Lymphopenia as a Prognostic Factor for Overall Survival in Advanced Carcinomas, Sarcomas, and Lymphomas

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Abstract

Lymphopenia is frequent in advanced cancers and predicts the toxicity of chemotherapy. Its effect on relapse and survival is uncertain. Its prognostic value for survival was analyzed in three databases of previously reported prospective multicenter studies: (*a*) FEC chemotherapy in metastatic breast carcinoma; (*b*) CYVADIC in advanced soft tissue sarcoma (European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group 62791); and (*c*) prospective, consecutive phase III studies of aggressive diffuse large-cell non–Hodgkin's lymphomas conducted at Centre Léon Bérard between 1987 and 1993. Univariate and multivariate analyses of prognostic factors for survival were performed. The incidence of lymphopenia of <1,000/μL before treatment was constant among the series: 25%, 24%, and 27%, respectively. Lymphopenia was significantly more frequent ($P < 0.05$) in metastatic breast cancer patients with performance status (PS) of >1, non–Hodgkin's lymphoma patients with international prognostic index (IPI) of > 0, and advanced soft tissue sarcoma and metastatic breast cancer patients with bone metastases. In univariate analysis, lymphopenia of <1,000/μL significantly correlated to overall survival in patients with metastatic breast cancer (median, 10 versus 14 mo; $P < 0.0001$), advanced soft tissue sarcoma (median, 5 versus 10 months; $P < 0.01$), and non–Hodgkin lymphoma (median, 11 versus 94 months; $P < 0.0001$). In multivariate analysis (Cox model), lymphopenia was an independent prognostic factor for overall survival in metastatic breast cancer [RR (relative risk), 1.8; 95% CI (confidence interval), 1.3–2.4] along with liver metastases and PS; in advanced soft tissue sarcoma (RR, 1.46; 95% CI, 1.0–2.1) along with liver metastases, lung metastases, and PS; and in non–Hodgkin's lymphoma (RR, 1.48; 95% CI, 1.03–2.1) along with IPI. Our findings show that lymphopenia is an independent prognostic factor for overall and progression-free survival in several cancers. [Cancer Res 2009;69(13):5383–91]

Introduction

Factors related to (*a*) disease extent and dissemination (stage, tumor size, tumor markers), (*b*) patient characteristics [age, gender, associated comorbidities, performance status (performance status)], and (*c*) treatment (quality of surgery, radiotherapy, type of chemotherapy) have prognostic significance for survival from cancer. Long-term survival (e.g., >5 years) is generally observed in patients with favorable prognostic factors in all categories. Five to 10% of patients with metastatic soft tissue sarcoma or metastatic breast cancer (MBC), and 50% of non–Hodgkin's lymphoma (NHL) patients, are still alive 10 years after the diagnosis of metastasis (1–6).

Previously published studies have shown that lymphopenia is frequently observed in patients with advanced cancers and is a powerful predictor of chemotherapy-induced toxicity, in addition to patient characteristics, disease characteristics, biological parameters, and previous treatments. Lymphopenia has also been found associated with an increased risk of febrile neutropenia (7–11), thrombocytopenia requiring platelet transfusion (12), severe anaemia requiring red cell transfusion in adults and children (13, 14), and early death (15). All subsets of lymphocytes are altered in lymphopenic patients, whereas CD4+ and, to a lesser extent, CD56+ lymphopenia have been found to be the most powerful predictors of toxicity (16).

In the present study, we retrospectively investigated the prognostic value of lymphopenia for overall survival and progression-free survival in three prospectively collected series: (*a*) untreated aggressive NHL patients receiving first-line cyclophosphamide-Adriamycin-vincristine-prednisone (CHOP) or a CHOP-derived regimen, (*b*) hormone-resistant MBC patients receiving first-line FEC chemotherapy, and (*c*) untreated advanced soft tissue sarcoma (ASTS) patients treated in the 62761 trial of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group with the CYVADIC regimen.

Materials and Methods

Objectives

The study aimed to determine the prognostic value of lymphopenia for progression-free and overall survival in patients treated with chemotherapy for MBC, NHL, and advanced sarcoma.

Patients

NHLs. We analyzed the data from non-pretreated, HIV-negative patients with intermediate or high-grade NHL who were included in two prospective multicenter phase III trials of the Groupe d' Etude des Lymphomes de

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Table 1. Non–Hodgkin lymphoma (n = 322)

