PAPERS AND ORIGINALS

Chronic Granulocytic Leukaemia: Multiple-drug Chemotherapy for Acute Transformation

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Summary

The response to 60 trials of therapy in 50 patients with chronic granulocytic leukaemia (C.G.L.) in acute transformation is reported. None of the 13 patients who received single-agent chemotherapy had a satisfactory response. The use of two drugs in combination produced only one satisfactory response in 30 patients. Various types of multiple-drug treatments in eight patients achieved one good response which lasted four months. In contrast when nine patients with rapidly progressive acute transformation of C.G.L. received a regimen—TRAMPCO(L)—incorporating seven or eight drugs (thioguanine, daunorubicin, cytarabine, methotrexate, prednisolone, cyclophosphamide, and vincristine, with or without L-asparaginase colaspase) five improved significantly. Four patients had a good clinical and haematological response with survival for over three, eight, over 12, and 14 and a half months; and one patient had a partial response. Toxicity was not extreme and maintenance therapy with the same regimen was given on an outpatient basis. TRAMPCO(L) seems superior to previously reported regimens and should be considered for rapidly progressive transformation of C.G.L. especially when simpler treatments have failed.

Introduction

Advances in antileukaemic chemotherapy have radically improved the prognosis of acute lymphoblastic leukaemia and produced a modest but definite increase in survival of

patients with various forms of acute myeloid leukaemia (Galton and Spiers, 1971). In contrast, the survival of patients with chronic granulocytic leukaemia (C.G.L.) remains little better than that observed 50 years ago in untreated patients (Minot *et al.*, 1924). In one controlled trial half of all patients receiving busulphan were dead within 170 weeks of beginning treatment, while patients receiving radiotherapy fared significantly worse (Medical Research Council, 1968). In over 70% of patients in the M.R.C.'s trial death was due to uncontrolled leukaemia. The disease underwent a change best described as metamorphosis (Baikie, 1969) in which the features of C.G.L. in its chronic phase were partly or wholly lost and the neoplasm behaved in a more malignant fashion. Metamorphosis of C.G.L. has many variants, with refractoriness to previously effective therapy as their only common denominator, but in about half the cases in the M.R.C. series the process was characterized by the accumulation of primitive cells in the bone marrow and peripheral blood and an acute course terminating within six months. This picture is usually termed acute transformation of C.G.L. and its most rapidly progressive form, with sudden onset and very rapid deterioration, used to be termed "blastic crisis" and is easily recognized though fortunately relatively uncommon.

Two major factors limit survival in C.G.L. Conventional therapy for the chronic phase, usually with busulphan, improves the quality of life but fails to postpone substantially the onset of metamorphosis. Treatment for metamorphosis, particularly when of the acute transformation type, is unsatisfactory and has had no significant effect on the median survival. Prolonged deferment of metamorphosis would improve the prognosis in C.G.L. and this is being attempted—for example, by active immunotherapy during the chronic phase (Sokal *et al.*, 1973). Improved treatment for acute transformation would also increase survival but in the past the disease has proved singularly refractory. Because of the wide range of variation in the mode of onset of metamorphosis and the lack of generally accepted criteria for defining its establishment or for separating the more acute from the less rapidly progressive cases it is difficult to compare different series of patients. Furthermore, there are no agreed criteria for assessing the extent of benefit conferred by treatment. Remission in the sense of a conversion to apparent haematological normality, as in the de novo acute leukaemias,

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is exceptionally rare. Return of the peripheral blood and bone marrow to the appearances of C.G.L. in its chronic phase might be an acceptable criterion of benefit, but intensive chemotherapy would prevent this from occurring. Cytogenetic evidence of the suppression of aberrant cell lines (Canellos *et al.*, 1971) is only useful in cases possessing such lines and not all laboratories have facilities for finding such evidence.

There are few reports of the results of therapy in series of patients with acute transformation of C.G.L. Satisfactory response to the use of a single agent is rare. In patients treated with single agents such as mercaptopurine, demecolcine, dibromannitol, and colaspase only rare responses have been reported, and the information has been mainly anecdotal. Mercaptopurine seems to be the "least bad" available single agent but it is nowhere recommended more strongly, and standard texts unenthusiastically recommend its use, usually without data to support the recommendation. Myelotoxic combinations such as prednisolone, vincristine, mercaptopurine, and methotrexate "pomp" produce occasional satisfactory responses at the price of severe and sometimes fatal toxicity. In a study of 13 cases treated with this combination (Foley *et al.*, 1969) there was one complete remission and three partial remissions. The nine failures included four deaths attributed to drug toxicity.

