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Chromosome Pattern and Survival in Acute Non-Lymphocytic Leukaemia in Relation to Age and Occupational Exposure to Potential Mutagenic/Carcinogenic Agents

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The bone marrow karyotype was investigated in 98 patients with acute non-lymphocytic leukaemia (ANLL). The patients were divided into two groups according to age.

(1) 47 patients were 20–54 (median 40) years old. 21 had a history of occupational exposure to chemical solvents, insecticides, or petrol products. and 26 were considered occupationally not having been exposed to such agents. In 4 exposed patients (19%) all bone marrow cells had clonal chromosomal aberrations (designated AA), while also 4 of the non-exposed patients (15%) were AA. Thus in young ANLL patients. there was no significant association between occupational exposure to potential mutagenic/carcinogenic agents and the AA constitution of the leukaemic cells.

(2) 51 patients were 55 years of age or older (median 65 years). 16 were exposed and 8 of these (50%) had the AA constitution. 35 patients were non-exposed and only 4 (11%) were AA. It is known from previous studies that the survival of ANLL patients with AA is extraordinarily short. Accordingly the overrepresentation of AA in exposed patients 55 years or older, was associated with a shorter survival than that of the non-exposed elderly patients. The results suggest that etiologic factors may influence the clinical course of ANLL. especially in elderly patients.

Key words: acute leukaemia – cytogenetics – occupational exposure – survival

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Adult acute non-lymphocytic leukaemia (ANLL) is characterized by the incidence of chromosome abnormalities in some 50% of the cases (First International Workshop on Chromosomes in Leukemia 1978); about half of these patients have a mixture of normal and abnormal bone marrow metaphases (AN) and half have only abnormal metaphases (AX). It is known that survival is especially short in the AA patients (Sakurai & Sandberg 1976, First International Workshop on Chromosomes in Leukemia 1978, Mitelman et al 1978, 1981).

Chromosomal abnormality is decidedly more common in patients with a history of occupational exposure to potential mutagenic/

carcinogenic agents than in those without such exposure (Mitelman et al 1978, 1979, 1981). Below we present data indicating that the presence or absence of chromosomal abnormality may be related to age: at the time of diagnosis, the proportion of **AA** patients is especially large in exposed patients who are 55 years or older.

MATERIAL AND METHODS

This report is based on 98 adult patients with ANLL (47 women and 51 men) aged 20–84 years (median 56 years) in whom the bone marrow karyotype was established by banding technique. and whose case records contained sufficient information on present or previous occupations to make it possible to classify each of them as either professionally exposed or not exposed to mutagenic/carcinogenic chemical agents. The material comprised about 75–80 % of all ANLL patients in the age group studied who were treated at our hospital during the period 1972–1981. About 20–25 % of the total number of patients studied cytogenetically during this period had to be excluded because ambigous or no data were available regarding their previous profession(s) or because chromosome banding examination failed.

The case records of all patients were reviewed and the occupation categorized by one of us without any knowledge of the clinical and cytogenetic data. The exposure criteria have been described and discussed previously (Mitelman et al 1978. 1981). Whenever possible, the information contained in the case records was supplemented by interviews with patients or relatives. or both. Social and private habits were not considered. Patients with leukaemia developing after treatment for another malignant disease. or after a myeloproliferative disorder, were not included. The patients were divided into 2 categories: exposed and non-exposed. Patients occupationally exposed to chemical solvents. insecticides, and petrol products or their combustion residues were referred to the exposed groups. The non-exposed group included mainly house-wives, students and white-collar workers but also some other occupations were represented where no history of exposure to chemical agents was apparent.

The chromosomes were studied at the time of diagnosis in direct bone marrow preparations or after short term (12–20 h) cultures of bone marrow: the preparation and staining methods were described previously (Mitelman et al 1981). Only clonal chromosomal aberrations were recorded. An abnormal clone was defined as at least 2 cells with the same extra chromosome or structural rearrangement, or 3 cells with the same missing chromosome. The detailed karyotype findings in 89 of the patients were reported previously (Mitelman et al 1981).

In the total material of 98 patients the number of metaphases analyzed varied between 5–108 (mean 30). The patients were divided into 2 groups: 20 patients with abnormal metaphases only and 78 patients with either only normal metaphases or a mixture of normal and abnormal metaphases. The mean numbers of metaphases analyzed in the 2 groups were 29.3 and 29.7 respectively.

All patients were classified according to the criteria established by the French-American-British (FAB) cooperative group [Bennett et al 1976). Survival time was calculated from the day of diagnosis. Response to treatment was not evaluated since different chemotherapy schedules were used during the period of study.

RESULTS

The proportions of patients with abnormal metaphases only **(AA)** were recorded in 2 age groups. 1 group comprised 47 patients 20–54 years old (median 40 years) and the other group 51 patients aged 55 years or older (median 65 years). Among **21** exposed patients in the young age group.

TABLE 1

Number** of AA-patients* **(in *whom all bone marrow cells had clonal chromosome aberrations)* *in relation to occuparional exposure and age

	Age	
	20–54 years	≧ **55** years
Exposed patients	4/21 (19%)	8/16 (50 %)*
Non-exposed patients	4/26 (15%)	4/35 (11 %)
Total no. of patients	47	51

* $P < 0.01$

there were 4 (19%) with the AA constitution. 4 out of the 26 non-exposed young patients (15%) had this chromosomal pattern, i.e. the proportion of AA patients was similar in young exposed and non-exposed patients.

