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Relationship of the Duration of the Chronic Phase in Chronic Granulocytic Leukaemia to the Need for Treatment During the First Year After Diagnosis

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Summary. *From a data base of 203 patients with chronic granulocytic leukaemia (CGL) seen at our institution during the period 1972–1981, we identified 25 patients in whom duration of the chronic phase could be accurately determined and who had received only busulphan or no treatment at all during the first year after diagnosis. Twenty-one of the patients had Ph^1 chomosome-positive disease but in four patients the Ph^1 status was unknown. We found a significant correlation between the total dose of busulphan administered during the first year of disease (range 300–1,300 mg) and the duration of chronic phase disease (range 13–72 months). In confirmation of this relationship, we identified a further 11 patients in chronic phase continuing 47–136 months after diagnosis in whom the total dose of busulphan administered in the first year of disease ranged from 0 to 300 mg. We conclude that calculation of the total dose of busulphan administered in the first year after diagnosis of chronic phase disease might allow prediction of the duration of the chronic phase in other patients and could be of value in selecting candidates for experimental therapeutic approaches, such as bone marrow transplantation.*

Introduction

The survival of patients with CGL ranges from a few months to 15 or more years after diagnosis, and many attempts have been made to predict prognosis in individual patients. Some writers have tried to identify 'static' clinical or haematological features assessed at diagnosis which correlate with survival [6, 7, 9, 11, 16], but results obtained by analysis of one series of patients have not in general been applicable to other series. Perhaps more logically, others have examined 'dynamic' features of the disease, e.g., the kinetic characteristics of blast cells at diagnosis [15], the leucocyte count halving time with standardised treatment [4], or the doubling time following treatment [1]; these analyses, however, take no account of the extent of disease at the time of diagnosis. We report in this paper the results of examining the relationship between the duration of chronic phase in 25 patients with previously untreated CGL and the amount of busulphan administered during the first year after diagnosis – a measure that might reflect both static and dynamic features of the disease.

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Patients and Methods

Patients with Chronic Phase of Known Duration. We have collated clinical and haematological data on 203 patients with CGL seen on one or more occasions in the MRC Leukaemia Unit during the period 1972–1981; in fact the majority of these patients were diagnosed during the period 1976–1981 and 110 of these are alive still in the chronic phase of their disease. From this patient population, we sought to identify patients who satisfied the following criteria:

1. They were diagnosed as having CGL in chronic phase but later underwent transformation to an acute phase as defined by Canellos et al. 1971 [2]. Patients were excluded from consideration if they presented in transformation, if they entered transformation within 1 year of diagnosis, or if the transformation was so insidious that its date of onset could not be accurately assessed. They were also excluded if adequate follow-up data including details of treatment could not be obtained from the referring hospital.

2. They were treated exclusively with busulphan during the first year after diagnosis. Patients who during the first year after diagnosis received other cytotoxic drugs in addition to or instead of busulphan were excluded from analysis. (In practice patients were treated initially by leucapheresis to collect blood stem cells for cryopreservation; they started busulphan usually soon after the fourth collection procedure.)

3. They were known to have Ph^1 chromosome-positive disease (21 cases) or had haematologically typical CGL without cytogenetic confirmation of the Ph^1 chromosome (4 cases). Patients with haematologically atypical disease or those known to be Ph^1-negative were excluded from the analysis.

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Of the 203 patients for whom we had data, 178 were excluded from further consideration on the basis of one or more of the above criteria. Further analysis was based on the remaining 25 patients.

Busulphan Treatment. Busulphan was administered during the first year after diagnosis in one of three ways: (1) Ten patients received busulphan at a low dosage (2–8 mg/day) until the leucocyte count was normal or near-normal, at which point treatment was interrupted until the leucocyte count began to rise again [4]; in general treatment was reinstituted before the leucocyte count rose to 20 × 10^9/l; (2) Twelve patients were treated with single 50, 100, or 150 mg doses at monthly or greater intervals; the exact dose of busulphan was determined by the leucocyte count in accordance with a standard scheme [17]; (3) Three patients received busulphan at a low dosage, i.e., busulphan was continued on a 'maintenance' basis to control the leucocyte count in the range 4–10 × 10^9/l.

