Henry Ford Hospital Medical Journal

Volume 25 | Number 4 Article 6

12-1977

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Henry Ford Hosp Med Journal
Vol 25, No 4, 1977

Long-term survival after onset of blast crisis in chronic granulocytic leukemia

Case report and therapeutic considerations

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Current analysis indicates a median survival of 3.6 months in 356 cases of chronic granulocytic leukemia after onset of blast transformation. Thirty-five (10.0%) complete remissions (CR), all of short duration, were observed. Closer scrutiny of the reported clinical experience offers clues for improving this poor outlook. A 16% CR rate can be extracted from this total experience by identifying cases treated with cytosine arabinoside combined with one or more other agents. In isolated reports, weekly vincristine and prednisone have yielded good remission rates. Two general morphologic types of blasts can be distinguished by cytochemical stains and other features: lymphoid and nonlymphoid (myeloid, monocytoid).

We suggest that the lymphoid type of blast crisis is more responsive to vincristine-prednisone, whereas combination chemotherapy, containing cytosine arabinoside, is more effective in nonlymphoid crises.

We report a blast crisis in which two CRs occurred. The patient survived 19 months after onset, possibly because he also received BCG.

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DESPITE striking improvement in the complete remission rates in both the lymphocytic and nonlymphocytic acute leukemias during the past decade, the management of patients with blast crisis of chronic granulocytic leukemia (CGL) has remained discouragingly unchanged. Therapeutic regimes, which have a 60% complete remission rate in acute granulocytic leukemia, apparently can produce only short-lived complete remissions in about 10% of patients with blast crisis. However, recent attention to morphologic features of the blast cells seen in blastic transformation of CGL and renewed interest in cytochemical staining methods, attended by some surprisingly good results in a few clinical experiences,[1-3] may suggest a rational approach to more effective treatment.

Our recent experience with a patient who obtained a gratifying response to treatment of his blast crisis demonstrates some of the points we wish to make.

Case Report

A 62-year-old man with mild diabetes was found to have typical Philadelphia chromosome-positive CGL with hepatosplenomegaly in February, 1973. His initial white blood cell count was 52 x 10^9/liter. The leukocyte alkaline phosphatase score was 4. Excellent control (WBC 10 x 10^9/liter) was accomplished with brief courses of intermittent myleran in doses no larger than 4 mgs/day.

On May 31, 1974 the white blood count abruptly rose to 25 x 10^9/liter with 30% myeloblasts. Concomitantly, the bone marrow was hypercellular with 50% blasts. Treatment with vincristine 2 mg single IV injection, cytosine arabinoside 200 mgs/day for 10 days, and prednisone 120 mgs daily for 5 days (10 day OAP) produced severe bone-marrow hypoplasia with associated complications of sepsis and gastrointestinal hemorrhage. However, with the recovery of marrow cellularity the patient reached complete remission status by July 18, 48 days after treatment of the blast crisis had been started. Philadelphia chromosome was still demonstrated.

This remission was maintained with monthly cytosine arabinoside, vincristine and prednisone (5 day OAP), and intermittent BCG scarification. Blast crisis again supervened on February 10, 1975, after a seven-month remission. This crisis was resistant to intensification of OAP treatment, but after treatment in early March with adriamycin 75 mg/m^2, given twice 14 days apart, a complete remission status was recaptured in early April. This remission, maintained with 6-mercaptopurine and methotrexate orally, lasted until October 20, 1975 (6.5 months). During this interval a transient episode of asymptomatic cholestatic jaundice was related to 6-mercaptopurine toxicity. Subsequent responses to adriamycin were only partial and brief. The patient died on December 10, 1975 from sepsis, 19 months after the onset of blast transformation of CGL.

Comment

This case is noteworthy on two counts, one of which may be related to the other: 1) the length of remissions was unusually long and the survival duration was exceeded by only one other report found in the literature;[4] and 2) the patient received immunotherapy in the form of BCG scarification during his first complete remission. This adjuvant therapy has now had widespread use in the acute leukemias, but as yet, not in blast crisis of CGL. In retrospect and in light of current knowledge, this patient's blast crisis should have been characterized by additional study *(vide infra)*. The good response to the par-

BLAST CRISIS OF CHRONIC GRANULOCYTIC LEUKEMIA
Complete Remission and Median Survival Data

Yr.	Source	No. of Pts.	Complete Remission	Median Survival (in mos.)
69	Hayes, Ellison[5]	24	4	-
69	Foley[6]	13	2	3
71	Canellos[1]	30	6	4
73	Resegotti[7]	7	1	4
73	Marmont[2]	24	9	-
73	Monfardini[8]	70	0	1
74	Spiers[9]	50	6	-
74	Vallejos[10]	39	4	3.3
74	Levin[11]	14	0	-
74	SWOG[12]	21	0	-
75	Duhamel[13]	45	3	3
76	Peterson[14]	19	0	2
	TOTAL	356	35 (10.0%)	2.9

Figure 1

ticular therapy given suggests that the blast crisis was myeloid.