In the old age group. 8 out of 16 exposed patients had the AA-constitution (50%) whereas only 4 out of 35 non-exposed elderly patients (11%) were AA. The difference between exposed and non-exposed elderly patients is significant ($\chi^2 = 9.08$. $P = 0.01$). The results are summarized in Table 1. Because there was a predominance of men (12 men and 4 women) in the group of elderly exposed patients compared to the non-exposed elderly group (17 men and 18 women) it was considered possible that the AA constitution might be characteristic for elderly men with ANLL, thereby explaining the difference between exposed and non-exposed patients in the old age group. However, among the non-exposed elderly nine out of 17 had the AA constitution (52%) whereas 7 out of the 12 exposed elderly men (58%) had this cytogenetic pattern ($\chi^2 = 7.13$, $P < 0.01$). Thus the over-representation of the AA constitution among elderly patients was related to exposure but not to sex distribution.

As expected, the different frequency of AA-patients was associated with a different prognosis in the exposed and non-exposed elderly patients. 15 exposed (median age 63 years) and 34 non-exposed patients (median age 68.5 years) in the old age group have been followed after diagnosis. All exposed patients died within 9 months with a median survival time of 2 months. Among the 34 elderly non-exposed patients, 10 survived for 9 months or longer with a median survival time of 4.5 months ($P = 0.02$). The median survival in the young exposed and non-exposed patients was not significantly different, 11 and 9 months. respectively.

DISCUSSION

Most of the patients in the present study were analyzed with techniques that do not yield an adequate number of metaphases with elongated chromosomes, and therefore subtle rearrangements. such as those recently reported by Yunis et al (1981). would have been overlooked. It is therefore possible that the incidence of chromosomal abnormality is underestimated. Nevertheless, the data collected in this investigation support observations made previously by us and others. We have shown that patients with a history of occupational exposure to potential mutagenic/carcinogenic agents have a higher incidence of chromosomal abnormality in their leukaemic cells than those without any such history (Mitelman et al 1978, 1979. 1981). Thus. clonal chromosomal aberrations were present in 39 of 52 (75%) exposed patients, but in only 35 of 110 (32%) non-exposed patients. This observation was recently confirmed by Golomb et al (1982). These authors analyzed 74 patients on the basis of occupational data classified in the same manner as by our group and found that 25 of the 58 (43%) non-exposed patients had a clonal chromosomal abnormality, compared with 12 of 16 (75%) exposed patients, i.e. similar figures as found by our group. The present stud! contributes the additional information that the proportion of AA-patients is significantly higher among elderly exposed, patients. compared to non-exposed patients of this age group. Such difference was not found among younger ANLL patients.

The reason(s) why chromosome aberrations develop more frequently in exposed as compared to non-exposed patients, and the virtual absence of cells with a normal karyotype in a large proportion of elderly exposed patients can only be speculated upon at present. One possibility is that the rate of the chromosomal progression from a normal to an abnormal karyotype may be influenced by the type of exposure, or age itself, or both. This idea may be supported by some cytogenetic observations in animals and man: studies on experimental tumors have demonstrated that these may start with a normal karyotype that eventually changes to an abnormal one, by a predetermined stepwise karyotypic evolution (Mitelman 1972), and the rate of this chromosomal progression may depend on the inducing agent. Thus, chemically induced sarcomas of the rat are characterized by a much higher incidence of normal karyotypes than histologically identical virus-induced sarcomas (Mitelman 1971, Mitelman & Levan 1972, Levan & Levan 1975). In this context it may be important to recall that almost all patients with acute leukaemia after previous cytotoxic and/or radiation therapy for a primary malignancy had chromosomally abnormal clones when bone marrow cells were studied in the leukaemic phase (Rowley et al 1981).

It is possible that in addition to the inducing factor, age may also influence the rate of the chromosomal evolution from a normal to an abnormal karyotype. If mitotic errors of DNA-damage more often occur spontaneously, or are produced more easily in older individuals, the likelihood that an abnormal clone emerges will be increased. Indeed, there is some evidence supporting both possibilities. Thus, the frequency of hyper-and hypodiploid cells, i.e. the products of non-disjunctional even (Jarvik et al 1976, Fitzgerald & McEwa 1977) as well as structural chromosom aberrations (Hedner et al 1983) have bee found to be age-related. There is also ev dence that aging cells are more sensiti to the effects of DNA-damaging agen Studies of human diploid fibroblasts fro young and old individuals (Schneider & G man 1979) indicated an age-dependent i crease in the frequency of sister chromat exchanges following challenge with mit mycin-C and N-acetoxy-2-acetylaminofluore (N-AAF). Moreover Pero et al (1978) fou an age-related increase in DNA-dama caused by N-AAF.

The results mentioned above suggest a increased susceptibility and/or decrease resistance of cells from elderly individuals chromosome-damaging effects of extern agents. Both factors may favor the appea ance of chromosomally abnormal cells an these mechanisms, as well as age itself, ma also increase the rate of the chromosom evolution from a normal to an abnorm karyotype in malignant cells. Obviousl older exposed patients have usually bee exposed for a longer period of time, an therefore the results from the present stud may well be explained by a combination the 2 factors: inducing agent and age.

Results from studies of ANLL seconda to radiotherapy and/or chemotherapy i dicate that the course of ANLL may b influenced by the previous treatment. I these patients remissions are rarely obtain and their survival is short compared t ANLL de novo (Pedersen-Bjergaard et 1981). It is reasonable to assume that di ferent etiologic factors were responsible f the development of ANLL in our expose and non-exposed patients. The present fin ing of a shorter survival in the elderly e

p than in the non-exposed patients may therefore support the concept that etiologic factors may influence the clinical course of XNLL.

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