Papers and Originals

Chronic Granulocytic Leukaemia: Comparison of Radiotherapy and Busulphan Therapy

Report of the Medical Research Council's Working Party for Therapeutic Trials in Leukaemia*

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In 1957 a conference on the evaluation of different methods of cancer therapy was arranged by the Medical Research Council. One of the consequences of this conference was the formation of a working party to evaluate different methods of treatment in leukaemia. Though the conference had been specially concerned with the value of new forms of radiotherapy in malignant disease and the demands that were likely to be made for them, the Working Party on Leukaemia was faced with the problem of the extent to which chemotherapy might displace radiotherapy in the treatment of leukaemia. One of its first actions, therefore, was to initiate a long-term comparison of radiotherapy and chemotherapy in chronic granulocytic leukaemia, and the present paper is a report on this study.

The Working Party has also carried out therapeutic trials in acute leukaemia on which two reports have already been published (M.R.C., 1963, 1966). The trials have been made on a co-operative basis, and the methods used, which are common to all the trials, have been described in the previous two reports.

Purpose of the Trial

The purpose of the trial was to compare the quality of life and the survival in two randomly selected groups of hitherto untreated patients diagnosed as suffering from chronic granulocytic leukaemia. The patients in one group (B) were to be treated by busulphan, and those in the other (R) by radiation therapy. In both groups the allotted treatment was to be used as long as it seemed to be beneficial, but the physician or radiotherapist was free to change the treatment when a patient was no longer responding.

Diagnostic Criteria.—Patients were accepted if the clinical findings, blood counts, blood film morphology, and bone-marrow picture indicated a diagnosis of chronic granulocytic leukaemia. The trial was begun on 1 September 1959, before the discovery of the specific chromosomal defect involving the long arm of one of the 21st pair of autosomes (the Ph^1 abnormality), now thought to be characteristic of chronic granulocytic leukaemia, and perhaps confined to it. The proportion of patients whose blood and bone marrow were examined for the presence of the Ph^1 chromosome increased during the later years of the trial, but in 64 cases—27 in group B and 37 in group R—the examination was not made. Chromosome preparations were made in 38 cases (21 in group B, 17 in group R). The Ph^1 chromosome was present in 34, was not identified in two, and in two cases the preparations were not satisfactory. Thus an unknown but probably small number of Ph^1-negative cases might have been included in the trial. The classical haematological investigations sufficed for the exclusion of cases of acute myeloid or myelomonocytic leukaemia, and of myelosclerosis.

Treatment Schedules.—The form of treatment was determined by opening a sealed envelope after it had been decided to include the patient in the trial. Sets of numbered envelopes were held at each centre, each of which contained a card indicating either busulphan (B) or radiotherapy (R), the cards indicating the two forms of treatment being in random order in each set.

Busulphan.—This was to be administered orally at a daily dose of 4 mg. or 0.065 mg./kg. of body weight, whichever was the less, until the total leucocyte count had fallen to between 15,000 and 20,000/cu. mm., when the treatment was to be discontinued. The trend of the leucocyte count was to be observed in the ensuing period, with a view to resuming treatment, if necessary indefinitely, so as to stabilize the total leucocyte count at approximately 10,000/cu. mm. Apart from the blood count no check was made to discover if the patients took their tablets regularly. The clinician was free to abandon the treatment allocated if it seemed in the interest of the patient to do so.

Radiotherapy.—The precise technique of external radiotherapy was left to the radiotherapists at each centre. Irradiation of the spleen was the usual method employed, but at one centre some patients received abdominal "baths" or total body *x*-irradiation. The radiotherapy was administered in courses, the indications for treatment being left to the discretion of each radiotherapist.

Patients Admitted to the Trial.—Between 30 September 1959 and 1 January 1964 107 notifications were received. Five patients were excluded from the trial for the following reasons: one patient (B) was lost to follow-up after only one attendance; two died within 48 hours of admission (both R); the diagnosis in one case (B) was revised to myelosclerosis, and in another (R) to acute myeloid leukaemia. Thus 102 cases were available for analysis—48 in the busulphan group (B) and 54 in the radiotherapy group (R). This report records the state of the trial on 1 January 1967, when the minimum follow-up period was three years and the maximum period seven years and three months. Twelve patients were still living—eight in group B and four in group R.

Presenting Features

History of Illness

Of the 102 patients, 54 had had slowly progressive symptoms for periods up to two years. They eventually sought advice

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because one or other symptom became oppressive. The chief symptoms were lassitude, tiredness, malaise, loss of weight, increasing dyspnoea on exertion, discomfort after meals, sweating, swelling of the abdomen, or abdominal or lower chest pain. Five of these patients presented with acute pain, but admitted to long-standing symptoms on questioning.

Eighteen patients presented with symptoms of less than eight weeks' duration.

Thirteen patients presented with haemorrhagic manifestations, including haematomata, bleeding after minor surgery, or bruising. Eight of these patients admitted previous symptoms.

In 17 cases, including two prospective blood donors, the diagnosis was made by chance. Two of these patients admitted to minor symptoms.

There were no major differences in the incidence of the various types of presentation in the two groups, B and R. Comparisons of the two series in respect of the age and sex distribution and pretreatment features, spleen size (shortest distance in centimetres from the tip of the spleen to the costal margin), haemoglobin concentration, and total leucocyte, platelet, and blast-cell counts are shown in Tables I to IV.

Age and Sex

There were 52 males, 26 in each group, and 50 females (22 in group B, 28 in group R).

The age range was from 21 to 79 years, and the distribution among the males and females in each treatment group is shown in Table I.

TABLE I.—*Age Distribution of 102 Patients Suffering from Chronic Granulocytic Leukaemia at the Start of a Therapeutic Trial in Which 54 Patients Received X-irradiation and 48 Busulphan*

Treatment Group	Sex	No. of Patients Aged (in years)						Total No. of Patients in Each Group
		20–29	30–39	40–49	50–59	60–69	70–79	
Busulphan	M	4	5	5	7	4	1	26
	F	0	3	5	7	4	3	22
Radiotherapy	M	2	5	5	5	5	4	26
	F	2	2	5	8	9	2	28
All groups	M and F	8	15	20	27	22	10	102

Spleen Size

The spleen was palpable in every case, and the recorded distances of the tip of the spleen from the costal margin in centimetres at right angles to the left costal margin are given in Table II. The distance was 10 cm. or more in 70% of all the cases.

