MYLERAN IN TREATMENT OF CHRONIC MYELOID LEUKAEMIA

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"Myleran" (1:4-dimethanesulphonyloxybutane) was synthesized by Haddow and Timmis (1953) in the hope that its biological action might resemble that of the nitrogen mustards because of a common ability to alkylate. It showed a depressive influence on the granulocytic series both in the rat and in man at a much lower dosage than most of the other members of the sulphoncic acid esters which they elaborated. Galton (1953) demonstrated that it is an effective palliative in the treatment of chronic myeloid leukaemia. Here we record our experiences during the past four and a half years with this drug in the treatment of 17 cases of chronic myeloid leukaemia and one case of neutrophilic leukaemia.

Methods

All the patients were treated initially in hospital and later as out-patients. The clinical diagnosis of chronic myeloid leukaemia and of acute relapse was confirmed by examination of peripheral blood and bone marrow. Estimations of the haemoglobin, and erythrocyte, leucocyte, and platelet counts, were made thrice weekly in the earlier phases of therapy and less frequently afterwards. Patients in good clinical remission and not on maintenance doses have been seen at monthly intervals.

Myleran was given as tablets by mouth. Early in the trial, doses of 10-25 mg. were given at varying intervals depending upon the clinical and haematological response (see Table). Cases 1-3 were treated with these doses throughout, and Cases 4, 11, and 12 for the first few months only, while the maximum single doses early in the treatment of Cases 7 and 10 never exceeded 10 mg. Because thrombocytopenia developed in Cases 2, 3, 4, 10, and 11, we ceased using high single dosage and gave thereafter 0.06 mg. per kg. body weight. This meant an average dose of 4 mg. daily, which was then continued as long as clinical and haematological improvement continued. Occasionally 6 mg. daily was given for a few days when a rapid response was desired, and lower amounts of the order of 2 mg. a day to patients with an unusually sensitive therapeutic response.

Symptomatic treatment was given as required. Roentgen therapy, when given, consisted of irradiation of the splenic area.

Results

Patients Not Previously Treated

Detailed results are shown in the Table. Eight cases (Nos. 3, 5, 6, 10, 11, 15, 16, and 18) which would otherwise have had radiotherapy were treated with myleran, and, with the exception of the case of neutrophilic leukaemia (Case 10), satisfactory remissions were obtained. In Case 3 a single course of 180 mg. of the drug was given over a period of five months. The patient responded well, but developed irreversible thrombocytopenia one month after cessation of the course. As the leukaemic process also relapsed at this time she was given splenic irradiation. Although the haemoglobin then rose following a satisfactory fall in leucocyte count and the spleen diminished in size, the thrombocyto-

penia remained, and she died from cerebral haemorrhage eight months after starting myleran therapy. In Case 5 the patient relapsed five weeks after the end of the first course of myleran (1,666 mg. over 18 months), but responded well to further treatment with 360 mg. over five months. He then developed acute myeloblastic relapse, from which he died. After 18 months on myleran therapy (1,104 mg.), Case 6 developed resistance to the drug, as shown by a progressive fall in haemoglobin, a steady rise in the leucocyte count, and increase in size of the spleen. In no other instance within this group, apart from acute relapse, was this phenomenon seen. Splenic irradiation gave him temporary relief, but he died from myeloblastic leukaemia three months after the cessation of myleran treatment.

The case of neutrophilic leukaemia (No. 10) was resistant to both myleran and irradiation. In Case 11 a first course of 350 mg. of myleran was given over six months. The patient quickly relapsed on the cessation of the therapy and also developed thrombocytopenia at this time. In view of the latter, radiotherapy was begun. He improved with each of five courses given during the ensuing 16 months, but the thrombocytopenia persisted. A partial remission then followed 160 mg. of myleran given over three months. This was followed by terminal acute myeloblastic relapse. In Case 15, pernicious anaemia had been treated successfully for 17 months with parenteral vitamin B₁₂ before the patient developed leukaemia. She and Cases 16 and 18 were treated with myleran for three and a half months. Remissions have been maintained to date for 13, 12½, and 13½ months respectively.