Discussion

Review of 356 cases of blast crisis (Figure 1) from 13 different sources in this country and Europe[1,2,5-14] shows a complete remission rate of 10% with a median survival of only 2.9 months. However, by identifying a subset of patients who were treated with regimes that included cytosine arabinoside (perhaps the most effective single agent in nonlymphocytic leukemias) in combination with other drugs, one obtains a complete remission rate of 16% (Figure 2). This improved response rate suggests that, as a general mode of therapy in blast crisis, cytosine arabinoside combined with one or more other antileukemic drugs, is superior to regimes that do not include cytosine arabinoside or use it only as a single agent. In fact, the 15 complete remissions in 91 cases treated with Ara-C combinations compared with the 20 complete remissions in 265 cases treated with other regimes yields a highly significant p value of 0.026 that favors the former (see Appendix).

BLAST CRISIS OF CHRONIC GRANULOCYTIC LEUKEMIA

DATA ON CASES TREATED WITH COMBINATION CHEMOTHERAPY CONTAINING Ara C

Yr.	Source	No. Pts.	R_x	Complete Remission
69	Hayes	24	AraC+BCNU	4
73	Resegotti	7	TRAP	1
74	Spiers	14	TRAMPCO (L)	4
74	Vallejos	24	COAP DOAP, OAP	3
75	Duhamel	22	AraC+Pred.	3
	TOTAL	91		15 (16%)

A, AraC = Cytosine Arabinoside; P, Pred. = prednisone
BCNU = 1,3 Bis (2 chloroethyl) 1-nitrosourea
T = Thioguanine; R, D = Daunorubicin; M = Methotrexate
C = cyclophosphamide; O = Oncovin; L = L-asparaginase

Figure 2

On the other hand, Canellos et al,[1] Marmont,[2] and Howes and Emerson[3] have reported excellent results (combined complete remission rate of 29%) using only vincristine and prednisone. Other investigators have been unable to duplicate these results, which suggests that there may exist a subpopulation of blast crisis patients whose disease is sensitive to these latter agents, similar to most lymphoid leukemias in this respect. It is therefore pertinent that Mathé et al[15] had noted in 1967 that the morphology of the blasts in patients undergoing transformation from CGL had lymphoid characteristics in most cases. Boggs[16] theorized that during the aggressive or acute leukemic phase, a clone of pluripotential stem cells expands and dominates the morphologic picture. These cells may take on characteristics of lymphoid, myeloid, or monocytoid differentiation to a greater or lesser extent. Subsequently, Beard et al[17] described seven cases of acute leukemia, six lymphocytic and one undifferentiated, in whom the Philadelphia chromosome was demonstrated, with pseudo-Pelger-Huet and hypogranular characteristics present in the circulating granulocytes. Two of the seven cases developed a CGL-like picture while in remission from the acute leukemia, but five did not. Beard and his investigators postulated that all these cases represent a blast crisis of CGL, with suppression of the usual chronic phase. Marmont and Damasio[2] noted that hypogranular blasts were present in the patients who had the best response in their series. Howes and Emerson[3] described a patient whose blast cells morphologically appeared lymphoid and in which the cytoplasm showed positivity with the periodic acid Schiff (PAS) stain. This patient obtained a prompt and prolonged remission initiated by high doses of vincristine and prednisone alone.

Further evidence favoring the lymphoid origin of the occasional blast crisis comes from the recent recognition of the enzyme, terminal deoxynucleotidyl transferase, in the blast cells of several cases of blast crisis of CGL.[18,19] This enzyme is normally found in lymphoid cells of thymic origin and has also been identified in leukemic cells from 12 of 14 cases of acute lymphoblastic leukemia, but not in leukocytes from other types of leukemia.

A recent review[20] of the clinical characteristics of 67 cases of blast crisis of CGL subdivided the blast cell line as follows: 38 myeloblastic, 21 lymphoblastic, 7 erythroblastic, and one unique blast cell type.

