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Regression Analyses of Prognostic Factors in Metastatic Malignant Melanoma

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Abstract—*Patients entered into phase II trials in metastatic malignant melanoma should be carefully selected in order to ensure that they live long enough to permit a meaningful evaluation of the efficacy of a given drug. In this selection emphasis has been put on performance status. However, also for patients with a good performance status, survival is often short. The purpose of this study has been to identify supplementary prognostic factors as these could be of help in the design of phase II trials.*

From 1978–1986, 177 *consecutive patients were given various chemotherapy regimens for metastatic malignant melanoma in the Norwegian Radium Hospital. About* 92% *had a performance status of ECOG* 0–2. *Median survival was* 4.0 *months* (0–30 *months*). *Multivariate survival analysis selected lactate dehydrogenase* (*LDH*) >450 U/l, *presence of brain metastases, leukocyte count* $>10 \times 10^9$/l, *and erythrocyte sedimentation rate* (*ESR*) >15 mm/h *as significant prognostic factors indicating short survival with low probability of surviving* 3 *months. Patients with normal values of LDH, leukocyte count, and ESR had a median survival of* 11.5 *months with* 94% *surviving* 3 *months. We conclude that this information could have an impact on the design of phase II trials.*

INTRODUCTION

CHEMOTHERAPY is of limited benefit in malignant melanoma and the prognosis is dismal when the disease is disseminated. A mean survival of 16–18 weeks has consistently been reported for patients entered into first-drug trials with chemotherapeutic agents. Single-agent treatment with DTIC or nitrosoureas in several studies have yielded response rates of 10–20%. Encouraging results of new regimens are rarely confirmed in sizable series [1]. In view of these observations it is increasingly recognized that in advanced disease, clinical trials aimed at identifying new active compounds should have high priority. In order to ensure that patients live long enough to permit a meaningful evaluation of the therapeutic efficacy of a given drug it is important to select patients carefully. In phase II trials, protocols are, therefore, designed so that patients with expected survival less than 3 months are excluded. Especially, emphasis has been put on performance status and protocols normally require an ECOG status of 2 or better. It is, nevertheless, a common experience that many patients are not evaluable because of early progressive disease and early death.

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The purpose of this study was to identify supplementary prognostic variables that can predict short survival and thus be of help in the design of phase II trials.

PATIENTS AND METHODS

This is a follow up study of all evaluable patients treated with chemotherapy for metastatic disease from histologically proven malignant melanoma in the Norwegian Radium Hospital during the period 1978–1986. It has been the policy of the institution to give chemotherapy only to patients in good general condition and an expected survival of more than 3 months. Thus, 92% of the patients had a performance status as estimated by retrospective review of their records of ECOG 0–2. Patients with multiple metastases localized to one extremity only are usually treated with a combination of intraarterial chemotherapy and radiotherapy. Patients with metastases to regional lymph nodes are usually treated with surgery/radiotherapy. These two groups of patients have, therefore, not been included in the analysis. There were no patients with brain metastases only. All patients treated were considered no longer to be candidates for surgical procedures. Patients were evaluated as to the extent of disease by history, physical examination, chest

X-ray and standard biochemical tests, and, if indicated, by ultrasound, CT scan or scintigraphy of liver, abdomen, bones or brain. The material was analysed with respect to response and survival using standard response criteria. Patients dying before first evaluation (4 weeks) were coded as non-evaluable for response but included in analyses with patients with progressive disease. Response was coded by patient and not by location, that is, if the patients experienced PD in one localization, the response was coded as PD regardless of disease status in alternative locations present at the same time. 'Response' as used in the analyses was defined as complete plus partial remissions. Response duration is from start of chemotherapy until documented progression. Survival was estimated from start of chemotherapy and calculated with the life table method [2]. One patient died outside the hospital few days after the first course of chemotherapy. This case was considered possible toxic death and excluded from analysis. Otherwise all deaths were considered deaths due to malignant melanoma. Differences between survival curves were tested by the log-rank test [3].

