Meeting Report

First International Workshop on Chromosomes in Leukemia

This workshop, in which 7 laboratories participated, was organized for review of the clinical and cytogenetic data on CML and ANLL with the aims of: (a) correlating clinical findings and chromosome constitution in a large series of cases; (b) identifying techniques that could provide useful information for future studies; and (c) determining which hematological diseases should be studied in the future on a multicenter basis.

Prerequisites for inclusion of patients in the series were that bone marrow mitoses had been studied by banding and that sufficient clinical data were available for classification of the disease according to the FAB criteria (1). Questionnaires on both clinical and cytogenetic data were filled out in advance for all patients included in the workshop. Karyotypes of the patients were exchanged prior to, or were reviewed at, the workshop.

Summary of Findings in CML

Data on 223 patients with Ph'-positive CML were included. Of these, 122 patients were studied in the chronic phase only; 59 were studied in both the chronic and the blast phase; 37 patients who were known to have CML were studied cytogenetically only in the blast phase; and 5 patients were seen in the blast phase but had no prior history of CML. A detailed report on these patients will appear elsewhere, and only the major findings are summarized here.

The translocation between chromosomes 9 and 22 ([t(9q+;22q-)]) was found in 92% (205) of all patients; of the remainder, 8 patients had a 2-way translocation involving chromosome 22 with another chromosome, and 9 had 3- or 4-way translocations, all of which involved both chromosomes 9 and 22 with some other chromosome(s). One patient with a 22q− chromosome lacked an obvious translocation. Fewer than 10% of the patients in the chronic phase had other karyotypic abnormalities. In contrast, at least 75% of those in the acute phase showed a change in their karyotype. In some instances, such changes preceded the onset of clinically apparent blast crisis by up to 18 months, although the usual interval was 1 to 4 months.

The additional abnormalities seen in the chronic phase, most often a double Ph' chromosome (5%) or +8 (2.4%), were also those most frequently seen in the blast phase. The possible isochromosome for the long arm of 17 [i(17q)] was considered to be a reliable marker for the blast phase. Other structural rearrangements independent of the Ph' translocation occurred in about 10% of the patients. Such rearrangements may cause difficulty in the identification of complex Ph' translocations.

Summary of Findings in ANLL

Data were available on 279 patients with ANLL, 140 of whom had an apparently normal karyotype and 139 of whom were chromosomally abnormal. These latter patients were classified according to the type of abnormality, specifically +8 (22 cases), −7 (20 cases), t(8q−; 21q+) (11 cases), t(15q+; 17q−) (9 cases), and t(9q+; 22q−) (5 cases). The remaining patients were classified according to chromosome numbers as follows: modal number less than 46 (19 cases); equal to 46 (30 cases); and greater than 46 (23 cases). The details of the correlations of the types of leukemia (FAB classification), with the types of karyotypic changes, incidence of a preleukemic phase, and survival are the subjects of a separate report. The most significant findings are summarized here.

The survival of patients was related to the karyotypes of the marrow cells. Patients with only NN, with AN, and with only AA had median survival times of 6, 5, and 4 months, respectively. The correlation between karyotype and survival was most significant for patients with acute myelocytic leukemia, in which the median survival was 8 months for NN patients, but 2 and 3 months for AN and AA patients, respectively. Of all the NN and AN patients, 21% were alive 1 year after the diagnosis had been made, compared with only 5% of AA patients. A major difficulty in comparisons of survival data among individual investigators is the variability in the types of chemotherapy used and the difference in support systems available for patient care. Despite these problems, the data appear to support previous observations on the clinical correlations between karyotype and survival.

Although the patients who were over 60 years old appeared to be distributed equally between those with normal (36%) and those with abnormal (29%) karyotypes, some subgroups showed a different distribution. For example, of 25 patients with either t(8q−; 21q+), t(15q+; 17q−), or t(9q+; 22q−), only 3 were above age 60.