Out of 24 cases of C.G.L. in acute transformation treated with a combination of cytarabine and carmustine there were four complete remissions and four partial ones. There were 16 failures and drug toxicity was severe (Hayes and Ellison, 1969).

The more encouraging results of Canellos *et al.* (1971) and of Marmont and Damasio (1973) suggest that about one-third of patients may benefit from a combination of vincristine and prednisolone, which has low myelotoxicity but significant neurotoxicity and metabolic effects. In 30 cases studied by Canellos *et al.* treatment with prednisolone and vincristine produced six complete remissions and three partial ones. They found that chromosomal hypodiploidy apparently favoured a good response. Marmont and Damasio found that patients with acute transformation characterized by agranular blast cells were more likely to respond well to this regimen. Out of their 24 cases there were nine complete remissions and seven partial ones. Nine out of 15 patients with agranular blast cells had complete remissions while none of the nine patients with granulated blast cells did so.

We studied the response to treatment of 50 patients with C.G.L. which had undergone metamorphosis of the acute transformation type. Patients in whom metamorphosis was a subacute or chronic process with a long course despite the presence of an excess of immature cells in the blood or bone marrow were excluded from this series; in some instances this exclusion was only possible on retrospective analysis. Some of the 50 patients had two different treatments, separated by a definite interval, and thus were studied twice. We report here the results of 60 trials of therapy, with special reference to the use of an eight-drug combination which shows considerable promise.

Patients and Methods

All the patients were aged between 17 and 74 years and had typical C.G.L. at presentation, with marked leucocytosis and a differential leucocyte count which showed a complete spectrum of granulocytic cells with characteristic peaks in the percentages of myelocytes and neutrophils. In all patients the Philadelphia chromosome had been identified in direct preparations of bone marrow cells.

Acute Transformation was defined as the complex of clinical deterioration, usually with splenomegaly, resistance to

busulphan therapy, and progressive, rapid—that is, over a period of weeks—accumulation of primitive granulocytic cells in the peripheral blood or bone marrow or both.

Therapeutic Response was defined from the patients' viewpoint. Good response indicated the abolition of symptoms attributable to leukaemia, the ability to live at home with no special measures or with minimal support—for example, infrequent outpatient transfusions—and regression of splenomegaly, hepatomegaly, and lymphadenopathy. Partial response was rated as any improvement less than this but with definite subjective and objective benefit—for example, remission of symptoms and regression of organomegaly but requiring transfusion more than once a month. Haematological response signified reduction of bone marrow hypercellularity and the peripheral blood blast cell count, sometimes with improvement in the neutrophil count and regression of enlarged viscera, but without substantial improvement in wellbeing. Minor improvement in the symptoms of the disease accompanied by severe symptoms attributable to drug therapy was scored as a haematological response only, and all responses rated as haematological only were considered to be therapeutic failures. In practice all patients achieving a good or partial response showed concurrent haematological improvement, and no patient failed to show even a haematological response.

Therapy was of four main types. Before 1970, patients received either a single agent (see table I) or prednisolone (60 mg daily) plus a second drug (see table II). During 1970 because various types of multiple-drug chemotherapy had achieved improved results in *de novo* acute myeloid leukaemia several drug combinations were tested in patients with acute transformation (see table III). In 1971 a new regimen was devised (Spiers, 1972). Its name, TRAMPCO(L), is an acronym derived from the eight component drugs (see table IV). During initial therapy courses were given at 14-day intervals (five days' treatment and nine days' rest). The frequency of maintenance courses was determined by response and varied from three to 12 weeks. Nine patients with C.G.L. in acute transformation have so far been treated with this combination (see table V).

