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Determinants of Myelosuppression in the Treatment of Non-small Cell Lung Cancer with Cisplatin-containing Chemotherapy

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Data on 16 potential risk factors for myelosuppression were assessed in 134 patients who received either vindesine and cisplatin (VP) or mitomycin C, vindesine and cisplatin (MVP) for inoperable stage III or IV non-small cell lung cancer in a randomized trial. Determinant factors for myelosuppression were evaluated by using univariate analysis and the logistic regression model. Recursive partitioning and amalgamation (RPA) was also used to define patient subgroups frequently suffering from severe bone marrow toxicity. Overall, 33 (25%) of 134 patients experienced at least one episode of grade 4 leukopenia. In univariate analysis, age, body surface area, serum creatinine, and pretreatment hemoglobin concentration were associated with severe leukopenia. A multivariate analysis using the logistic regression method showed that only raised creatinine level was an independent predictor for grade 4 leukopenia ($P=0.049$). The RPA model generated three distinct subgroups based on age, body surface area and regimen. The three subgroups were distinguished by the frequency of severe (grade 4) leukopenia (50%, 25%, and 2.4%, respectively) ($P<0.001$). Grade 4 leukopenia occurred more frequently in patients in class 3 (age ≥ 65 years and treatment with MVP). The RPA model was useful in identifying the risk factors for myelosuppression induced by cisplatin-based chemotherapy, and in defining patient subgroups with elevated risk of toxicity.

Key words: Cisplatin-based chemotherapy — Non-small cell lung cancer — Bone marrow suppression — Elderly patient — Recursive partitioning and amalgamation

The combination of cisplatin and vindesine (VP)[1,2] or mitomycin C, vindesine and cisplatin (MVP)[3–5] has been reported to produce response rates of between 20% and 73% in patients with advanced non-small cell lung cancer (NSCLC), and has also been used as preoperative chemotherapy for operable patients.[6] Although cisplatin-containing regimens have provided greater effectiveness in patients with advanced NSCLC than had formerly been possible, complete response is rarely attained and there have been only small improvements in survival. While pretreatment patient characteristics usually have a greater impact on survival than the therapy itself, definite benefit from chemotherapy may be expected in some patients. Toxicity is among the great problems faced by patients receiving chemotherapy, with considerable variation in toxic effects even among patients assigned to the same chemotherapy regimen. Much effort has been made to identify factors that may predispose patients to increased likelihood of toxicity. Chronological age has often been proposed as a risk factor for serious toxicity, especially for myelosuppression.[7,8] However, the joint effect of age and other prognostic factors, and their interactions with treatment, on grade 4 bone marrow suppression in the treatment of NSCLC remains unclear.

The objectives of this study were (1) to identify significant risk factors for myelosuppression through univariate analysis of patients registered in a randomized trial;[9] (2) to assess the interactions of these factors by multiple regression analysis; and (3) to use recursive partitioning and amalgamation (RPA) analysis to construct homogeneous subgroups of patients with significant myelotoxicity differences.

PATIENTS AND METHODS

Patient selection and chemotherapeutic regimen The patients included in this analysis were patients registered into a three-arm randomized trial on inoperable NSCLC conducted from June 1986 to April 1988. The eligibility criteria included cytologic or histologic diagnosis of NSCLC; stage IIIA, IIIB, or IV disease; age younger than 75 years; performance status better than 3 in the Eastern Cooperative Oncology Group scale; adequate pretreatment renal, hepatic, bone marrow and cardiac function (serum creatinine <1.5 mg/ml, serum alanine aminotransaminase-aspartate aminotransferase <2 times

