Chromosome Studies in Preleukemic States

V. Prognostic Significance of Single versus Multiple Abnormalities

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The prognostic value of marrow chromosome findings was examined in 242 patients with preleukemic myelodysplastic syndromes (MDS) or myeloproliferative disorders (MPD), with emphasis on the significance of single versus multiple karyotypic changes. In both groups, the results showed that patients with multiple chromosome abnormalities in a marrow clone had a very high probability of early death, from progression to leukemia or from other complications of hematopoietic dysfunction. Conversely, in patients with a hemic clone having only one karyotypic alteration (involving a single chromosome or single translocation), survival over 2 years was only slightly reduced as compared to those without chromosome abnormality. The only single karyotypic alteration perhaps associated with a markedly shortened survival was monosomy 7. These findings suggest that the conclusions of previous studies concerning the grave consequences of chromosome alterations in preleukemia largely reflect the clinical significance of clones with multiple cytogenetic changes. Prior knowledge of the karyotypic status of preleukemic patients should be helpful in evaluating current attempts to find effective treatment for these difficult disorders.


Previous reports from this laboratory and elsewhere have demonstrated the prognostic value of chromosome studies in those hematologic disorders that carry an increased risk for the subsequent development of leukemia. In general, the data have indicated that the presence of a chromosomally abnormal clone in the bone marrow is a grave prognostic sign with respect to the subsequent development of leukemia for patients with myelodysplastic syndromes (MDS), but of less prognostic value for patients with myeloproliferative disorders (MPD). Results have been less definitive concerning the relationship of chromosome abnormalities to death from other causes or the significance of particular chromosome patterns.

Preliminary data from our longitudinal study of patients with preleukemic disorders suggested that multiple karyotypic alterations indicated an unusually poor prognosis, with respect to overall survival as well as leukemia, for patients with both MDS and MPD. The current study confirms this conclusion in a large series of patients with these disorders, providing correlation between the extent of cytogenetic abnormality and patient survival during the 2 years after the chromosome study.

Materials and Methods

Clinical Characteristics

The current summary includes a total of 242 adult patients who have been followed for at least 2 years, or until death, after an initial cytogenetic investigation. They have been classified as having a MDS (144 patients) or a MPD (98 patients), based on the classification of the French-American-British (FAB) group and the Polycythemia Vera Study Group, respectively. Patients from our previous reports have been included when available data permitted appropriate classification.

Our MDS group includes patients with refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), and refractory anemia with excess blasts (RAEB) when first studied. Forty-two patients were considered as RA or RARS; 102 were classified as RAEB. We have not included patients presenting as “refractory anemia with excess blasts in transition” (RAEBT) in the FAB classification, with greater than 20% blasts in the bone marrow and more than 5% blasts in the blood, since they were considered “leukemia” rather than “preleukemia” in our earlier reports. In our MDS group, 58% were

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males, and the median age of the entire group was 66 years at the time of study.

The 98 patients with MPD were subclassified as polycythemia vera (27 patients), myelofibrosis (27 patients), undifferentiated myeloproliferative disorder (23 patients), and essential thrombocythemia (21 patients), as defined by the Polycythemia Vera Study Group. Of this group of patients, 54% were males and the median age was 61 years.

After the initial chromosome study, all patients were followed for at least 2 years, or until death, with progression to leukemia and the cause of death determined through the referring physician.

Cytogenetic Studies

To examine for the presence of a chromosomally abnormal clone in the bone marrow, direct preparations and 24-hour cultures, without mitogen, were done on marrow aspirates. Where appropriate, 24-hour cultures, without mitogen, were also done on peripheral blood. Slide preparation and chromosome banding, by the trypsin-Giemsa method, were carried out as previously described. In nearly all cases, at least 25 counts and three karyotype analyses were obtained. No clone was identified in this series that constituted less than 20% of the metaphases examined. In many instances, serial chromosome studies were done on patients during the follow-up period.