MORPHOLOGY OF BLASTS IN BLASTIC TRANSFORMATION

	LYMPHOID	MYELOID	MONOCYTOID
High N:C	+	±	-
Dark Blue Cytoplasm	+	±	-
Blue Grey Cytoplasm	-	±	+
Coarse Granules	-	+	-
Fine Granules	-	-	+
Auer Rods	-	+	+

N : C = nuclear cytoplasmic ratio

Figure 3

Morphology and Cytochemical Staining

Shaw et al[21] stressed the heterogeneity of the morphological and cytochemical features of the blasts in eight cases of blast crisis of CGL, but Hammouda et al[22] found lymphoid staining behavior in their four cases. Peterson, Bloomfield, and Brunning[14] were able to divide their cases into those with lymphoid characteristics and those with nonlymphoid characteristics. The morphologic features, which help in this differentiation, include: the nuclear cytoplasmic ratio; the presence of coarse cytoplasmic granulation, as opposed to fine or absent granulation; the staining character of the cytoplasm with ordinary hematologic stains; and the presence of Auer rods (Figure 3). There has been an upsurge in interest in cytochemical staining as an additional means of making distinctions between the types of blasts. Admittedly, there are some blast cells whose behavior to cytochemical stains is ambiguous or heterogonous, but some cases clearly show blast cells which stain with lymphoid characteristics, although these are probably in the minority. Figure 4 reviews the most useful stains for this purpose. Peroxidase and Sudan Black positivity in the myeloid type of blasts is helpful, whereas Oil Red O stains lymphoid but not myeloid cells. The particulate block-like positivity to PAS in the lymphoid type of cell is quite characteristic, provided it persists after diastase digestion for 30 minutes. Finer PAS positive granules have less specificity and for that reason less significance. Specific and nonspecific esterase stains may be difficult to interpret until one develops experience with them, but they may be helpfully confirmatory for the other stains. Unequivocal nonspecific esterase positivity identifies blast cells of monocyte origin.

CYTOCHEMICAL STAINS IN BLAST CRISIS OF CGL

	LYMPHOID	MYELOID	MONOCYTOID
Peroxidase	-	+	V
Sudan Black	-	+	V
Oil Red O	+	-	V
PAS*	$+^{1}$	V	V
Specific Esterase**	-	+	V
Non-sp'fic est'ase***	V	V	+

*PAS=PERIODIC ACID-Schiff; **Specific Esterase=Naphthol AS-D Chloroacetate esterase; ***Non-sp'fic est'ase=Alpha Naphthol Butyrate method; $+^{1}$ = Block - like particulate positivity; V = variable reaction.

Figure 4

Cytogenetics

Although Rowley[23] has recently stressed that in acute granulocytic leukemia patients who demonstrate no chromosomal abnormalities in their blasts have a therapeutic advantage over patients who do show abnormalities, the situation is not so clear in the blast crisis of CGL. With few exceptions, all of these blast-crisis patients have a Philadelphia chromosome present and the majority of them have an additional chromosomal abnormality. A double Philadelphia chromosome is sometimes observed. An extra chromosome 8 and abnormalities of chromosome 17 occur less frequently, but as a rule the further changes are heterogeneous with no useful prognostic pattern as yet identified. A possible exception to this last statement may be found in the observation of Canellos et al[1,24] that better results were obtained with vincristine-prednisone in patients with hypodiploidy in their blast karyotypes. These investigators did not correlate the presence of hypodiploidy with the possible lymphoid character of blasts as determined by other morphologic and cytochemical staining features. In the future this correlation should be made in analyses of data.

Our experience with the management of blast transformation identifies other features which seem to predict a favorable result. One of these, as in the case reported here, is the abruptness of the transformation. This generally correlates with the percentage of blasts appearing in the marrow, the total marrow cellularity, and the lack of marrow fibrosis. Contrariwise, a gradual increase in the aggressiveness of the chronic leukemia combined with a slowly increasing percentage of blasts would seem to imply a poor prognosis, as does increased marrow fibrosis demonstrated by bone marrow biopsy.

Plan for Therapy

Both the foregoing data and our own experience encourage us to propose the following strategy for therapy of blast crisis, which, although admittedly speculative, might improve the rate of complete remission and the length of survival:

1. The presence of blast crisis should be established by means of the following factors: marrow blasts greater than 30%, rising leukocyte alkaline phosphatase (LAP), cytogenetic aneuploidy, and associated clinical changes.

