

This Week's Citation Classic®

Canellos G P, DeVita V T, Whang-Peng J & Carbone P P. Hematologic and cytogenetic remission of blastic transformation in chronic granulocytic leukemia. *Blood* 38:671-9, 1971.

[Solid Tumor Service, Medicine Branch, and Human Tumor Cell Biology Branch, National Cancer Institute, Bethesda, MD]

This paper demonstrated that 30 percent of patients in the blastic phase of chronic granulocytic leukemia could be treated to clinical remission with vincristine and prednisone. The treatment also results in a hematologic cytogenetic reversion to the chronic phase coincident with the disappearance of the blast cells. [The SCI® indicates that this paper has been cited in over 210 publications.]

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Until the early 1970s the human leukemias were rarely subclassified beyond acute or chronic, lymphoid or myeloid. The vast majority of patients with chronic myelogenous (CML) or granulocytic (CGL) leukemia had a disease consisting of two generally definable clinical phases.

The chronic phase consisted of excessive proliferation of granulocytes and in some cases, platelets, and thus was considered a leukemia disorder of the precursor of cells of myeloid origin. Demonstration of the Philadelphia chromosome abnormality in erythroid, granulocytic, and platelet precursors confirmed this. It was not demonstrated, by routine techniques, in circulating lymphoid cells transformable by mitogenic agents *in vitro*, and thus CML was considered to be a disease of the myeloid stem cell related to other myeloproliferative disorders.

The blastic or terminal phase was considered a variant of acute myeloblastic leukemia and was treated accordingly. The response to therapy was poor, and patients died within two or three months after conversion of CML to the blastic phase. The latter was characterized by an excess proliferation of blastic cells with compromise of differentiated hemopoietic function resulting in anemia, thrombocytopenia, and granulocytopenia. Therapy added further to the suppression of hemopoiesis without selective destruction of the blast cells. These cells were variously described as "myeloblasts" but did

not necessarily have all of the features of myeloblasts of acute myeloblastic leukemia. In addition to retaining the Philadelphia chromosome, the blastic phase has other chromosomal abnormalities, such as deletion or addition of extra chromosomes (aneuploidy).

In the late 1960s we undertook a comprehensive study of the blastic phase of CML. The technology to study the malignant cells was limited to cytochemistry and cytogenetics. There emerged a consistent minority of patients whose blastic cells had some of the morphologic features of the lymphoblastic cells seen in acute lymphoblastic leukemia. Antilymphoblastic therapy available at that time was mainly vincristine and prednisone. In a series of 30 consecutive patients, 30 percent responded with a complete or partial remission, with responders surviving a median duration of 10.5 months. We demonstrated that this response was accompanied by disappearance of the aneuploidy coincident with elimination of blast cells and return to chronic phase hemopoiesis and cytogenetics. Hematologic remission occurred in a full 50 percent of patients with lymphoblastic transformation. Up until that time, the remission rate was close to nonexistent when treatment appropriate for acute myeloblastic leukemia was used.

The paper is cited because it was the first to demonstrate the effective treatment for the blastic phase of CML and that remission can be accompanied by the cytogenetic changes consistent with the disappearance of blastic cells and restoration of the chronic phase. It further gave impetus to the possibility that CML may be a disorder of the stem cell common to lymphoid and myeloid cells. Subsequent investigations have defined that the morphologic lymphoid transformation of CML is indeed lymphoid, as defined by enzymic markers, indicating a pre-B-lymphocytic phenotype.¹⁻³ Other researchers separated lymphoid cells of B lineage and demonstrated the presence of the Philadelphia chromosome in these cells.⁴

Recent study of the blast cells of individual patients with lymphoblastic transformation has shown blast cells with immature T-lymphoid phenotype.⁵ Thus, detailed study of blastic phase provides evidence that CML may be a disease of the totipotential hemopoietic stem cell and that such a common stem cell normally exists in man.

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