Correlation between Selected Environmental Exposures and Karyotype in Acute Myelocytic Leukemia

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Abstract

Many bone marrow cytogenetic abnormalities in acute myelogenous leukemia (AML) are tumor specific, clonal, nonrandom, and related to prognosis; it has been hypothesized that they may be markers of exposure to etiological agents. A previous report from our institution revealed several such associations; the purpose of the current study was to determine whether previous findings were present in a new group of patients. Subjects included 84 newly diagnosed AML patients (French-American-British M, and M2); exposure data were gathered using self-report questionnaires at the time of registration. Two sets of comparisons were made: (a) patients with all (AA) or some (AN) cytogenetically abnormal cells versus those with normal karyotypes (NN) and (b) patients with specific abnormalities [-5/5q-, -7/7q-, +8, t(8;21)] versus all others. Odds ratios (ORs) were 4.64 for the association between prior cytotoxic therapy and -5/5q- and 6.38 for the association with -7/7q-, but were <1.00 for +8 and t(8;21). There were no ORs >2.0 for specific abnormalities in any of the other exposures evaluated (cigarette smoking, alcohol use, occupational exposure to organic chemicals, paints, or pesticides/herbicides), with the exception of exposure to paints and -7/7q- (OR, 7.50). The ORs for AA/AN versus NN patients were 1.43 and 3.81 for smoking and alcohol use, and weak dose-response trends were present. The most consistent positive associations between the two series were for prior cytotoxic therapy (-5/5q-; -7/7q-), cigarette smoking (AA/AN versus NN) and alcohol use (AA/AN versus NN). Reasoning from the known association between prior cytotoxic therapy and -7/7q-, we would have predicted relatively high ORs (>4.0) if specific abnormalities acted as markers for the exposures assessed, but none were present. However, in both series, AA/AN patients were more likely to smoke and use alcohol than were NN patients, and weak dose-response patterns were present for both. This finding suggests that both smoking and alcohol use may play a role in the pathogenesis of cytogenetic abnormalities in AML-M5/M2; however, the mechanism by which they work and whether they are involved in the etiology of these diseases remain unclear.

Introduction

Chromosomal abnormalities are detectable in the bone marrow of most patients with AML3 (1, 2). Abnormalities are clonal, nonrandom, confined to tumor tissue, and, for the most part, disease-specific (3). Previously detectable abnormalities disappear from the marrow of patients in remission, and their reappearance presages relapse (4). Sites of abnormalities map very closely to locations of proto-oncogenes (3). Many of these same abnormalities occur in preleukemic conditions, some of which are at exceptionally high risk of evolving into acute leukemia (5).

In recent years, extensive research has indicated that chromosomal abnormalities have prognostic significance in leukemia independent of other factors such as age or histological subtype (6, 7). Patients with 100% abnormal cells (AA) in their marrow have a much reduced survival compared to those with cytogenetically normal marrow (NN); patients with mixtures of abnormal and normal-appearing cells (AN) have intermediate prognoses. Furthermore, this survival advantage is associated with specific abnormalities: rearrangements of chromosome 16 inv(16) and translocations between chromosomes 8 and 21 t(8;21) are relatively favorable; normal marrow, translocation between chromosomes 15 and 17, and loss of the Y chromosome in males carry an intermediate prognosis; abnormalities involving the long arm of chromosome 11 (11q23), loss of all or part of chromosomes 7 (-7/7q- or 5 (-5/5q-) are unfavorable (5–7).

Because chromosomal abnormalities have clinical and prognostic relevance, it has been proposed that they may have etiological importance as well, and that specific exposures may be associated with particular karyotypes (8, 9). Secondary leukemias due to prior cytotoxic therapy have a high frequency of -7/7q- as compared to de novo cases (3, 10). A population-based case-control study has revealed an unadjusted OR of 7.91 for cigarette smoking in patients with the same abnormality versus nondiseased controls (11). Other researchers have reported a history of occupational exposure to mutagens to be more frequent in AA/AN versus NN patients (10, 12–14), but...
these findings have not always been consistent (15, 16), and none of these studies included a nondiseased control group.

