Chromosome 8, Occupational Exposures, Smoking, and Acute Nonlymphocytic Leukemias: A Population-based Study

Laura Davico, Carlotta Sacerdote, Giovannino Ciccone, Luigi Pegoraro, Simonetta Kerim, Giorgio Ponzi, and Paolo Vineis

Units of Cancer Epidemiology (L. D., C. S., G. C., P. V.) and Pathology (S. K.), Department of Oncology, Ospedale S. Giovanni Battista and University of Torino, and Departments of Genetics (G. P.) and Internal Medicine (L. P.), University of Torino, 1-10126 Turin, Italy

Abstract

In a previous epidemiological study on acute myelocytic leukemia (M. M. Crane et al., Cancer Epidemiol. Biomark. Prev., 5: 639–644, 1996), clonal aberrations in chromosome 8 have been reported to be in excess in smokers and in workers exposed to paints. In that study, cytogenetics was performed after therapy. In our report, we describe a population-based survey on nonlymphocytic leukemias in northern Italy, in which 79 patients (acute myelocytic leukemia, myelodysplastic syndromes, or other nonlymphocytic leukemias) were studied before cytotoxic therapy. We found 9 aberrations involving chromosome 8 (six +8, two −8, and one translocation), whereas abnormalities involving chromosomes 5 and 7 occurred with a low frequency compared with previous studies.

Aberrations involving chromosome 8 were associated with smoking (odds ratio, 6.3; 95% confidence interval, 0.9–42.3; among smokers of 10 or more cigarettes/day: odds ratio, 14.2; 95% confidence interval, 1.4–142.3); +8 aberrations were found in 1 of 24 nonsmokers and in 5 of 38 smokers. Three +8 aberrations were found in 22 subjects potentially exposed to solvents or polycyclic aromatic hydrocarbons.

The low frequency of chromosome 5 and 7 aberrations in our population-based series (compared with other studies) can be attributed to the recruitment before cytotoxic therapies. Aberrations involving chromosome 8 (particularly +8) were associated with smoking habits. Chromosome 8 includes the c-myc oncogene.

Introduction

Known risk factors for AML3 include benzene and ionizing radiation; the role of tobacco smoking, occupational exposure to organic solvents other than benzene, and low-frequency electromagnetic fields is still controversial (1). Several authors have reported an excess of chromosome aberrations among subjects with AML who had been exposed to chemicals and/or mutagens (for a review see Ref. 2).

In a survey among 213 patients affected by AML, Crane et al. (3) found an association between prior cytotoxic therapies, exposure to paints or cigarette smoking, and the presence of chromosome aberrations. In the case of smoking, the association was particularly strong when chromosome 8 was involved, with relative risks of 2.17 (95% CI, 0.72–6.51) for the +8 karyotype and of 1.81 (CI, 0.59–5.50) for the t(8;21) translocation. An excess of t(8;21) translocations was observed also in patients exposed to paints that contain organic solvents (OR, 2.95; CI, 0.82–10.55). Aberrations involving chromosomes 5 or 7 were more common in association with prior cytotoxic therapy, alcohol use, or exposure to pesticides. The study by Crane et al. suggests that different chromosome aberrations may be expression of the action of different leukemogenic agents.

In a previous hospital-based pilot investigation (4), we found a weak association between smoking habits or exposure to PAHs and all chromosome aberrations, with no peculiar pattern of aberrations. We report here on a population-based study involving 79 patients with newly diagnosed nonlymphocytic leukemia or MDS who had not been treated at the time of the execution of the karyotype.

Subjects and Methods

In the context of a multicenter population-based case-control study on hematopoietic cancers in Italy (5), all of the subjects suspected of being affected by leukemia were identified through periodical surveys in the hematology departments of three hospitals in Turin, Italy. Only newly diagnosed cases occurring in the study period (late 1989–1992) were included (both sexes, aged 20–74, residents of the areas under study). In each hospital department, a reference physician was identified and cooperated in case finding. Case ascertainment was based also on periodical surveys in the Pathology Departments. In addition, cancer institutes and departments of hematology and pathology located in Milan and Pavia, Italy (i.e., external to the study areas) were periodically surveyed. A timely recruitment was necessary to keep as high as possible the proportion of cases who were alive at interview. All of the suspected cases were identified and the subjects interviewed; the status of each case was further evaluated after the interview.

Information about the known or suspected risk factors for

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2 To whom requests for reprints should be addressed. At Unit of Cancer Epidemiology, Department of Oncology, Ospedale S. Giovanni Battista, via Santena 7, 1-10126 Turin, Italy. Fax: 11-6706692.

3 The abbreviations used are: AML, acute myelocytic leukemia; MDS, myelodysplastic syndrome; OR, odds ratio; CI, confidence interval; PAH, polycyclic aromatic hydrocarbon.

the pathologies under investigation was collected through person-to-person interviews. Interviews were done preferably at the patient’s home. The only exceptions were interviews with patients who were seriously ill, which were mostly done in the hospital.