Patients' characteristics	No (%)	Overall survival			
		Univariate analysis		Multivariate analysis*	
		Median (mo)	P	HR (95%CI)	P
Age (y)	322				
<60	160 (50)	>165	<0.0001	—	NS
≥60	162 (50)	21	—	—	—
Gender	322				
Male	187 (58)	30	NS	—	NS
Female	135 (42)	69	—	—	—
Ann Arbor stage	321				
I	30 (9)	>123	<0.0001	—	NS
II	107 (33)	112	—	—	—
III	37 (12)	39	—	—	—
IV	147(46)	18	—	—	—
PS (ECOG)	286				
0–1	199 (70)	112	<0.0001	—	NS
>1	87 (30)	12	—	—	—
B symptoms	277				
No	227 (82)	78	0.002	—	NS
Yes	50 (18)	11	—	—	—
Extra nodal involv.	322				
0–1	311 (97)	52	NS	—	NS
>1	11 (3)	14	—	—	—
Serum LDH level	314				
≤Normal	115 (37)	94	0.02	—	NS
>Normal	199 (63)	29	—	—	—
Bone marrow involv.	321				
No	277 (86)	56	NS	—	NS
Yes	44 (14)	16			
β^2 microglob. level	252				
≤Normal	207 (82)	89	<0.0001	—	NS
>Normal	45 (18)	11	—	—	—
IPI	279				
0–1 †	96 (34)	>165	—	—	—
2	106 (38)	94	<0.0001	1.99 (1.3–3.1)	<0.0001
3	47 (17)	30	—	3.22 (1.9–5.4)	—
4–5	30 (11)	4	—	7.25 (4.2–12.6)	—
Lymphocytes (/μL)	322	—	—	—	—
≥1,000 †	234 (73)	94	—	—	—
<1,000	88 (27)	11	<0.0001	1.48 (1.03–2.1)	

Abbreviations: HR, hazard ratio; NS, not significant; Involv., involvement; ECOG, Eastern Cooperative Oncology Group; microglob., microglobulin.
*The final model was performed on 279 patients.
†Reference modality.

l'Adulte at Centre Léon Bérard cancer center between 1986 and 1997. All patients were treated with the CHOP or ACVBP regimens.

MBCs. The second series included non-pretreated patients with MBC included in the prospective multicenter phase III trial ERASME, who received first-line chemotherapy with FEC at Centre Léon Bérard cancer center between 1986 and 1990 (17).

ASTS. The third series involved non-pretreated patients with metastatic soft tissue sarcoma included in the prospective multicenter phase III trial of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (trial 62791; ref. 18).

Prognostic Factors

Previously validated prognostic factors for overall survival had been collected for the three series of patients. For non–Hodgkin's lymphoma, prognostic factors were those of the International Prognosis Index (IPI; ref. 19); for MBC, they included age at diagnosis, menopausal status, presence or absence of hormone receptors, metastasis-free interval, site of metastasis, number of metastatic sites, and previous adjuvant treatments (1); for soft tissue sarcoma, the factors were age over 60 y, gender, histologic subtype, site of metastasis, and histologic grade (3, 4). In all patients, lymphocyte counts immediately before initiation of systemic treatment had been prospectively recorded in the case report form of the different trials and were available for analysis. Lymphopenia was defined as a lymphocyte count below 1,500/μL, but the relevant threshold value in this series was found to be 1,000/μL.

Statistics

Survival analysis. Overall survival was defined as the time from treatment initiation (or from date of diagnosis for NHL patients) to the date

of death or the date of last follow-up for patients alive at last contact. Progression-free survival was defined as the time from treatment initiation (or from date of diagnosis for NHL patients) to the date of disease progression or death, or to the date of last follow-up for patients alive at last contact. Survival distributions were estimated by the Kaplan-Meier method (20).

Univariate analysis. To evaluate the relationship between survival and all biological and/or clinical factors known to be relevant in each disease, potential prognostic factors were included in univariate Cox proportional hazard regression models. The risk factors most commonly used in previous studies (e.g., PS, >1) were dichotomized. Lymphopenia was also included in the models as a dichotomous variable (<1,000/μL versus ≥1,000/μL). These categories were defined by first determining the quartiles of the distribution of lymphocyte counts for each tumor type. The overall survival distributions of these quartiles were further examined using the Kaplan-Meier method. The conclusion was that the threshold corresponding to the lower quartile (close to 1,000/μL for each tumor type) was the most discriminative parameter to predict overall survival in the three tumor types studied. Candidate prognostic factors with a 0.05 level of significance in univariate analysis were then selected for inclusion in the multivariate analysis.

Multivariate analysis. Independent prognostic variables of overall survival and progression-free survival were respectively identified by a Cox regression analysis using a backward selection procedure (21, 22). The add-value of lymphopenia in each model where it was found to be an independent prognostic factor was evaluated using a likelihood ratio test (LRT): likelihood scores of the model evaluated with and without lymphopenia were compared, considering that lower likelihood scores indicate better fitting models (23).

All statistical analyses were performed using SPSS12.1 and SAS v.9.1 (Cary).

Results

Patient Characteristics

The characteristics of patients with NHL, MBC, and metastatic sarcoma are given in Tables 1, 2, and 3, respectively. In total, 322 NHL, 287 MBC, and 193 ASTS patients were analyzed.

The incidence of lymphopenia was remarkably similar among the studied patient populations, i.e., 27%, 25%, and 24%, respectively (Table 4).

