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Treatment of Chronic Granulocytic Leukaemia with Repeated Single Doses of Busulphan

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Abstract—*We have treated* 15 *patients with chronic granulocytic leukaemia in the chronic phase with single doses of* 50, 100 *or* 150 mg *of busulphan repeated as necessary every* 4 weeks. *The mean leucocyte halving time after the first dose of busulphan was* 13.4 days (*range* 4–39). *The mean time for patients to achieve a leucocyte count of* $11 \times 10^9/l$ *was* 7.2 weeks (*range* 2–19). *There were no immediate side-effects of the drug given in this manner. Marrow hypoplasia, which proved reversible, occurred in one patient but was not directly attributable to treatment with busulphan. The results of this and previous studies suggest that the administration of busulphan in intermittent high doses is convenient for the patient and probably as safe as longer term low dosage treatment. There is no evidence that it prolongs the duration of the chronic phase or survival.*

INTRODUCTION

PATIENTS with newly diagnosed chronic granulocytic leukaemia (CGL) who have symptoms are usually treated initially with busulphan at daily doses of 4–6 mg continued for several weeks. An alternative dosage schedule in which busulphan is administered in single large doses might be more convenient for the patient and might in the long term prove less toxic. Sullivan and his colleagues recently reported the use of such a schedule in a series of 17 patients whose mean survival was 137 weeks [1]. They concluded that the method was at least as effective as continuous low-dose busulphan. Douglas and Wiltshaw have arrived at the same conclusion [2]. In the last three years we have treated 15 patients with repeated high doses of busulphan and their initial response to therapy is reported here.

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MATERIALS AND METHODS

Patients

Fifteen patients with Philadelphia-chromosome-positive CGL were entered in this pilot study. Their mean age at diagnosis was 39.9 yr: 7 were female and 8 were male. Further clinical and haematological details are given in Table 1. Thirteen of the patients were treated initially by leucapheresis on the continuous-flow blood-cell separator [3] but only two patients had previously received cytotoxic drugs, hydroxyurea in one case and hydroxyurea and busulphan in the other (Table 2). The median interval between diagnosis and beginning treatment with high-dose busulphan was 8 weeks (range 1–250 weeks). Busulphan was given initially as a single large dose and the need for further doses was assessed thereafter at four week intervals; the actual dose that a patient received was based on the scheme shown in Table 3, which the clinician was free to modify in the light of the patient's previous response. For the convenience of the patients special capsules each containing 50 mg busulphan were prepared in the hospital pharmacy.

One criterion of response was the time

Table 1. Clinical and haematological details of 15 patients with CGL at diagnosis

Patient	Sex	Age (yr)	Liver (cm)	Spleen (cm)	Hb (g/dl)	WBC ($\times 10^{-9}$/l)	Blast cells (%)	Platelets ($\times 10^{-9}$/l)
1. CC	M	34	6	16	9.0	360	1	745
2. WW	M	65	6	14	9.4	176	3	308
3. BH	M	20	0	21	6.3	319	4	236
4. SB	F	24	0	11	9.6	277	5	386
5. KT	F	22	0	11	7.4	449	1	745
6. JN	M	42	1	0	13.5	80	0	600
7. GD	F	68	2	14	10.7	136	1	640
8. RC	F	42	0	2	9.3	187	2	188
9. DC	M	33	0	3	8.0	180	2	400
10. GSW	M	50	0	0	15.1	15	0	NA
11. GB	M	66	6	12	7.4	217	1	200
12. NB	F	45	0	0	13.9	55	2	1080
13. KD	M	17	0	8	8.9	151	0.4	41
14. KK	F	32	0	1	13.5	124	3	500
15. RMcN	F	37	edge	tip	12.2	44	0	760

NA—Not available.