TABLE II.—*Distance of Spleen (cm.) Below Left Costal Margin in 102 Cases of Chronic Granulocytic Leukaemia*

Treatment Group	No. of Patients with Spleen Size (cm.)				Total No. of Patients in Each Group
	<5	5–10	10–20	20+	
Busulphan	4	8	31	5	48
Radiotherapy ..	9	10	25	10	54
	13	18	56	15	102

Haematological Values

Haemoglobin Concentration (Table III).—The haemoglobin concentration at presentation ranged from 5.3 to 13 g./100 ml. In one case the value before the patient received blood transfusions was not known, and in one case the patient had bled into an enormous subcutaneous haematoma before the first blood sample was taken. In 15 cases the haemoglobin concentration was less than 7.5 g./100 ml. (seven males, eight females), in 18 it was 11.5 g./100 ml. or more (15 males, 3 females), in 68 it lay between these values, and in one it was not measured.

TABLE III.—*Haemoglobin Concentration at the Start of the Trial in 102 Cases of Chronic Granulocytic Leukaemia*

Treatment Group	Sex	No. of Patients with Haemoglobin (g./100 ml.)					Total No. of Patients in Each Group
		Not Measured Before Transfusion	<7·5	7·5–9	9–11·5	11·5–13	
Busulphan	M	0	2	6	10	8	26
	F	1	3	6	11	1	22
Radiotherapy	M	0	5*	7	7	7	26
	F	0	5	9	12	2	28
All groups	M and F	1	15	28	40	18	102

* After a large soft-tissue haematoma in one case.

Total Leucocyte Count (Table IV).—The leucocyte counts ranged from 25,000 to 760,000/cu. mm.; they were below 100,000 in only 11 cases, above 350,000 in 28, and between these limits in 63.

TABLE IV.—*Total Leucocyte, Platelet, and Blast-cell Counts at the Start of the Trial in 102 Cases of Chronic Granulocytic Leukaemia*

Cells	Counts (/cu. mm.)	No. of Patients Treated With		
		Busulphan	Radiotherapy	All Treatments
Total leucocytes	<100,000	4	7	11
	100,000–350,000	30	33	63
	350,000–700,000	13	13	26
	700,000+	1	1	2
	All counts	48	54	102
Platelets	Not known	2	8	10
	<100,000	1	3	4
	100,000–350,000	25	22	47
	350,000–700,000	15	9	24
	700,000+	5	12	17
	All counts	48	54	102
Blast cells	Not known	2	0	2
	0	5	9	14
	<5,000	13	15	28
	5,000–20,000	23	26	49
	20,000–50,000	4	4	8
	50,000+	1	0	1
	All counts	48	54	102

Platelet Counts (Table IV).—The platelet counts ranged from 43,000 to 1,856,000/cu. mm., but no initial counts were available in 10 cases. In four cases the counts were less than 100,000/cu. mm.; in 47 they were between 100,000 and 350,000, in 24 between 350,000 and 700,000, and in 17 above 700,000/cu. mm.

Blast-cell Counts (Table IV).—Differential counts are not available for the initial leucocyte counts in two cases. In 14 cases (five males, nine females) differential counts were made but no blast cells were recorded. Of the remaining 86 cases the blast-cell count was less than 5,000/cu. mm. in 28, between 5,000 and 20,000 in 49, between 20,000 and 50,000 in 8, and 100,000/cu. mm. in 1 case (13% of 760,000 total leucocytes per cu. mm.).

Adherence to Treatment Schedules

Fig. 1 shows the treatments other than blood transfusions, antibiotics, and other supportive therapy received by each patient until death or, in the case of the 12 surviving patients, to 1 January 1967. There was no suggestion that the two groups differed in the supportive treatment, especially blood transfusion, administered during the terminal stage of the disease. Changes in treatment made within four weeks of death have been omitted from Fig. 1.

The majority of patients in the busulphan group received no other form of treatment during the greater part of the course

of their disease, though 13 received mercaptopurine, prednisone, or splenic irradiation (four cases) within six months of death. Six other patients received these or other forms of treatment (radioactive phosphorus, one case; mannitol-Myleran and demecolcine, one case) from 6 months to 90 weeks before death. Busulphan therapy was continued for at least 14 weeks from entry into the trial in all patients who survived beyond this period.

In the radiotherapy group the treatment was abandoned in favour of busulphan in seven cases within six months of entry into the trial. A total of 28 patients received busulphan, prednisone, mercaptopurine, or azathioprine for longer than six months before death. A further nine patients received one or more of these drugs within six months of death.

Results

The two groups of patients have been compared in respect of (1) survival from the first day of treatment, (2) the effect of the treatment on the size of the spleen, (3) the haemoglobin concentration, (4) the total leucocyte count, and (5) the platelet count.

Survival

Table V shows the 50% and 20% survival times for the two groups of patients. Fig. 2 shows the survival curves for all the patients in the two groups, Fig. 3 the survival of the male, and Fig. 4 survival of the female patients. The curves refer to the state of the trial on 1 January 1967, when 12 patients were still alive (indicated by arrows). Each point corresponds with the time at which the patient died, or with 1 January 1967 in the case of the living patients.

Fifty per cent. of the patients in the busulphan group were alive 170 weeks after the first day of their treatment, compared with 120 weeks for the radiotherapy group. The 20% survival times were, respectively, 263 weeks and 182 weeks. Thus the median survival of the busulphan-treated group of patients was almost one year longer, and the period for which 20% survived was 18 months longer. In both groups the 20% survival was longer in males, and the 50% survival was longer in males in the radiotherapy group.