In view of recent reports on the specificity of t(15q+; 17q−) in APL, it is noteworthy that each of 9 patients with this translocation had APL. Of the remaining 8 patients with APL, 6 were normal and 2 had other abnormalities. The t(8q−; 21q+) was noted in 11 patients, 10 of whom had acute myelocytic leukemia and 1 of whom had acute myelomonocytic leukemia.

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Specific Recommendations for Future Study of Patients with CML and ANLL.

It is often very difficult to determine the precise karyotype of leukemic cells. Analysis of the chromosome banding pattern is essential. Every attempt should be made to count 30 cells from each patient and to photograph and analyze 10 banded cells in detail. An abnormal clone is defined as 2 cells with the same extra chromosome or with the same structural rearrangement, or 3 cells with the same missing chromosome. Some of the problems associated with the nomenclature of acquired chromosome abnormalities in cancer are being reviewed by the Standing Committee on Human Cytogenetic Nomenclature, and new recommendations may be forthcoming.

It is quite important for cytogeneticists to recognize the fine balance required between overinterpreting the banding analysis and being too conservative and not identifying fairly clear abnormalities. An example is the frequent identification of a possible isochromosome for the long arm of chromosome 17 ([i(17q)]; in some cases the banding pattern supports this determination, whereas in others it is quite clear that one arm is different from the other and that the abnormality therefore is not an i(17q).

The frequency and significance of the Ph1 chromosome in patients who do not have typical CML require further clarification. In the workshop, the findings on 5 patients were thought to represent CML with the onset in the acute phase without a prior chronic phase, and 5 patients were classified as having Ph1-positive ANLL. The distinction was made primarily on clinical grounds; those patients with clinical signs suggestive of a chronic phase, such as splenomegaly, were considered to have CML, whereas those lacking these signs were considered to have ANLL. Three of the latter also had a significant number (more than 20%) of chromosomally normal marrow cells.

One of the latter patients was studied in remission; the bone marrow cells showed a normal karyotype, which is not seen in CML. Detailed clinical, morphological, and cytogenetic analysis, performed both initially and during remission, should provide the information necessary for a more precise delineation of these 2 conditions. The relationship of Ph1-positive acute lymphoid leukemia to CML in the blast phase, although not discussed in the workshop, also requires further investigation.

It is necessary to investigate carefully the various characteristics of the proliferating cells and to correlate the data obtained with the results of the cytogenetic investigation.

Differentiation between the types of acute leukemia should be based on the FAB classification. Cytochemical analyses should include peroxidase or Sudan black, periodic acid-Schiff, naphthyl acetate esterase, and naphthyl AS-D acetate esterase both with and without fluoride. Other tests that may be of value are the growth pattern in vitro of colony-forming cells obtained from bone marrow and peripheral blood, transmission electron microscopic analysis of bone marrow cells, and HLA typing.

For identification of the cells involved in the blast phase of CML, as well as in some undifferentiated forms of acute leukemia, tests for cell surface markers (T, B, and null) should be used. These may be supplemented, whenever possible, with a determination of terminal deoxynucleotidyl transferase.

The usefulness of cytogenetically abnormal clones of bone marrow origin for gene mapping should be kept in mind.

The following genetic factors and exposure to mutagenic agents in the environment should be recorded and correlated with the karyotypic changes: (a) family history of cancer; (b) exposure to radiation, occupational hazards, drug treatment, or other potentially mutagenic agents; (c) history of a previous hematological disorder, or of a previously treated cancer, such as malignant lymphoma, multiple myeloma, or carcinoma.

Conclusions

Chromosome analysis is important in the investigation of patients with leukemia. It may help to establish the patient’s diagnosis, and it is useful in the evaluation of the prognosis. If the full potential of this contribution is to be realized, cytogeneticists and hematologists must appreciate their interdependence. It is therefore recommended that cytogenetic studies be combined with the analysis of other parameters of cell morphology and cell function. Identification of new, important, but more subtle correlations will probably only result from comparison of the cytogenetic findings with careful observations of patients, particularly those who have unique clinical features.

REFERENCES

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