Table 2. Clinical and haematological details of 15 patients at start of high-dose busulphan treatment

		At start of high-dose busulphan						
Patient	Previous treatment	Time from diagnosis (weeks)	Liver (cm)	Spleen (cm)	Hb (g/dl)	WBC ($\times 10^{-9}$/l)	Blasts (%)	Platelets ($\times 10^{-9}$/l)
1. CC*	CFC × 4	4	6	16	8.8	362	2	270
2. WW	CFC × 26, HU, BUS	250	4	7	8.6	251	9	230
3. BH	CFC × 6	8	0	21	7.0	220	4	150
4. SB*	CFC × 5	3	4	9	10.8	218	3	600
5. KT	CFC × 6	2	2	12	11.7	217	1	935
6. JN	Nil	71	0	17	9.5	210	6	840
7. GD	Nil	4	2	14	11.4	180	2	180
8. RC*	CFC × 4	3	0	5	11.7	160	1	200
9. DC*	CFC × 5	4	0	3	10.7	147	2	230
10. DSW	CFC × 5	86	3	8	11.1	98	1	270
11. GB	CFC × 3, HU	65	0	0	11.4	72	0	286
12. NB	CFC × 4	13	0	0	11.2	62	0	848
13. KD*	CFC × 9	14	0	4	8.2	55	0	95
14. KK	CFC × 3	1	0	1	13.2	43	1	300
15. RMcN	CFC × 4	17	0	0	14.1	33	0	740

*Five patients were splenectomised after starting high-dose busulphan.
CFC—Continuous flow centrifugation leucapheresis; BUS—Busulphan; HU—Hydroxyurea.

taken for a patient's leucocyte count to return to 11×10^9/l or less. Another criterion, the leucocyte count "halving time", was the time in days for leucocyte numbers to fall to half their initial value after a single standard dose of 100 mg of busulphan. For patients who had received no busulphan during the previous 8 or more weeks and whose leucocyte count had risen again above 20×10^9/l, it was possible to calculate the halving time on more than one occasion.

Table 3. High-dose busulphan protocol

Leucocyte count ($\times 10^{-9}$/l)	Busulphan dosage (mg)
>200	150
50–200	100
20–50	100 or 50
<20	50 or nil

Dosage in the leucocyte range 20–50 was based on the patient's previous response. Below 20 the patient usually received no busulphan.

RESULTS

The total leucocyte count fell rapidly following the first dose of busulphan in almost all patients (Table 4). The median time to reach a leucocyte count of $11 \times 10^9/l$ was 7 weeks. Six patients reached this level after only a single dose of busulphan. The slowest response was seen in patient JN who received 450 mg of busulphan: his leucocyte count fell to normal levels only after 19 weeks. By the time the leucocyte count was restored to normal the haemoglobin had risen in 10 of the 15 patients. Initially high platelet counts in 2 patients (KT and JN) had also fallen to normal levels. The platelet count rose to high levels in patient NB.

The leucocyte-halving time could be assessed after the first 100 mg dose of busulphan in 11 patients (Table 4). The mean value was 13.4 days (range 4–39 days). In 7 patients the leucocyte count halving time could be assessed on more than one occasion (Fig. 1). Two such patients were of special interest. Patient GD received two doses of 100 mg and then required no further busulphan for 27 months. The halving times after the first and after the third 100 mg doses were the same, 7 days. In patient KD halving times were assessed on 5 occasions over a 14 month period during the chronic phase; values ranged between 7 and 17 days. In 4 other patients there was a tendency for the halving time to lengthen with successive doses of busulphan but in the seventh patient (DC), whose halving time at first lengthened, the halving time after a total of 1050 mg busulphan was almost as short as that after initial treatment.

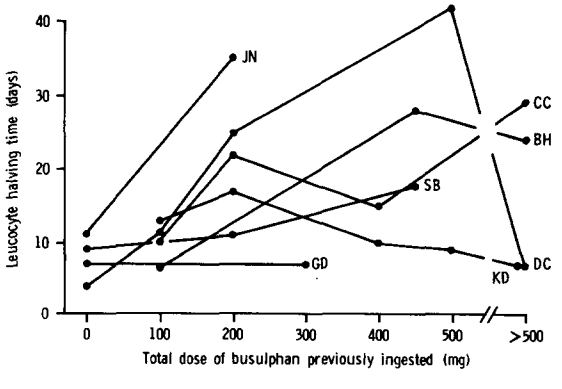

Fig. 1. Leucocyte count halving times in 7 patients related to cumulative dose of busulphan.

The administration of busulphan in high dosage proved to be free of toxicity. No patient complained of vomiting or other gastrointestinal disturbance. Marrow hypoplasia occurred in only one patient. He had received his most recent dose of busulphan 10 weeks previously. This patient (DC) recovered rapidly from his hypoplasia but then entered blast-cell transformation 8 weeks after the hypoplastic phase. Two patients became noticeably pigmented (WW and DC).