Results

The clinical and haematological data for the 25 patients with chronic phase of finite duration are

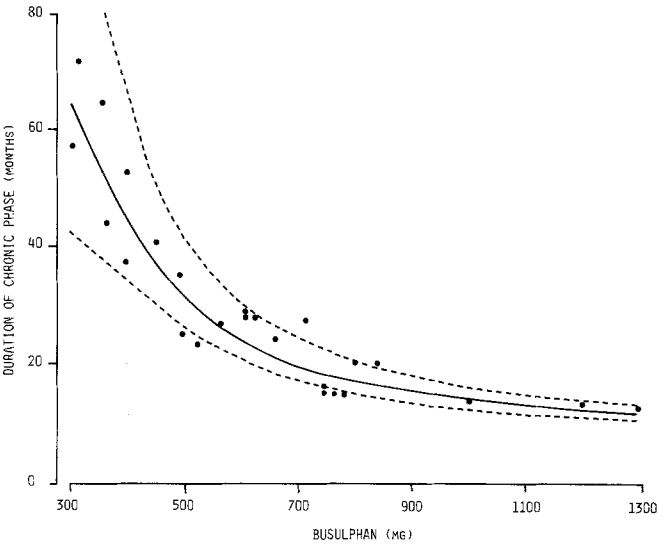

Fig. 1. The relationship between total dose of busulphan administered during the first year after diagnosis and duration of chronic phase in 25 patients with CGL. The *dashed lines* define the 90% prediction bands (see Appendix)

Table 1. Clinical and haematological data on 25 patients with CGL treated only with busulphan in their first year of diagnosis

Patients	Sex	Age at diagnosis (years)	Spleen[b] (cm)	Liver[c] (cm)	Leucocyte count (× 10^9/l)	Blasts (%)	Granulocyte[d] precursors (%)	Haemoglobin (g/dl)	Platelets (× 10^9/l)
1 RN	M	26	1	0	160.0	2	30	10.1	320
2 VM	F	43	15	0	256.0	12	40	7.7	450
3 KD	M	17	7	0	151.2	0	12	8.9	41
4 TW	M	23	20	–	190.0	2	–	8.6	1,200
5 AG[a]	M	35	5	0	99.4	0	25	15.6	400
6 MC	F	29	20	0	269.0	1	12	7.3	634
7 MW	M	31	14	0	197.0	4	40	9.8	350
8 RZ[a]	M	17	11	0	230.4	2	27	11.4	680
9 DC[a]	M	33	3	0	180.0	2	14	10.5	425
10 HB	F	56	14	6	322.0	1	28	12.0	1,045
11 AO	F	61	10	0	240.0	8	34	9.1	350
12 GS[a]	M	69	4	4	99.4	1	21	11.1	510
13 PC	M	17	18	0	99.0	2	6	11.4	508
14 MS	F	53	11	7	32.1	11	19	8.2	455
15 GG	M	29	25	5	505.0	6	49	7.1	320
16 DP	M	40	9	6	290.0	0	24	9.1	155
17 TP	F	19	25	1	253.5	10	22	7.6	560
18 DF	M	34	20	–	223.0	2	20	6.3	174
19 SB[a]	F	24	11	0	277.0	5	24	9.3	786
20 RB	M	37	12	0	348.0	5	35	8.5	1,300
21 RH	M	60	17	3	241.0	2	7	8.2	1,164
22 CC	M	34	15	6	400.0	1	34	10.1	142
23 BH	M	20	25	0	319.2	4	25	6.3	236
24 AM	F	58	15	5	399.0	3	39	10.7	417
25 IW	M	18	–	–	620.0	–	–	7.2	900
Mean		35.3	13.6	1.9	25.6	3.6	25.5	9.3	541
Range		17–69	1–25	0–7	32.1–620.0	0–12	6–49	6.3–15.6	41–1,300

[a] Incidental diagnosis, e.g., at routine blood test for pregnancy, blood donor or insurance examination
[b] Spleen size measured from the left costal margin
[c] Liver size measured from the right costal margin
[d] Granulocyte precursors = promyelocytes + myelocytes
– Data not available

summarised in Table 1. In five cases diagnosis occurred 'incidentally' at times when the patient was free of symptoms; the other patients had a variety of symptoms that led to diagnosis. The total dose of busulphan administered in the first year after diagnosis ranged from 300 to 1,300 mg (Table 2); the duration of chronic phase disease ranged from 13 to 72 months. The relationship between the total dose of busulphan administered in the first year and the overall duration of chronic phase is shown in Fig. 1.