Techniques for the motivation of subjects to participate, such as contacts with the general practitioners, were applied. They were particularly successful in keeping the response rate high.4

The interview was face-to-face and lasted approximately 1 h. The personnel in charge of the interviews were trained specifically for this study through a residential 3-day course at the Siena University.5

The whole occupational and smoking history of each patient was investigated. Each working period lasting more than 6 months was sought, and detailed information was collected on job titles. Up to 12 different jobs were recorded for each subject. Job titles were coded according to the ILO coding system (6), and productive activities were coded according to the United Nations system (7). Each change in smoking habits was recorded; we investigated the number of cigarettes smoked, dates of start and quitting, and the presence of a filter. “Non-smokers” were subjects who had never smoked.

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Cytogenetic analysis was performed routinely for most patients with nonlymphocytic leukemia or MDS for diagnostic purposes. The analysis was done in three services of genetics: the pathologies under investigation was collected through person-to-person interviews. Interviews were done preferably at the patient’s home. The only exceptions were interviews with patients who were seriously ill, which were mostly done in the hospital.

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smokers and 8 of 38 smokers (age-adjusted OR, 6.3; 95% CI, 0.9–42.3). Aberrations +8 were one in nonsmokers and five in smokers, whereas two −8 aberrations and one translocation t(8;21) were observed in smokers only. Table 1 shows the relationship between chromosome 8 aberrations and the number of cigarettes smoked. Interestingly, the association between smoking and aberrations was much stronger for those who only smoked unfiltered cigarettes: among 38 smokers, aberrations were 5 of 6 subjects who had never used a filter versus 13 of 32 subjects who had ever used a filter (OR, 7.2; 95% CI, 1.3–39.0). Of the five aberrations in smokers of unfiltered cigarettes, two were in chromosome 8.

Twenty-one subjects (19 men, 2 women) had held jobs involving potential exposure to organic solvents or PAHs. Of these, 16 (76%) had a normal karyotype, and 5 (24%; all men: 1 was aged <45, and 4 were aged ≥65) had the aberrations shown in Table 2, three of which involved chromosome 8. No particular pattern was evident in the subjects who had worked in the electric/electronic industry or in hairdressing. A more formal evaluation of the risk associated with occupational exposures is impaired by small numbers, the unbalanced distribution by age groups, and the concurrent exposure to tobacco smoke.

The association between chromosome aberrations and smoking was equally distributed among AML, MDS, and other nonlymphocytic leukemias (P > 0.05).

Discussion

Several studies (1–3) have suggested that exposure to chemicals and/or mutagens can increase the risk of AML through the induction of chromosome aberrations. The strongest hypothesis is that each abnormality is attributable to a specific etiological agent. The best example is represented by prior cytotoxic treatment, which is associated with the loss of all or part of chromosomes 5 and 7 (3).

Our investigation had two advantages over the previous ones, i.e., it was population-based (all incident cases were identified), and leukemia cases were recruited before treatment. The cytogenetic tests were not influenced by therapies, and this can explain the low frequency of losses of chromosomes 5 or 7 in comparison e.g., with the paper by Crane et al. (3). The frequency of +8 aberrations (6 of 62) was comparable to that found in other series (approximately 8–9%; Refs. 3 and 10).

We have found a rather strong association between smoking habits and chromosome 8 aberrations. Five +8 aberrations were observed in smokers and one in a nonsmoker; three of the five occurred in subjects occupationally exposed to solvents or PAH. The association with smoking was stronger in smokers of unfiltered cigarettes. We can hypothesize that exposure to PAHs that occurs through tobacco smoking (particularly of unfiltered cigarettes) or for occupational reasons, can induce nonlymphocytic leukemia by interfering with chromosome 8. Our observation is of interest also because chromosome 8 includes the c-myc oncogene. The translocation t(8;14) that has been observed in Burkitt's lymphoma results in the translocation of the c-myc cellular proto-oncogene from chromosome 8 to chromosome 14 near the immunoglobulin heavy chain gene, which results in the activation of the c-myc gene (11).

Our observation may have alternative explanations. For example, rather than being involved in the causal pathway, chromosome 8 aberrations could be seen in excess among leukemia patients as a consequence of clonal selection. However, it is not clear why clonal selection should be more frequent in smokers than in nonsmokers. Clearly, this issue must be clarified in the context of longitudinal studies. Smoking has been associated with several types of genotoxic effects in animals (12) and in humans, including the observation of micronuclei (13), chromosome aberrations in lymphocytes (14, 15), and genetic alterations at chromosomal sites containing oncogenes or tumor suppressor genes in bronchial epithelium (16).

References

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