Results

Myelodysplastic Disorders

Clinical course: Survival data on the 144 patients with MDS during the 2 years after the initial chromosome study are given in Figure 1. The 63 patients (44%) with a cytogenetically abnormal clone are divided into two groups: 28 patients with a single karyotypic abnormality (defined as gain or loss of all or part of one chromosome or a single reciprocal translocation) and 35 patients with multiple karyotypic alterations in the clone. As is well recognized, the prognosis for the entire myelodysplastic group is poor, with fewer than 50% in this series surviving for 1 year. Figure 1 clearly indicates that those with multiple karyotypic alterations have a particularly grave prognosis, 80% being dead within 6 months, essentially all from leukemia or from other complications of their hematologic disorder. Conversely, the survival curve for MDS patients with a single chromosome abnormality is little different from that of the 81 MDS patients without a karyotypically abnormal clone in the bone marrow (Fig. 1).

The data on progression to leukemia, presented in Table 1, further indicate the bad prognostic significance of multiple cytogenetic abnormalities. The frequency of progression to frank leukemia in this group (74%) was twice that of the MDS population with normal chromosomes (37%), confirming previous reports by us and by others. Interestingly, the incidence of ultimate progression to leukemia was also high (64%) among the MDS patients with a single chromosome abnormality, indicating the lesser importance in this group of deaths from other hematologic complications.

Cytogenetics: The chromosome patterns observed in the myelodysplastic group were generally comparable to those previously reported. The most common single abnormalities were a 5q− chromosome and monosomy 7 (4 cases each), a t(2p;11q) translocation (3 cases), and two cases each with a 20q− chromosome and an isochromosome for the long arm of chromosome 17 (iso17q). Among the patients with multiple karyotypic changes, including a number where the MDS was apparently secondary to clastogenic therapy for an earlier neoplasm, the most common alterations were loss of all or part of chromosomes 5 and 7, as previously observed in many series. Multiple abnormalities were much more fre-
quent in myelodysplastic patients with RAEB (31% of 102 patients) as compared to individuals with RA or RARS (7% of 42 patients). This is consistent with the view that RAEB represents a later stage than RA in the progression of MDS toward frank leukemia, and that karyotypic evolution may contribute to this progression.3,5,11,18 In this regard, serial cytogenetic studies in several myelodysplastic patients documented sequential karyotypic changes, and these were typically associated with concomitant clinical progression.3

Myeloproliferative Disorders

Clinical course: Survival data in the MPD group are given in Figure 2. The overall prognosis in this group is clearly better than in patients with myelodysplastic syndromes,1 but the grave prognostic significance of a clone with multiple chromosome abnormalities is apparent with these patients also. Although the group is small, seven of these ten patients were dead by 6 months, and only one survived for 2 years. Among the 24 MPD patients with a single chromosome abnormality, there were several early deaths, but by 2 years, the survival was only slightly less than for the 64 MPD patients with a normal karyotype (Fig. 2).

The frequency of progression to leukemia among the patients with myeloproliferative disorders generally paralleled the survival data. As expected, the overall incidence of leukemia was much lower than in the MDS group.1,8-10 The excess of leukemias among all chromosomally abnormal MPD patients as compared to those with a normal karyotype (18% vs. 9%) was largely due to the 30% incidence in the small group with multiple karyotypic changes. The frequency in the group with single abnormalities (13%) was not significantly different from those with a normal karyotype (P > 0.70).

Cytogenetics: As in the MDS group, specific cytogenetic alterations seen among the MPD patients were similar to those previously reported from our laboratory and elsewhere.1,4,8-10 The most common single abnormalities were trisomy 8 (3 cases) and two cases each of trisomy 9 and a 20q− chromosome. The small numbers make prognostic statements concerning these individual alterations difficult, but our findings do tend to confirm previous reports of the relatively poor prognosis for preleukemic patients with monosomy 7.3,6,19 Combining the total MPD and MDS populations, we had five patients with monosomy 7 as the only karyotypic alteration, and only one survived for 12 months. Conversely, among the five patients with MDS or MPD having only a 5q− abnormality and the four patients with either trisomy 8 or 20q−, only one individual in each of these small groups died within 2 years after the study.

