define patient subgroups with similar prognoses using all patient data. The results formed the regression tree shown in Figure 1. The first and most significant prognostic split was by PS category (0 vs 1, 2). Age, hemoglobin, WBC, presence of chest pain, and weight loss defined further splits of the tree. The resulting tree included 10 terminal nodes (note: the terminal nodes are rectangular boxes in Fig 1) that were not split into smaller subgroups owing to their homogeneity of prognosis. A Cox regression model was used to determine which terminal nodes to combine or amalgamate without significantly reducing the overall log-likelihood for the model. Table 4 describes the resulting six prognostic groups, and Figure 2 shows the Kaplan-Meier survival curve for each of these subgroups. The patient subgroup with the best prognosis (group 1 in Table 4) consisted of patients with PS=0 and age younger than 49 years, and patients with PS=0, age 49 years or older, and hemoglobin level ≥14.6/μL. The median survival and 2-year survival in group 1 were 13.9 months and 38%, respectively. Prognostic groups 2 and 3 have similar median survival estimates; however, the 2-year survival of patients in group 2 (21%) is greater than that in group 3 (10%). The prognostic group with the worst prognosis includes patients with PS of 1 or 2 and elevated WBC count (*ie*, ≥15.6/μL). Median survival in group 6 was 1.4 months, with no patient living longer than 9 months.

### *Multivariate Analyses With Adjustment for Study Arm*

The analyses presented have considered the prognostic importance of patient characteristics unrelated to treatment. A natural question is whether the assigned study arm had any impact on survival beyond that predicted by nontreatment factors. In multivariate analysis limited to variables collected in all studies (N=309), there was no significant difference among the 10 treatment regimens. However, when study arm is considered in the analysis limited to studies collecting all variables (N=195), the prognosis with treatment on 9031 (cisplatin plus dihydroazacytidine [DHAC]) and 9234 (paclitaxel) is significantly worse than that on both arms of 9131 and 8933 ($p<0.05$). The power of these study arm comparisons is limited by the small number of patients treated under each regimen. In addition, the interpretation of these results is further complicated by any confounding secular trend in the natural history of the disease.

## Discussion

Numerous articles have examined the impact of various clinical factors on the prognosis or survival of patients diagnosed as having mesothelioma. Table 5[25-41] lists 17 of these articles, along with the time period during which these patient cohorts were diagnosed and the number of patients included in that cohort. The article by Spirtas et al,[31] which reported on the largest patient cohort of 1,475 patients, was based on information collected from

**Table 4—*Survival Tree Prognostic Groups****

| Group | Description | No. of Patients | Median Survival, mo | | 1-yr Survival | | 2-yr Survival | |
|---|---|---|---|---|---|---|---|---|
| | | | Est | 95% CI | Est | 95% CI | Est | 95% CI |
| 1 | PS=0, age <49 yr<br>PS=0, age ≥49 yr, HGB ≥14.6 | 36 | 13.9 | 11.1-31.4 | 0.63 | 0.46-0.77 | 0.38 | 0.23-0.55 |
| 2 | PS=1/2, WBC <8.7, no chest pain | 36 | 9.5 | 6.9-14.7 | 0.41 | 0.26-0.57 | 0.21 | 0.10-0.37 |
| 3 | PS=0, age ≥49 yr, HGB <14.6<br>PS=1/2, WBC<15.6, chest pain, no weight loss, HGB≥12.3<br>PS=1/2, 9.8≤WBC<15.6, chest pain, weight loss, HGB≥11.2 | 146 | 9.2 | 7.5-10.5 | 0.30 | 0.23-0.37 | 0.10 | 0.06-0.16 |
| 4 | PS=1/2, 8.7≤WBC<15.6, no chest pain | 33 | 6.5 | 3.7-9.4 | 0.25 | 0.14-0.42 | 0.06 | 0.02-0.17 |
| 5 | PS=1/2, WBC<15.6, chest pain, no weight loss, HGB<12.3<br>PS=1/2, 9.8≤WBC<15.6, chest pain, weight loss, HGB<11.2<br>PS=1/2, WBC<9.8, chest pain, weight loss | 73 | 4.4 | 3.4-5.1 | 0.07 | 0.03-0.15 | 0 | |
| 6 | PS=1/2, WBC≥15.6 | 13 | 1.4 | 0.5-3.6 | 0 | | 0 | |

*Est=estimate; CI=confidence interval; HGB=hemoglobin.