Results

The results of the first two approaches were very poor (tables I and II). Of the 43 patients 31 had only a haematological response. Reduction of grossly raised blast cell counts was often accompanied by relief of fever and bone pain, but responses were usually transient because neutropenia and thrombocytopenia precluded the continuation of drug therapy. Secondary drug resistance often developed rapidly, possibly because in many patients the C.G.L. had become a polyclonal neoplasm (Spiers and Baikie, 1968). Only 11 patients had sufficient benefit from treatment to be rated as partial responders, there was only one good result, and no response lasted longer than three months. Incomplete regression of splenomegaly with persisting thrombocytopenia, neutropenia, anaemia, and a high transfusion requirement,

TABLE I—Results of Treatment in 13 Patients with Chronic Granulocytic Leukaemia in Acute Transformation who received Single-agent Chemotherapy

Drugs Administered	Therapeutic Response		
	Good	Partial	Haematological Only
Dibromannitol	0	1	3
Mercaptopurine	0	1	4
Mannitol busulphan ..	0	0	2
Azathioprine	0	0	1
Methotrexate	0	0	1
Total	0	2	11

TABLE II—Results of Treatment in 30 Patients with Chronic Granulocytic Leukaemia in Acute Transformation who received Two Drugs Simultaneously

Drugs Administered	Therapeutic Response		
	Good	Partial	Haematological Only
Prednisolone + mercaptopurine 2.5 mg/kg/day	1	4	7
Prednisolone + mercaptopurine 1 g/wk	0	0	1
Prednisolone + demecolcine	0	2	5
Prednisolone + cyclophosphamide	0	0	1
Prednisolone + vincristine	0	1	6
Cytarabine + thioguanine	0	1	0
Hydroxyurea + mercaptopurine	0	1	0
Total	1	9	20

were major factors in preventing these patients from achieving a satisfactory clinical status.

The results of multiple-drug therapy during 1970 were little better (table III). One good response occurred and lasted four months, during which the patient lived at home and did not require transfusion. In the five patients whose response was haematological only—that is, clinical failures—it was notable that the circulating blast cells recovered rapidly from the effects of chemotherapy, while platelet and neutrophil counts suffered steady progressive decline. Repeated courses of chemotherapy aggravated pancytopenia while having progressively less effect on the blood and bone marrow populations of primitive cells. These observations suggested that an aggressive multiple-agent combination should be employed, with the objects of (a) inflicting maximal damage upon the blast cells at each treatment and allowing wider spacing of treatments and better opportunity for recovery of residual chronic-phase C.G.L. marrow, and (b) preventing the rapid emergence of secondary resistance to the anti-leukaemic drugs. The TRAMPCO(L) regimen was designed with this end in view and incorporates representatives of all the major types of drug known to be effective in the acute leukaemias (table IV).

TABLE III—Results of Treatment in Eight Patients with Chronic Granulocytic Leukaemia in Acute Transformation who received Three or More Drugs in Combination

Drugs Administered	Therapeutic Response		
	Good	Partial	Haematological Only
Prednisolone + vincristine + mercaptopurine	1	0	1
Prednisolone + daunorubicin + mercaptopurine + cytarabine	0	1	1
Prednisolone + thioguanine + hydroxyurea	0	0	1
Cyclophosphamide + demecolcine + dibromannitol	0	0	1
Prednisolone + daunorubicin + thioguanine + cytarabine + methotrexate	0	0	1
Prednisolone + vincristine + thioguanine + daunorubicin + cytarabine + cyclophosphamide + hydroxyurea	0	1	0
Total	1	2	5

TABLE V—Clinical Details of Nine Patients with Chronic Granulocytic Leukaemia in Acute Transformation treated with the TRAMPCO(L)

Case No.	Age	Sex	Duration of Chronic Phase (Months)	Treatment during Chronic Phase, in Chronological Order. Treatment after Transformation and before TRAMPCO(L)	Granular Blast Cells in Transformation Bone Marrow	Colaspase with TRAMPCO Therapy
1	26	F.	11	Busulphan, elective splenectomy,* busulphan, hydroxyurea (prednisolone + vincristine; no response)	+	+
2	25	F.	48	Busulphan (mercaptopurine; transient response)	+	—
3	21	F.	108	Busulphan (prednisolone + vincristine; no response)	—	—
4	56	F.	24	Busulphan (prednisolone + oxymetholone; no response)	+	—
5	40	F.	42	Busulphan	+	+
6	60	M.	36	Busulphan (splenectomy)	+	+
7	45	M.	12	Busulphan (hydroxyurea; no response)	+	—
8	16	M.	12	Busulphan, elective splenectomy,* busulphan, mercaptopurine, melphalan	+	—
9	25	M.	31	Methotrexate, mercaptopurine, elective splenectomy*	+	—