The current study seeks to extend results from one of the above uncontrolled studies (10). We evaluated prior cytotoxic therapy, cigarette smoking, alcohol use, and exposure to solvents and chemicals as risk factors in a series of 84 patients with acute myeloblastic leukemia FAB M1 and M2 and compared them to data derived from 123 patients in our original series with this diagnosis. We hypothesized that AA/AN patients were more likely to have been exposed to these agents than NN patients, and that exposure would be associated with a higher prevalence of abnormalities involving chromosomes 5 and 7.

**Patients and Methods**

**Patients.** Patients with confirmed diagnoses of acute myeloblastic leukemia (FAB subtypes M1, M2, and M3) were derived from two sources. The most recent group of patients consisted of 84 AML patients enrolled at MDACC between 1986 and 1990, who completed a self-administered risk factor questionnaire that is given to all newly registered patients at MDACC. About 60% of all newly registered patients completed the questionnaire (17, 18). The other group of patients was identified from a larger series of 440 ANLL patients enrolled for induction therapy by the Leukemia Service at MDACC between January 1, 1976 and June 1, 1983. An attempt was made to interview these individuals or their relatives either by in-person telephone, or mailed questionnaire between June 1982 and June 1984. Results have been reported previously for the entire group of ANLL patients (10).

**Chromosomal Abnormalities.** Cytogenetic studies are routinely obtained for all newly diagnosed patients seeking therapy at MDACC. The procedures in effect at the time both groups were presented have been described elsewhere (4). Briefly, unstimulated bone marrow cells were cultured for 24, 48, and 72 h in Ham's F10 medium supplemented with 10% fetal bovine serum. Peripheral lymphocytes were cultured in the above medium containing phytohemagglutinin (0.18 mg/ml). At the end of the culture period, demecolcine (0.04 µg/ml) was added for an additional 30 min to arrest cells at metaphase. Cells were then treated with a hypotonic solution of 0.075 M potassium chloride for 15 min, fixed with 3:1 methanol-glacial acetic acid, and dropped on glass slides to air dry. The slide preparations were Giemsa banded to allow differentiation of individual chromosomes according to the procedure of Seabright (19). Whenever possible, a minimum of 25 Giemsa-band metaphases were analyzed for chromosomal abnormalities, and such abnormalities were required to be in at least two cells to be counted. Supplementary quinacrine banding was used for some patients. Abnormalities were described using the nomenclature established by the International System for Cytogenetic Nomenclature (20).

**Exposure Assessment.** Each medical record was reviewed for evidence of a previous cancer or other condition that required cytotoxic therapy (chemotherapy, irradiation, or radiomimetic drugs). Exposure questionnaires, completed either by the patient or a family member, requested information concerning use of tobacco (cigarettes, other), use of alcohol (beer, wine, hard liquor), occupation, and occupational and avocational exposure to benzene and other organic solvents, paints, pesticides, and other substances such as dyes, glues, or varnishes.

Patient or surrogate interviews (early series) and self-report responses (later series) were obtained without knowledge of cytogenetic status; all exposure data were coded and entered into a data base without knowledge of the cytogenetic status.

The occupation in which a subject spent the longest number of years was coded according to the Dictionary of Occupational Titles at the level of the first digit. Alcohol was coded as ever/never consumption. Two beers, two glasses of wine, or two drinks were considered to be 1 ounce of alcohol, and these were totaled to obtain the number of ounces of alcohol consumed per month and then divided by 30 to obtain an average daily consumption. Cigarette smoking was coded as ever/never, and the number of cigarettes smoked per day was also noted. Chemical exposures were coded as yes or no.

**Statistics.** We made no attempt at separating cytogenetics results into mutually exclusive categories; each abnormality was treated as an independent event, and thus some patients with multiple abnormalities may be present in more than one subgroup.

