Chronic Myeloid leukemia (CML) in the chronic phase is a relatively benign disease. However, when patients develop the chronic phase (BP), the majority will have a very unfavorable prognosis due to the therapeutic refractoriness of the leukemia. To assess the therapeutic response and survival after the onset of the BP, various clinical, morphological, cytogenetic, enzymatic, and immunologic parameters have been studied and evaluated; the results have been reviewed by Barton and Conrad, Spiers and Woodruff. Several approaches based on cytogenetic findings in evaluating the BP of CML have been taken. However, whether all such approaches are effective, reliable, and consistent in estimating the response to therapy and/or survival after the onset of the BP of CML is still a moot point that requires further data and evaluation.

The present article represents an attempt at evaluating clinical, hematologic and cytogenetic parameters at the BP of CML, the results indicating that the chromosome findings constitute the most reliable and valuable index of the disease.

Materials and Methods

This study was based on observations in 64 Ph1-positive CML patients in the BP examined cytogenetically from January 1966 through December 1980. The group of patients was composed of 42 males and 22 females, ranging in age from 16 to 76 yr (median 44 yr) at the onset of the BP of the disease. All patients had clinically typical adult-type CML and a chronic phase ranging from 6 to 229 mo in duration (median 36 mo). The patients had a good response to busulfan and related therapy at least once during the chronic phase. The majority were treated at RPMI during their BP. Of the 64 patients, 1 patient (case 1) received only conservative therapy, whereas the other patients were treated predominantly with combinations of colchicinic acid derivatives [desacetylmycolcolchicine (Colcemide) and trimethylcolchicinic acid (TMCA)] and purine analogs [6-mercaptopurine (6-MP) and 6-thioguanine (6-TG)]. Other agents were used when these patients failed to respond to chemotherapy. Ten patients had a splenectomy before and 34 patients after the onset of BP of CML.

The BP was thought to exist when the percentage of myeloblasts in the bone marrow exceeded 20% and/or when the combined percentage of myeloblasts, promyelocytes, and promonocytes in the bone marrow exceeded 30%, criteria according to the First International Workshop on Chromosomes in Leukemia.

Evaluation of response to therapy was classified in the following four groups:

(A) Complete response (CR). Patient asymptomatic and fully functional; hemoglobin and platelets normal; marrow blasts less than 5%; peripheral blood differential counts normal or showing minor abnormalities consistent with the chronic phase of CML. Remission status must be maintained for at least 4 wk.

(B) Partial control (PC). Patient asymptomatic and fully functional, not requiring platelet transfusions, and with adequate numbers of mature neutrophils in peripheral blood. Excessive numbers of immature cells may persist in blood or marrow, and anemia requiring occasional transfusion may be present. Remission status must be maintained for at least 4 wk.

(C) Minor improvement (MI). Leukocytosis controlled and percentage of mature granulocytes increased, with symptomatic benefit. However, major hematologic abnormalities evident and functional status considerably impaired because of infectious complications or need for frequent erythrocyte or platelet transfusions.

(D) No response (NR). All other patients were classified in this group.

Therapeutic and Prognostic Value of Initial Chromosomal Findings at the Blastic Phase of Ph1-Positive Chronic Myeloid Leukemia

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To assess parameters of therapeutic response and of survival after the onset of the blastic phase (BP) in 64 patients with Ph1-positive chronic myeloid leukemia (CML), a number of clinical, hematologic, and cytogenetic parameters at the BP were evaluated. Among 10 parameters checked, only the chromosomal findings correlated with the therapeutic response and survival after the onset of the BP. The patients were divided into three groups on the basis of the chromosome findings in the bone marrow, blood, and spleen: (1) those with only a Ph1 (PP), (2) those having two types of clones, i.e., one clone with only a Ph1 and another with additional karyotypic changes (AP), and (3) those with only abnormal clones in addition to the Ph1 (AA). The number of patients in each group was 29 in PP, 15 in AP, and 20 in AA. The results were as follows. The percentage of patients with a good therapeutic response was 79% (23/29) in PP, 53% (8/15) in AP, and 30% (6/20) in AA. The median survival after the onset of the BP was 171 days (5.7 mo) in PP, 146 days (4.9 mo) in AP, and 74 days (2.5 mo) in AA. Statistically, there was a significant difference between the AA and the other two groups (p < 0.05). For further study, the AA and AP patients were divided into 4 subgroups each: those with 48 or more chromosomes, those with 47 chromosomes, those with pseudodiploidy, and those with hypodiploidy. A subgroup with 48 or more chromosomes in the AA patients had a very short survival (median, 25 days; 0.8 mo) and a poor therapeutic response (1/9, 11%). Our observations suggest that the lack of a clone with only a Ph1 (AA), particularly with more than 48 chromosomes, at the acute crisis or shortly after the onset of the BP indicates an unfavorable therapeutic response and a poor prognosis after the onset of the BP.