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upper limit of normal, WBC $\geq$4,000/μl, platelet count $\geq$100,000/μl); no prior radiotherapy or chemotherapy; no concurrent active malignancy; and informed consent. The results of the trial, including response and survival, have been reported in detail elsewhere.[9] Since patients treated with the etoposide and cisplatin alternating with vindesine and mitomycin regimen had a lower response rate and less severe myelosuppression than those treated with the other two regimens (VP or MVP), these patients were excluded from this analysis. Therefore, patients with stage III and IV NSCLC who were treated with the VP or MVP regimen were retrospectively evaluated for the study. The dosage and schedule of these regimens were as follows: VP (vindesine 3 mg/m^2 intravenously [i.v.] on days 1, 8 and 15 and cisplatin 100 mg/m^2 i.v. on day 1, repeated every 4 weeks), and MVP (mitomycin 8 mg/m^2 i.v. on days 1 and 29, vindesine 3 mg/m^2 days 1, 8, 29 and 36, cisplatin 80 mg/m^2 on days 1 and 29, repeated 6 weeks thereafter). To avoid cisplatin-induced renal damage, patients were intravenously hydrated on day 1 with 2,600 ml of 5% dextrose in 0.45% sodium chloride, and diuresis was induced with mannitol and furosemide. Hydration with 800 ml of 5% dextrose in 0.45% sodium chloride, given intravenously, continued for another 48 h as previously described.[9] In each group, the doses were reduced to 75% of the initial dose if the leukocyte nadir decreased below 1,000/μl or the platelet nadir $\leq$30,000/μl; doses were also modified as required to take account of renal dysfunction. Patients in whom response was seen were continued on chemotherapy until progression of disease or severe toxicity. Patients who stabilized received at least a second course, while patients with obvious evidence of disease progression were removed from the study. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not used at all because it was not commercially available at that time. Drug toxicities were classified in accordance with the World Health Organization (WHO) criteria.[10]

Statistical methods The influence of variables on myelosuppression was studied by univariate and multivariate analyses. For this purpose, we categorized all 16 potential prognostic variables into two groups. In most cases, the biologic values were dichotomized into normal and abnormal values according to standard laboratory norms (Table I). The two groups were tested for significant myelotoxicity differences using the χ^2 test or Fisher's exact probability test. Multivariate analysis of prognostic variables for myelosuppression was carried out using a logistic regression model.[11] The explanatory variables were selected using a stepwise forward procedure with the entry limit fixed as a significance probability of 95%. Confidence intervals for relative risks were calculated.

RPA was applied to identify subgroups of patients with similar myelosuppression within the subgroup, but different toxic effects across the groups.[12] RPA begins with the whole sample and finds the best split into two groups based on any of the variables at any possible cut point. The best split for the node was the one that corresponded to the χ^2 statistic having the smallest significance level. The split was carried out until the subdivision led to nodes that included more than 20 patients. When the partitioning process stopped, the node was called a terminal node. Since the resulting "tree" is an overfit to the data, an optimal subtree is chosen by a resampling technique. The final tree may contain subgroups or "terminal nodes" having a similar degree of myelosuppression that can then be combined to form the final groups. All P-values refer to a two-sided significance test. Values of less than 0.05 were considered to be statistically significant.

RESULTS

Data from 134 patients who received the VP or MVP regimen were analyzed for the nadir WBC counts, nadir platelet counts and anemia, together with possible risk factors. Grade 4 leukopenia (WBC $<$1,000/μl) was observed in 33 (24.6%) patients, and grade 4 thrombocytopenia in only three (2.2%). Grade 3 or worse anemia (hemoglobin $<$8 g/dl) was observed in 28 (21%) of 134 patients.

Univariate analysis of factors for leukopenia Of 16 variables evaluated, older age, low hemoglobin concentration, raised serum creatinine and low pretreatment body surface area were predictors for more severe leukopenia. Surprisingly, neither performance nor the regimen was a significant predictor for leukopenia. Further, sex, clinical stage, body weight loss, transaminases, serum albumin and the number of treatment courses were also not correlated with grade 4 leukopenia (Table I).

Multivariate analysis for leukopenia with a logistic regression model Factors whose P-values ($P<0.1$) approached significance according to univariate analysis were entered into a multivariate regression model. Multivariate analysis using a logistic regression model showed that only an elevated serum creatinine level was independently statistically significant for grade 4 leukopenia ($P=0.049$) (Table II). Older age and regimen (MVP) were marginally discriminant for leukopenia ($P=0.062$ and $P=0.096$).