ORs and 95% confidence intervals and trend tests (Mantel extension of Mantel-Haenszel procedure) were calculated using EPI INFO (Version 6; U. S. Distributors Inc., Stone Mountain, GA). ORs were first computed for AA/AN versus NN patients, and then for each specific abnormality versus all others, e.g., $q_{3q}$ versus all others without this abnormality. Logistic models were fit using EPILLOG software (EPICENTER SOFTWARE, Pasadena, CA).

**Results**

There were 84 patients from the later series who met the eligibility criteria [acute myeloblastic leukemia (FAB subtypes M1, M2, and M3)], age 18 years or older, cytogenetic data available, completed risk factor questionnaire) and 129 patients from the early series. Fifty-six percent of the responses in the early series were from relatives; all responses in the new series were self-reported. The proportions of abnormal karyotypes were similar in both series (55 and 58% for the early and later series, respectively) as were race (5 and 7% black, respectively) and sex (66% and 58% male, respectively). There was a higher proportion of patients ages 60 years and older in the later (44%) versus the early group (33%). These data are shown in Table 1.

Twenty patients (9 in the early series and 11 in the latter series) had received prior cytotoxic therapy; the reasons included prior malignancy (one breast cancer, two ovarian cancers, one cancer of the tongue, one ocular melanoma, five Hodgkin's disease, one uterine, one multiple myeloma, one prostate, one laryngeal, and one stomach), polycythemia (one patient), thyroid disease (one patient), and an ill-defined problem of the sinuses (one patient). The proportions of nonsmokers (42% in the early and 51% in the later series) and teetotalers (30% and 25%, respectively) were similar in both groups. However, a much higher proportion of respondents in the later series were coded as exposed to organic chemicals (45% versus 20%) and pesticides (27% versus 10%); conversely, a higher proportion of respondents in the early series reported exposure to dyes, glues, or lacquers (14% versus 5%), and the proportion of those exposed to paints was similar (10% in the early series and 8% in the later one).

ORs for AA/AN versus NN patients are shown in Table 2. The OR (and 95% confidence interval) for any prior cytotoxic therapy was 2.51 (0.82, 9.16). There were no apparent associations between chromosomal abnormalities and exposure to organic chemicals, pesticides, paints, and dyes/glues/lacquers or employment in blue collar occupations. There was a trend for an increasing proportion of AA/AN patients with increased use of both cigarettes and alcohol; ORs for the highest use group of...
smokers (>40 cigarettes/day) and alcohol users (>1.0 ounce/day) were 4.23 (0.81, 41.74) and 3.13 (0.99, 10.50), respectively.

In the 1976–1983 series, the distribution of AA/AN versus NN patients by smoking category was: nonsmokers (27/27), 1–20 cigarettes/day (14/16), 21–40 cigarettes/day (20/11), and >40 cigarettes/day (8/2); the corresponding ORs were 1.0, 0.9, 1.8, and 4.0 (P for trend = 0.07). The corresponding numbers for the more recent series were 23/20, 16/10, 6/4, and 1/0, respectively; the ORs for these categories were 1.0, 1.4, 1.3, and undefined (P for trend = 0.48). The data for alcohol followed a similar pattern. The numbers of AA/AN and NN patients in the early series were nonusers (16/22), 0.1–<0.5 ounce (30/19), 0.5–1.0 ounce (13/9), and >1.0 ounce (12/5); the corresponding numbers for the later series were 7/14, 37/18, 49/14, and 49/14, respectively. The ORs for smoking and alcohol consumption, the dose-response trends were stronger in the patients of the earlier series than in the patients of the later series.

Associations between exposures and specific chromosomal abnormalities are shown in Table 3 for each series separately and for both combined, adjusted by logistic regression for age, sex, and, where appropriate, prior cytotoxic therapy. The overall OR for prior cytotoxic therapy and –5/5q– was 4.38 (1.29, 14.89) and for –7/7q–, 9.68 (3.18, 29.49); ORs were above 2.0 for both abnormalities in each series. No other exposure-abnormality relationship demonstrated that same pattern (≥2.0 overall, >2.0 in both series). Overall ORs were >2.0 for +8 and smoking (2.17), –5/5q– and alcohol use (2.01), –7/7q– and alcohol use (2.08), t(8;21) and exposure to paints (2.95), and for –5/5q– and exposure to pesticides or herbicides (2.06).