Table 2. Breast cancer (n = 287)

Patients' characteristics	No (%)	Overall survival			
		Univariate analysis		Multivariate analysis*	
		Median (mo)	P	HR (95%CI)	P
Age (y)	286				
<60	193 (67)	11	NS	—	NS
≥60	93 (33)	13	—	—	—
Hormone receptor	181				
No	60 (33)	10	NS	—	NS
Yes	121 (67)	12	—	—	—
SBR grade	108				
I	22 (20)	13	NS	—	NS
II	60 (56)	12			
III	26 (24)	14	—	—	—
PS (ECOG)	265				
0–1 †	160 (60)	15	<0.0001		<0.0001
>1	105 (40)	8	—	1.99 (1.5–2.6)	—
Liver metastases	279				
No †	147 (53)	16	<0.0001	—	<0.0001
Yes	132 (47)	10	—	1.85 (1.4–2.4)	—
Bone metastases	279				
No	101 (36)	13	NS	—	NS
Yes	178 (64)	11	—	—	—
Skin metastases	279				
No	263 (94)	12	NS	—	NS
Yes	16 (6)	16	—	—	—
Bone marrow involv.	279				
No	269 (94)	12	0.03	—	NS
Yes	10 (6)	11			
Nb metastatic sites	281				
1	100 (36)	17	0.0002	—	NS
>1	181 (64)	11	—	—	—
Lymphocytes (/μL)	279				
≥1,000 †	208 (75)	14	<0.0001	—	0.0002
<1,000	71 (25)	10	—	1.8 (1.3–2.4)	—

*The final model was performed on 257 patients.
†Reference modality.

Table 3. Advanced soft tissue sarcoma (n = 193)

Patients' characteristics	No (%)	Overall survival			
		Univariate analysis		Multivariate analysis*	
		Median (mo)	P	HR (95%CI)	P
Age (y)	192				
<60	149 (78)	9	NS	—	NS
≥60	43 (22)	8			
Gender	192				
Male	100 (52)	8	NS	—	NS
Female	92 (48)	9			
Grade	145				
I	11 (8)	15	NS	—	NS
II	28 (19)	8			
III	106 (73)	9	—	—	—
Karnofsky index	184				
100–80 †	111 (60)	12	<0.0001		<0.0001
<80	73 (40)	4	—	2.33 (1.7–3.3)	—
Liver metastases	173				
No †	142 (82)	9	0.02		0.002
Yes	31 (18)	7	—	2.03 (1.3–3.1)	—
Bone metastases	183				
No	159 (87)	9	NS	—	NS
Yes	24 (13)	8	—	—	—
Lung metastases	189				
No †	80 (42)	9	0.02		0.03
Yes	109 (58)	9	—	1.49 (1.05–2.1)	—
Histotype	153				
Leiomyosarcoma	41 (27)	11	—	—	—
MFH	30 (20)	8			
Synovial sarcoma	5 (3)	24	0.01 ‡	—	—
Liposarcoma	15 (10)	16	—	—	—
Fibrosarcoma	18 (12)	10	—	—	—
Other	44 (29)	7			
Lymphocytes (/μL)	193				
≥1,000	147 (76)	10	—	—	0.05
<1,000	46 (24)	5	0.006	1.46 (1.0–2.1)	—

Abbreviation: MFH, malignant fibrous histocytosarcoma.
*The final model was performed on 162 patients.
†Reference modality.
‡Not included in the multivariate analysis because interpretation is difficult.

In patients with NHL, lymphopenia of <1,000/μL was more frequently associated with women (36% versus 21%; P = 0.002), age of >60 years (33% versus 22%; P = 0.03), increased pretreatment levels of serum β 2 microglobulin (49% versus 24%; P = 0.0007), clinical B symptoms (42% versus 24%; P = 0.009), lactate dehydrogenase level above normal (34% versus 16%; P = 0.0005), higher international prognostic index (P = 0.03), or hemoglobin levels of <12g/dL (38% versus 19%; P = 0.0002), but was not correlated to clinical stage or bone marrow involvement. In MBC patients, lymphopenia of <1,000/μL was more frequently associated

Table 4. Incidence of lymphopenia in the three groups of patients

	N (%) Lymphocyte count (/μL)			
	<400	[400–700]	]700–1,000[	≥1,000
Non–Hodgkin's lymphoma (n = 322)	9 (3)	45 (14)	34 (11)	234 (73)
MBC (n = 279)	10 (4)	23 (8)	38 (14)	208 (75)
Advanced soft tissue sarcoma (n = 193)	6 (3)	18 (9)	22 (11)	147 (76)