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category. A decrease in leukocytosis without improvement in the differential count was classified as no response.

The two former groups (CR + PC) were considered as a “good response group,” and the two latter groups (M1 + NR) as a “poor response group.”

The chromosomes in the cells of the bone marrow, blood, and spleen were analyzed by a direct method without phytohemagglutinin (PHA). 11

For chromosome analysis before 1972, a conventional staining method was used; after 1973 Q- and G-banding methods were used. 11 About 20 metaphases were examined in each specimen at the BP or shortly after the onset of the BP.

The patients were divided into three groups on the basis of the chromosome findings: (1) those with only a Ph1 clone (PP), (2) those having two types of clones, i.e., one clone with a Ph1 and another with additional karyotypic changes (AP), and (3) those with only abnormal clone(s) containing karyotypic abnormalities in addition to the Ph1 (AA). An abnormal clone was defined as two cells with the same extra chromosome or structural rearrangement, or three cells with the same missing chromosome.

The chromosome findings are based on data obtained on the day on which the diagnosis of the BP was made; however, when the samples for the cytogenetic study were not received at the time of the BP, we used the data obtained on the following specimens; with the exception of a few cases, these specimens were obtained before therapy for the blastic phase was begun.

For the further study, the AA and AP patients were divided into 4 subgroups each: those with 48 or more chromosomes (48-AA and 48-AP), those with 47 chromosomes (47-AA and 47-AP), those with pseudodiploidy (46-AA and 46-AP), and those with hypodiploidy (45-AA and 45-AP), although there was no case with 45-AP.

Statistical analysis was performed by standard methods.12

RESULTS

To assess the parameters of therapeutic response and of survival after the onset of the BP, the following data at the BP in this series of patients with CML were analyzed using the statistical method of stepwise regression: (1) age, (2) sex, (3) length of the chronic phase, (4) splenomegaly, (5) level of hemoglobin, (6) leukocyte counts, (7) percentage of myeloblasts in peripheral blood, (8) platelet count, and (9) percentage of myeloblasts in the bone marrow.

No statistically significant correlation was found between any of these nine parameters and the therapeutic response and/or survival after the onset of the BP. However, there was a significant correlation between the chromosome findings at the BP (or shortly after its onset) and therapeutic response and survival after the onset of the BP. Based on the chromosome findings, the patients were subdivided into the three groups (AA, AP, and PP) defined earlier. Among the patients, 20 (31%, 13 males, 7 females, ranging in age from 18 to 66 yr, with a median of 44 yr) were classified as AA, 15 (23%, 10 males, 5 females, ranging in age from 16 to 63 yr, with a median of 43 yr) as AP, and 29 (45%, 19 males, 10 females, ranging in age from 23 to 76 yr, with a median of 44 yr) as PP. No significant differences in age, sex, clinical and hematologic findings were present among these groups at the onset of the BP. The interval between the date of diagnosis of the acute crisis and that of chromosomal examination ranged from 0 (same day) to 165 days with a median of 3 days in AA, from 0 to 156 days with a median of 1 day (next day) in AP, and from 0 to 210 days with a median of 0 days in PP. In none of the calculations to follow was there a significant difference found whether the results were based on karyotypic findings obtained within 1 mo of the diagnosis of the BP or when the data of cases examined after that period were excluded. Thus, the differences among these three groups (AA, AP, and PP) were not significant.

The percentage of patients with a good therapeutic response (CR + PC) was 30% (6/20) in AA, 53% (8/15) in AP, and 79% (23/29) in PP. There was a significant difference ($\chi^2 = 11.96, df = 2, p < 0.01$) among these three groups by the Pearson chi-square test for a 2 × 3 table. There was also a significant difference between AA and PP, but not between AA and AP, and AP and PP. These results indicate that the response to the therapy depends on the cytogenetic type at the onset or shortly after the onset of the BP of CML.