The OR for cigarette smoking and AA/AN in both groups combined was 1.56, and this was consistent in both the early (1.47) and the later series (1.43). The ORs for smoking and specific abnormalities were moderately elevated in both the early and later series for –5/5q– (1.49 and 1.47, respectively), for +8 (2.06 and 1.62, respectively), for t(8;21) (1.73 and 2.40, respectively) but not for –7/7q– (0.86 and 0.67, respectively).
Environmental Exposures and Karyotype in AML

6-12

Environmental Exposures and Karyotype in AML

I, Unadjusted

Other two chromosomal abnormalities that were considered; atrogenic environmental exposures and -5/5q- or -7/7q- or added to the model). but there was little evidence of confound-

Discussion

In a logistic model comparing AA/AN versus NN patients that also contained age and sex, the ORs for prior cytotoxic therapy, ever smoked, ever use of alcohol, and exposure to organic chemicals were 4.76 (1.39, 16.37), 1.37 (0.74, 2.53), 2.85 (1.42, 5.74), and 1.00 (0.53, 1.90). There was a suggestion that prior cytotoxic therapy was confounded by cigarette smoking (the OR increased from 2.99 to 4.66 when smoking was added to the model), but there was little evidence of confounding for any of the other variables.

Table 4: ORs and 95% confidence intervals for selected exposures and specific abnormalities in 213 AML patients evaluated at M. D. Anderson Cancer Center, by period of diagnosis

<table>
<thead>
<tr>
<th>Occupational exposure to organic chemicals</th>
<th>1976–1983 (n = 129)*</th>
<th>1986–1990 (n = 84)*</th>
<th>Both groups combined a, b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior therapy</td>
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<tr>
<td>AA/AN</td>
<td>7.24</td>
<td>1.29</td>
<td>2.99 (1.02,8.75)</td>
</tr>
<tr>
<td>-5/5q-</td>
<td>2.88</td>
<td>4.64</td>
<td>4.38 (1.29,14.89)</td>
</tr>
<tr>
<td>-7/7q-</td>
<td>12.91</td>
<td>6.38</td>
<td>9.68 (3.18,29.49)</td>
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<tr>
<td>+X</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
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<tr>
<td>t(8;21)</td>
<td>1.13</td>
<td>0.74</td>
<td>0.91 (0.11,7.75)</td>
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<tr>
<td>Ever smoker</td>
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<tr>
<td>AA/AN</td>
<td>1.47</td>
<td>1.43</td>
<td>1.56 (0.88,2.76)</td>
</tr>
<tr>
<td>-5/5q-</td>
<td>1.49</td>
<td>1.47</td>
<td>1.74 (0.56,5.46)</td>
</tr>
<tr>
<td>-7/7q-</td>
<td>0.86</td>
<td>0.67</td>
<td>1.02 (0.36,2.92)</td>
</tr>
<tr>
<td>+X</td>
<td>2.06</td>
<td>1.62</td>
<td>2.17 (0.72,5.61)</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>1.73</td>
<td>2.40</td>
<td>1.81 (0.59,5.50)</td>
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<tr>
<td>Alcohol use, ever</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AA/AN</td>
<td>2.16</td>
<td>3.81</td>
<td>2.63 (1.37,5.08)</td>
</tr>
<tr>
<td>-5/5q-</td>
<td>2.18</td>
<td>1.64</td>
<td>2.01 (0.51,7.87)</td>
</tr>
<tr>
<td>-7/7q-</td>
<td>2.00</td>
<td>1.04</td>
<td>2.08 (0.59,7.27)</td>
</tr>
<tr>
<td>+X</td>
<td>0.47</td>
<td>und</td>
<td>0.93 (0.30,2.90)</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>1.46</td>
<td>0.68</td>
<td>0.89 (0.26,3.00)</td>
</tr>
<tr>
<td>Occupational exposure</td>
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<tr>
<td>to organic chemicals</td>
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<td></td>
<td></td>
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<tr>
<td>Paints</td>
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<td></td>
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<tr>
<td>AA/AN</td>
<td>1.18</td>
<td>0.97</td>
<td>0.93 (0.50,1.75)</td>
</tr>
<tr>
<td>-5/5q-</td>
<td>0.72</td>
<td>1.25</td>
<td>1.11 (0.35,3.56)</td>
</tr>
<tr>
<td>-7/7q-</td>
<td>0.38</td>
<td>1.97</td>
<td>1.01 (0.39,3.29)</td>
</tr>
<tr>
<td>+X</td>
<td>1.05</td>
<td>1.24</td>
<td>1.02 (0.33,3.15)</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>2.50</td>
<td>0.59</td>
<td>1.15 (0.39,3.40)</td>
</tr>
<tr>
<td>Pesticides, herbicides</td>
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</tr>
<tr>
<td>AA/AN</td>
<td>2.01</td>
<td>1.87</td>
<td>1.81 (0.65,6.49)</td>
</tr>
<tr>
<td>-5/5q-</td>
<td>0.00</td>
<td>2.68</td>
<td>1.43 (0.27,7.42)</td>
</tr>
<tr>
<td>-7/7q-</td>
<td>0.00</td>
<td>7.50</td>
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</tr>
<tr>
<td>+X</td>
<td>2.62</td>
<td>0.00</td>
<td>1.34 (0.28,5.52)</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>4.89</td>
<td>0.00</td>
<td>2.95 (0.82,10.55)</td>
</tr>
<tr>
<td>a Unadjusted OR</td>
<td></td>
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<tr>
<td>b Adjusted by logistic regression for age, sex, and prior cytotoxic therapy in lower five exposures.</td>
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<td></td>
<td></td>
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<td>c, d undefined.</td>
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</table>