Multiple karyotypic alterations were much less frequent in the myeloproliferative patients than in those with MDS, but again loss of all or part of chromosomes 5 and 7 were most common, including several individuals with polycythemia vera who had previously been exposed to clastogenic therapy.1,8,10

As in previous reports,1,3,8-10 the frequency of chromosome aberrations varied somewhat among the MPD subgroups. Karyotypic changes were most common among the myelofibrosis (MF) patients (54% of 27 patients) and least common in the essential thrombocythemia group (14% of 21 patients). Interestingly, progression to leukemia was rare in both of these subgroups (<5%) despite the high frequency of chromosome abnormalities in the MF patients. In part, this reflects the many early deaths from other hematologic complications secondary to myelofibrosis,4 reducing the population at risk for leukemia.

As with MDS, we have observed karyotypic evolution, associated with clinical progression, in the MPD group.1,20 Interestingly, in both an MF patient20 and an RA patient, evolution from a normal to an abnormal karyotype involved appearance of a single alteration, an iso17q, with subsequent progression to leukemia. This abnormality, presumably involving critical genes on both the short and long arms of chromosome 17,21 was also seen as the only alteration in two of our myelodysplastic patients at the time of initial study, and has been commonly associated with clinical progression of chronic myelogenous leukemia22 as well as with other hematologic neoplasms.21-23

Discussion

The current findings confirm and extend several reports of recent years on the prognostic value of chromosome
studies in preleukemic states.1–10 Most importantly, survival data on a large series of patients with myelodysplastic or myeloproliferative dyscrasias demonstrate clearly the extremely grave prognosis associated with a bone marrow clone having multiple karyotypic alterations. Three fourths of the patients with multiple abnormalities were dead within 6 months, and fewer than 10% survived for 2 years. Progression to leukemia was the major cause of death, but other hematologic complications contributed significantly.

By contrast, the current survival data indicate that preleukemic patients having a hemic clone with a single karyotypic alteration, involving only one chromosome or a single balanced translocation, are at only slightly increased risk for early death as compared to those without a demonstrable cytogenetic abnormality. There was increased frequency of leukemia in the MDS patients with a single alteration, and some early deaths in the MPD population, but the overall survival at 2 years in both of these single-abnormality groups was only slightly reduced (Figs. 1 and 2).

Previous studies of patients with MDS and MPD have demonstrated that chromosome alterations indicate a poor prognosis, particularly with respect to progression to leukemia.1,2,4,23 In some cases, it has been noted that an “unstable” karyotype, as evidenced by additional changes on sequential studies, was frequently associated with clinical progression.5,6,10 It has been generally difficult to follow enough patients to evaluate the significance of particular karyotypic alterations or the overall survival patterns, although some conclusions have been developed through international collaboration2,26 and through concentrating on a particular abnormality (e.g., 5q−).7,16 To date, no report has focused on the specific question addressed here: the significance, for survival, of single versus multiple alterations, although a trend for shorter survival was noted by Tricot et al.27 in MDS patients with “complex” chromosome abnormalities.

On the basis of our earlier data, we offered the view1,3 that preleukemic individuals with multiple karyotypic changes might be the most logical candidates for newer therapeutic approaches, because of their poor outlook. In the past few years, initial clinical trials with low doses of cytotoxic drugs, or with agents such as retinoic acid derivatives and androgenic compounds, have indicated that these measures may be of value for some preleukemic patients, particularly those with myelodysplasia.4,28–31 A number of these agents, however, require some months of treatment before an effect is demonstrable. Because the expected survival time, as indicated by the current series, may be so short for preleukemic patients with multiple chromosome alterations, it would seem appropriate that the cytogenetic status of prospective participants be known before they are entered in a therapeutic protocol of significant duration. Although the patients with multiple alterations are in the greatest need of effective treatment, they may not survive long enough to provide an adequate test of the agent under study.

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