RPA for leukopenia Fig. 1 shows the tree that resulted from the RPA analysis. The most significant split was by age category. In the subset with age younger than 65 years, the next most important split was by body surface area. No other significant splits occurred for these patients, so these subgroups became terminal nodes I and II. For patients age 65 years or older, treatment was the only significant covariate used for the construction of the partition: the frequency of grade 4 leukopenia in the VP group (terminal node III) was significantly less than that

Table I. Univariate Analysis for Grade 4 Leukopenia: Influence of Clinical and Laboratory Values

Variable	Category	No. of patients	Grade 4 leukopenia (%)	*P*-values
Age	<65 years	70	10 (14.3)	0.004
	≥ 65	64	23 (35.9)	
Body surface area	<1.5 m^2	74	25 (33.8)	0.006
	≥ 1.5	60	8 (13.3)	
Serum creatinine	<1 mg/ml	124	27 (21.8)	0.020
	≥ 1	10	6 (60.0)	
Hemoglobin	≥ 12 g/dl	86	16 (18.6)	0.030
	<12	46	17 (35.4)	
Regimen	VP	66	12 (18.2)	0.088
	MVP	68	21 (30.9)	
Leukocyte count	$\geq 6{,}000/\mu$l	105	23 (21.9)	0.164
	$<6{,}000/\mu$l	29	10 (34.5)	
Stage	IIIA, IIIB	77	22 (28.6)	0.218
	IV	57	11 (19.3)	
Sex	male	102	23 (22.5)	0.319
	female	32	10 (31.3)	
Albumin	normal	31	9 (29.0)	0.472
	abnormal	97	22 (22.7)	
Lactate dehydrogenase	not elevated	94	21 (22.3)	0.469
	elevated	34	10 (29.4)	
Performance status	0, 1	91	21 (23.1)	0.545
	2	43	12 (27.9)	
Alanine aminotransaminase	<40 U/ml	118	28 (23.7)	0.701
	>40	12	4 (25.0)	
Body weight loss	$\geq 10\%$	17	7 (41.2)	0.160
	<10	117	26 (22.2)	
Aspartate aminotransferase	<40 U/ml	117	28 (23.9)	0.839
	≥ 40	13	3 (23.1)	
Number of courses	1, 2	115	28 (20.9)	0.854
	≥ 3	19	5 (26.3)	
Alkaline phosphatase	not elevated	102	25 (24.5)	0.955
	elevated	32	8 (25.0)	

Abbreviations: VP, vindesine + cisplatin; MVP, mitomycin C+ vindesine + cisplatin.

Table II. Multivariate Analysis for Leukopenia with a Logistic Regression Model

Covariate[a)]	Value = 1	Relative risk	95% Confidence interval		
			Lower	Upper	*P*-value
Creatinine	≥ 1 mg/ml	0.23	0.05	0.99	0.049
Age	≥ 65 years	0.41	0.16	1.04	0.062
Regimen	MVP[b)]	0.47	0.19	1.14	0.096
Body surface area	<1.5 m^2	0.46	0.17	1.23	0.121
Hemoglobin	<12 g/dl	0.56	0.23	1.36	0.199

a) Each covariate in the model is expressed as 0 or 1. The relative risk of leukopenia refers to persons with a value of 1 for that covariate relative to persons with a value of 0.
b) Mitomycin C + vindesine + cisplatin.

in the MVP group (terminal node IV). Terminal nodes I to IV represented 42, 28, 28, and 36 patients, respectively.

After application of an amalgamation of the four terminal nodes, we identified three classes of patients heterogeneous for grade 4 leukopenia. The least one (class 1) included 42 patients under 65 years of age with body surface area of ≥ 1.5 m^2. Class 2 included 28 patients under age 65 but with body surface area of < 1.5 m^2, and 28 patients age 65 years or older and receiving the VP regimen. Class 3 included 36 patients age 65 years or older in the MVP-treated group. The frequencies of

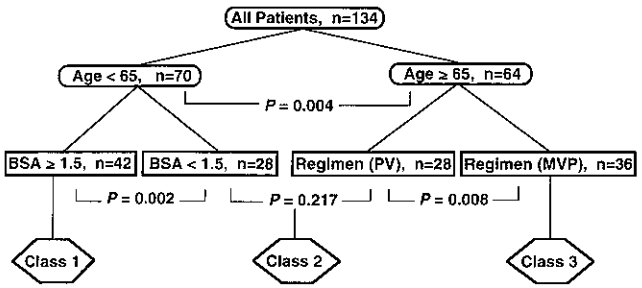

Fig. 1. Recursive partitioning and amalgamation paradigm of leukopenia for 134 patients with NSCLC.