Another explanation for the lack of positive findings is that the exposures examined were not leukemogenic. The search for noniatrogenic risk factors in leukemia has been disappointing, and is currently limited to occupational exposure to benzene and ionizing radiation and perhaps to other organic solvents and chemicals, and possibly cigarette smoking. Benzene is a well-documented leukemogen, although there is controversy as to the intensity of exposure required to induce disease (25, 26).

In a case series and reports have linked abnormalities of chromosomes 5 and 7 with benzene exposure. Van den Berghe et al. (27) reported cytogenetic studies from two benzene-exposed workers diagnosed with malignant blood disorders who had a preleukemic phase; one individual had t(9;10) and t(4;15) abnormalities superimposed upon a constitutional abnormality of t(3;16), whereas the other was -7/7q-. Two benzene-exposed patients from a series of secondary leukemias in France (28) were AA/AN; one patient was -21 with two marker chromosomes and loss of another chromosome, possibly chromosome 8; the other had losses of chromosomes 5, 8, and 17 as well as 6q- and 7q- and a ring chromosome. By contrast, none of the 12 ANLL patients with well-documented occupational exposures in our previous study (10) had a lesion of either chromosome 5 or 7. A case-control study of AML, chronic myelo-
and myelodysplastic syndrome cases and both clinic and population-based controls reported only two patients with definite or probable benzene exposure, both of whom had chromosomal abnormalities (type not mentioned); the OR for benzene exposure was 1.7 (0.6, 5.5) in males (29).

Eight patients in the above-mentioned French study (Ref. 28; including the two already described) were exposed either to benzene, solvents, or hydrocarbons; seven of them were AA/AN, four were -5q/-5q, and two were -7q/-7q. Unfortunately, it was not possible to estimate ORs for specific abnormalities. The OR for -5q/-5q and solvent exposure in a case-control study involving 70 patients (calculated by us from Tables 3 and 4 in the original source) was 0.72 (0.01, 6.67; Ref. 30), which was quite close to the OR for chemical exposure of 0.91 (0.29, 2.84) in a case-control study of ANLL patients with abnormalities of chromosomes 5 and/or 7 and NN controls (16). These results are similar to those for solvent exposure in Table 3 (OR, 1.11 and 1.14 for -5q/-5q and -7q/-7q, respectively) but much lower than the 4.37 (1.77, 10.29) for lesions of chromosomes 5 and/or 7 in the Fourth International Workshop on Chromosomes in Leukemia (14).

