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Chromosomal Abnormalities in Untreated Patients With Non-Hodgkin's Lymphoma: Associations With Histology, Clinical Characteristics, and Treatment Outcome

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We describe the chromosomal abnormalities found in 104 previously untreated patients with non-Hodgkin's lymphoma (NHL) and the correlations of these abnormalities with disease characteristics. The cytogenetic method used was a 24- to 48-hour culture, followed by G-banding. Several significant associations were discovered. A trisomy 3 was correlated with high-grade NHL. In the patients with an immunoblastic NHL, an abnormal chromosome no. 3 or 6 was found significantly more frequently. As previously described, a t(14;18) was significantly correlated with a follicular growth pattern. Abnormalities on chromosome no. 17 were correlated with a diffuse histology and a shorter survival. A shorter survival was also correlated with a +5, +6, +18, all abnormalities on chromosome no.

EARLY IN this century, Boveri¹ hypothesized that all cells of malignant tumors had karyotypic abnormalities, and that any event leading to chromosomal abnormalities would result in a malignant tumor. However, it took many decades before the Philadelphia chromosome in chronic myelogenous leukemia was described.² Since then, cytogenetic abnormalities have been found in several diseases, including acute leukemias,^{3,4} myelodysplastic syndromes,⁵ and non-Hodgkin's lymphomas (NHL).⁶⁻²³

Several karyotypic abnormalities in NHL are associated with a particular histology, localization of disease, or treatment outcome.²⁴ However, many reports have included only small numbers of patients or patients analyzed at relapse. We analyzed 104 patients with cytogenetic abnormalities in newly diagnosed NHL that were treated according to Nebraska Lymphoma Study Group protocols. We describe the cytogenetic abnormalities found in these patients and correlate them with histology, clinical characteristics, and response to therapy.

MATERIALS AND METHODS

Patient Characteristics

Between October 1982 and April 1988, the lymph nodes or other sites of disease of 123 patients with histologically confirmed and previously untreated NHL were studied cytogenetically. In 10 patients the results were inconclusive, in 9 patients they were normal, and abnormal in 104. All of the tissues examined were involved by lymphoma. A piece of the same tissue used for cytogenetic analysis was studied for histology and B-cell and T-cell markers, using an immunoperoxidase technique. The Working Formulation Classification was used.²⁵ Staging consisted of a complete history and physical examination, chest radiograph, computed tomography scan of the abdomen, and bone marrow biopsy. The patients were staged according to the Ann Arbor system.²⁶

In all patients, the tumor was studied at the time of primary diagnosis. No selection criteria other than the availability of cytogenetic data at the time of diagnosis and treatment according to Nebraska Lymphoma Study Group protocols were used. No patients with a human immunodeficiency virus (HIV)-related lymphoma were included.

5, or involvement of breakpoint 14q11-12. In a multivariate analysis, these chromosomal abnormalities appeared to be independent prognostic factors and correlated with survival more strongly than any traditional prognostic variable. Patients with a t(11;14)(q13;q32) had an elevated lactate dehydrogenase (LDH). Skin infiltration was correlated with abnormalities on 2p. Abnormalities involving breakpoints 6q11-16 were correlated with B symptoms. Patients with abnormalities involving breakpoints 3q21-25 and 13q21-24 had more frequent bulky disease. The correlations of certain clinical findings with specific chromosomal abnormalities might help unveil the pathogenetic mechanism of NHL and tailor treatment regimens. © 1990 by The American Society of Hematology.

The clinical characteristics of the patients with abnormal cytogenetic analysis are listed in Table 1. Similar data from the patients with the normal chromosome studies are also listed in Table 1 for comparison. The patients with the inconclusive results were excluded from analysis. The follow-up of the patients was 1 to 55 months (median 16 months).

Treatment

Patients were treated according to protocols of the Nebraska Lymphoma Study Group. Patients with pathologically confirmed stage I disease were treated with radiation therapy until 1986, and more recently with radiation after two or three cycles of chemotherapy. The patients with stage II, III, and IV disease were all treated with chemotherapy directly after the diagnosis was made. The chemotherapy regimens consisted of CAP-BOP (cyclophosphamide, adriamycin, procarbazine, bleomycin, vincristine, and decarbazine) for the intermediate- and high-grade malignant lymphomas, or CHVP (chlorambucil 12 mg/m² [maximal dose 20 mg] administered orally on days 1 through 5, vincristine 1 mg/m² intravenously [IV] on day 1, and prednisone 100 mg orally on days 1 through 5, every 3 to 4 weeks) for the lymphomas of low-grade malignancy. A complete remission (CR) was defined as the absence of