TABLE V.—*Survival of 102 Patients Suffering from Chronic Granulocytic Leukaemia Three Years after the Entry of the Last Patient into the Trial*

Treatment Group	Sex	No. of Patients	50% Alive at (weeks)	20% Alive at (weeks)
Busulphan	M	26	170	272
	F	22	170	206
	M and F	48	170	263
Radiotherapy	M	26	127	187
	F	28	114	176
	M and F	54	120	182

The difference between the survival curves for the two treatment groups was tested by Gehan's extension of the Wilcoxon test (Gehan, 1965; Mantel, 1967). For both sexes taken together the busulphan group showed a significantly longer survival time ($P<0.03$), and the same trend appeared when the males and females were considered separately, but was less significant ($P<0.09$ for males, $P<0.14$ for females).

The minimum follow-up period was three years. At this time 30 of the 48 patients in the busulphan group were alive (62.5%) compared with 18 of the 54 patients in the radiotherapy group (33.3%), and similar differences were observed

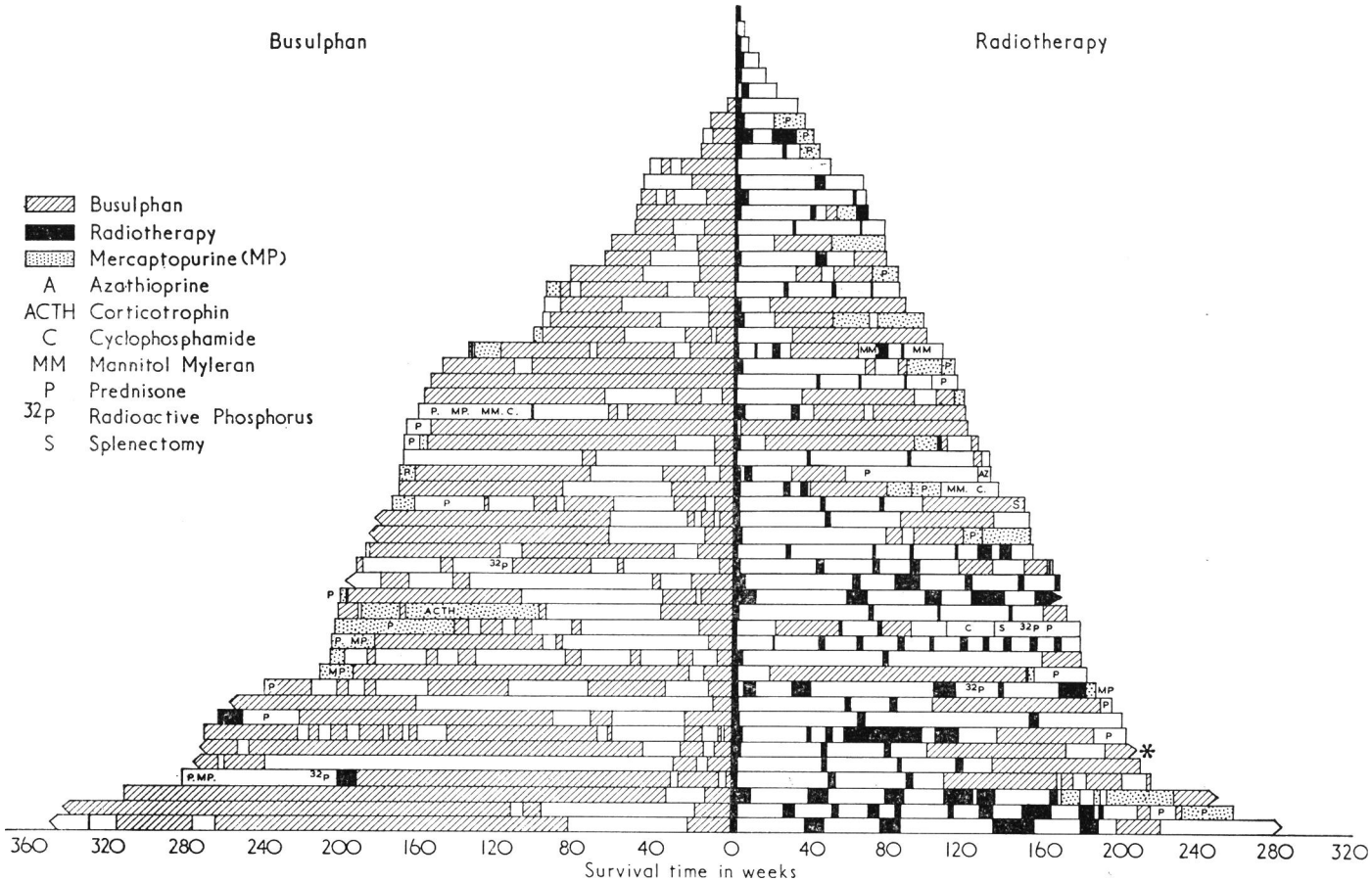
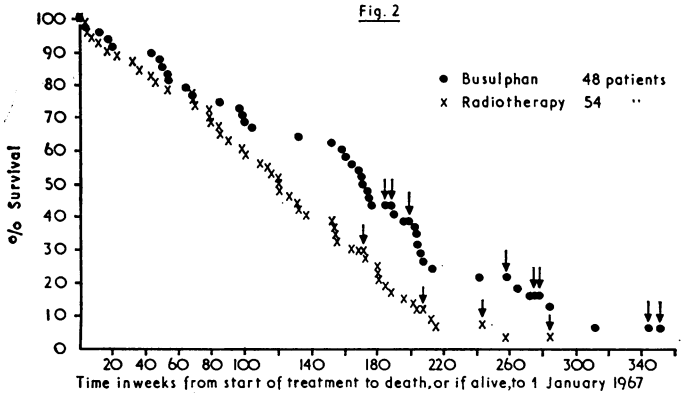