Patients Previously Treated by Radiotherapy

Of the remaining ten patients, six had become resistant to splenic irradiation (Nos. 2, 4, 7, 8, 9, and 12). They had had repeated courses of such therapy with gradually lessening periods of remission until they had failed to respond at all to the treatment. Cases 8 and 12 were also found to be resistant to myleran, but the other four obtained satisfactory remissions. However, of the four patients, one (Case 2) died of monoblastic relapse after a course of 500 mg. of myleran over four months, while two (Cases 4 and 7) developed myeloblastic relapse after courses of 593 mg. over 14 months and of 748 mg. over 17 months respectively. In Case 9 thrombocytopenia occurred even before the beginning of myleran therapy, and the patient died of bronchopneumonia 12 months after chemotherapy was begun.

Myleran had no effect in Case 13, who was, however, admitted to hospital extremely ill. Case 1 developed myeloblastic leukaemia after a course of 867 mg. of myleran given over 14 months, while Case 14 has responded well to 378 mg. of the drug given over three months. A course of 262 mg. given over nine weeks has resulted in a remission of 11 months to date in Case 17.

Data Relating to All Patients

Remission with myleran therapy was heralded in each case by relief of general symptoms such as malaise and night sweats and by a falling leucocyte count. The haemoglobin level did not rise significantly at this stage but rose subsequently. Splenic regression was often slower than with radiotherapy, but the rate of increase in haemoglobin was just as satisfactory.

Dangerous granulopenia was not seen. Five cases, however, developed significant thrombocytopenia, but this has not occurred since smaller individual doses of the order of 4 mg. a day have been given. Aplastic anaemia has not developed, and no toxic effects have been noted in this series with the smaller doses.

Of the 13 patients who have died, the terminal event in six was myeloblastic leukaemia and in one monoblastic leukaemia. Four of these seven (Cases 1, 2, 4, and 7) had had prior courses of radiotherapy, while a fifth (Case 11) was irradiated subsequent to myleran therapy. The remaining two patients had myleran alone throughout (Cases 5 and 6).

RESULTS ACHIEVED IN 10 CASES

Case No.	Age and Sex	Last Specific Therapy	Duration of Disease Before Myleran (Months)	General Con- dition Before Myleran	Effect of Myleran On												Remissions			Total Given (mg.)	Duration of Course (Months)	Toxic Effects	Comments						
					Spleen (Inches below costal margin)						Haemoglobin (G./100 ml.)						Total W.B.C. (10^9 /c.mm.)							Platelets (10^9 /c.mm.)					
					3 Mths.		6 Mths.		Start	3 Mths.	6 Mths.	Start	3 Mths.	6 Mths.	Start	3 Mths.	6 Mths.	Start	3 Mths.					6 Mths.					
					1st	2nd	1st	2nd																	1st	2nd			
1	36 M	RT	6	Good	3.5	1	1	11.8	14.8	14.5	250	30	44	480	500	520	14	—	867	14	—	Large doses. Died acute leukaemia 18 months after myleran begun							
2	28 M	RT	—	Poor	10	7.5	—	9.2	12.9	—	400	100	—	300	125	—	3.5	T	500	4	T	Large doses. Died acute leukaemia 5 months after starting myleran							
3	73 F	—	—	Fair	6.5	4	8.5	8.1	11.8	9.9	350	190	110	150	400	50	5.5	T	180	5	T	Large doses. Died cerebral haemorrhage 8 months after myleran begun							
4	34 F	RT	—	"	9	9	8	11.4	11.7	11.1	30	46	26	210	220	300	13.5	T	593	14	T	Large doses earlier. Died acute leukaemia 16 months after myleran begun							
5	35 M	—	—	"	4.5	2	1.5	11.8	11.8	13.0	300	100	12	380	420	300	17	—	1,666	18	—	Small doses. Died acute relapse after 3 months on second course							
6	47 M	—	—	Good	1	—	—	10.5	14.2	14.5	125	70	14	500	500	700	17.5	—	1,104	18	—	Small doses. Became resistant. RT temporarily beneficial. Died acute relapse 3 months after cessation of myleran treatment							
7	41 F	RT	—	Fair	2	0.5	0.5	8.7	11.1	10.1	133	20	51	650	850	700	16	—	748	17	—	Mainly small doses. Died acute relapse 184 months after myleran begun							
8	60 F	RT	—	Poor	10	—	—	7.8	—	—	15	—	—	50	—	—	—	—	60	1	—	Small doses. Resistant. Acute relapse after further RT							
9	72 F	RT	—	Fair	7.5	8	8	11	9.2	12.1	25	17	17	90	160	50	7.5	T	110	8	—	Small doses. Resistant to further RT							
10	47 M	—	—	"	2	1	2	8.9	8.3	8.0	24	15	13	300	250	90	—	—	50	0.25	—	Neutrophilic leukaemia. Mainly small doses. Resistant to myleran and RT							
11	22 M	—	—	Good	8	7	9.5	9.1	13.3	9.5	300	288	400	100	360	120	5.5	T	350	6	T	Large doses earlier. Responded to RT for 16 months between courses of myleran. Died acute relapse 22 months after drug begun							
12	64 F	RT	—	Poor	7	7	7	8.9	8.8	10.4	20	54	12	60	80	50	—	—	155	7	—	Resistant. Big doses earlier							
13	49 M	RT	4	Very poor	10	—	—	7.4	—	—	500	—	—	250	—	—	—	—	48	0.3	—	Died 10 days after drug begun							
14	58 F	RT	9	Good	5	1	1	13.9	13.3	11.9	40	15	54	300	550	1000	5.5+	—	378	3	—	Small doses							
15	60 F	—	—	"	3	1.5	0.5	13.8	13.6	14.8	100	12	17	180	225	240	13+	—	376	3.5	—	Small doses. Had pernicious anaemia for 17 months—on vitamin B ₁₂							
16	49 F	—	—	Fair	5	0.5	—	8.9	13.0	14.8	250	16	7	600	275	220	12.5+	—	368	3.5	—	Small doses							
17	63 M	RT	11	"	4	1.5	—	9.6	12.1	14.8	75	10	18	200	130	110	11+	—	262	2.25	—	"							
18	30 M	—	—	Good	2	0.5	0.5	12.1	14.8	15.1	250	9	5	510	330	250	13.5+	—	270	3.5	—	"							