The median survival after the onset of the BP was 74 days (2.5 mo) for AA, 146 days (4.9 mo) for AP, and 171 days (5.7 mo) for PP. Statistical examination revealed that there is a significant difference among the three groups ($p < 0.05$). No significant difference between AP and PP existed. The results indicate that the median survival for the AA as a group was shorter than that for AP and PP (Fig. 1).

In a further evaluation, the AA and PP patients were divided into seven subgroups (48-AA, 47-AA, 46-AA, 45-AA, 48-AP, 47-AP, and 46-AP); there was no 45-AP patient in this series. Among the patients, 9 (6 males, 3 females, cases 1, 3, 4, 5, 6, 12, 16, 30, and 36) were classified as 48-AA, 6 (2 males, 4 females, cases 11, 22, 32, 37, 41, and 59) as 47-AA, 4 (4 males, cases 8, 14, 48, and 51) as 46-AA, 1 (male, case 13) as 45-AA, 5 (3 males, 2 females, cases 10, 15, 20, 26, and 50) as 48-AP, 5 (4 males, 1 female, cases 21, 31, 33, 43, and 47) as 47-AP, and 5 (3 males, 2 females, cases 24, 44, 55, 58, and 63) as 46-AP. The percentage of patients with a good therapeutic response was only 11% (1/9) in 48-AA and ranged from 40% to 60% in the other 5 subgroups (47-AA, 46-AA, 48-AP, 47-AP, and 46-AP). The 45-AA patient (case 13) with a missing Y, the only such patient in this series, did not respond to therapy and had a short survival (53 days, 1.8 mo).

The median survival after the onset of the BP was 25 days (0.8 mo) in 48-AA, 143 days (4.8 mo) in 47-AA,
Fig. 1. Actuarial survival after the onset of BP in 64 Ph'-positive CML according to cytogenetic classifications (PP: patients with only a Ph' clone; AP: patients with one clone with a Ph' and another with additional karyotypic changes; AA: patients in whom all the cells had karyotypic changes in addition to the Ph'). Statistically, there was a significant difference between the AA and the other groups ($p < 0.05$).

66 or 232 days (2.2 or 7.7 mo) in 46-AA, 108 days (3.6 mo) in 45-AA (only 1 case), 82 days (2.7 mo) in 48-AP, 146 days (4.9 mo) in 47-AP, and 286 days (9.5 mo) in 46-AP.

Thus, the combination of the chromosome classification (AP) and the number of chromosomes in the AA and AP patients revealed a tendency for 48-AA patients to have a very poor response to therapy and very short survival after the onset of the BP of CML.

DISCUSSION

A number of therapeutic and prognostic parameters for the BP of CML has been reported. The blast-cell morphology (i.e., lymphoid versus myeloid),$^{13,14}$ the activity of the enzymes neutrophil alkaline phosphatase$^{15-17}$ and terminal deoxynucleotidyl transferase (TdT)$^{18,19}$ and the cytogenetic findings appear to be useful therapeutic and/or prognostic parameters. In particular, the cytogenetic data have been a fruitful index of therapeutic and prognostic parameters for the BP of CML.$^{2,5,9,20-22}$

The purpose of the present study was to determine whether clinical, hematologic, and cytologic features at the onset of the BP could be correlated with the therapeutic response and survival after the onset of this phase.

In this series, except for the cytogenetic observations, there was no correlation between the therapeutic response and/or prognosis after the onset of the BP and a number of parameters evaluated, i.e., age, sex, length of the chronic phase, splenomegaly, level of hemoglobin, leukocyte count, percentage of blasts in the peripheral blood, platelet count, and the percentage of myeloblasts in the bone marrow. However, there was a significant correlation between the chromosome findings at the BP (or shortly after its onset) and the therapeutic response and survival after the onset of the BP.

Several investigators$^{5-8,20-22}$ have reported a correlation between the therapeutic response and/or survival after the onset of the BP of Ph'-positive CML and the chromosome patterns. The patients were classified either on the basis of the modal chromosome number (i.e., hyperdiploidy, pseudodiploidy, or hypodiploidy) or the presence of specific marker chromosomes (such as ring chromosomes) and an extra Y.