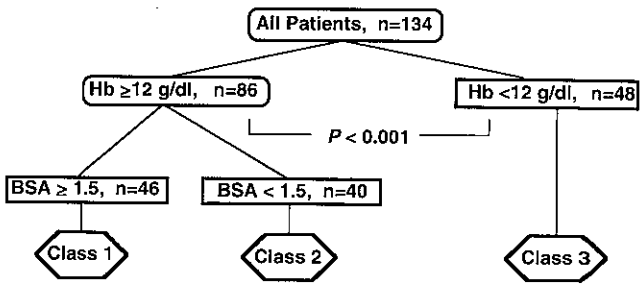

Fig. 2. Results of recursive partitioning and amalgamation for anemia.

Table III. Recursive Partitioning and Amalgamation Classification of Leukopenia

Class	No. of patients	Grade 4 leukopenia	*P*-value	Response rate (%)	Median survival time (weeks)
1	42	1 (2.4)[a]		33	42
2	56	14 (25)	<0.001	34	46
3	36	18 (50)		47	47

a) Figures in parentheses are percentages.
Class 1: Patients younger than 65 years with body surface area of ≥ 1.5 m^2.
Class 2: Patients younger than 65 years with body surface area of < 1.5 m^2 or patients age 65 years or older in the vindesine and cisplatin (VP)-treated group.
Class 3: Patients 65 years of age or older in the mitomycin, vindesine and cisplatin (MVP)-treated group.

grade 4 leukopenia observed in the three heterogeneous classes were 2.4% in class 1, 25% in class 2, and 50% in class 3 (Table III). However, there were no statistically significant differences in response rate or median survival time among these three classes.

Analysis for thrombocytopenia Thrombocytopenia was observed in only three (2.2%) patients. The number of patients who experienced grade 4 thrombocytopenia was too small to analyze with multivariate analysis.

Analysis for anemia Grade 3 or worse anemia (hemoglobin <8.0 g/dl) was observed in 28 (21%) patients. Univariate analysis showed the importance of pretreatment hemoglobin level ($P<0.001$), body surface area ($P=0.003$), performance status ($P=0.022$), and alkaline phosphatase level ($P=0.043$) for anemia. The most important determinant factor for anemia was pretreatment hemoglobin level. A logistic regression model identified pretreatment hemoglobin level ($P<0.001$), leukocyte count ($P=0.037$), and body surface area ($P=0.042$) as significant predictors for anemia. We therefore constructed a similar classification with the first subdivision based on the hemoglobin level. At the next (last) step, body surface area was the variable involved in the partitioning algorithm. Application of the amalgamation led to the construction of three classes that were homogeneous for anemia (Fig 2). The frequencies of grade 3 or worse anemia were 13%, 33%, and 58% for classes 1, 2, and 3, respectively (Table IV).

Table IV. Recursive Partitioning and Amalgamation Classification of Anemia

Class	No. of patients	Grade 3 anemia (%)	*P*-value
1	46	6 (13)	
2	40	13 (32.5)	<0.001
3	48	28 (58.3)	

Class 1: Patients with a hemoglobin concentration of ≥ 12 g/dl and body surface area of ≥ 1.5 m^2.
Class 2: Patients with a hemoglobin concentration of ≥ 12 g/dl and body surface area of < 1.5 m^2 or patients aged 65 years or older in the VP-treated group.
Class 3: Patients aged 65 years or older in the MVP-treated group.

DISCUSSION

Mortality rates for patients with NSCLC remain high. A small proportion of these patients is potentially curable with surgery. Since the likelihood of cure unfortunately

remains remote for most patients with unresectable disease, improvement in symptoms and quality of life, in addition to an increase in survival, should be the major goals of treatment for NSCLC. One of the main arguments against the use of chemotherapy for NSCLC concerns the considerable toxicity of treatment with only modest survival benefits. A major toxicity is hematologic; it is therefore important to identify risk factors that may predispose NSCLC patients to increased likelihood of severe myelosuppression, and to minimize the severe toxicities of treatment, including treatment-related death.