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Table 4. Statistically Significant Correlations Between Breakpoints Occurring in More Than Five Percent of the Patients and Characteristics of Disease

Breakpoint (Chromosome)	Clinical Correlations	P Value
1q21-25	No marrow involvement	.005
3q21-25	Bulky disease	.005
6q11-16	B symptoms	<.001
11q13	Elevated LDH	.01
11q23-24	B cell	.01
13q21-24	Bulky disease	.001
14q11-12	Shorter median survival	<.001
14q32	Follicular histology	.01
18q21	Follicular histology	.005

Chromosome no. 11. Abnormalities of breakpoint 11q13 were found in five patients, always as a part of a t(11;14)(q13;q32). This abnormality was correlated with a higher frequency of LDH elevation ($P = .01$) without a correlation with other parameters for tumor load. Five other patients had a breakpoint at 11q23-24. This abnormality was related with a B-cell phenotype ($P = .01$).

Chromosome no. 13. Five patients had an abnormality involving breakpoint 13q21-24. They were more likely to have bulky disease ($P = .001$).

Chromosome no. 14. Five patients had a breakpoint involving 14q11-12 and they had a significantly shorter median survival (8 months v 26 months; $P = .001$). Only one of these patients had a T-cell phenotype. Forty-three patients had a breakpoint at 14q32. They were more likely to have a follicular growth pattern ($P = .01$), but there was no relation with survival or disease-free survival. Of these 43 patients with a breakpoint at 14q32, 26 had a t(14;18) and they were more likely to have a follicular growth pattern ($P = .005$), but there was no correlation with survival or disease-free survival. Fifty-four patients had an abnormality in chromosome no. 14q. These patients were less likely to have stage I disease ($P = .01$) or skin infiltration ($P = .01$). In patients with a diffuse histology, the abnormalities on chromosome 14q combined were correlated with the absence of skin infiltration ($P = .005$). This correlation was not present for breakpoints 14q11-12 or 14q32.

Chromosome no. 17. No specific breakpoints involving at least 5% of the patients were recognized. All patients with an abnormal chromosome no. 17 combined ($n = 20$) had a higher frequency of diffuse pathology ($P = .01$) and a shorter median survival (7 months v 42 months; $P < .0001$) compared with the patients without this abnormality.

Chromosome no. 18. Twenty-six patients had a breakpoint at 18q21, all as a part of a t(14;18). For correlation see Chromosome no. 14 section. A trisomy 18 ($n = 20$) was correlated with a shorter median survival of 6 months versus 41 months ($P = .008$) for all other patients. The presence of an abnormal chromosome no. 18 in patients with an immunoblastic NHL was correlated with a lower frequency of stage IV disease ($P = .01$). In the same histologic subgroup, a t(18) was correlated with a lower frequency of extra nodal disease ($P = .005$).

For all other chromosomes, the number of patients with an

abnormality was less than 5% or there was no significant correlation with the tested disease characteristics.

Importance of Normal Metaphases

In 58 patients only abnormal karyotypes were found, while in 46 patients there was an admixture of normal cells. There was no significant correlation between the presence or absence of normal cells and histologic type. Also, there was no difference in survival between the patients with only abnormal karyotypes and those with an admixture of normal karyotypes and those with only normal karyotypes. This was also the case in subgroups as follicular, diffuse, low-grade, or intermediate- and high-grade NHL.

Multivariate Analysis

A multivariate analysis of survival using the proportional hazards model of Cox was conducted to assess the independent prognostic influence of the various patient characteristics on survival. Four patient characteristics were significantly associated with patient survival (ie, LDH > 1.5 high normal; B symptoms; stage IV disease; and age greater than 70) (Table 5). After adjustment for these variables, neither gender, bulky disease, or histology were significantly associated with survival. The abnormalities that were correlated with survival (+5, +6, +18, all on no. 5, all on no. 17, and breakpoints 14q11-12) were then analyzed to assess the prognostic significance (Table 5). The presence of these cytogenetic abnormalities is an indication of a significant poorer survival ($P = .0000007$), even after adjusting for other features of considerable prognostic importance. The number of patients with any specific chromosomal abnormality was too small to allow for the assessment of the individual cytogenetic abnormalities' prognostic significance.