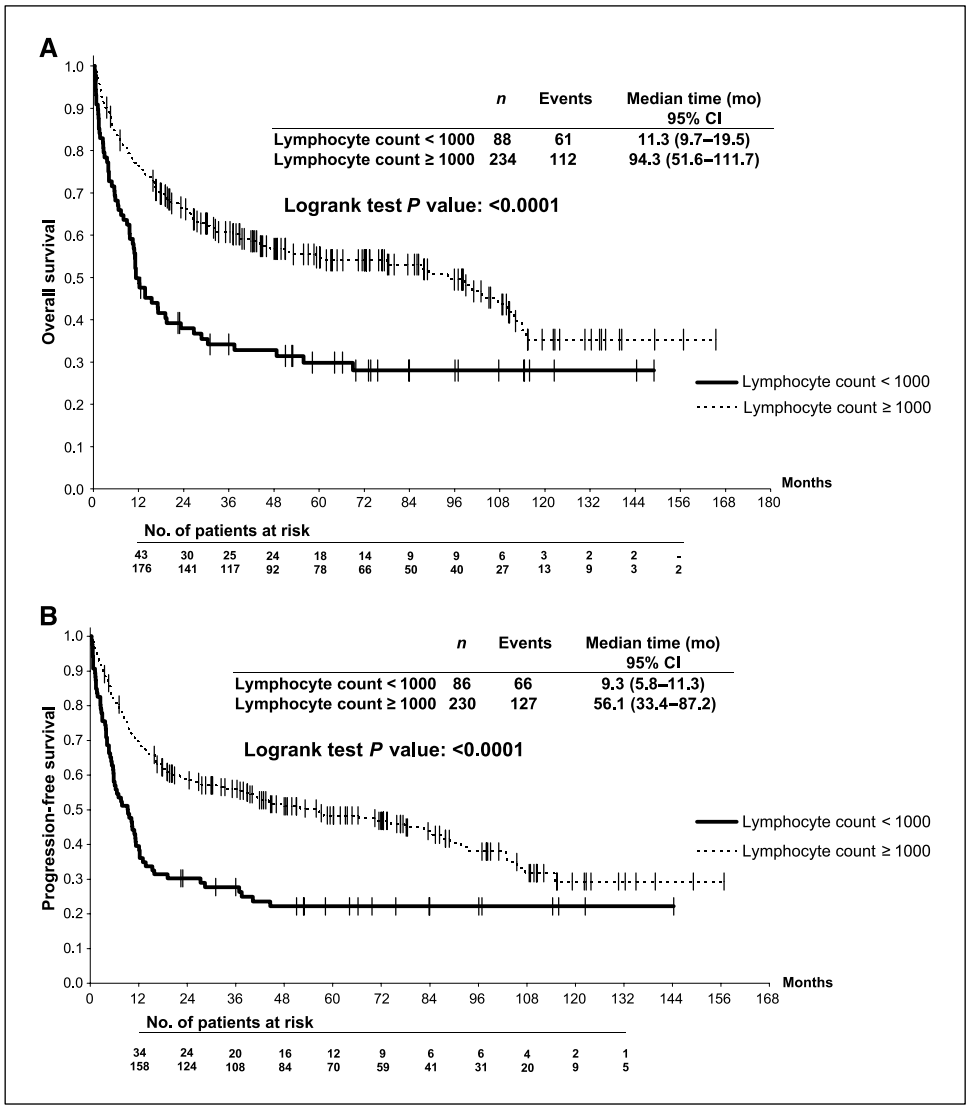

Figure 1. Overall (*A*) and progression-free (*B*) survival of non–Hodgkin's lymphoma patients according to baseline lymphocyte counts.

with PS of >1 (34% versus 20%; $P = 0.01$), postmenopausal status (28% versus 6%; $P = 0.01$), bone marrow involvement (67% versus 24%; $P = 0.009$), bone metastasis (29% versus 18%; $P = 0.04$), or more than one metastatic site (30% versus 18%; $P = 0.03$), but not with age. In sarcoma patients, lymphopenia was correlated only to the presence of bone metastases (46% versus 21%; $P = 0.01$) but not to age, gender, histologic grade of the primary tumor, or liver metastases.

Overall Survival

NHL. In the univariate analysis, age over 60 years, PS of >1, presence of B symptoms, Ann Arbor stage of >III, serum LDH level above normal, β2 microglobulin level above normal, IPI score ($P < 0.05$; Table 1), and baseline lymphocyte count of <1,000/μL were found to be correlated to overall survival (Fig. 1*A*). In the multivariate analysis, only the IPI score ($P < 0.0001$) and lymphocyte counts below 1,000/μL [RR, 1.48; 95% confidence interval (CI), 1.03–2.1; $P = 0.04$] were found to be independently correlated to overall survival (Table 1). Results of the LRT indicated that this multivariate model fitted the data significantly better than the same model without lymphopenia ($P = 0.05$). Lymphopenia was found significantly correlated to progression-free survival, with a median interval of 9 versus 56 months ($P < 0.0001$; Fig. 1*B*). Using the Cox model, the IPI score ($P < 0.0001$) and lymphopenia (RR, 1.71; 95% CI, 1.2–2.4; $P = 0.002$) were independently correlated to progression-free survival. Results of the LRT indicated a better fitting model when including lymphopenia ($P = 0.003$).