*Elective splenectomies were performed in cases 1, 8, and 9 during chronic phase of C.G.L. as part of another therapeutic study

TABLE IV—The TRAMPCO(L) Regimen

Drug	Dose	Route	Duration*
Thioguanine	100 mg/m ² /day	By mouth	3-5 Days
Rubidomycin (daunorubicin)	40 mg/m ²	I.V.	Day 1 only
Ara-C (cytarabine)	100 mg/m ² /day	I.V. (push)	3-5 Days
Methotrexate	7.5 mg/m ² /day	I.V. (push)	3-5 Days
Prednisolone	200 mg/day	By mouth	Days 1-5
Cyclophosphamide	100 mg/m ² /day	I.V.	3-5 Days
Oncovin (vincristine)	2 mg	I.V.	Day 1 only
L-asparaginase (colaspase)	8,000 U/m ² /day	I.V.	Days 1-28

*Where a variable duration is indicated, drugs were usually given for three days on course 1, four days on course 2, and five days on course 3, if tolerated. After course 3 drugs other than prednisolone, vincristine, and colaspase could be given in augmented dosage if tolerated.

This treatment has been used in nine patients with C.G.L. in acute transformation (table V). An attempt was made to classify the predominant primitive cell in each patient as "granular" or "agranular" after Marmont and Damasio (1973). Classification as "agranular" signified undifferentiated blast cells with cytoplasmic basophilia and no granules; these cells could not with confidence have been identified as of myeloid origin without knowledge of the antecedent diagnosis of C.G.L. "Granularity" signified that a proportion of the blast cells had cytoplasmic granulation; inevitably such cells had a more "myeloid" appearance. Four patients had a good response with complete remission of symptoms and signs, peripheral blood counts with no abnormality other than mild anaemia, and substantial reduction in the number of primitive cells in the bone marrow. They were able to resume normal activities and to continue treatment as outpatients. The outcome of the therapy in each patient is given below.

Case 1.—This patient had a good response. Blast cells cleared from her blood after the second course of treatment. She maintained hypocellular bone marrow and normal peripheral blood values without transfusion for 14 weeks. She returned to work, but the blast cells returned at the 15th week. She had eight courses of treatment altogether, and afterwards she received high-dose busulphan with carmustine and thiotepe. Her haemoglobin was well maintained with few transfusions, and she survived for 14½ months after transformation.

Case 2.—The blast cells cleared from this patient's peripheral blood, splenomegaly regressed, and her symptoms were abolished. Her response was good, and she was able to travel extensively between the 12 courses of treatment she was given. Her leukaemia finally became progressively more resistant and after more intensive TRAMPCO therapy she succumbed with septicæmia and renal failure eight months after transformation.

Case 3.—The partial response of this woman consisted in prompt and complete regression of splenomegaly, blasts cleared from peripheral blood with the first course and did not return, and her symptoms improved. Three courses of TRAMPCO were given. The platelet count improved but did not become normal, and transfusions were necessary to maintain haemoglobin, but

she was able to live at home. She eventually died four months after transformation from klebsiella septicaemia.

Case 4.—The response in this patient was haematological only. After one course of treatment peripheral blood cleared of blast cells, but she died with a pulmonary embolus before the second course was due, having survived three months of transformation.

Case 5.—There was a rapid fall of blast cells after each treatment in this patient with haematological response but an equally rapid return to high values. There was some relief of symptoms. Doses were escalated on successive courses and neutropenia and thrombocytopenia were severe. She died of hypostatic pneumonia three months after transformation and shortly after the third course of TRAMPCO(L).

Case 6.—The response of this patient was haematological only. Splenectomy was performed before TRAMPCO(L) was begun. Post-operatively blast cells fell and neutrophils and platelets rose. The first course of TRAMPCO(L) caused a 90% fall in blast cells with no decline in neutrophils or platelets, but the patient died of bilateral bronchopneumonia before the second course, having survived transformation for three months.