In this study, we have presented a new cytogenetic classification of CML patients (AA, AP, and PP) for evaluating the therapeutic response and survival after the onset of the BP in 64 patients with Ph'-positive CML. This cytogenetic classification was based on that for acute myelogenous leukemia (AML) described by Sakurai and Sandberg.$^{23,24}$ These authors found a correlation between the various subgroups of AML patients (AA, AN, and NN) and their survival. The significance of this AML classification in acute nonlymphocytic leukemia (ANLL) was confirmed by the First and Second International Workshops on Chromosomes in Leukemia.$^{25,26}$

We reported a near correlation between the chromosome pattern (using the AP classification) during the course of the BP and survival after the onset of the BP of the 64 Ph'-positive CML of this series.$^{27}$ The survival in the previous study reported by us$^{27}$ was very similar to that of the present study, which means that the median survival for the AA group was significantly shorter than that for the other two groups: there was no significant difference between the AP and PP groups. These facts indicate that the initial chromosome findings at the onset or shortly after the onset of the BP may reflect the chromosomal features during the course of the BP and could also be a useful index for survival after the onset of the BP of CML.

Sakurai and Sandberg$^{23,24}$ suggested that the relatively long survival and good response to therapy in AN and NN patients with AML indicated that in most of these cases the marrow contained a significant number of normal cells needed to repopulate the bone marrow after the eradication of the leukemic cells by chemotherapy. In the present series, only one (case 46) out of 64 samples had a normal clone, i.e., a minimum of two cells that were karyotypically normal. This
patient, who might be subgrouped as a PN, had a relatively long survival and a good response to therapy (196 days and a complete remission). In Ph'-positive CML patients who undergo the BP, the presence of karyotypically normal cells may point to a much better response to therapy and relatively longer survival than in those patients without normal cells.

For further chromosomal study, the AA and AP patients were divided into seven subgroups (i.e., 48-AA, 47-AA, 46-AA, 45-AA, 48-AP, 47-AP, and 46-AP); there was no 45-AP patient. This subclassification revealed that 48-AA as a subgroup had a most unfavorable therapeutic response (1/9, 11%) and a very short median survival (25 days, 0.8 mo). Even though 48-AP patients had a short survival (median, 82 days, 2.7 mo), the percentage with a good therapeutic response was about the same as that of 47-AA, 46-AA, 47-AP, and 46-AP (40%–60%).

From the results of our study, we postulate the existence, in neoplastic terms, of aggressive and nonaggressive types of cells in the karyotypically abnormal cell populations in the BP of CML. The fact that 8 of 29 cases (28%), on whom cytogenetic examinations were performed on the same day as when the BP was diagnosed, were revealed to belong to the AA group indicates the presence of aggressive type cells. In particular, of 9 examinations on 48-AA cases, 5 were performed on the day of diagnosis of the BP, 1 on the next day, and the other 3 on the third day after the onset of the BP. Thus, 48-AA cells seem to be the most aggressive.

On the other hand, some cells with karyotypic abnormalities in AP patients appear to be of the nonaggressive type. Of 5 46-AP patients, 3 (cases 44, 55, and 63) had only an i(17q) in addition to Ph' and a survival ranging from 185 to 387 days. Two cases had a poor therapeutic response. Thus, the cells with only an i(17q) in addition to Ph' may be of the nonaggressive type, though Prigogina suggested that i(17q) is an unfavorable chromosome. One patient (case 64) in whom a new clone with only an extra Ph' appeared during the BP (though he was grouped into PP in this study) had the longest survival (626 days, 20.9 mo) in this series and a good therapeutic response. The cells with only an extra Ph' must be also of a nonaggressive type.

Our observations on the 64 Ph'-positive CML patients suggest that the initial chromosomal findings at the BP or shortly after the onset of this phase are useful parameters for assessing the therapeutic response and survival after the onset of the BP of CML. The other clinical and hematologic data at the onset of the BP in this series did not correlate significantly. The lack of a clone with only a Ph' at the BP or shortly after its onset (AA group) indicates a subsequent unfavorable response and a poor prognosis. In particular, AA patients with 48 or more chromosomes (48-AA) had a very unfavorable response and a very poor prognosis after the onset of the BP. Thus, the karyotypic findings at the onset of the BP may be very useful to clinicians in planning the therapy for such cases, including bone marrow transplantation. However, more cases in the BP of CML will have to be classified and studied cytogenetically before more definitive conclusions can be reached regarding the various parameters covered in this article.

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Therapeutic and prognostic value of initial chromosomal findings at the blastic phase of Ph1-positive chronic myeloid leukemia

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