MBC. In the univariate analysis, PS of >1, presence of liver metastases, number of metastatic sites of >1, presence of bone marrow involvement, and lymphocyte count <1,000/μL were correlated to overall survival (Table 2). Figure 2 shows the overall survival of MBC patients according to lymphocyte count. Median survival was significantly better for patients with lymphocyte counts of ≥1,000/μL compared with <1,000/μL (14 versus 10 months; $P < 0.0001$). In the multivariate analysis, only performance status (RR, 1.99; 95% CI, 1.5–2.6; $P < 0.0001$), presence of liver metastases (RR, 1.85; 95% CI, 1.4 – 2.4; $P < 0.0001$), and lymphocyte count (RR, 1.8; 95% CI, 1.3 – 2.4; $P = 0.0002$) were found to be correlated to survival. Progression-free survival was also significantly shorter in patients with lymphocyte counts of <1,000/μL compared with ≥1,000/μL (7 versus 9 months; $P = 0.0001$; Fig. 2*B*). Using the Cox model, PS (RR, 1.6; 95% CI, 1.2–2.1; $P = 0.0004$), presence of liver metastases (RR, 1.67; 95% CI, 1.3–2.2; $P < 0.0001$), and lymphocyte count (RR, 1.48; 95% CI, 1.1–2.0; $P = 0.01$) were

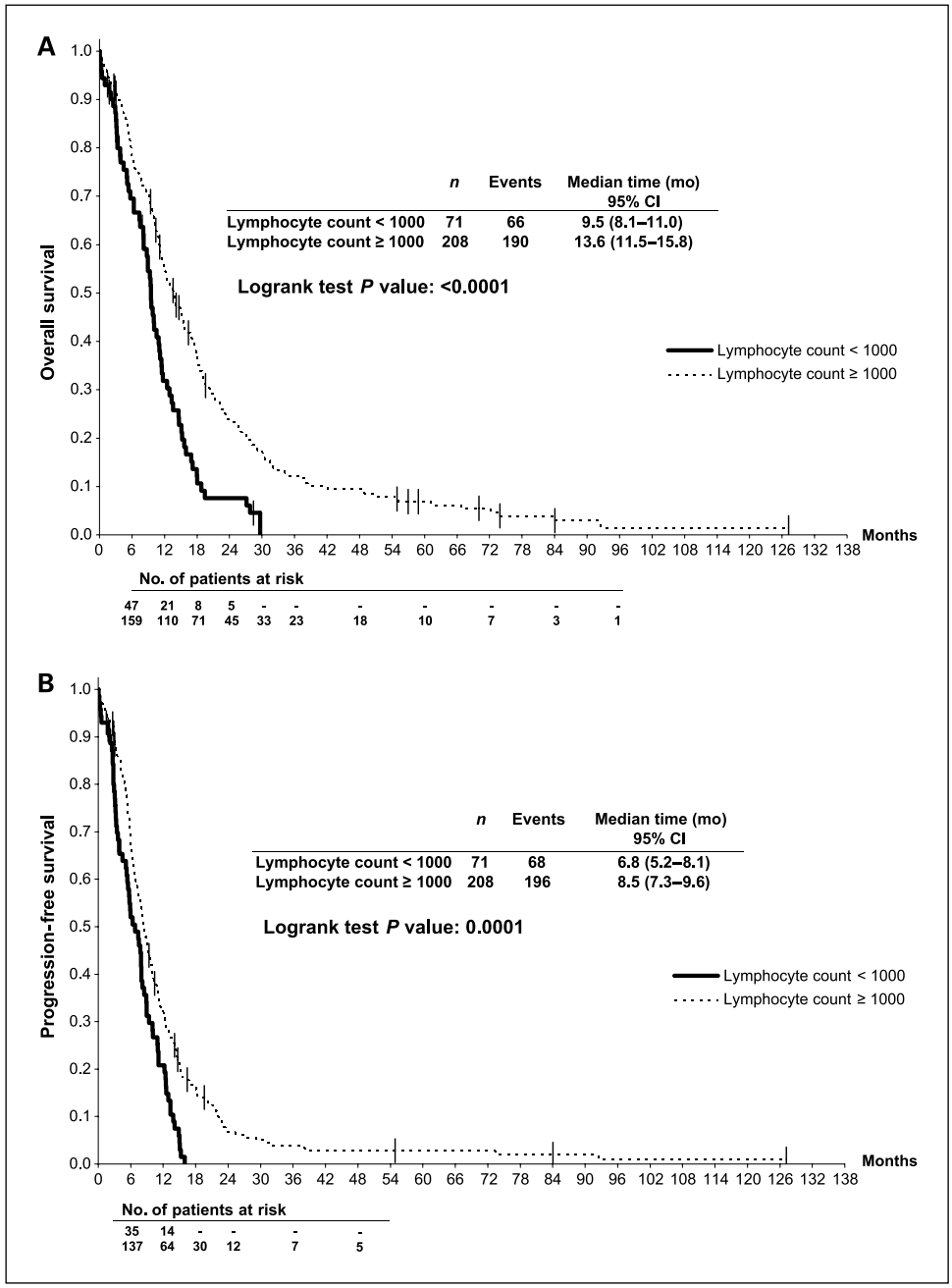

Figure 2. Overall (*A*) and progression-free survival (*B*) of hormone-resistant MBC patients according to baseline lymphocyte counts.

found to be correlated to progression-free survival. For both multivariate models, results of the LRT showed an improved goodness of fit of the models compared with the same models without lymphopenia ($P < 0.0001$).