Table 2. Busulphan dosage and duration of chronic phase in 25 patients treated with busulphan

Patients	Total amount of busulphan taken within a year of diagnosis (mg)	Method of administration of the busulphan[a]	Splenectomised in chronic phase[b]	Splenectomy performed within a year of diagnosis[b]	Duration of chronic phase (months)
1 RN	308	IH	Y	N	72
2 VM	353	IL	Y	Y	65
3 KD	300	IH	Y	Y	57
4 TW	392	IL	Y	Y	53
5 AG	366	IH	N	–	44
6 MC	450	IL	N	–	41
7 MW	400	IH	Y	N	37
8 RZ	496	CL	Y	N	35
9 DC	600	IH	Y	Y	29
10 HB	626	IL	Y	N	28
11 AO	717	CL	N	–	28
12 GS	600	IH	N	–	28
13 PC	560	IL	Y	N	27
14 MS	500	IH	Y	Y	25
15 GG	666	IL	Y	Y	24
16 DP	524	IH	N	–	22
17 TP	802	IL	Y	Y	20
18 DF	835	IL	N	–	20
19 SB	750	IH	Y	Y	16
20 RB	750	IL	N	–	15
21 RH	787	IH	N	–	15
22 CC	800	IH	Y	Y	15
23 BH	1,000	IH	N	–	14
24 AM	1,200	IL	Y	Y	14
25 IW	1,300	CL	N	–	13

[a] IH, intermittent high-dose busulphan; IL, intermittent low-dose busulphan; CL, continuous low-dose busulphan
[b] Y, yes; N, no

Table 3. Clinical, haematological, and treatment data for 11 patients continuing in chronic phase for 47 months or longer

Patients	Sex	Age (years)	Diagnostic information			Amount of busulphan taken in 1st year (mg)	Duration of 1st chronic phase (months)[a]	Method of administration[b]
			Leucocytes $\times 10^9$/l	Spleen (cm)	Liver (cm)			
1 JG	F	51	13.3	2	0	0	136	–
2 EA	M	37	42.0	1	0	0	123	–
3 LH	F	24	47.0	–	–	0	118	–
4 RM	F	36	43.6	1	1	100	55	IH
5 SP	M	46	107.0	3	0	140	60	IL
6 FM	F	27	328.9	23	1	152	60	IL
7 PG	F	30	400.0	20	1	180	72	IL
8 KK	F	31	80.6	1	0	200	59	IH
9 RC	F	42	182.0	2	0	200	47	IH
10 DD	M	30	315.0	15	0	268	60	IL
11 GD	F	68	180.0	1	0	300	81	IH

[a] Data analysed on 9th July 1981
[b] All abbreviations as in Table 2

The continuous line shown in the figure was obtained by trial and error. When an empirical formula (see Appendix) was used, a straight line with a correlation coefficient of -0.92 and a P-value less than 0.0001 could be derived. We attempted also to relate the duration of chronic phase disease to the total dose of busulphan administered within the first year of diagnosis after correction of the dosage for the patients' body weight. The correlation was less good (data not shown).

For the 11 patients in whon chronic phase disease was relatively protracted, its duration ranged from 47 to 136 months (Table 3). The dose of busulphan administered to these patients during the first year after diagnosis ranged from 0–300 mg.

Discussion

It has in the past been suggested that transformation occurs in a random manner [12]; more probably the occurrence of transformation depends on features intrinsic in the patient's disease, some or all of which cannot be accurately measured [10, 13]. In practice the duration of chronic phase disease may be related to at least two characteristics of a patient's disease: (1) the rate ('tempo') at which it evolves, which may differ from patient to patient; and (2) the point to which the disease has progressed at the time of diagnosis. These characteristics may or may not be interdependent. It follows, however, that to assess either of them alone is unlikely to yield meaningful results: for example, any attempt at a correlation between duration of survival and specific features assessed at diagnosis could only be expected to yield reproducible results if the tempo of disease was the same in all patients, which is unlikely to be the case; conversely, to attempt to assess prognosis on the basis solely of a kinetic measurement, such as the leucocyte count doubling time assessed after one course of treatment, could be unreliable because it takes no account of the extent of disease at diagnosis, which may vary from patient to patient. For a priori reasons a parameter that takes account of both the tempo of disease and the extent of disease at diagnosis would be expected to give the clinician a good guide to prognosis. It seemed to us that the amount of treatment, in this case busulphan, necessary to control a patient's disease during a finite period after diagnosis might reflect both the tempo and the extent of the disease; it might also reflect other unrecognised factors peculiar to an individual patient that also influence prognosis. In the 25 patients in this study busulphan dosage in the first year after diagnosis was significantly related to the duration of their first chronic phase.