Recursive Partitioning

Based on variables most prognostic for survival (presence of B symptoms and LDH), the prognostic influence of the presence of 1 of the 6 cytogenetic abnormalities correlated with survival (+5, +6, +18, all on no. 5, all on no. 17, and breakpoints 14q11-12) was then assessed within each of the three prognostic subgroups. The presence of 1 of these 6 chromosomal abnormalities was significantly associated with survival in all three prognostic subgroups (Figs 1 through 3).

DISCUSSION

In 104 of 123 (84.6%) patients with proven and previously untreated NHL, the karyotypes showed one or more abnormalities. This yield of abnormal metaphases is compar-

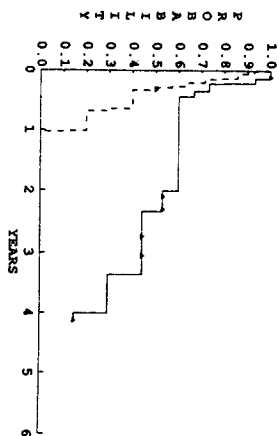


Fig 1. The influence on survival for the presence (---) or absence (—) of one of the chromosomal abnormalities that were correlated with survival (ie, +5; +6; +18; breakpoints 14q11-12; all abnormalities on chromosomes nos. 5 or 17) in patients with B symptoms. This difference is significant ($P = .004$).

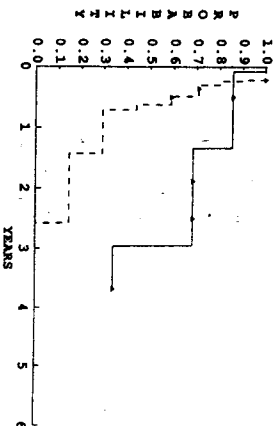


Fig 3. The influence on survival for the presence (---) or absence (—) of one of the chromosomal abnormalities that were correlated with survival (ie, +5; +6; +18; breakpoints 14q11-12; all abnormalities on chromosomes nos. 5 or 17) in patients with no B symptoms and high LDH. This difference is significant ($P = .03$).

ble with previous studies.^{11,12,16} However, in contrast to others,^{10,12,23} we did not find any difference for survival or disease-free survival between patients that had only normal karyotypes, only abnormal karyotypes, or a mixture. Also in contrast with others,¹¹ there was no difference in outcome between patients with only abnormal karyotypes and patients with an admixture of normal cells in the subgroup of the follicular NHL.

Cytogenetic findings in lymphomas might be helpful in unveiling the pathogenesis of these disorders. Several of the breakpoints we and others have found correlate with the presence of known oncogenes. The fact that there are breakpoints that correlate with disease characteristics, but not with known oncogenes, could suggest the presence of new, yet undiscovered, regulatory genes on these chromosomes. Also of potential importance are several correlations with disease characteristics found for combinations of abnor-

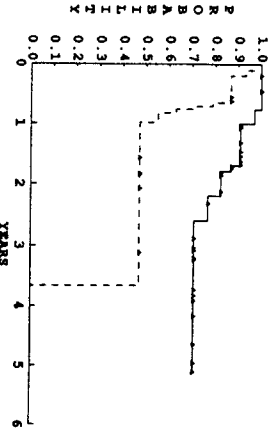


Fig 2. The influence on survival for the presence (---) or absence (—) of one of the chromosomal abnormalities that were correlated with survival (ie, +5; +6; +18; breakpoints 14q11-12; all abnormalities on chromosomes nos. 5 or 17) in patients with no B symptoms and low LDH. This difference is significant ($P = .0008$).

malities involving arms or complete chromosomes, which were not present for specific breakpoints. This suggests that in larger series a significant correlation with disease parameters for a more defined breakpoint might be found. Another possibility is that structural changes on that chromosome related with a particular disease phenomenon are not located on the same place on the chromosome in every patient, or that different changes on that particular chromosome can cause the same manifestation of the disease.