Soft tissue sarcoma. In the univariate analysis, Karnofsky Index of <80, presence of liver and/or lung metastases, histotype, and lymphocyte count of <1,000/μL were correlated to overall survival (Table 3). Figure 3 shows the overall survival of ASTS patients according to pretreatment lymphocyte count. Median survival was significantly better for patients with lymphocyte counts of ≥1,000/μL compared with <1,000/μL (10 versus 5 months; $P = 0.006$). In the multivariate analysis, Karnofsky Index of <80 (RR, 2.33; 95% CI, 1.7–3.3; $P < 0.0001$), presence of liver metastases (RR, 2.03; 95% CI, 1.3–3.1; $P = 0.002$), presence of lung metastases (RR, 1.49; 95% CI, 1.05–2.1; $P = 0.03$), and lymphocyte count (RR, 1.46; 95% CI, 1.0–2.1; $P = 0.05$) were found to be independently correlated to overall survival (Table 3). Results of the LRT showed that this multivariate model fitted the data significantly better than the same model without lymphopenia ($P = 0.05$). In the univariate analysis, progression-free survival was not significantly different between the two groups, although the median interval was shorter for lymphopenic patients (2 versus 3 months; $P = 0.17$). In the multivariate analysis, only Karnofsky Index of <80 (RR, 1.97; 95% CI, 1.3–2.9; $P = 0.0007$), presence of liver metastases (RR, 1.91; 95% CI, 1.1–3.2; $P = 0.01$), and tumor grade of >2 (RR, 1.58; 95% CI, 1.04–2.4; $P = 0.03$) were found correlated to progression-free survival.

Discussion

Several different parameters may influence survival in cancer patients: variables related to the characteristics of the tumor

(tumor size, stage, biological characteristics including molecular alterations), those related to the characteristics of the patient (age, gender, comorbidities), and those directly related to the nature and quality of treatment. Some of these prognostic factors, such as age, clinical stage, and performance status, are common across tumor types and represent the basis of treatment decision for health care providers, as well as the major inclusion criteria for entering patients into clinical trials.

In the present study, we identified lymphopenia as a simple prognostic factor for overall survival shared by the three tumor types studied: MBC, advanced sarcoma, and NHL. Lymphopenia before initiation of systemic treatment was found to independently correlate to overall survival in all patients, and to progression-free survival in MBC and NHL patients. We and others have previously reported the prognostic effect of lymphopenia on hematologic toxicity from chemotherapy, especially for neutropenia, severe thrombocytopenia, severe anemia requiring red cell transfusion, and early death after chemotherapy (7, 12–15, 24). Most previous studies have used a threshold level of 700 lymphocytes per microliter, which has been identified as the most discriminative predictive value for hematologic toxicities, although a cutoff value of 1,000/μL retains predictive value for toxicity (data not shown). The biological significance of this threshold remains unclear: it may select a larger proportion of patients with CD4 counts of <450/μL, later identified as the most discriminative factor to predict toxicity (16).

In the present study, the threshold of 1,000/μL was found to be more discriminative to predict overall survival in the three tumor types studied. The first interesting observation was that the frequency of lymphopenia of <1,000/μL in all three cancer patient populations was very similar, with 24% to 27% of the patients presenting a lymphocyte count of <1,000/μL before any systemic treatment. Interestingly, the incidence of lymphopenia of <1,000/μL was lower in patients with localized breast cancer or sarcoma, with a rate of 3% to 5% for the series of patients treated in our institution (data not shown). Lymphopenia was found correlated with performance status, as well as with specific prognostic factors for NHL (β 2 microglobulin, B symptoms), breast cancer (bone and bone marrow involvement, number of metastatic sites, menopausal status), and sarcoma (bone metastases). These observations