2. The predominant number of the blasts should be segregated into either lymphoid or nonlymphoid (i.e., myeloid, myelomonocytic, monocytoid, erythroblastic, etc.) cell types. This step will require the use of the morphological and cytochemical methods described above.

3. Patients with lymphoid blasts should be treated with high dose intravenous vincristine and oral prednisone. Nonlymphoid (myeloid) crises should be managed with cytosine arabinoside combined with one or more other agents, such as thioguanine,[25] cyclophosphamide,[26] adriamycin,[27] vincristine, and prednisone.

4. We would suggest that those patients in whom cytogenetic analysis indicates hypodiploidy be included in the lymphoid group and receive vincristine-prednisone alone as initial therapy, but we realize that this data may not be available when the decision to start treatment must be made.

5. Lastly, we have been encouraged by the reports of Sokal[28,29] and Gutterman et al[30] on the favorable responses in chronic and acute granulocytic leukemia with BCG scarification during maintenance of the remission state. We also are tempted to believe that the BCG administered to our patient may have favorably influenced the length of his remission. If subsequent experience substantiates the value of immunotherapy in this clinical setting, we further suggest that it be considered as adjuvant therapy in patients who attain complete remission.

While one can hardly expect to attain remission rates and survival durations comparable to those for acute granulocytic leu-

kemia, we feel nonetheless that significant improvement will result from following these guidelines.

Acknowledgment

W.R. McCrum, PhD, Department of Neurosurgery and Neurology, Henry Ford Hospital, Detroit, performed the statistical analysis.

References

1. Canellos GP, DeVita VT, Whang-Peng J, Carbone PP: Hematologic and cytogenetic remission of blastic transformation in chronic granulocytic leukemia. *Blood* **38**:671, 1971

2. Marmont AM, Damasio EE: The treatment of terminal metamorphosis of chronic granulocytic leukemia with corticosteroids and vincristine. *Acta Haemat* **50**:1, 1973

3. Howes D, Emerson P: Blast-cell transformation in chronic granulocytic leukaemia. Abstracted, *Lancet* **2**:1302, 1975

4. Canellos GP, Whang-Peng J, Schnipper L, Brown CH III: Prolonged cytogenetic and hematologic remission of blastic transformation in chronic granulocytic leukemia. *Cancer* **30**:288, 1972

5. Hayes DM, Ellison RR: Production of remissions in blastic phase of chronic myelocytic leukemia (CML) and acute myelocytic leukemia (AML) by arabinosyl cytosine (Ara-C) plus 1,3 BIS-B-(2-Chloroethyl)-1-Nitrosourea (BCNU). Abstracted, *Blood* **34**:840, 1969

6. Foley HT, Bennett JM, Carbone PP: Combination chemotherapy in accelerated phase of chronic granulocytic leukemia. *Arch Intern Med* **123**:166, 1969

7. Resegotti L, Falda M, Rossi M, Infelise VE: The management of blastic crisis of chronic myeloid leukaemia with thioguanine, rubidomycin, Ara-C and prednisone (TRAP regimen). *Panminerva Medica* **15**:275, 1973

8. Monfardini S, Gee TS, Fried J, Clarkson BD: Survival of chronic myelogenous leukemia: influence of treatment and extent of disease at diagnosis. *Cancer* **31**:492, 1973

9. Spiers ADS, Costello C, Catovsky D, Galton DAG, Goldman JM: Chronic granulocytic leukaemia: multiple-drug chemotherapy for acute transformation. *Brit J Med* **3**:77, 1974

10. Vallejos CS, Trujillo JM, Cork A, Bodey GP, McCredie KB, Freireich EJ: Blastic crisis in chronic granulocytic leukemia: experience in 39 patients. *Cancer* **34**:1806, 1974

11. Levin MC, Mims CH, Haut A: Dibromomannitol (NSC-94100): a clinical study of previously treated patients with refractory chronic myelocytic leukemia and blastic transformation. *Cancer Chemother Rep* **58**:223, 1974

12. Southwest Oncology Group: Cytarabine for acute leukemia in adults. *Arch Intern Med* **133**:251, 1974

13. Duhamel G, Najman A, Gorin N, Delous J, Elghouzi M: Etude de la transformation aiguë dans 45 cas de leucémie myéloïde chronique. *Nouv Rev Fr Hematol* **15**:301, 1975

14. Peterson LN, Bloomfield CD, Brunning RD: Blast crisis as an initial or terminal manifestation of chronic myeloid leukemia. *Am J Med* **60**:209,1976