Case 7.—A good response in this patient resulted in an immediate complete regression of 9-cm splenomegaly and gross cervical lymphadenopathy. Abnormal monocytoid blast cells cleared from peripheral blood and reduced to 10% in bone marrow. Clinical improvement was sufficient to justify a splenectomy. Since the splenectomy he has been working and has maintained a normal blood count without transfusion. He has had six courses of TRAMPCO—the last three at three-month intervals—and radiotherapy for recurrent cervical lymphadenopathy. At the time of this report he was alive and well, over 12 months after the start of transformation.

Case 8.—The response in this patient was haematological only. The blast cell count fell but rebounded after each of two courses of TRAMPCO. Nevertheless, symptoms attributable to uncontrolled leukaemia were relieved. Severe oral moniliasis and bacterial glossitis precluded further therapy with drugs likely to exacerbate his stomatitis, so TRAMPCO was abandoned. At the time of this report he had survived transformation for over two months.

Case 9.—After the first course of TRAMPCO the response in this patient was good, and blast cells cleared from peripheral blood. His bone marrow became less cellular and previous excess of primitive cells was no longer present. The patient lived at home, and had normal platelet and neutrophil counts: haemoglobin was 10 g/100 ml, and he has had no blood transfusion at any stage. He was alive at the time of this report, over three months after the start of transformation.

In the only patient with "agranular" blast cells (case 3) the peripheral blast cell count had fallen with prednisolone and vincristine, but splenomegaly and marrow hypercellularity with 80% of primitive cells persisted. Major improvement resulted from TRAMPCO(L) therapy with complete regression of 5-cm splenomegaly, but transfusions were still needed and response was rated as partial. Survival in the four patients achieving a good response was unexpectedly long considering the acute onset and rapid progression of metamorphosis in each. Prolonged survival and absence of pancytopenia in case 1 seemed possibly related to the previous splenectomy; for this reason splenectomy was performed before TRAMPCO(L) was begun in case 6. The patient in case 7 was splenectomized after an excellent response to chemotherapy. The operation was uncomplicated and it is hoped that the absence of a spleen will ameliorate his future

course. This patient, a professional man, was in active practice at the time of writing.

TOXICITY

Though inspection of the TRAMPCO(L) schedule (see table IV) suggests that the toxicity of this regimen might be extreme this was not the case. Nausea and vomiting occurred in six patients, but it was severe and protracted only in the three patients who received colapsase (TRAMPCO(L)). In six patients the colapsase was omitted (TRAMPCO). Three patients had mouth ulcers and one had considerable alopecia. Pancytopenia occurred in all patients but was not more severe than had been observed in patients treated with only two to four drugs. In most patients it was in fact possible to make one or more increments in dosage on successive courses of TRAMPCO(L). Steroid side effects were uncommon; the steroid dose was high but maintained for only five days, with intervals of 2-12 weeks (mean three weeks) between courses. No patient refused to continue therapy with TRAMPCO(L).

Discussion

The results of treatment in our first 43 patients confirm the widespread impression that acute transformation of C.G.L. rarely responds to steroids or mercaptopurine. No complete remissions occurred in seven patients who received prednisolone and vincristine. The more elaborate drug combinations used in the next eight patients possessed no clear advantage over the earlier treatments. The use of seven or eight drugs in combination (TRAMPCO or TRAMPCO(L)), however, in nine patients produced four unexpectedly satisfactory responses with a mean survival of more than nine months. All nine patients had rapidly progressive acute transformation of C.G.L. and most were seriously ill when treatment began. The only patient with "agranular" blast cells did not have a satisfactory response to treatment. Three of the four patients who achieved a good response with TRAMPCO(L) had failed to respond to other regimens which have been advocated for acute transformation.

These results can only be regarded as preliminary. Nevertheless, the TRAMPCO(L) regimen is acceptable to patients and toxicity is not prohibitive. The responses produced in acute transformation of C.G.L. were of good quality and of a duration unusual in this disease. While the less aggressive combination of prednisolone with vincristine may be preferred for the initial treatment of acute transformation some 70% of patients will not respond and in these the TRAMPCO(L) regimen should be tried.

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