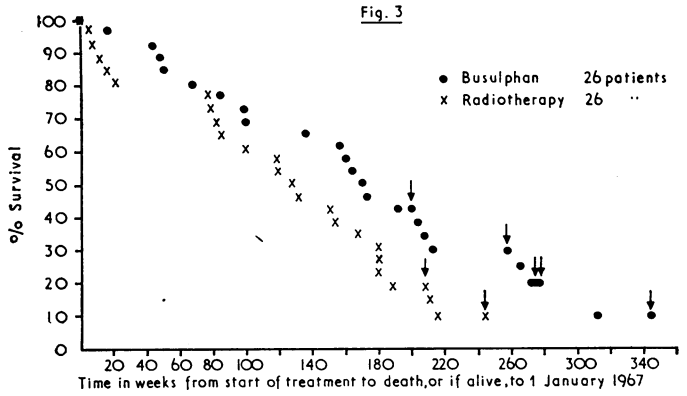
FIG. 1.—Treatments given to 48 patients who received busulphan on entering the trial and 54 patients who received radiotherapy. Each bar refers to one patient. Square-ended bars indicate deceased patients, pointed bars indicate patients alive on 1 January 1967. Treatments administered within four weeks of death, and blood transfusions, antibiotics, and other supportive measures are not shown. The asterisk refers to the case illustrated in Fig. 7.

separately for patients of each sex. For both sexes taken together the difference between the proportions of survivors is statistically highly significant ($P<0.01$).

Spleen Size

In the initial course of treatment busulphan and radiotherapy were equally effective in reducing the size of the spleen. There was no evidence that radiotherapy was more effective in relieving the pain of infarction or of perisplenitis. Rapid shrinkage of the spleen, however, gave no guarantee of long survival. The spleen became impalpable or regressed to within 5 cm. of the costal margin in 14 of the 21 patients who died within the first 12 months; 10 of these 14 died in blast-cell crisis. Of the remaining seven patients four died before any reduction in the size of the spleen occurred, in one case (busulphan) of peritonitis secondary to carcinoma of the colon, in three cases (radiotherapy) in blast-cell crisis. Thus, though failure of the spleen to diminish notably in size on treatment is a bad prognostic sign, it cannot be assumed that when the spleen regresses the patient will necessarily do well.





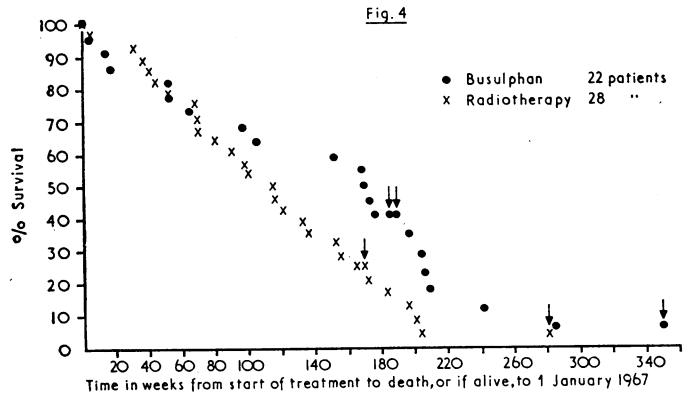


FIG. 2.—Survival of 102 patients suffering from chronic granulocytic leukaemia from the first day of treatment by busulphan or radiotherapy until 1 January 1967. Each point represents one patient. Arrows indicate living patients. FIG. 3.—Survival of 52 male patients suffering from chronic granulocytic leukaemia from the first day of treatment by busulphan or radiotherapy until 1 January 1967. See legend to Fig 2. FIG. 4.—Survival of 50 female patients suffering from chronic granulocytic leukaemia from the first day of treatment by busulphan or radiotherapy until 1 January 1967. See legend to Fig. 2.

The minimal recorded spleen size in each year from the start of treatment provides a rough basis for comparing the efficacy of busulphan and radiotherapy in controlling the tendency of the spleen to enlarge during the course of the disease. Thus for varying periods in each of the first two years the spleen was not palpable in 35 of the 65 patients (33 busulphan, 32 radiotherapy) who survived two years or more. Of the 35 patients, 21 were in the busulphan group and 14 in the radiotherapy group. Forty-eight patients (30 busulphan, 18 radiotherapy) survived three years or more. The spleen was not palpable for varying periods in each of the first three years in 24 of these (15 busulphan, 9 radiotherapy). It remained palpable in 22 (13 busulphan, 9 radiotherapy) (some measurements are missing in the remaining two). But the minimal size was less in the third year than in the second in four cases (three busulphan, one radiotherapy), was unchanged in six (three in each group), and was larger in 12 (seven busulphan, five radiotherapy).

Thus there was little difference in the efficacy of busulphan and radiotherapy in reducing the size of the spleen in the first three years, but the method of recording takes no account of the intermittent character of the effect of radiotherapy and of the tendency of the spleen to increase in size during the interval between two courses of irradiation. In the busulphan-treated patients the spleen was more often maintained at a small size for long periods.

Haemoglobin Concentration

Perhaps the most objective criterion of treatment is its effect in causing the haemoglobin concentration to rise and in preventing it from falling again. In a preliminary analysis we tried to compare the effect of the two treatments in maintaining the haemoglobin concentration at or above arbitrary "normal" levels throughout the course of the disease. For males, 14 g./100 ml. was selected as the normal level, and for females 13 g./100 ml. For each patient the number of days during which the haemoglobin concentration was at or above normal was expressed as a percentage of the total observation period. The scores so obtained were considerably higher in the busulphan group. However, reliance on a single arbitrary level of "normality" is undesirable, and we have therefore used a refinement of the method, suggested by Dr. M. C. Pike, which describes the ability of patients to maintain haemoglobin levels within the range 12–14 g./100 ml. or more for males and 11.5–13 g./100 ml. or more for females.

Periods during which the haemoglobin concentration was below 12 g./100 ml. (males) or 11.5 g. (females) were scored 0; when it was between 12 and 13 g. (males) or 11.5 and 12.25 (females) a score of 1 was allotted; a score of 2 represented periods during which the haemoglobin concentration was between 13 and 14 g. (males) or 12.25–13 g. (females), while a score of 3 represented levels of 14 g.+ (males) and 13 g.+ (females).

