

## Aberrations of chromosome No. 1 in blastic phase of chronic myeloid leukemia

G. ALIMENA, B. DALLAPICCOLA, F. MITELMAN and A. MONTUORO

*Department of Hematology and Institute of Medical Genetics, University of Rome, Italy, and Department of Clinical Genetics, University Hospital, Lund, Sweden*

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Aberrations of chromosome No. 1 were detected at the time of blastic crisis in 7 patients with Ph<sup>1</sup>-positive chronic myeloid leukemia (CML). Two patients had trisomy 1; trisomy for a long arm segment of chromosome No. 1 was present in 2 patients; trisomy for a short arm segment occurred in 2 patients; and one patient had an apparently balanced translocation affecting chromosome No. 1. All patients with extra material of chromosome No. 1 were trisomic for the region 1p22–1pter or 1q21–1qter. A survey of abnormalities of chromosome No. 1 in this series and in other patients with CML previously reported show, in all patients, a relative increase or decrease of genetic material of two specific regions: 1q32–1q42 and 1p36–1pter.

*Giuliana Alimena, Department of Hematology, University of Rome, Via Lancisi, 3, 00161 Roma, Italy*

Chromosome aberrations occurring during blastic crisis (BC) of chronic myeloid leukemia (CML) are strictly nonrandom. The most common pattern of chromosome evolution includes trisomy 8, iso(17q) and/or Ph<sup>1</sup>-duplication. All together, at least one of these aberrations is present in about 85 % of the patients (MITELMAN and LEVAN 1978; PRIGOGINA et al. 1978; ROWLEY 1978). We have recently shown that patients treated with intensive chemotherapeutic schedules during the chronic phase develop additional structural changes of chromosome No. 1 in about 50 % of the cases (ALIMENA et al. 1979). The present study indicates that only certain regions of chromosome 1 are selectively affected in CML and that such patients may have an unfavourable prognosis.

### Material and methods

This study is based on 7 Ph<sup>1</sup>-positive CML patients studied at the Department of Hematology, Rome, Italy, in whom abnormalities of chromosome No. 1 developed at the onset or during BC. All patients except Case No. 2 were briefly reported in ALIMENA et al. (1979). The patients were selected from a group of 50 Ph<sup>1</sup>-positive patients with CML in blastic crisis and/or with chromo-

some aberrations in addition to the Ph<sup>1</sup> studied in our laboratories since 1972. Twenty-three patients, including 6 of the patients reported here, were treated with intensive chemotherapeutic schedules during the chronic phase; the other 27 patients were treated with busulphan and/or hydroxyurea only during the chronic phase. The patients were selected at random for intensive treatment.

Cytogenetic analyses were performed on direct bone marrow preparations and/or after short term (16–20 h) bone marrow cultures. Banding studies were carried out using the GTG, GAG, CBG and/or RBA-techniques (PARIS CONFERENCE 1971) previously described (MITELMAN et al. 1976; ALIMENA et al. 1977; DALLAPICCOLA and ALIMENA 1979). The chromosome numbers were determined in 50 metaphases. Karyotype analyses of at least 10 banded metaphases from each case were made by photography.

### Case reports

*Case No. 1.* — 42-year-old female; CML diagnosed in July 1973. During the chronic phase, the patient was treated with hydroxyurea (HU) perorally 0.5–1.5 g daily (total dose 900 g) and bimonth-

ly courses of vincristine (VCR), 1.4 mg/m<sup>2</sup> × 2 (total dose 40.5 mg), cytarabine (CA), 80 mg/m<sup>2</sup> × 2 × 4 days (total dose 9.4 g), and prednisone. Splenectomy was performed in September 1973. BC was diagnosed in September 1976. Following treatment with HU, 1–2 g daily (total dose 720 g), and 6-Mercaptopurine (6-MP), 100–150 mg daily (total dose 72 g), partial remission was obtained which persisted until October 1977. From this period, no response to treatment was achieved and the patient died in December 1977.