Table 1. Patient characteristics

Total number of patients		178
Male	115	
Female	63	
Evaluable for response		177
Excluded (toxic death?)	1	
Previous chemotherapy		None
Previous or concomitant radiotherapy to only evaluable lesion		None
Distribution of metastases		
Brain	17	
Lung	58	
Liver	71	
Abdominal viscera other than liver	34	
Cutaneous/subcutaneous	118	
Skeletal system	28	
Other	8	

Table 2. Types of chemotherapy

Single drug (varying dose schedules) $n = 142$	
DTIC	92
CCNU	17
Velbe	7
Procarbazine	1
Mitozolomide*	5
TGU*	11
Dfur*	3
Azo*	4
Menogaril*	2
Combination chemotherapy $n = 35$	
DTIC/CCNU	7
DTIC/5-fluorouracil	1
CCNU/procarbazine	2
Velbe/procarbazine	1
Cis-platinum/bleomycin	4
Cis-platinum/bleomycin/5-fluorouracil	4
Cis-platinum/vindesine/DTIC (CiViDic)	16

Drugs marked with * were given in phase II trials in cooperation with EORTC. The results are published elsewhere.

There were 177 patients, 114 men and 63 women, age 5–78 years (mean age 51 years). None had received previous chemotherapy and patients with lesions in previously irradiated fields only were excluded. The metastases were distributed to the organ systems as outlined in Table 1. The patients had lesions in one to six organ systems (mean 2.2), three patients having metastases to five or more organ systems. Chemotherapy was given according to the protocol run in the department at the time (Table 2). Most patients ($n = 142$) were treated with single drugs, by far the greatest number with DTIC ($n = 92$), but in the later years some patients had received combination chemotherapy, most notably *cis*-platinum-containing regimens ($n = 20$).

To simultaneously analyse the importance of several prognostic factors, the Cox proportional hazards model [4] with a stepwise procedure was used. The following variables were included in the analyses (Table 3): age, sex, location of primary, metastatic site, number of organ systems involved, interval from primary melanoma to start of chemotherapy, interval from first metastasis to start of chemotherapy, weight loss of more than 10% during the last 6 months before chemotherapy, type of chemotherapy (single drug vs. combination chemotherapy, DTIC vs. others, CCNU vs. others, CiViDic vs. others), haemoglobin, erythrocyte sedimentation rate (ESR), leukocyte count, thrombocyte count, and serum lactate dehydrogenase (LDH). The proportional assumptions in the Cox model were tested with plot, and continuous variables were grouped with cutpoints at quartiles. None of the laboratory variables nor age could be used in the continuous form without neglecting the proportional assumption. These variables were divided into two groups with a cutpoint near the quartile giving the best plot of cumulative hazards. All variables were first tested individually. Only significant variables from the univariate analyses were included in the multivariate survival analyses. Stepwise logistic regression was used to relate possible explanatory variables to response to chemotherapy [5]. Statistical analyses were performed with the BMDP statistical software package [6].

RESULTS

All but two patients had died at the time of analysis (March 1987). Survival ranged from zero to 30 months, mean survival was 6.2 months,

Table 3. Continuous variables included in analyses

Variable	Lowest	Mean	Median	Highest
Haemoglobin (g/dl)	7.0	12.8	12.9	16.4
ESR (mm/h)	1	7	31	110
Leukocytes ($\times 10^9$/ml)	3.8	9.6	8.0	68.0
Thrombocytes ($\times 10^9$/ml)	94	396	365	785
LDH (U/l)	171	1227	624	20,060
Interval from primary diagnosis to first metastasis (months)	0	26	7	200
Interval from first metastasis to chemotherapy (months)	0	14	7	147

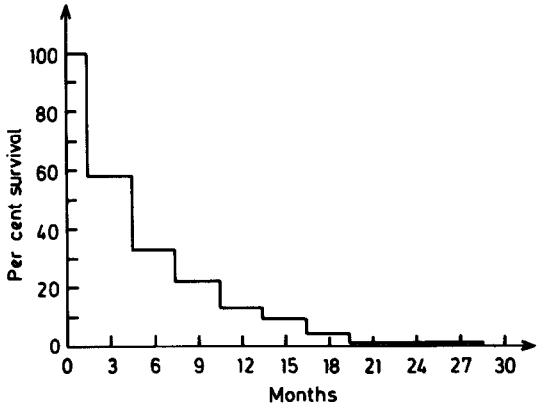

Fig. 1. Survival of patients with metastatic malignant melanoma.

median survival 4.0 months with two patients alive at 19+ and 9+ months (Fig. 1). The death rate in this material was awesome: 27 patients (15%) died within 1 month. Another 19 (11%) died during the 2nd month, 29 (16%) during the third month, and 20 (11%) during the 4th month. Thus, 75 patients (42%) died before 3 months had elapsed and more than half of the patients died within 4 months (54%).

