Chronic Myelogenous Leukemia with p190BCR-ABL Expression: The Missing Link with Monocytosis

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Chronic myelogenous leukemia (CML) is a clonal myelo-proliferative disorder, which involves myeloid, monocytic, erythroid, megakaryocytic, B-lymphoid, and occasionally T-lymphoid lineages. It was the first human disease in which a specific abnormality of karyotype - the Philadelphia (Ph) chromosome, t(9;22)(q34;q11) translocation - could be linked to pathogenetic events of leukemogenesis. The BCR-ABL hybrid gene, the product of the Ph chromosome, is found in the leukemic clone of at least 95% of CML patients diagnosed by conventional clinical features. The fusion protein encoded by BCR-ABL varies in size, depending on the breakpoint in the BCR gene. Three breakpoint cluster regions have been characterized to date: major (M-bcr), minor (m-bcr) and micro (μ-bcr) (1).

The smallest of the fusion proteins, p190BCR-ABL (m-bcr breakpoint), is principally associated with Ph-positive ALL. Rare cases of CML are due to a p190-type of BCR-ABL gene and the disease tends to have a prominent monocytic component, resembling chronic myelomonocytic leukemia (CMML). Melo et al first reported the missing link of p190BCR-ABL CML with CMML and pointed out that acute myeloid leukemia with m-bcr breakpoint also had a myelomonocytic phenotype (FAB M4) (2). They speculated that it might indicate that the presence of p190BCR-ABL in a committed early myeloid cell resulted in a myeloproliferative defect including monocytic lineage, whereas p210 BCR-ABL, the product of M-bcr breakpoint, in the same type of progenitor restricted the excessive proliferation to the granulocytic pathway.

Thereafter sporadic cases of CML with p190BCR-ABL have been reported. Although the dual expression of major and minor BCR-ABL fusion transcript could be detectable in the vast majority of CML patients, CML expressing exclusively a minor BCR-ABL transcript had been rare and the incidence of this condition was observed in 5 of the 1,384 (0.36%) CML cases in one study (3). Ohsaka et al reported a rare case of CML with p190BCR-ABL and reviewed the literature of similar cases (4).

See also p 1183.

They grouped these 18 cases into two categories according to having prominent monocytosis or not. Ten patients with monocytosis had similar hematological and clinical features except monocytosis to those of the other 8 patients without it. Hur et al published a similar review including 23 patients with p190BCR-ABL CML (5). They suggested that the absence of basophilia, and no or mild splenomegaly were the additional clinical features. Both authors pointed out the tendency to progression to lymphoid crisis. We can know the hematological data of 16 patients except for the blastic phase according to these reports after all. All except one patient had absolute monocytosis higher than 1.0×10^9/L; 11 (69%) had relative monocytosis greater than 8%. There were additional cases with p190BCR-ABL who had shown monocytosis during the course of their illness who had first presented at first as blastic phase of CML (6), myeloproliferative (7) or myelodysplastic syndrome (7, 8). Therefore, it may be of clinical and biological significance that CML patients with p190BCR-ABL have monocytosis.

The diversity of BCR-ABL fusion proteins and their relationship to clinical features are still unclear. In a murine bone marrow transduction/transplantation model (9), the three forms of BCR-ABL were equally potent in the induction of a CML-like myeloproliferative syndrome, and p190BCR-ABL could also induce lymphoid leukemia with a shorter latency than p210. It is suggested that the rarity of p190BCR-ABL in human CML may reflect the infrequent BCR intron 1 breakpoints during the genesis of the Ph chromosome in stem cells, rather than intrinsic differences in myeloid leukemogenicity between p190 and p210. In another murine model, Honda et al generated transgenic mice expressing p210BCR-ABL driven by the promoter of the mouse tec gene, which enabled expression of a cytoplasmic tyrosine kinase preferentially in early hematopoietic progenitors (10). The transgenic progeny reproducibly exhibited marked granulocyte hyperplasia with thrombocytopenia after a long latent period, which closely resembles the clinical course of human CML. This model may be useful to elucidate the real biological nature of p190BCR-ABL.

According to the new classification schema proposed by The World Health Organization (11), CML is defined as a myeloproliferative disease consistently associated with Ph chromosome and/or the BCR-ABL fusion gene. If we encounter a CML patient who had monocytosis, or atypical clinical features (no or mild splenomegaly, or absence of basophilia), we should analyze 3 forms of BCR-ABL transcript by sensitive reverse transcriptase polymerase chain reaction (RT-PCR).
References