At diagnosis of BC all bone marrow cells had the karyotype 46,X,-X,+der(X), t(X;9;22)(q27;q34;q12). During the 14th month of BC, a clone with trisomy 1 appeared. This clone rapidly increased in frequency and at the last sampling occasion in December 1977 60% of metaphases showed trisomy 1, and, in addition, trisomy 4, 8, 9, Ph<sup>1</sup>-duplication and i(17q) (Fig. 1).

*Case No. 2.* — 59-year-old male; diagnosed as having BC of CML without a detectable chronic phase in October 1977. He was treated with courses of VCR, 2 mg/m<sup>2</sup> weekly, and prednisone. Death occurred one month later.

Trisomy for chromosome 1 was observed in 55% of metaphases examined at diagnosis. Additional clones showing trisomy for chromosomes 5, 8, 9, 17, 18, 19, 21, duplication of Ph<sup>1</sup>, monosomy 16 and the presence of several unidentifiable marker chromosomes were found during BC.

*Case No. 3* — 54-year-old male; CML was diagnosed in February 1975. The patient was treated with busulphan perorally, 2 mg daily (total dose 280 mg) and courses of daunorubicine (DNR), 2 mg/kg (total dose 420 mg), CA and 6-Thioguanine (6-TG), both at doses of 1.5 mg/kg × 2 × 5 days (total dose 3 g). BC was diagnosed in September 1975 and the patient was treated with weekly courses of methotrexate (MTX), 60–200 mg/m<sup>2</sup>, and asparaginase (Asp), 10 000 IU/m<sup>2</sup>. Death occurred in January 1976.

Cytogenetic analysis at diagnosis of BC showed a del(1)(q21-qter) in 30% of the cells examined. Additional karyotypic changes included trisomy 8, 9 and a Ph<sup>1</sup>-duplication. At the next sampling occasion, during the 4th month of BC, a karyotypic evolution had occurred. In addition to the initial clone, a new clone with another abnormal chromosome 1 and monosomy 14, 16 and 21 was present in 10% of the cells. The second abnormal chromosome 1 had a duplication of the region 1q21-qter.

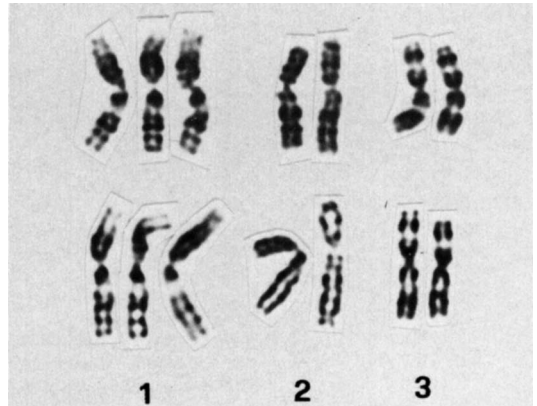


Fig. 1. Partial karyotypes of two cells from Case 1 showing trisomy 1.

*Case No. 4.* — 8-year-old female; CML diagnosed in October 1974. During the chronic phase the patient was treated with HU 1–2 g daily (total dose 120 g), and subsequently with busulphan 1 mg daily, and bimonthly courses of DNR, 1.5 mg/kg (total dose 500 mg), CA and 6-TG, both at doses of 1.5 mg/kg × 2 × 5 days (total dose 11.2 g). BC was diagnosed in April 1978 and death occurred in June 1978.

Cytogenetic analysis in May 1978 showed that 10% of the metaphases had a translocation of part of the long arm of chromosome 1 onto the long arm of chromosome 8: t(1;8)(q23;qter). Additional structural changes included a 5q+ and a 17p+ marker chromosome; the extra material could not be positively identified.

*Case No. 5.* — 29-year-old female; CML was diagnosed in November 1975. The patient was treated with HU 1.5–2.5 g daily, and courses of VCR 1 mg × 2 (total dose 30 mg), CA 4 mg/kg × 5 days (total dose 11.2 mg) and prednisone. BC occurred in April 1978. Following treatment with HU, 1.5 g daily and 6-MP, 150 mg daily, no response was achieved and the patient died in the 45th day of BC.