For each patient the maximum possible rating was the number of days he lived from the start of treatment multiplied by three. For example, a male patient who lived for 100 days and whose haemoglobin concentration never fell below 14 g./100 ml. would score the maximum rating of 300. The actual rating was expressed as a percentage of the maximum possible rating. The actual rating was obtained as follows: first, the number of days at which the haemoglobin levels were in the ranges required for each score from 0 to 3 were determined from the available readings, and these were multiplied by the appropriate scores. The products were then added together, and the total obtained was expressed as a percentage of the maximum possible rating for that patient.

Histograms of the patients' ratings are shown in Figs. 5 and 6. In Fig. 5 the ratings for both sexes are combined, though, as already stated, the ratings are based on different ranges of haemoglobin levels for the two sexes. Fig. 6 shows the ratings for each sex. All but one patient in the busulphan group achieved a positive rating, but the rating of seven radiotherapy patients was 0, which means that the haemoglobin concentration of these patients never rose to 11.5 g./100 ml. in four females or to 12 g./100 ml. in three males.

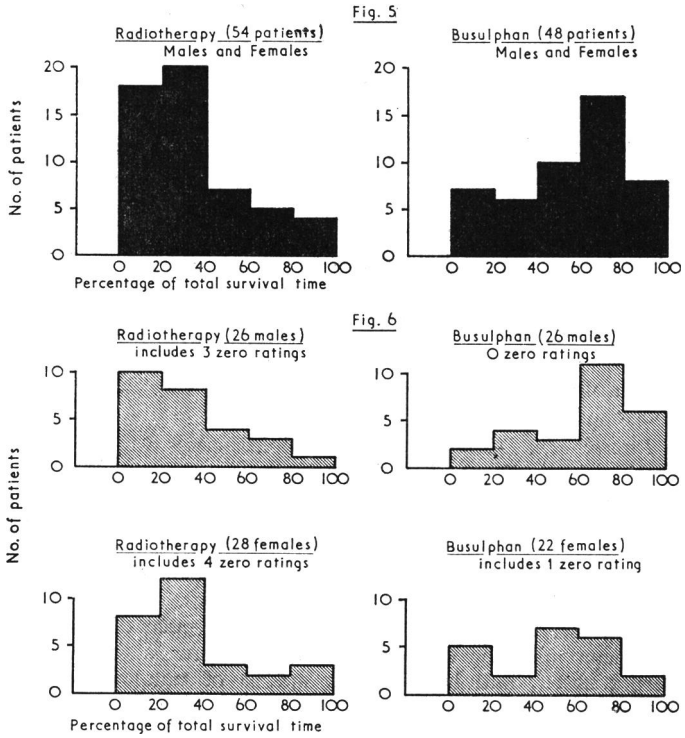


FIG. 5.—Frequency distributions of haemoglobin level ratings of 102 patients suffering from chronic granulocytic leukaemia treated by busulphan or radiotherapy. For calculation of ratings see text. Higher columns on the right indicate longer maintenance of haemoglobin concentration at higher levels. FIG. 6.—Frequency distribution of haemoglobin level ratings of 52 male and 50 female patients treated by busulphan or radiotherapy. For calculation of ratings see text.

To test the difference between the two forms of treatment a rank test was carried out on the ratings obtained. This gave a difference for males with probability $P<0.00003$ and for females with probability $P<0.02$, indicating that in both sexes busulphan therapy was significantly better at maintaining a higher level of haemoglobin concentration.

Though there was much variation the haemoglobin concentration was usually sustained at high levels more consistently in the first two years, and we have tested the difference between the two treatments in the haemoglobin ratings of the second year compared with the first. Table VI shows the number of patients in each group surviving longer than two years whose haemoglobin ratings during the second year were higher or lower than the ratings for the first year. Twice as many patients in the busulphan group achieved better ratings in their second year as those whose ratings decreased, but in the radiotherapy group twice as many patients had decreased ratings in the second year as those whose ratings increased. The probability of the difference in the two treatment groups being due to chance is less than one in a hundred. Thus busulphan therapy was much more effective than radiotherapy in sustaining a "normal" haemoglobin concentration during the second year.

TABLE VI.—*Haemoglobin Maintenance Ratings for the Second Year Compared With Those of the First Year in 65 Patients who Survived Longer than Two Years*

Treatment Group	Increased Rating	Decreased Rating	Totals
Busulphan	22	11	33
Radiotherapy ..	11	21	32
All groups	33	32	65

Toxicity of Busulphan and Radiotherapy

Apart from the bone-marrow toxicity on which its therapeutic efficacy depends, busulphan has few side-effects. Pigmentation and amenorrhoea are the commonest, but are not in themselves contraindications to treatment. More serious are the wasting syndrome with features resembling Addison's disease and pulmonary fibrosis; both may occur in the same patient, and are more likely the longer treatment is continued. Both complications are rare, and not a single case was reported in the present series.

The dosage of busulphan was carefully supervised for every patient, and no accidents resulting from overdosage occurred in the busulphan group. One patient, however, received a prolonged course at high dosage in relation to his body weight. In addition to prolonged leucopenia, the platelet count fell for 13 weeks, the lowest value being 4,000/cu. mm.; it was still only 10,000/cu. mm. in the 16th week but had risen to 130,000/cu. mm. in the 19th week. A few patients were unusually sensitive to busulphan administered at standard dosage and suffered some degree of neutropenia and thrombocytopenia after their first course of treatment. Busulphan therapy thus requires unrelenting vigilance, and the danger of unsupervised therapy can hardly be exaggerated.

Radiotherapy has a long tradition of stringently supervised dosimetry. One patient received splenic irradiation through two 15 by 10-cm. fields to a total dose of 1,200 rad and 1,100 rad administered in 15 days; the rate and extent of fall in the leucocyte count in the first five weeks after the end of treatment were exactly similar to what occurred in other patients whose leucocyte counts subsequently recovered, even when counts as low as 1,500/cu. mm. were obtained around the 35th day. But the count continued to fall, reaching 900 at the end of the sixth week and 550 at the end of the seventh week. The pancytopenia proved fatal and was probably a result of the high rate of dosage.