Several chromosomal abnormalities had a strong correlation with disease characteristics (Table 3). A trisomy 3 was significantly correlated with a high-grade histology. Yunis et al¹ found that a +3 was almost exclusively present in follicular large cell NHL; however, in our series, only 1 of 16 patients had this type and 8 had the immunoblastic type. The Fifth Workshop² found a +3 predominantly among diffuse mixed lymphomas. In our series, 25% of the patients with a +3 had this histologic subtype. Recently, a correlation between dup 3p or a +3 with a good prognosis in large cell NHL was reported.²⁴ We did not observe a survival advantage for these patients. Correlations between a trisomy of chromosome nos. 5, 6, 18, all abnormalities on no. 5, the breakpoints 14q11-12, and shorter survival found in a multivariate analysis to be independent of the usual clinical prognostic factors, have not been previously reported. Yunis et al¹ found an association for one of these abnormalities (+18) with the follicular large cell type. The correlations between a t(11;14)(q13;q32) and also for breakpoint 11q13 and elevated LDH was not suggested before and, in our series, was not related with tumor load, as reflected by stage, bulky disease, or B symptoms. Several investigators^{1,2,25} described a correlation between a t(8;14) and high-grade, more specifically small noncleaved NHL. In our series, only two patients had a t(8;14), but they both had a small noncleaved NHL. In contrast to Yunis et al,² patients with a dup 2p or a +2 and large cell NHL had no significantly different treatment outcome compared with the other patients. Analyzing the breakpoints of the chromosomes requires

of the cytogenetic abnormality, we found several significant correlations (Table 4). Breakpoints 14q32 and 18q21 were correlated with a follicular histology. The breakpoints 11q23-24 were correlated with a B-cell phenotype. Bulky disease was correlated with breakpoints 3q21-25 and 13q21-24. Also, B symptoms were correlated with breakpoints 6q11-16. Patients with breakpoints 1q21-25 were less likely to have marrow involvement. Patients with breakpoints at 14q11-12 had a poorer treatment result. Because of the location of the α gene T-cell receptor on 14q11-13 and the poorer outcome in patients with a T-cell lymphoma, this would not be of a surprise; however, only 1 of the 5 patients with this breakpoint had a T-cell NHL. In other studies, breakpoint 6q21-25 was present in the majority of patients with large cell histology^{14,15}, however, only in 33% of our patients with large cell NHL. Also, this breakpoint was reported to be correlated with bone marrow involvement¹⁴; however, this could not be confirmed by our results. In a recent study, several other correlations between chromosomal abnormalities and extranodal localizations of disease including sites of relapse were described as 1p32-36 and marrow infiltration, chromosome no. 14 abnormalities and spleen infiltration, and bone localizations.²¹ These observations were not confirmed in this study, probably because the sites of relapse were not included in our analysis.

In combining all abnormalities on one arm, or all of the abnormalities on one chromosome, we found several significant correlations. Patients with an abnormal 2p had more skin involvement. All patients with an abnormal chromosome no. 5 combined were found to have a shorter survival, as was also detected for patients with a +5. All patients with an abnormal chromosome 6q combined had a significant correlation with B symptoms, also found for breakpoints 6q11-16. The patients with abnormal chromosome no. 14 or 14q combined showed a correlation with the absence of skin

infiltration and, less frequently, stage I disease. This correlation was not found for any specific abnormality involving chromosome no. 14. Levine et al¹³ Cabanillas et al²² and our study observed that patients with an abnormal chromosome no. 17 less often reached a CR and had a shorter survival. However, Cabanillas et al's results were limited to the -17 and isochromosome 17q.²² In addition, we found a correlation with a diffuse histology. Both correlations were also found for 17p. In combining all abnormalities on the short arm of chromosome no. 1, the Fifth Workshop⁹ found a significant correlation with a T-cell phenotype. In our series, only 2 of 9 patients with this abnormality had a T-cell phenotype. Interestingly, of the 27 patients with a follicular lymphoma, only 13 had a (1;4;18) and 14 other patients with a (1;4;18) had a diffuse histology. Although there is a significant correlation in our study between a (1;4;18) and follicular growth pattern, this correlation is reported to be very strong for the patients with follicular small-cleaved NHL.²³ In our study, only one patient had a follicular small-cleaved NHL, which might explain the lower frequency than expected.

We were able to demonstrate several new correlations between chromosome abnormalities and disease characteristics. Also, we observed that the chromosomal abnormalities that were correlated with survival were independent risk factors in a multivariate analysis. This can be explained by the large number of patients studied and the fact that the analysis was done at diagnosis excluding secondary abnormalities, induced by disease evolution or treatment. This is also a possible explanation for the fact that we could not confirm all the abnormalities found by others. Clearly, further studies should be done. With the addition of molecular biologic studies, these data might be of importance in explaining and unveiling more of the pathobiology of malignant lymphoma. Also, the prognostic factors related with survival might be of help in designing new treatment strategies.

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