Cytogenetic analysis at the onset of BC disclosed the presence of an elongated short arm of one chromosome 1 in 60% of the cells, interpreted as a duplication of region 1p22–1pter (Fig. 2).

*Case No. 6.* — 30-year-old male; CML diagnosed in May 1971. During the chronic phase the patient was treated with busulphan 1 mg daily (total dose



Fig. 2. Partial karyotypes of three cells from Case 5 showing duplication of region 1p22-pter.



Fig. 3. Partial karyotype of three cells from Case 6 showing duplication of region 1p22-pter.

1 680 mg) and bimonthly courses of VCR, 1.4 mg/m<sup>2</sup> × 2 (total dose 27 mg) and CA 80 mg/m<sup>2</sup> × 2 × 4 days (total dose 6 g). In October 1976, BC was diagnosed. No response was achieved to treatment with HU, 1–2 g daily, and 6-MP, 100 mg daily. The patient died in February 1976.

Cytogenetic analysis at the onset of BC demonstrated the presence of a structural rearrangement of chromosome 1 similar to that found in Case 5, i.e. dup(1p22-pter) (Fig. 3). This abnormality was observed in about 60 % of the cells examined on subsequent analyses during BC. Additional changes included trisomy 8, 9, 19, 20, 21, Ph<sup>1</sup>-duplication and i(17q).

**Case No. 7.** — 78-year-old female. From the diagnosis of CML in October 1972 she was treated with busulphan 3–4 mg daily (total dose 448 mg) and HU 1–2 g daily (total dose 1 950 g) and courses of VCR 1 mg × 2 (total dose 72 mg) CA 2 mg/kg × 5 days (total dose 25 g) and prednisone. In September 1978, the patient developed BC and was treated with HU, 1.5 g daily, and 6-MP, 150 mg daily. She is still (June 1979) in a fairly good condition on this therapy.

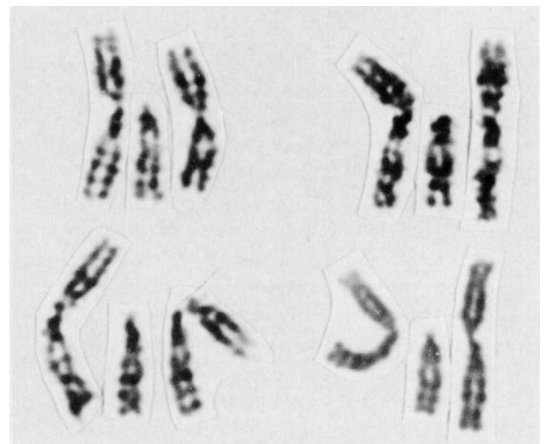


Fig. 4. Trisomy of the region 1p11-lqter in four metaphases of Case 7.

Cytogenetic analysis on two occasions during BC showed in all cells examined an extra marker chromosome, identified as a deleted chromosome 1: del(1)(p11) (Fig. 4).

## Discussion

An increasing number of observations have demonstrated that the karyotypic changes in human neoplasms are nonrandom and tend to cluster to a few specific chromosomes (MITELMAN and LEVAN 1978). Interest has been focused, by recent reports, on abnormalities affecting chromosome No. 1 in different malignant disorders. In a recent review of 856 human neoplasms with chromosome aberrations, including myeloproliferative disorders, lymphoproliferative disorders and various solid tumors, chromosome No. 1 was affected in 139 cases, i.e. 16.2 % (MITELMAN and LEVAN 1978). In certain malignant disorders, such as polycythemia vera, non-Burkitt lymphomas, acute lymphocytic leukemia, chronic lymphocytic leukemia, monoclonal gammopathies, malignant melanomas, neurogenic tumors, and carcinomas, abnormalities of chromosome No. 1, numerical and/or structural, were present in 25–75 % of the cases. In addition, ROWLEY (1977) and KOVACS (1978) have presented evidence indicating that certain regions of chromosome No. 1, namely 1q21–1q32, are selectively affected in malignant cells and, therefore, may be of crucial importance in the development of different tumor types. A similar nonrandom involvement of specific chromosome regions has previously been noticed also in experimental tumors (LEVAN et al. 1974).