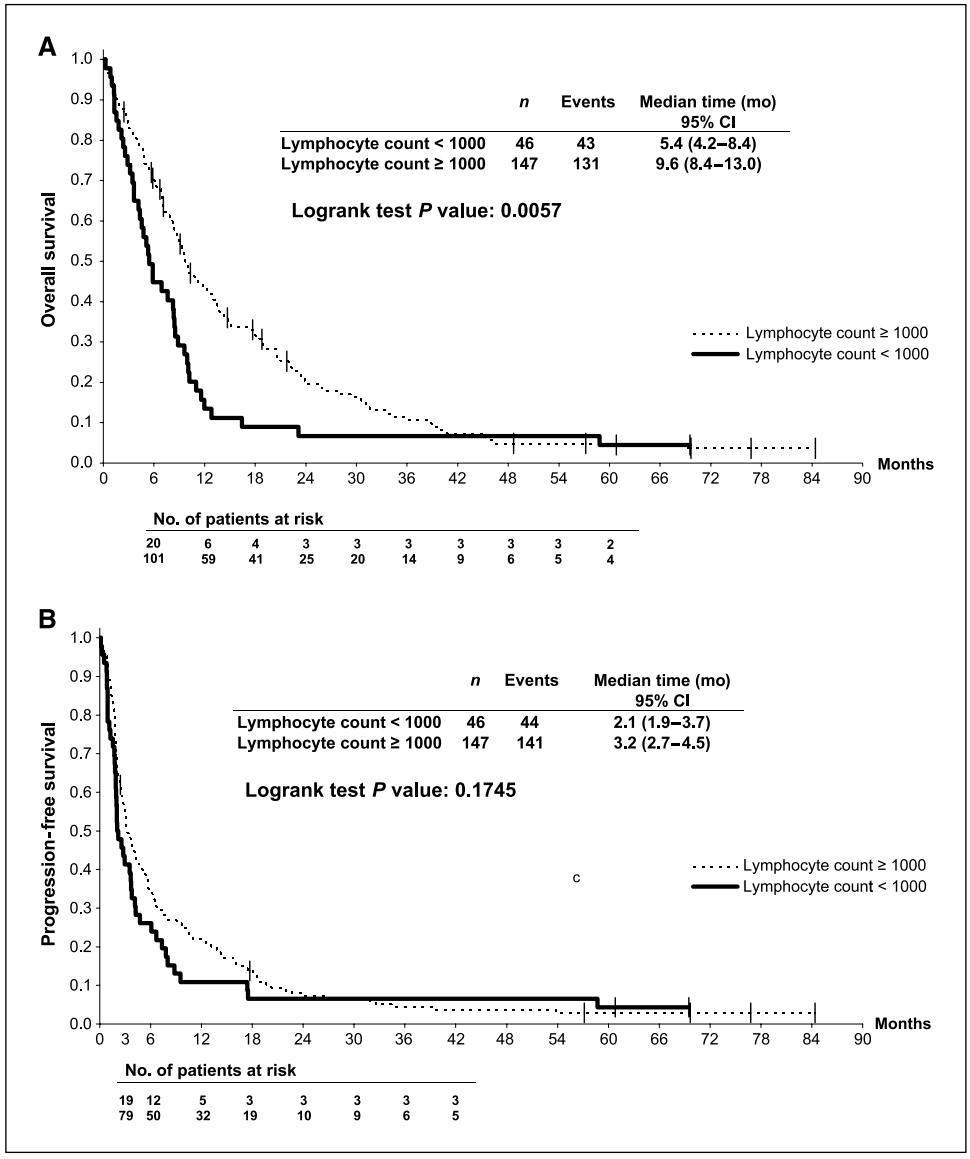

Figure 3. Overall (*A*) and progression-free survival (*B*) of advanced soft tissue sarcoma patients according to baseline lymphocyte counts.

strongly show that lymphopenia is related to tumor cell mass, metastatic sites, and paraneoplastic inflammatory syndrome, but also to host characteristics (menopausal status or age).

Although the actual mechanisms of the association between low lymphocyte count and poor prognosis is unclear, the different possibilities are as follows: (*a*) the low lymphocyte count may be associated with a preexisting immunosuppressed condition, suggesting that the host tends to have an inadequate immunologic reaction; (*b*) the low lymphocyte count may be a consequence of lympholytic cytokines produced by the lymphoma cells, and such lymphoma may itself be resistant; or (*c*) a combination of both or other factors. Effectively, the mechanisms of lymphopenia in cancer patients remain unclear and are probably multifactorial. The three series studied included only previously untreated patients; therefore, lymphopenia was not due to exposure to cytotoxic agents. Lymphopenia may have resulted from a destruction of lymphocytes elicited by the tumor (25, 26) and/or an altered homeostasis of lymphocyte pools in cancer patients (27). In support of the first hypothesis, it has been reported that the lymphocytes of cancer patients undergo activation-induced death *in vivo* and that proapoptotic ligands such as FasL or tumor necrosis factor (TNF) β are produced *in vivo* in cancer patients (25, 28–30). Physiologic lymphocyte homeostasis and maintenance of lymphocyte subset pools in adult patients are dependent on the presence and function of dendritic cells (27). The differentiation of dendritic cells is impaired by the overproduction of numerous cytokines and mediators such as interleukin (IL)-6, PGE2, IL-10, and transforming growth factor β, which are produced within the tumor environment and are released in the blood stream in breast carcinoma, lymphoma, and other tumors (31). The correlations between lymphopenia and inflammatory B symptoms as well as serum IL-6, IL-10, and TNF levels in breast carcinoma, lymphoma, and other neoplastic diseases are consistent with this hypothesis (32–38).