Another patient left the district and was subsequently treated with busulphan. Infrequent blood counts were performed during 11 months of continuous therapy; the haemoglobin concentration and leucocyte count continued to fall in the next four months, and the patient died. The trends are compatible with busulphan toxicity; platelet counts of 170,000 and 185,000/cu. mm. were obtained in the third week before death, though in the last week of life the count was only 54,000/cu. mm.

Table VII gives an indication of the trends in the leucocyte and platelet counts after the end of the initial course of radiotherapy or busulphan.

Total Leucocyte Count

Leucocyte Counts after First Course of Treatment.—Table VII shows the total leucocyte counts at the end of the first course of treatment; the number of patients whose counts rose, fell, or remained stationary in the period immediately following the end of the treatment; the lowest levels to which the counts fell; and the duration of the fall in those cases in which falls occurred.

In both treatment groups the counts varied greatly at the time of stopping treatment, but the median values for both males and females in the radiotherapy group were rather higher. However, the proportion of patients whose counts continued to fall subsequently was similar in both groups and the median values of the lowest recorded counts were in the same range in both groups. The median duration of the fall was about

TABLE VII.—*Total Leucocyte and Platelet Counts at End of First Course of Treatment, Their Subsequent Trends, and Lowest Levels in Cases of Continued Fall in the Counts*

Cells	Treatment Group	Counts at End of Treatment (thousands/cu. mm.)			No. of Patients Showing Stated Trends After End of Treatment				Lowest Counts After End of Treatment* (thousands/cu. mm.)			Total No. of Patients in Each Group
		Highest	Lowest	Median	Upwards	Unchanged	Downwards	Insufficient Counts	Highest	Lowest	Median	
Total leucocyte count	Busulphan	260	3·8	8·4	15	4	28 (16–106, median 46 days)	1	20	2·1	5·4	48
	Radiotherapy	180	3·4	18·5	11	0	42 (2–92, median 28)	1	68	0·55	6·0	54
Platelet count	Busulphan	1,000	30	180	3	16	19 (7–90, 37)	10	350	4	60	48
	Radiotherapy	1,500	49	190	3	4	27 (4–72, 22)	20	550	10	110	54

* In cases of continued fall in the counts.

three weeks longer in the busulphan-treated patients than in those treated by radiotherapy.

Platelet Counts After the First Course of Treatment

Table VII also shows the highest, lowest, and median platelet counts at the end of the first course of treatments; the number of patients whose counts subsequently fell, rose, or remained unchanged; the highest, lowest, and median counts of those whose counts fell; and the longest, shortest, and median duration of the fall. There was a tendency for the fall to continue longer and to reach lower levels in the busulphan group. The lowest median values were obtained about three weeks later in the busulphan group.

Causes of Death

Table VIII shows the causes of death, so far as they could be determined, in the 90 patients (40 busulphan, 50 radiotherapy) who had died by 1 January 1967.

TABLE VIII.—*Causes of Death of 90 Patients Who Died Before 1 January 1967*

Cause		Busulphan	Radiotherapy	Total
Leukaemia	Acute blast-cell	14 (3)	18 (2)	32 (5)
	Chronic blast-cell	14 (10)	18 (5)	32 (15)
	Resistant to busulphan	4	0	4
Intercurrent disease		7 (5)	8 (2)	15 (7)
Busulphan toxicity		0	1	1
Unknown		1	5	6
Total		40	50	90

Figures in parentheses refer to patients who had become resistant to busulphan.

In 68 cases (32 busulphan, 36 radiotherapy) death was due to uncontrolled leukaemia. However, death occurred when the leukaemia was apparently well controlled in 15 cases, and was due to conditions that were not obviously related to the leukaemia. The immediate cause of death was not known in six cases (all but one in the radiotherapy group), and was probably a result of busulphan toxicity in one other (radiotherapy) case.

Thus the causes of death were similar in the two treatment groups, and there was no evidence to suggest that the blast-cell transformation, the commonest cause of death, was provoked by one treatment more than another. The survival curves, however (Figs. 2, 3, and 4), indicate that the onset of the terminal phase occurred earlier in the radiotherapy series.

Leukaemia.—Of the 68 deaths attributable to leukaemia definite evidence of progressive blast-cell transformation was available in 64 cases (28 busulphan, 36 radiotherapy). In its extreme forms this phase presented as an acute phenomenon, causing death in a few weeks, or was protracted for as long as 18 months, during which control of the clinical and haematological manifestations of the disease was progressively lost. The two extreme forms were linked by a range of intermediate cases. In Table VIII the terminal blast-cell phase is described as "acute" when its duration was less than six months as estimated from inspection of the haematological charts, and "chronic" when more than six months. In both series blast-cell transformation accounted for 70% of the deaths, and the distribution of acute and chronic cases was the same. Twenty of the 64 patients who died in the blast-cell phase were already resistant to busulphan before its onset, but in four other cases in the busulphan series definite evidence of blast-cell transformation was not obtained, though the patients had become resistant to busulphan and the leukaemic process was never again controlled.

Intercurrent Disease.—In the busulphan series death was due to chronic cardiovascular disease in three cases, and to pneumonia, renal failure, a bladder tumour, and peritonitis from carcinoma of the colon in one case each. In all seven cases the leukaemia was apparently well controlled at the time of the terminal illness, though five patients had become resistant to busulphan and were receiving other treatment. In the radiotherapy series two patients died of cardiovascular disease, two of pneumonia, one each of bronchial carcinoma, generalized herpes zoster, and bone-marrow aplasia of unknown origin. An eighth patient committed suicide.

Discussion

For half a century splenic *x*-irradiation has been the preferred treatment for chronic granulocytic leukaemia. Fowler's solution, though often effective, was not well tolerated, and benzene never became popular. In the 1940s the first of several new groups of cytotoxic drugs became available, and some of these were found to be of value in the treatment of chronic granulocytic leukaemia, though it soon became apparent that, as in the case of radiotherapy, the benefit was only temporary. Even so, radiotherapy had the disadvantage that its administration required specialized permanent installations to which the patient had to be brought. Chemotherapy has no such limitation, though it does require careful laboratory control.