Abnormalities of chromosome No. 1 have so far been identified in only 6 patients with CML (HAYATA et al. 1975; PRIGOGINA et al. 1978; SEABRIGHT and PEARSON 1978; SONTA and SANDBERG 1978). Our findings suggest that this may be yet another specific subgroup, possibly related to treatment. Recent evidence presented by us (ALIMENA et al. 1979) has indicated that new stable clones with a preferential engagement of chromosome No. 1 may be produced by intensive chemotherapy during the chronic phase. In the present series, 6 of the 7 patients with abnormalities of chromosome No. 1 had received such treatment.

The abnormalities of chromosome 1 found in the present series are rather homogeneous and include trisomy for the long arm of chromosome 1 (Cases 1, 2 and 7), duplication/deficiency of region 1q21–qter (Case 3) and duplication of region 1p22–pter (Cases 5 and 6). One patient had an apparently balanced translocation, t(1;8), the break point on chromosome 1 being located at band 1q23 (Case 4). It has been speculated (MITELMAN and LEVAN 1978) that the observable chromosomal changes in malignant cells are of

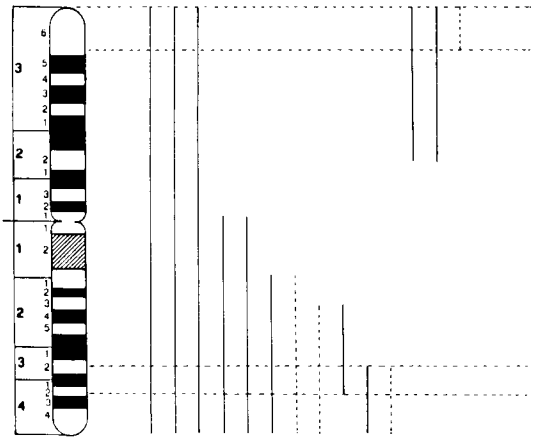


Fig. 5. Survey of abnormalities of chromosome 1 in 13 patients with CML. For each patient a relative increase of genetic material (trisomy or duplication) is indicated by a full line; a relative decrease of genetic material (deletion or translocation) is represented by a dashed line. Seven cases are derived from the present study (both abnormal chromosomes 1 present in Case No. 3 are included); six cases from the following sources: HAYATA et al (1975), PRIGOGINA et al. (1978), SEABRIGHT and PEARSON (1978), SONTA and SANDBERG (1978). The dashed horizontal lines enclose shared segments that are trisomic or monosomic.

two essentially different kinds; active and passive. The former take place in specific loci that must be manipulated to affect the malignant transformation; the passive changes act to enhance the effect of the primary change. This can be achieved either by increasing the number of chromosome loci, in which the active change has occurred, or eliminating the normal, unchanged homologue. Fig. 5 shows a survey of the trisomic and monosomic regions of chromosome 1 in our patients and in the 6 patients previously reported. It is striking that all patients show a relative increase or decrease of genetic material of two specific regions: 1q32–1q42 and 1p36–1pter. Based on the reasoning above, this might indicate that these particular regions contain genes which may be important for the progression of CML. It should be noticed that in patients with duplication of part of chromosome 1, the adjacent region between bands q25 and q32 appears to be crucial in other hematologic disorders (ROWLEY 1977).

OSHIMURA et al. (1976) and NAJFELD et al. (1978) have suggested that abnormalities of chromosome 1 may represent an unfavourable prognostic sign in acute myeloid leukemia. Six patients of the present series died 25–108 days from the detection

of chromosome 1 abnormalities, indicating that the appearance of aberrations of chromosome 1 at the beginning of and/or during BC, irrespective of whether or not other changes are present, may mark a poor response to therapy also in CML. It must be emphasized that the material is scanty and the results presented on this aspect need to be confirmed on a larger series of patients.

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