It has been proposed (31, 32) that cigarette smoking is a risk factor for myeloid leukemia. A large population-based case-control study by Sandler et al. (11) revealed a very low excess risk for ever having smoked cigarettes in AML patients (OR calculated by us from their Table 1 was 1.18), although the risk increased with amount smoked (from 1.21 for ≤1 packs/day to 1.42 for >2 packs/day; Ref. 11). The OR for smoking in M1 and M2 patients with -7q/-7q versus all other patients was calculated from Table 5 by us to be 4.66 (and was reported by the authors to be 7.12 in comparison to the nonleukemic controls); the analogous OR for +8 was 1.30 (2.11 versus controls). By contrast, the corresponding values from the current study were 1.02 (-7q/-7q) and 2.17 (+8).

The OR for having ever used alcohol in AA/AN versus NN patients in the current study was 2.63 (1.37, 5.08), and was present in both the early (2.16) and the later series (3.81). None of the four specific abnormalities evaluated in this study were associated with alcohol use in both series. A small case-control study (60 matched pairs) by one of us (M. M. C.) noted ORs of 1.5, 1.2, and 2.2 for consumption of beer, wine, and hard liquor, respectively; however, the OR for current use of alcohol in M1/M2 patients was 0.7 (33). Thus, the relevance of alcohol to the overall risk of leukemia is unclear.

In addition to the lack of well-defined leukemogenic exposures, another possible source of error is the potentially high false-negative rate for detecting chromosomal abnormalities. Studies using high-resolution methods (34) suggest that the proportion of diploid patients is much lower than in this study, perhaps on the order of 5-10%. The effect of this misclassification error would be strongest in the AA/AN versus NN comparisons and would depend on the distribution of exposures in the incorrectly classified NN patients. Comparisons involving specific abnormalities versus all others (Table 3) would not be affected unless certain abnormalities in exposed individuals were less likely to be detected, which would force ORs toward the null.

A final potential explanation for our lack of positive findings is the differing data collection methods between the two data sets (high proportion of surrogate respondents in the early data; substantial nonresponse rates in both). In general, the ORs based on self-reports were greater than or equal to those based on surrogate responses for all exposure variables. However, the magnitude of the differences was small, and it seems unlikely that the high proportion of surrogate respondents in the early data was responsible for the lack of exposure abnormality associations. As for the second patient group, evaluations of the overall data base have indicated that respondents are representative of all MDACC patients with respect to age, sex, and race and that the questionnaire is reasonably reliable (17, 18). Finally, we note that both the investigators and the respondents

\* Unpublished data.
were blind to the cytogenetic status of the subjects at the time of data collection.

On the other hand, the experience of patients in our sample may be quite different from a population-based sample of AML-M2/M2 patients, since the catchment area and referral patterns for these diseases at MDACC are not well defined. The proportion of AA/AN patients in the current study was quite similar to that of AML-M2/M2 patients in the population-based study of Sandler et al. (Ref. 11, 56% versus 58%, respectively) as were the proportions of -7/-7q (10% versus 7%) and +8 (9% versus 8%) patients. Finally, cytogenetic studies were not available for a significant number of patients (5–10%) due to insufficient metaphases and other technical reasons. To what extent this influenced the results is unclear.

A recent review of cytogenetic abnormalities and occupational exposures also noted inconsistencies among reports. The authors attributed these inconsistencies to differences in ascertainment of patients, definition of exposure, and lack of appropriate controls and consistent data collection methods. The authors concluded that the optimal approach to fully evaluate these issues.

References

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