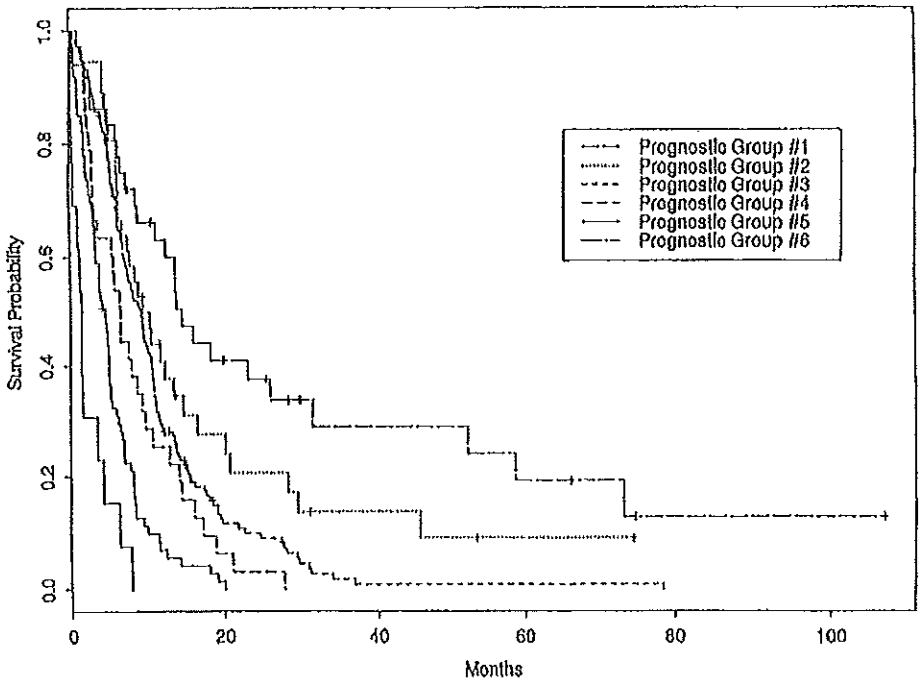


FIGURE 2. Kaplan-Meier survival curves for prognostic subgroups

the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. The remaining 16 references included in Table 5 consider smaller patient cohorts in which a more comprehensive list of clinical data is generally available to incorporate into a prognostic factor analysis. The limitations of most of these studies are their small size. Most of these 16 references report on analyses involving <200 patients, with only 2 studies having >200 patients. The patient cohort described in the current article is slightly larger than the largest study[29] not based on Surveillance, Epidemiology, and End Results data (337 vs 332).

Table 5—*References Reporting Analyses on Prognostic Factors for Malignant Mesothelioma*

| Source | Years Accrued | No. of Patients |
|---|---|---|
| Chailleux et al[25] | 1955-1985 | 167 |
| Tammilehto et al[26] | 1960-1980 | 65 |
| Schildge et al[27] | 1964-1986 | 84 |
| Alberts et al[28] | 1965-1985 | 262 |
| Ruffie et al[29] | 1965-1984 | 332 |
| Antman et al[30] | 1965-1985 | 180 |
| Spirtas et al[31] | 1973-1984 | 1476 |
| Chahinian et al[32] | 1974-1980 | 69 |
| Boutin et al[33], Viallat et al[34] | 1973-1990 | 188 |
| Fusco et al[35] | 1979-1985 | 113 |
| Manzini et al[36] | 1979-1991 | 80 |
| Calavrezos et al[37] | 1981-1993 | 132 |
| Tammilehto[38] | 1981-1990 | 98 |
| Van Gelder et al[39] | 1987-1989 | 168 |
| Chahinian et al[40] | ? | 59 |
| Rusch et al[41] | 1985-1988 | 83 |

Table 6 summarizes the factors that have been reported in the literature as having prognostic importance in mesothelioma. Most of these prognostic factors were considered in the analyses presented in the current article, along with hemoglobin, WBC, and LDH.

As presented in Table 6, age, stage, PS, and epithelial histology were commonly reported as having a significant impact on survival. The current study has confirmed the importance of these factors in univariate and multivariate analyses. Patients who are older, have a poor ECOG PS, or have disease with nonepithelial histology have a significantly poorer prognosis. The current study has also confirmed in univariate analyses, and at times in multivariate analyses, the prognostic importance of chest pain, weight loss, platelet counts, and pleural disease involvement. Hemoglobin, WBC, and LDH, factors previously not considered in the analyses of prognostic factors for mesothelioma, were shown to be important in predicting survival.