In univariate analysis the following nine out of 22 variables tested were associated with short survival, $P < 0.05$ (Table 4): LDH >450 U/l, metastases to the liver, metastases in three or more organs, ESR >15 mm/h, leukocyte count $>10 \times 10^9$/l, thrombocyte count $>450 \times 10^9$/l, metastases to brain, long interval (>40 months) from primary melanoma diagnosis to start chemotherapy, primary melanoma in ENT area. The multivariate analyses selected only four of these nine variables: LDH >450 U/l, metastases to the brain, leukocyte count $>10 \times 10^9$/l and ESR >15 mm/h as independent prognostic factors (Table 5).

The survival curves and median survival for patients positive for one or more predictors of short survival is given in Fig. 2 and Table 6. It will be seen from the figures that the differences in survival are highly significant: if the LDH was ≤450 U/l, 83% of patients survived 3 months, among the

Table 4. Results of univariate survival analysis (n = 168–177)

	P values
LDH >450 U/l	<0.0001
Metastases to liver	<0.0001
Three or more organs involved	<0.0001
ESR >15 mm/h	<0.0001
Leukocytes $>10 \times 10^9$/l	<0.001
Thrombocytes $\leq 450 \times 10^9$/l	<0.01
Metastases to brain	<0.01
Interval from primary diagnosis to first metastasis >40 months	<0.05
Primary melanoma in ENT area	<0.05

patients with LDH >450 U/l, the corresponding percentage was 46. Sixty-one per cent of the patients without brain metastases were alive after 3 months. Twenty-four per cent of the patients with brain metastases survived 3 months. The corresponding data showed a 3-month survival of 71% with leukocytes $\leq 10 \times 10^9$/l, 24% with leukocytes $>10 \times 10^9$/l, 52% with ESR >15 mm/h, and 76% with ESR ≤15 mm/h. Thirty-four patients had LDH >450 U/l, leukocytes $>10 \times 10^9$/l, and ESR >15 mm/h. These patients had a median survival of 1.8 months and only 18% were alive after 3 months. The corresponding data for the rest of the patient population was median survival 4.8 months, 67% survivors at 3 months. In contrast, the patients with LDH ≤450 U/l, leukocytes $\leq 10 \times 10^9$/l, and ESR ≤15 mm/h had a median survival of 11.5 months with 94% surviving 3 months.

The response rate was 11.3% (three complete and 17 partial remissions). The responses were short, lasting from 2 to 11 months, median five months. Stepwise logistic regression analysis selected the CiViDIC regimen as the only significant variable associated with response to treatment.

DISCUSSION

Even though most of our patients had a good performance status and were judged fit to receive chemotherapy, 42% died within 3 months after commencement of treatment. If these patients had been included in phase II trials, a large proportion

Table 5. Results of multivariate survival analyses (n = 168)

Variables		Regression coefficient	Standard error	*P* values
LDH >450 U/l	vs. others	0.81	0.18	<0.0001
Metastases to brain	vs. others	1.07	0.28	<0.001
Leukocytes >10 × 10^9/l	vs. others	0.49	0.18	<0.01
ESR >15 mm/h	vs. others	0.57	0.22	<0.01