To attempt to predict the duration of chronic phase for patients treated with busulphan doses outside the limits of our sample population is not necessarily valid. If, however, the general relationship that we postulate does apply, one might expect patients with low requirements for busulphan during their first year of disease to fare especially well. The data in Table 3 confirm that patients requiring little or no treatment within the first year after diagnosis have an excellent chance of becoming long survivors.

We cannot as a result of this study say whether the requirement for a drug other than busulphan, e.g., hydroxyurea, would correlate equally well with duration of chronic phase. It is possible that busulphan may have accelerated that onset of transformation in patients who, if treated with drugs with a less pronounced mutagenic potential, might have survived longer. It is clear, however, that for the 25 patients included in this study the requirement of busulphan allowed a reasonable estimate of the duration of the chronic phase; further studies will show whether the relationship between treatment and duration of chronic phase can be extended to other series of patients and to the use of other drugs.

Methods for treating patients with CGL are relatively unsatifactory [14]. The use of busulphan or hydroxyurea alleviates symptoms for patients with chronic phase disease but does not greatly prolong survival. Combinations of cytotoxic drugs or treatment by autografting offer modest benefit for some patients in transformation. Successful eradication, at least temporarily, of the Ph^1-positive clone of myeloid cells can be achieved by bone marrow transplantation where the patient has an identical twin [3, 5], and allografting with marrow from HLA-compatible sibs is now being undertaken for patients still in the chronic phase of their disease. If one could reliably predict the duration of chronic phase for an individual patient it would greatly facilitate the difficult decision of whether or not to recommend allogeneic marrow transplantation in an individual case.

Appendix

In Fig. 1 the duration of the chronic phase in months is plotted as the ordinate, y, and the total amount of busulphan (mg) administered in the first year after diagnosis as the abscissa, x. The *continuous line* shown on Fig. 1, which was found by trial and error

to give an adequate description of the observed data, is one of a family of curves with the empirical formula:

$$y = 10^{e^{e^{mx+c}}}$$

where m and c are constants. The values of these constants were determined by computation of the regression line for the relationship between z and x where:

$$\text{since } z = \ln[\ln(\log y)] \quad \ln[\ln(\log y)] = mx + c \quad z = mx + c.$$

This relationship should approximate to a straight line if the original assumption about the nature of the curve was correct: in practice the correlation coefficient between z and x is -0.92, which gives a P-value of < 0.0001 for the t-test, so that the assumption was justified. m and c were calculated as the gradient and the intercept, respectively, on the z-axis of the regression line. This regression line, calculated by the method of least squares, is shown in Fig. 2, from which:

and $m = -1.954 \times 10^{-3} \cdot \text{mg}^{-1}$
and $c = 0.067$.

The difference between the observed and expected data, calculated from the line of best fit, is not significant at the 5% level when tested by the chi-square test. The dashed lines in Fig. 1 are the boundary lines of the 90% prediction bands, i.e., they indicate the area within which one can be 90% confident that a new value of y will fall for an observed value of x [8]. They are defined as:

$$z_{x_i} = \bar{z} + m \cdot (x_i - \bar{x}) \pm t_{n-2 \cdot 1-a/2} \cdot S \cdot \frac{z}{x} \sqrt{1 + \frac{1}{n} \frac{(x_i - \bar{x})^2}{n-1 \cdot Sx^2}}$$