15. Mathé G, Tubiana M, Colman R, Schlumberger JR, Berumen L, Choquet C, Cattan A, Schneider M: Les syndromes de leucémie aiguë (SLA) apparaissant au cours de l'evolution des hematosarcomes et des leucémies chroniques (Analyse Clinique). *Nouv Rev Fr Hematol* **7**:543, 1967

16. Boggs, DR: Hematopoietic stem cell theory in relation to possible lymphoblastic conversion of chronic myeloid leukemia. *Blood* **44**:449, 1974

17. Beard MEJ, Durrant J, Catovsky D, Wiltshaw E, Amess JL, Brearley, RL, Kirk B, Wrigley PFM, Janossy G, Greaves MF, Galton DAG: Blast crisis of chronic myeloid leukaemia (CML) 1. Presentation simulating acute lymphoid leukaemia (ALL). *Brit J Haemat* **34**:167, 1976

18. Sarin PS, Gallo RC: Terminal deoxynucleotidyltransferase in chronic myelogenous leukemia. *J Biol Chem* **249**:8051, 1974

19. McCaffrey R, Harrison TA, Parkman R, Baltimore D; Terminal deoxynucleotidyl transferase activity in human leukemic cells and in normal human thymocytes. *N Engl J Med* **292**:775, 1975

20. Rosenthal S, Canellos GP, DeVita VT Jr, Gralnick HR: Characteristics of blast crisis in chronic granulocytic leukemia. *Blood* **49**:705, 1977

21. Shaw MT, Bottomley RH, Grozia PN, Nordquist RE: Heterogeneity of morphological, cytochemical, and cytogenetic features in the blastic phase of chronic granulocytic leukemia. *Cancer* **35**:199, 1975

22. Hammouda F, Quaglino D, Hayhoe FGJ: Blastic crisis in chronic granulocytic leukaemia. Cytochemical, cytogenetic and autoradiographic studies in four cases. *Brit Med J* **1**:1275, 1964

23. Rowley JD: The role of cytogenetics in hematology. *Blood* **48**:1, 1974

24. Canellos GP, DeVita VT, Whang-Peng J, Chabner BA, Schein PS, Young RC: Chemotherapy of the blastic phase of chronic leukemia: Hypodiploidy and response to therapy. *Blood* **47**:1003, 1976

25. Clarkson BN, Dowling MD, Gee TS, Cunningham IB, Burchenal JH: Treatment of acute leukemia in adults. *Cancer* **36**:775, 1975

26. Whitecar HP Jr, Bodey GP, Friereich EJ, McCredie KB, Hart JS: Cyclophosphamide, vincristine, cytosine arabinoside and prednisone (COAP) combination chemotherapy for acute leukemia in adults. *Cancer Chemother Rep* **56**:543, 1972

27. McCredie KB, Bodey GP, Gutterman JU, Rodriguez V, Freireich EJ: Sequential adriamycin-Ara-C (A-OAP) for remission induction of adult leukemia. Abstracted, *Proc Am Assoc Cancer Res* **15**:62, 1974

28. Sokal JE, Aungst CW, Grace JT Jr: Immunotherapy of chronic myelocytic leukemia. *Natl Cancer Inst Monogr* **39**:195, 1973

29. Sokal JE: Immunologic studies in lymphoma and leukemia, and exploration of antitumor immunotherapy. *J Surg Oncol* **5**:557, 1973

30. Gutterman JU, et al: Chemoimmunotherapy of adult acute leukaemia prolongation of remission in myeloblastic leukaemia with BCG. *Lancet* **2**:1405, 1974

Appendix

Two by Two contingency table for determining $x2$ value for Ara-C combination treatment compared either to no treatment or to single-drug treatment.

TREATMENT	REMISSIONS		FAILURES		TOTAL
	Observed	Expected	Observed	Expected	
Ara-C combin.	15	8.95	76	82.05	91
None or One	20	26.05	245	238.95	265
TOTAL	35		321		356

$$x^2 \text{ (adjusted)} = S \frac{(\text{deviation}-0.5)^2}{\text{expectation}}$$

$$x^2 = \frac{(15-8.95-0.5)^2}{8.95} + \frac{(26.05-20-0.5)^2}{26.05} + \frac{(82.05-76-0.5)^2}{82.05}$$

$$+ \frac{(245-238.95-0.5)^2}{238.95} = 5.13$$

$x^2 = 3.841 \rightarrow p = 0.05$

$x^2 = 5.412 \rightarrow p = 0.02$

$x^2 = 5.13 \rightarrow p \text{ (interpolated)} = 0.026$