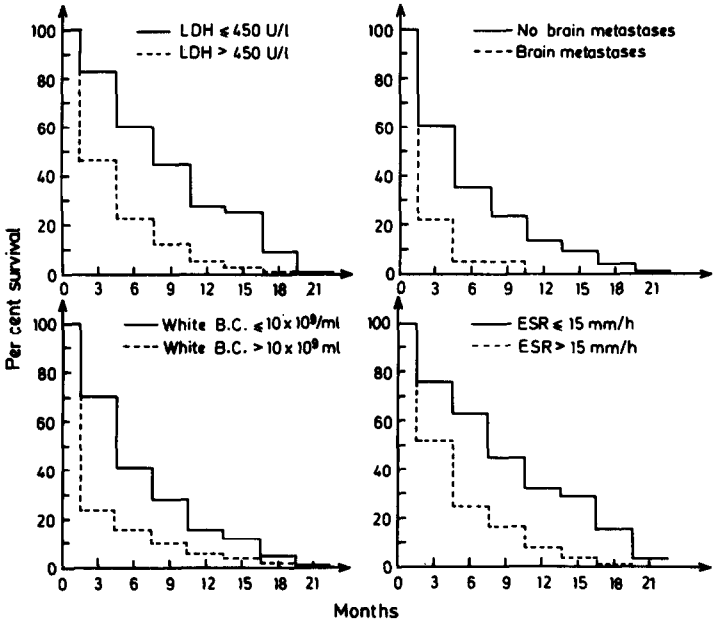

Fig. 2. Metastatic malignant melanoma. Survival of patients in different prognostic groups.

Table 6. Survival in different prognostic groups

Prognostic factor	Median survival (months) Yes	No
LDH >450 U/l	2.8 (*n* = 123)	7.9 (*n* = 47)
Metastases to brain	2.0 (*n* = 17)	4.4 (*n* = 160)
Leukocytes >10 × 10^9/l	2.0 (*n* = 51)	5.1 (*n* = 125)
ESR >15 mm/h	3.2 (*n* = 138)	8.1 (*n* = 38)

of them would have died before they could have been evaluated with the danger of erroneously rejecting drugs with some activity. Accordingly, there seems to be a need to identify supplementary prognostic factors with respect to survival. We have identified four factors of significance, namely: elevated LDH, presence of metastases to the brain, leukocytosis, and elevated ESR, an elevated LDH being the most important one. The identification of LDH, leukocytosis and ESR as independent prognostic factors has, to our knowledge, not been reported previously. LDH has traditionally been correlated to liver metastases by other investigators [7, 8], and the presence of metastases to liver has been known to be associated with short survival [7, 9]. Also in this study, there was a correlation between elevated LDH and presence of liver metastases. In addition, we found that elevated LDH and the variable for heavy tumour burden (metastatic involvement of three or more regions) were correlated. In the multivariate survival analyses LDH always entered before liver metastases and the variable for heavy tumour burden. These variables then did not contribute further to explain variation in survival. LDH is, thus, more closely linked to survival than is the presence of liver metastases or involvement of many organs. We, therefore, believe that elevated LDH can be used as an easily obtainable, quantitative indicator of expected survival.

We also found leukocytosis and elevated ESR to be prognostic variables indicating short survival. Leukocytosis has been associated with short survival in other malignant diseases such as colorectal carcinomas [10–12], primary lung cancer [13], and in patients with liver metastases from unselected primaries [14]. Elevated ESR has been noted as a

prognostic factor in renal carcinoma [15], non-Hodgkin lymphoma [16], and chronic lymphocytic leukaemia [17]. It is not known why leukocytosis and elevation of the ESR seem to be associated with poor prognosis in several cancer forms. Their presence may signal a rather uniform reaction by the body upon severe malignant disease.

The presence of brain metastases also was a prognostic indicator for short survival. This is in accordance with earlier studies [7].

We find elevated LDH, metastases to the brain, leukocytosis and elevated ESR to be strong prognosticators including short survival as illustrated by the large difference in median survival for patients positive and negative for the factor. The presence of these poor prognostic factors in the individual patient is easily established by means of clinical examination and simple laboratory tests. The presence of one or more of these factors can, unlike the estimation of a performance status, be established by objective measures. These findings could have an impact on the design of protocols for experimental chemotherapy in melanoma. We would also suggest that the distribution of these prognostic factors could be stated when reporting the results of chemotherapy trials to facilitate interpretation of the results. Finally, we think that, in the individual patient, the identification of these factors could influence clinical decision making in palliative management of metastatic malignant melanoma.

CONCLUSION

In this study elevated LDH, metastases to brain, leukocytosis and elevated ESR were significant independent prognostic factors indicating short survival of less than 3 months. These patients should not be entered into chemotherapy trials. The distribution of these factors in a patient population should be stated when reporting the results of future chemotherapy trials. We would be hesitant to give toxic combination chemotherapy to a patient exhibiting one or more of these factors.

We were not able to demonstrate any clinically useful prognostic factors for response to chemotherapy in this material.

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