RT = Roentgen therapy. T = Thrombocytopenia.

Of a separate series (unpublished) of 16 fatal cases of chronic myeloid leukaemia, all of whom had been treated by upper abdominal irradiation only, over the years 1946–50, only four died in acute relapse. It is interesting to compare this group of cases with the present myleran series. However, the number of cases developing acute relapse is too small in each series to obtain statistical significance.

Discussion

The best palliative therapy for chronic myeloid leukaemia that has stood the test of time is radiotherapy. Is myleran an effective substitute? As none of these cases on myleran therapy alone has been observed for more than three years from the start of the illness, and as the mean survival for the disease in general is three to four years (Shimkin *et al.*, 1951; and others), this question cannot yet be answered. There is general agreement that myleran is easier to administer than radiotherapy, and that it is free from undesirable side-effects (Galton, 1953; Hansen, 1954; Kurrle, 1955; Petrakis *et al.*, 1954; Videbaek, 1955; and others). It is undoubtedly effective in many cases. However, the relatively high incidence of acute relapse in this series sounds a note of caution. If radiotherapy is not available or is contraindicated, or if the patient is radio-resistant, then it can be used with justification.

From our own experience and perusal of the literature, myleran is preferable to urethane, to the nitrogen mustard group of drugs, and to arsenic and benzene, because it is free from side-effects, remissions are longer, and response is not so erratic. The place of demecolcine ("colcemid") in this range of therapeutic drugs has yet to be determined.

It may be preferable to give interrupted rather than continuous courses of myleran, because resistance to the drug may develop (Galton, 1955; our Case 6). Furthermore, five of our patients who developed an acute relapse had had continuous therapy.

Summary

Our experiences are described in the treatment with "myleran" of 17 cases of chronic myeloid leukaemia and one case of neutrophilic leukaemia. Optimum dosage appears to average 0.06 mg. per kg. body weight per day by mouth. With larger doses thrombocytopenia may occur. Of eight cases not previously treated, seven had satisfactory remissions. The eighth case was one of neutrophilic leukaemia. Four out of six radio-resistant patients and three out of four who had had previous irradiation but were not radio-resistant had satisfactory remissions.

Of the 13 patients who have died, the terminal event in seven was acute relapse.

If radiotherapy is not available or is contraindicated, or if the patient is radio-resistant, then myleran can be used justifiably. Although it is preferable to other

chemotherapeutic agents, with the possible exception of demecolcine, the best palliative therapy for chronic myeloid leukaemia that has stood the test of time is radiotherapy. Myleran at present does not appear to be superior to radiotherapy, but we cannot yet answer the question, "Is myleran an effective substitute?"