Bone marrow involvement and the presence of bone metastases are likely contributing factors in some patients because they were found correlated to lymphopenia in our breast cancer series. Cachexia associated with tumor progression may also contribute to decreased lymphocyte counts, although weight loss and hypoalbuminemia were observed in <40% of our lymphopenic breast and lymphoma patients for whom this information was available (data not shown). Partial correlation between lymphopenia and hypoalbuminemia has also been reported in a recent series of metastatic carcinomas with unknown primary (39).

Several of the prognostic parameters previously reported in the literature for each tumor type were found to be correlated to overall survival: liver metastases, number of metastatic sites, and PS in breast carcinoma; IPI score (40) in NHL; and histotype, liver metastases, and PS in sarcomas (1–6, 17–19). In the three populations, the prognostic value of lymphopenia was found to be independent of these factors in the multivariate analysis using the Cox model. Moreover, we also showed that the three models better fitted the data when they included lymphopenia as a prognostic factor. Lymphopenia had been previously found correlated to overall survival. In a study published in 1970, Riesco (41) reported a significant positive correlation between cancer curability and the total number of peripheral lymphocytes in miscellaneous cancer patients (n = 589), notably those with localized cervix and breast cancers, with a threshold level of 1,000/μL similar to the threshold identified in our study. Ownby and colleagues (42) analyzed recurrences in a series of patients with breast cancer: patients with preoperative lymphocyte counts of ≤1,500/mm^3 and/or eosinophil counts of <55/mm^3 had a significantly higher risk of recurrent disease than those with normal or high levels of eosinophils and/or lymphocytes. In Hodgkin's disease and diffuse large B-cell lymphomas, lymphopenia has been reported to be correlated to overall survival (40, 43, 44). We previously reported that lymphopenia is not restricted to a specific lymphocyte subset and involves the CD4, CD8, CD19, and CD56 cell compartments, although correlation to patient outcome is mainly associated with CD4 and CD56 depletion (16). In 1999, Ayoub and colleagues (43) also reported a series of 238 newly diagnosed patients with Hodgkin's disease and showed a correlation between quantitative changes of B, T, and natural killer cells and patients' clinical characteristics: WBC counts were higher in patients with advanced disease, whereas peripheral blood lymphocytes and CD4, CD8, and CD3−/CD56+/CD16+ subsets were decreased in advanced stages.

Lymphopenia may not only be a parameter correlated to survival but also a biological mechanism stimulating tumor progression, both in NHL where immune suppression is clearly involved in tumor progression and etiology, and in other tumor types, including melanoma and head and neck carcinoma (25, 26, 45). In addition to the increased risk of death due to treatment toxicity (15), the poor outcome observed in lymphopenic patients may also result from the loss of an antitumor specific immune response (46). The other fundamental question about the results presented here and previous studies (8, 12, 15) is the link between drug toxicity, lower dose intensity of treatment (due to toxicity), or spontaneous poor prognosis. Unfortunately this question remains unclear because data on treatment intensity and chemotherapy were not available from the data sets used in the present study. It will be very important to explore this point in further studies.

Determining whether lymphopenia represents a cause as well as a consequence of tumor progression will be of importance in the perspective of the correction of lymphopenia using lymphocyte growth factors such as IL-7 (47–50). Indeed, exogenous recombinant IL-7 can enhance T-cell recovery following lymphocyte depletion (40, 41). This cytokine, like IL-2, is being developed therapeutically as an immunorestorative agent in lymphopenic patients and deserves to be tested in a clinical setting (47–49). In melanoma patients, a partial correction of lymphopenia has been observed following tumor antigen vaccination in those patients in whom tumor control had been achieved (25). Of note, we observed a normalization or correction of lymphocyte counts after complete remission only in lymphoma patients; lymphocyte counts dropped again in the 10 patients who subsequently relapsed (data not shown). Not surprisingly, normalization could not be observed in breast carcinoma series where complete remission was not achieved. In conclusion, our results show that, in addition to its predictive value for hematologic toxicity and early death, lymphopenia is a general prognostic factor for overall survival in patients with different types of cancers. The final question is how to use these findings in routine practice. First, although the prognostic value of lymphocyte counts is now well established for NLH, their add-value for other cancers (sarcoma, MBC, but also lung cancer, etc.) needs to be confirmed by others. Second, only the results of randomized clinical trials comparing homogeneous groups of patients treated or not with potential correctors of lymphopenia (anti-CTLA4 antibody, IL-7 LGF, etc.) could modify clinical practice and thereby permit to use lymphopenia for decision making in routine practice. Currently, we plan to evaluate this prognostic factor in other solid tumors (ovarian carcinoma,

lung cancer; ref. 51) and also to explore the mechanisms of such lymphopenia.

The understanding of mechanisms involved in lymphopenia and of its consequences on patient outcome may facilitate the development of corrective measures with the aim of reducing treatment toxicity and improving patient survival.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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