When the present trial was planned there was a choice of several cytotoxic drugs, including urethane, nitrogen mustard, nitromin chlorambucil, tretamine, thiotepa, demecolcine, mercaptopurine, and busulphan. Busulphan (Haddow and Timmis, 1953), with its relative freedom from side-effects and known efficacy and ease of handling in the treatment of chronic granulocytic leukaemia, was thought by many physicians to be at least as effective as radiotherapy, and perhaps more effective. Furthermore, busulphan therapy was already known to be beneficial in some cases in which radiotherapy had lost its efficacy. It had also been suggested from observations on a small uncontrolled series that patients who received radiotherapy and busulphan in sequence survived longer than those who were treated by either method alone (Wiltshaw and Galton, 1958). It was not known whether particular manifestations of the disease might indicate the use of one method rather than the other, and there was a suspicion that busulphan was more prone to produce blast-cell crisis than radiotherapy.

The two methods had never been compared on a random basis in a controlled clinical trial, and such a trial was clearly desirable. Therapeutic trials almost inevitably raise ethical questions, but in this trial the observers knew the treatment the patients were receiving and had complete freedom to change it if they were not satisfied with the patients' progress. Analyses of the data were made at intervals, but the intake of patients was slow; it was not until early in 1964 that the superiority of busulphan over radiotherapy became evident, and no further patients were admitted to the trial.

In planning the trial it was decided to compare the two methods in respect of a few easily measured objective features, particularly survival, control of spleen size, and efficacy in restoring and maintaining satisfactory levels of haemoglobin concentration. The precise technique of radiotherapy was to be left to each radiotherapist, but it was decided to standardize the administration of busulphan.

The results indicate that busulphan was superior to radiotherapy in respect of each feature analysed, except perhaps in the long-term control of the size of the spleen, in which little difference between the two forms of treatment was found. The median survival and the 20% survival were longer, and the maintenance of satisfactory haemoglobin levels, especially in the second year of the disease, was also superior in the group of patients allocated to busulphan therapy. It is to be noted also that whereas treatment with busulphan was in the majority of cases continued until the late stage of the disease, a high proportion of patients in the radiotherapy group were transferred to some other form of treatment, in most cases busulphan, at an earlier stage. In two cases the change to busulphan was requested by the patient on grounds of convenience, though in the majority the disease was no longer adequately controlled by radiotherapy. Moreover, in spite of the availability and use of other forms of treatment, the overall survival of the patients who were started on radiotherapy was shorter than those who were started on busulphan therapy.

Part, at least, of the difference between the two forms of treatment may reflect the different ways in which they were used. With radiotherapy, relapse was more often allowed to proceed to an advanced stage before a further course of treatment was begun, by which time the advantage conferred by the previous course had been lost.

With busulphan the advantage gained by the initial therapy was more often consolidated by embarking on a further course or on maintenance therapy at an early stage of relapse. The difference is illustrated in Fig. 7, which shows the haemoglobin concentration, platelet, and total leucocyte counts of a patient in the radiotherapy series (case denoted by asterisk in Fig. 1) who was transferred to busulphan therapy after the third course of splenic *x*-irradiation. The haemoglobin concentration rose after each course of radiotherapy, but fell as the leucocyte count rose; during continuous busulphan therapy the haemoglobin concentration was maintained at a normal level. The Chart also shows how the interval between successive courses of radiotherapy became less.

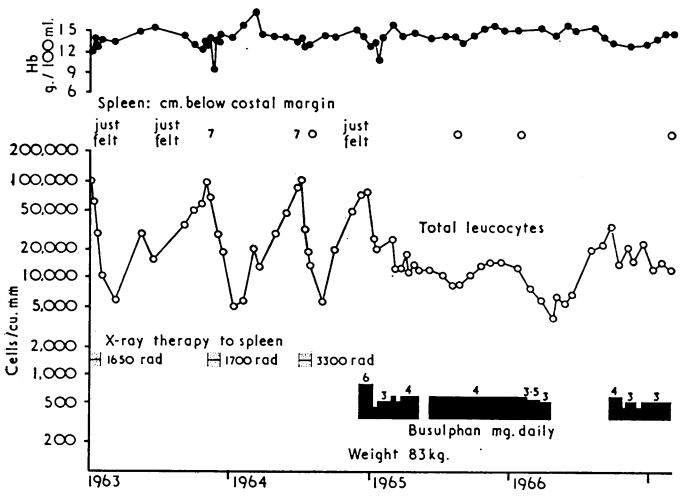


FIG. 7.—Case 49R. Male, 38 years. Haemoglobin concentration, size of spleen (cm. below costal margin), total leucocyte count, over four-year period from entry into trial. Patient received three courses of *x*-ray therapy to the spleen in the first two years and was subsequently treated by busulphan

The commonest cause of death in both groups was a change in the character of the leukaemia resulting from the emergence of undifferentiated blast cells. The blast-cell transformation accounted for the terminal illness in 70% of the 90 patients who died, and the incidence was equal in the two series. However, the transformation must have arisen earlier in the radiotherapy group, in which the survival at all times from the start of treatment was shorter than in the busulphan group.

Comparison With Other Series

The only series of untreated patients for which survival data are available is that of Minot, Buckman, and Isaacs (1924). The survival of 52 untreated patients was compared with that of 78 patients treated by irradiation, chiefly from radium. At that time adequate supportive therapy such as blood transfusion, antibiotics, or diuretics was not available. It is therefore difficult to compare our results and those of other recently published series with the data of Minot *et al.* Reinhard, Neely, and Samples (1959) have described the results of treatment with radioactive phosphorus, and Haut, Abbott, Wintrobe, and Cartwright (1961) used intermittent busulphan therapy. In both series the survival data were calculated from the estimated onset of the disease. The median survival times for both treatment groups in our series calculated from the estimated onset of the disease (188 weeks for busulphan, 156 weeks for radiotherapy) were of the same order as those given by Reinhard *et al.* and by Haut *et al.*, though rather longer. However, the insidious onset of symptoms in the majority of cases makes an estimate of onset a matter of guesswork, and in this report we have therefore presented our survival data only from the day on which treatment was begun. Tivey (1954) studied several published reports on chronic granulocytic and chronic lymphocytic leukaemia treated by various methods and concluded that the prospects for survival in the two diseases were almost identical. The median survival from the start of treatment was 1.6 years —considerably shorter than in the more recent series, including our own.