Where:

y = duration of the chronic phase
x = total amount of busulphan (mg) taken within a year of diagnosis
z = $\ln[\ln(\log y)]$
z_{x_i} = limits of the predicted value of z from a newly observed value of x
z_i = observed value of z
z_x = expected value of z calculated from regression line
$\bar{z}$ = mean of z
$\bar{x}$ = mean of x
x_i = observed value of x
m = gradient of the regression line of z against x
$t_{n-2 \cdot 1-a/2}$ = the $100.(1-a/2)\%$ point of the t distribution with $n-2$ degrees of freedom
n = number of patients

$$S^2_{z/x} = \frac{1}{n-2} \cdot \sum_1^n (z_i - z_x)^2$$

$$S^2_x = \frac{1}{n-1} \cdot \sum_1^n (z_i - \bar{z})^2 .$$

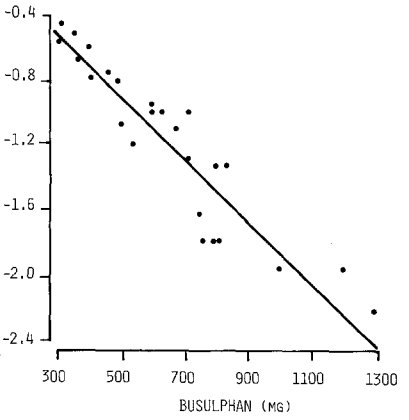

Fig. 2. Relationship between z (see Appendix) and total dose of busulphan administered during the first year of diagnosis in 25 patients with CGL. ($R = 0.92$, $P < 0.0001$)

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References

1. Bergsagel DE (1967) The chronic leukaemias: A review of disease manifestations and the aims of therapy. Can Med Assoc J 96: 1615
2. Canellos GP, DeVita VT, Whang-Peng J, Carbone PP (1971) Hematologic and cytogenetic remission of blastic transformation in chronic granulocytic leukemia. Blood 38: 671
3. Fefer A, Cheever MA, Thomas ED, Boyd C, Ramberg R, Glucksberg H, Buckner CD, Storb R (1979) Disappearance of Ph^1-positive cells in four patients with chronic granulocytic leukemia after chemotherapy, irradiation and marrow transplantation from an identical twin. N Engl J Med 300: 333
4. Galton DAG (1959) Treatment of the chronic leukaemias. Br Med Bull 15: 79
5. Goldman JM, Johnson SA, Catovsky D, Agnarsdottir G, Goolden AWG, Galton DAG (1981) Identical twin marrow transplantation for patients with leukemia and lymphoma. Transplantation 31: 140
6. Jacquillat C, Chastang C, Tanzer J, Briere J, Weil M, Pereira-Neto M, Gemon-Auclerc MF, Schaison G, Domingo A, Boiron M, Bernard J (1978) Prognostic factors in chronic granulocytic leukemia. A study of 798 cases. Boll Ist Sieroter Milan 57: 237
7. Kardinal CG, Bateman JR, Weiner J (1976) Chronic granulocytic leukemia. Review of 536 cases. Arch Intern Med 136: 305
8. Kleanbaun DG, Kupper LL (1978) Applied regression analysis and other multivariable methods. Duxbery Press, MA, USA
9. Monfardini S, Gee T, Fried J, Clarkson B (1973) Survival in chronic myelogenous leukemia: Influence of treatment and extent of disease at diagnosis. Cancer 31: 492
10. Preisler HD, Reese PA (1980) Another look at survival curves in chronic myelocytic leukemia. Am J Hematol 9: 123
11. Schilling RF, Crowley JJ (1979) Prognostic signs in chronic myelocytic leukemia. Am J Hematol 7: 10

12. Sokal JE (1976) Evaluation of survival data for chronic myelocytic leukemia. Am J Hematol 1: 493
13. Spiers ASD (1976) The problem of acute transformation in chronic granulocytic leukaemia: A hypothesis concerning its genesis and manoeuvres to postpone its onset. Haematologica (Pavia) 61: 488
14. Spiers ASD (1978) Improved therapy for chronic granulocytic leukemia. Boll Ist Sieroter Milan 57: 370
15. Stryckmans PA (1974) Current concepts in chronic myelogenous leukemia. Semin Hematol 11: 101
16. Tura S, Baccarani M, Corbelli G and the Italian Cooperative Study Group on Chronic Myeloid Leukaemia (1981) Staging of chronic myeloid leukaemia. Br J Haematol 47: 105
17. Vicariot M, Goldman JM, Catovsky D, Galton DAG (1979) Treatment of chronic granulocytic leukaemia with repeated single doses of busulphan. Eur J Cancer 15: 559

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