The advantage of RPA analysis, compared with a classical logistic regression approach is, first, the ability to include a patient with missing data on any factor. Second, with RPA the grouping of patients is a natural outcome of the analysis, whereas use of the regression model to form homogeneous subsets requires grouping in arbitrary ways based on the estimated values of the model coefficients. The tree paradigm derived from RPA is easily understood by eye and can be useful for decision making in clinical settings. Finally, the exploration of interactions between factors, while clearly possible with the Cox model, is automatic with RPA without having been specified before analysis. Therefore, we applied the newer and less conventional analysis model of RPA to our data.

Our multivariate analysis using a logistic regression model revealed that a serum creatinine level of ≥ 1.0 mg/ml was the only significant predictor for leukopenia (Table II). The association of grade 4 leukopenia and a raised serum creatinine level is due to lower glomerular filtration. However, normal serum creatinine values may occur in spite of reduced glomerular filtration because the relationship between serum creatinine and glomerular filtration is described by a rectangular hyperbola.[13] Diminished renal clearance causes serious adverse effects by prolonging drug elimination, with a consequent increase in drug exposure time. Since only ten (7%) patients showed a pretreatment serum creatinine level of ≥ 1 mg/dl, this variable seems to play only a small role in the majority of patients who experienced leukopenia. Older age and treatment with MVP were associated with a trend towards developing severe leukopenia ($P=0.062$ and 0.096, respectively). Our logistic regression results are not completely confirmed by the application to our data of the RPA technique. This may be due to the relatively small number of patients ($n=134$), which provides only a low statistical power for detecting differences of moderate magnitude among the factors. Our RPA (Fig. 1) defined four major subgroups that were amalgamated into three subsets with rates of grade 4 leukopenia of 2.4%, 25%, and 50%, respectively. Chronologic age was the most important split (Fig. 1). Although there was no consistent trend in severe toxicities in relation to age, age has often been proposed as a risk factor for myelosuppression.[14, 15] Hoagland[16] stated that increased age should be anticipated as a risk factor for hematologic toxicity because it is a decrease in the number of bone marrow stem cells, which typically accompanies aging, which generally determines the degree of tolerance to cytotoxic drugs. However, because of the great variation in tolerance to chemotherapy among elderly patients, more work is needed to identify those factors which carry a high risk of toxicities for elderly patients, as well as to determine more clearly what factors associated with the aging process account for the increased risk.

Within the subgroup of patients below 65 years of age, body surface area was the next most important determinant of myelosuppression (Fig. 1). The median body surface area in this trial of 1.52 m^2 was smaller than those in trials conducted in European and North American countries. MTD of several anticancer agents, of which the dose limiting toxicity is leukopenia, were frequently lower in Japan than those reported from other European and North American countries. Low body surface area in Japanese may well explain this difference in MTD among these countries.

Only treatment regimen (MVP regimen) was important for leukopenia in the older age (≥ 65 years) subset (Table III). For these patients, less aggressive chemotherapy, with a meaningful effect on quality of life and with acceptable toxicity, may be recommended.

Unlike other researchers,[17, 18] we did not find that patients with poorer performance status had a significantly greater chance of experiencing severe toxicity in any of our analyses.

Since December 1991, rhG-CSF has become commercially available for patients with lung cancer undergoing cytotoxic treatment in Japan. With its availability, it has become possible to reduce the severity and duration of the leukopenia induced by cytotoxic chemotherapy. However, according to The American Society of Clinical Oncology Recommendations for the use of hematopoietic colony-stimulating factors,[19] the strategies for noncurable malignancies including NSCLC involve initial chemotherapy dose reduction and delay or the use of a less myelosuppressive chemotherapy regimen in the high-risk patients to avoid intolerable side effects. Standard supportive care measures, including antibiotics, remain the primary alternatives to use of rhG-CSF. Therefore, it is important to identify significant risk factors for myelosuppression through univariate analysis and to define homogeneous groups of patients with significant myelotoxicity using RPA analysis.

In conclusion, this study on predictors of myelosuppression with 16 potential covariates in 134 patients with unresectable advanced NSCLC identified elevated serum creatinine level as a risk factor for leukopenia in multivariate analysis (logistic regression model). The results of our RPA for the first time suggest the highest impor-

tance of age as a predictor of leukopenia over performance status, sex and other factors. Our RPA defines three subgroups of patients, with the most severe leukopenia for patients aged 65 years or more in the MVP-treated group. These classifications may allow us to select the most suitable treatment for an individual patient to avoid unnecessary and severe myelosuppressive toxicity.

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