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THERAPEUTIC AND PSYCHOLOGICAL APPROACH TO CASES OF UNCONSUMMATED MARRIAGE

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In a paper read before the 19th International Psycho-analytical Congress at Geneva I attempted to formulate the scientific findings derived from the psychotherapeutic treatment of about 50 cases of unconsummated marriage (Abraham, 1956). Much of this work was carried out at the South London Hospital for Women, and was made possible by the co-operation of Miss Edith Hall and her department. First I shall give an account of my therapeutic approach. Much of the description may seem to be commonplace, but later I shall demonstrate that each step was taken on the basis of psychological reasoning and that it was through my knowledge of psycho-analytical theory that I was able to understand and handle my patients.

The women referred to me had been married for periods varying from two months to about eleven years. Most of them had been seen by one or several general practitioners, some by marriage guidance centres, and all by a gynaecologist who had not succeeded in carrying out a vaginal examination. Several patients had had a dilatation under general anaesthesia without any result.

Technique of Treatment

My technique was evolved under the pressure of a busy out-patient department, where such patients, so obviously unsuitable for a waiting-list, had to be dealt with quickly. The early cases were handled in a more tentative manner than the later ones and with greater expenditure of time. When the flow of such cases became continuous I gradually shortened and modified my procedure. Two points should here be stressed. First, my success largely depended on team-work, and the understanding and co-operation of Miss Hall and Miss Croxford were invaluable. Secondly, in no case was I content with the achievement of intercourse, for I continued to see the patients until, in most cases, some measure of orgasmic satisfaction was reported, although this naturally varied in degree and in a few cases remained poor. If pregnancy was not desired, birth-control was introduced before intercourse took place, so as to obviate any conscious reasons for apprehension and restraint. If

pregnancy was desired and achieved the patients were seen throughout that time, since it was assumed that women who had denied their femininity so strongly would need help in adjusting to their maternal role. Also, the management of the expected infant was discussed, in the hope that this might protect it from the mother's fate.

When seeing such patients the first efforts must be directed towards gaining their confidence. Often they have had their fears derided by doctors, and are therefore surprised by a sympathetic approach, and the assurance that I have seen other patients with similar fears serves to relieve tension and to gain the necessary co-operation. From the outset it is made clear that my treatment consists merely of a discussion of their anxiety, which I hope may lead to an understanding of the root of their trouble, and that they have been referred to me because I have the necessary time and experience. I then get them to tell me of their marriage and of their home background in their own way, and with as little prompting as possible. This gives me an idea of the strength of the symptom and of the time I shall need to help them to overcome it. As stated below, I have come to recognize two groups into which these cases fall.

At the end of the first interview, which generally lasts about 30 minutes, I invariably ask the patient to refrain from all further attempts at intercourse until we both agree that she is ready for it. This again is contrary to all previous advice, and is received with relief. I always add that it will not take us long to overcome her fears and that she should ask her husband to be patient for a few more weeks. Such a statement has a twofold purpose: it introduces the husband's point of view, and it helps inhibited patients to talk about a topic they have often avoided discussing with their husbands and which has been banned. In psycho-analytical language, we would say that in this way I come to represent a tolerant and permissive mother-figure. This line is followed throughout.

During the first or second interview the question of menstruation and the first menstrual period is raised as a routine matter. It is in fact used as an entry into a discussion of the patient's relationship to her mother and of her own attitude to sexuality. I ask why we have a period, thus helping her again to identify with me. I am usually told from whom or how she found out, and often assured that she knows all about it. I have learnt never to accept this, but to get her to tell me what she knows. This knowledge is as a rule incomplete and quite often absurdly distorted. Most patients are, however, keenly interested to learn something about the anatomy and physiology of their own body, a subject they had hitherto regarded as forbidden. By the end of the second interview most patients are relaxed and ready to ask questions, and in the third a plan of procedure can safely be laid before them. They are told that they will need a vaginal examination and that they would be shown how to use glass dilators—not, it is stressed, because they need stretching, but to help them to gain self-confidence. As a rule I suggest that they might help by investigating these parts of their body by themselves and trying to identify the structures I have sketched for them. This often leads to a discussion about clean and dirty parts of the body. Here I have found the use of the mouth for purposes of analogy very helpful, not merely to correct the existing ideas about clean or dirty body openings, but also for a discussion of their fear of being hurt. They readily understand that it hurts to push any object into the mouth if the lips are tightly pursed and that mouth and vagina alike may become parched with apprehensive fear and so become chafed.

Examination by Gynaecologist

With the first series of patients referred to me I used to be present during their examination by the gynaecologist, because I wanted to observe their reaction and because I believed the use of the transference relationship to me, already established, might help to shorten the treatment. I have gradually cut the preparatory phase from six to one