Based on the multivariate Cox analyses, one can conclude that pleural disease involvement, LDH level >500 IU/L, poor PS, chest pain, platelet count

Table 6—*Favorable Prognostic Factors Reported in the Literature**

| Favorable Factor | Reference Reporting Factor as Important† | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Young age | 25 | | | | (29) | (30) | (31) | 32 | | | (36) | (37) | 38 | (39) | | |
| Early stage (Butchart) | | (26) | | (28) | (29) | 30 | | | (33) | | (36) | (37) | (38) | (39) | | |
| Good PS | | (26) | | (28) | | (30) | | (32) | | | 36 | (37) | (38) | | | |
| Epithelial histology | | | 27 | | | (30) | | 32 | (33) | 35 | | (37) | (38) | (39) | | 41 |
| Epithelial or mixed histology | | | | | 29 | | | | | | (36) | | | | | |
| Female gender | | | | 28 | | 30 | (31) | | | | | | (38) | | | |
| Duration of symptoms >6 mo | 25‡ | 26 | | (28) | | | | | | | | | (38) | | | |
| No asbestos exposure | | | | | (29) | | | | | | | | 38 | | | |
| No weight loss | | | | | 29 | | | | (33) | | 36 | | | | | |
| Absence of chest pain | | | | | | (30) | | | | | | | | | | |
| Absence of dyspnea | | | | | | | | | | | | (37) | | | | |
| No symptoms | | | | | (29) | | | | | | | | | | | |
| Localized tumor | | | | | | | (31) | | 33 | | | | | | | |
| Low platelet count | | | | | (29) | | | | | | | | | | 40 | 41 |
| Lack of a smoking history | | | | | | 30 | | | | | | | | | | |
| Origins on left side | 25 | | | | | | | | | | | | | | | |
| Small tumor | | 26 | | | | | | | | | | | | | | |
| Pleural site | | | | | | | | 32 | | | | | | | | |
| Normal visceral pleura | | | | | | | | 32 | | | | | | | | |
| Presence of pleural fluid with mesothelioma cells without neoplastic cells | | | | | | | | | | | 36 | | | | | |

*Does not include treatment-related factors predictive of survival.
†Numbers listed in chart correspond to the manuscript's reference list. Please see Table 5 or this article's reference list for more detailed references. Numbers in parentheses are significant in multivariate analyses.
‡Duration of symptoms >2 mo.

>400,000/μL, nonepithelial histology, and increasing age older than 75 years independently predict poorer survival.

Patient groups with similar prognoses were developed using exponential regression trees. This method generated six patient groups with significantly different survival experiences, where these patient groups were defined by PS, age, hemoglobin, chest pain, weight loss, and WBC. Patients having the best prognosis with a median survival of 13.9 months were those with PS=0 and age younger than 49 years, or PS=0, age of 49 years or older, and hemoglobin ≥14.6/μL. Patients with PS=1 or PS=2, and a WBC ≥15.6/μL had the worst prognosis with a median survival of 1.4 months.

The interpretation of phase II clinical trials relative to previously conducted mesothelioma studies is difficult given the continually changing patient population. Patient characteristics and/or prognostic factors are often carefully scrutinized to assess whether they had any potential impact on response differences. Given the number of factors that might potentially affect prognosis, the interpretation of these individual phase II trials is often difficult. However, the information from the important prognostic factors has been integrated into the definition of prognostic groups. Hence, an examination of the distribution of patients among the prognostic groups may be sufficient to understand differences across phase II trials. It should be noted that phase II studies are not designed to have a sufficient number of patients to make definitive comparisons within and between studies. However, identification of the patient's prognostic group might be useful in understanding and interpreting a phase II study. For instance, a poor response rate relative to other treatment regimens might be explainable by a large percentage of patients with extremely poor prognosis (*eg*, prognostic group 6). Such an observation would suggest that an examination of the treatment regimen in a "healthier" population (*ie*, a population with a better prognosis) might allow a more objective assessment of a given regimen's effectiveness *vis-à-vis* other available regimens. These data can serve as a type of "historical control" against which to assess new agents and regimens.

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# Factors Predictive of Survival Among 337 Patients With Mesothelioma Treated Between 1984 and 1994 by the Cancer and Leukemia Group B

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