In the past it has sometimes been questioned whether treatment actually increases the duration of life in chronic granulocytic leukaemia, and some doubt remains. Tivey, commenting on the increased median survival reported by Osgood and Seaman (1952) in their series of patients treated by radioactive phosphorus or radiotherapy, emphasized the importance of improved supportive therapy in comparison with that available to patients in earlier series. It is now quite clear, however, that busulphan therapy improves the quality of life, and it probably increases its duration. To a less extent this is also true of radiotherapy.

Summary

One hundred and two untreated patients suffering from chronic granulocytic leukaemia were allocated at random to one of two treatment schedules. Forty-eight patients started treatment with busulphan and 54 with external *x*-irradiation, usually to the spleen. The minimal follow-up was three years. The two groups are compared in respect of: (1) survival from

the first day of treatment; (2) the effect of the treatments on the size of the spleen during the first three years; (3) the haemoglobin concentration during the first two years; and (4) the total leucocyte and platelet counts after the first course of treatment.

Three years after the entry of the last patient into the trial 30 of the 48 patients in the busulphan group (62.5%) and 18 of the 54 patients in the radiotherapy group (33.3%) were alive.

The median survival of the busulphan group was 170 weeks and of the radiotherapy group 120 weeks after the start of treatment; 20% of the busulphan group survived 263 weeks and 20% of the radiotherapy group 182 weeks.

In the radiotherapy group the median survival was superior in males, the values for the busulphan (26 male patients) and radiotherapy (26 male patients) groups being 170 and 127 weeks respectively, compared with 170 and 114 weeks respectively for the females in the busulphan (22 patients) and radiotherapy (28 patients) groups.

Busulphan and radiotherapy were equally effective in reducing the size of the spleen in the initial course of therapy, and there was little difference in their efficacy in controlling the tendency of the spleen to enlarge during the first three years. The spleen was impalpable for varying periods during each of the first three years in 50% of the patients in each group (30 busulphan, 18 radiotherapy) who survived three years.

Busulphan was superior in causing the haemoglobin concentration to rise to arbitrarily chosen "normal" levels. Only one of 48 patients failed to reach the lower range of normal levels, compared with seven of 54 patients in the radiotherapy group.

Busulphan was significantly better than radiotherapy at maintaining the haemoglobin concentration within an arbitrarily chosen normal range, the probability of the difference being due to chance being less than 0.00003 in the case of males and 0.02 in the case of females.

Busulphan was also more effective than radiotherapy in sustaining normal haemoglobin levels during the second year, the probability of the difference being due to chance being less than 0.01.

The leucocyte and platelet counts at the end of the first course of treatment continued to fall in a similar proportion of patients in both groups, but the fall continued, on average, three weeks longer in the busulphan group.

When the trial was ended 90 patients had died. Death resulted from blast-cell transformation in 70% of the patients. The incidence was the same in both treatment groups, but the transformation arose earlier in the radiotherapy group.

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REFERENCES

Gehan, E. A. (1965). *Biometrika*, **52**, 203.
Haddow, A., and Timmis, G. M. (1953). *Lancet*, **1**, 207.
Haut, A., Abbott, W. S., Wintrobe, M. M., and Cartwright, G. E. (1961). *Blood*, **17**, 1.
Mantel, N. (1967). *Biometrics*, **23**, 65.
Medical Research Council (1963). *Brit. med. J.*, **1**, 7.
—— (1966). Ibid., **1**, 1383.
Minot, G. R., Buckman, T. E., and Isaacs, R. (1924). *J. Amer. med. Ass.*, **82**, 1489.
Osgood, E. E., and Seaman, A. J. (1952). Ibid., **150**, 1372.
Reinhard, E. H., Neely, C. L., and Samples, D. M. (1959). *Ann. intern. Med.*, **50**, 942.
Tivey, H. (1954). *Amer. J. Roentgenol.*, **72**, 68.
Wiltshaw, E., and Galton, D. A. G. (1958). In *Proceedings of the VIth International Congress of International Society of Haematology*, p. 164. New York.

Secretion of Androgens and Oestrogens in Testicular Feminization: Studies in Vivo and in Vitro in Two Cases*

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Patients with so-called testicular feminization have a female body habitus with apparently well-developed breasts, a lack of body hair being a marked feature. There is no uterus, and the gonads are testes situated within either the abdomen or the inguinal canal. They present superficially as females with primary amenorrhoea. These observations led to the term "testicular feminization" being adopted for these patients (Morris, 1953). The sex chromosome pattern is a normal male one, 46 XY (Jones, 1965); the condition is familial, being inherited, probably as a sex-linked recessive.

Despite the early supposition that the abnormality in testicular feminization lay in the testis, which was producing oestrogen rather than androgen, it has been known for some years that urinary 17-oxosteroid and oestrogen excretions are in the ranges for normal men (Morris, 1953). Griffiths *et al.* (1963) reported the first in-vitro study on a testis which showed the ability to form androstenedione and testosterone, but not oestrogen. In the same year Morris and Mahesh (1963) reported the isolation of testosterone from testicular venous blood in the condition.

In the present study androgen and oestrogen secretion in two patients with testicular feminization has been assessed by the measurement of production rates in vivo by isotope dilution, by synthesis in vitro from ^{14}C-progesterone, and in one case by the concentration of steroids in testicular vein plasma and of free testosterone in peripheral plasma.

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Case Histories

Case 1.—This patient was aged 17. A "sister," two years older, also had testicular feminization. At operation one gonad was found in the abdomen, the other in the inguinal canal; both were removed. Buccal squames were chromatin-negative.

Case 2.—This patient was aged 16. A sister, one year younger, was normal. At the age of 6 the patient had had a herniorrhaphy, and an "ovary" had been found in the inguinal canal. Ten years later both gonads were within the abdomen, and were removed.