At the time of analysis five patients in the series have entered blast-cell transformation: three of these (WW, SB and BH) died but two patients (CC and DC) in myeloblastic transformation were successfully restored to chronic-phase disease by autografting cryopreserved buffy-coat cells after treatment aimed at destroying the blast cells [4, 5]. Ten patients remain in the original chronic phase of their disease.

DISCUSSION

Since its introduction in 1953 [6] busulphan has gained wide acceptance in the treatment of patients with CGL. A Medical Research Council study [7] showed in 1968 that busulphan gave results superior to those of radiotherapy, and intermittent or continuous therapy with busulphan at low dosage is now routine initial treatment for CGL. As a result of the observation that one patient treated with large single doses of busulphan showed a partial restoration of Ph^1-negative myeloid precursors in his marrow, pilot studies employing high-dose busulphan were initiated at the Hammersmith and Royal Marsden Hospitals. In the event reduction in the proportion of Ph^1-positive marrow metaphases was observed only in one patient in the Royal Marsden series [2] and in patient (GD) in our series. The Royal Marsden patients were usually treated with busulphan every two weeks and the actual dosage was based on the platelet count. The aim was to keep the total leucocyte count below $5 \times 10^9/l$. Our patients were assessed for treatment every 4 weeks and the indications for treatment were less strict. In the Royal Marsden series the mean time for the leucocyte count to fall to $10 \times 10^9/l$ was 11 weeks which compared with a mean time of 18 weeks for treatment at conventional dosage. The mean time for the leucocyte count to fall to $11 \times 10^9/l$ in our 15 cases was 7 weeks.

The administration of busulphan in this manner allows one to recognize any change in

Table 4. Clinical and haematological data for 15 patients when WBC has fallen to or below 11×10^9/l after starting high-dose busulphan

Patient	Time to achieve 11×10^9/l (weeks)	Halving time (days)	Spleen size (cm)	Busulphan dosage (mg) Total	per m^2SA	Hb (g/dl)	Platelets ($\times 10^{-9}$/l)
1. CC	7	NE‡	4	200	115	12.1	300
2. WW	10	NE	4	200	114	11.9	450
3. BH	8	NE	13	250	150	11.2	440
4. SB	4	9	0	200	118	12.5	920
5. KT	3	13	6	100	63	10.2	400
6. JN	19	11	0	450	237	14.0	340
7. GD	7	7	10	200	114	13.8	420
8. RC	16	23	0	200	108	12.7	183
9. DC	7	4	0	200	122	12.0	300
10. DSW	11	39	tip	200	100	15.3	300
11. GB	3	8	0	100	55	9.4	110
12. NB	3	9	0	100	63	11.9	1300
13. KD	4	NE	0	50	27	7.9	85
14. KK	2	9	1	100	63	10.5*	350
15. RMcN	4	15	0	100	59	14.5	570
Mean ± S.D.:	7.2 ± 5.0	13.4 ± 9.9	—	177 ± 96.1	101 ± 50.6	—	—

*Following blood transfusion

‡NE = Not evaluable. In 2 patients a leucapheresis procedure coinciding with the first dose of busulphan complicated the assessment and in 2 other patients the initial dose of busulphan was only 50 mg.

sensitivity to the drug that may occur in individual patients after successive doses. In two patients no change in the leucocyte halving time in response to identical doses of busulphan was observed over 27 and 14 months respectively. This accords well with the observations of Stryckmans [8] who found that the circulating immature myeloid-cell halving time remained constant in a patient treated with 4 courses of busulphan over a 10-yr span. It contrasts with the finding that the leucocyte "doubling time" after successive courses of busulphan tends to shorten [9, 10]. In our other 5 patients there was a tendency for the leucocyte halving time to lengthen after successive doses of busulphan but this trend was not consistent. In two patients the development of relative insensitivity to 100 and 150 mg doses of busulphan respectively heralded the advent of blast-cell transformation.

We conclude from the results of this small series that the administration of busulphan in single high doses at 4 week intervals is clinically convenient and rapidly restores high leucocyte counts to normal. We cannot say that it will avoid the serious problem of busulphan-related hypoplasia in the rare patient who is especially sensitive to this drug and we cannot yet comment on the duration of the chronic phase or the survival of our patients.

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