Therapy of Polycythemia Vera with Myleran

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MYLERAN* was developed in the course of a study of the tumor-inhibiting effect of various sulfonic acid esters by Haddow and Timmis.[1] Because of the neutropenia, unaccompanied by other side effects, which was observed during its ineffective clinical trial in various types of cancer in man, Myleran was employed in the treatment of chronic granulocytic leukemia by Galton[2] in 1950. His successful results in the control of this disease have been duplicated and reported subsequently by many other workers.[3]

The use of Myleran in chronic granulocytic leukemia at the Atomic Bomb Casualty Commission, Hiroshima, Japan, was started in 1953 by Moloney and Fujii.[4] In 1954 they, with Sears, extended its use to two cases of polycythemia vera having elevated white counts and found that a reduction of the leukocytosis occurred.[5] Since then we have used Myleran in polycythemic relapses regardless of the leukocyte level, primarily for its effect on the erythropoietic system. In five cases of polycythemia vera, it was possible to study nine polycythemic relapses through courses of Myleran therapy into clinical and hematologic remissions.

METHODS

The diagnosis of polycythemia vera was made in five Japanese patients examined at the Atomic Bomb Casualty Commission, Hiroshima, on the basis of clinical history, physical findings and laboratory data. In addition to routine blood and bone marrow examinations, blood volume[6] and red cell survival measurements[7] with Cr^{51}, and red cell production[8] and iron turnover determinations[9] with Fe^{59} were carried out in three of the cases before and after Myleran therapy. Details of the tracer technics used have been reported elsewhere.[10] Myleran was given orally in 2 mg. tablets, in a dosage determined by clinical and laboratory findings.

RESULTS

The amount of Myleran given in nine relapses of polycythemia vera in the five cases studied is listed in table 1, together with the duration of remissions produced. The average dosage of Myleran that produced full remission was 29.4 mg. per week, ranging from 22 to 40 mg. per week. Only partial remissions resulted in two instances when 14 and 17 mg. per week were used. It should be noted that in the cases where more than one fully effective course of Myleran treatment was given, subsequent remissions were produced without any significant dosage increase.

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TABLE 1.—*Duration of Remissions in Five Cases of Polycythemia Vera Treated with Myleran*

Case No.	Sex	Age	Course of Therapy	Total Dose (mg.)	Therapy Duration (weeks)	Average Dose (mg./week)	Remission Duration (months)
1	F	56	First	114	8	14	3*
			Second	288	12	24	19†
2	F	58	First	84	5	17	4*
			Second	268	10	27	19
			Third	364	12	30	6†
3	F	54	First	160	4	40	20
			Second	268	12	22	7†
4	M	46	First	408	14	29	6†
5	M	46	First	238	7	34	3†

*Partial remission. Observation period interrupted by further therapy.
†Remission still present at time of this report.

Complete remissions, occurring in seven instances, were characterized by disappearance of clinical symptoms and of abnormal physical findings, including hypertension and splenomegaly when these were present. Improvement in hematologic tests was also seen. In the two instances of incomplete remission, clinical improvement occurred, but hematologic tests showed a fall in leukocytes and platelets without much change in red cell values.

The effect of Myleran on various pertinent blood constituents is demonstrated in table 2. Individual variation in the response to a given dose level is evident, but no significant difficulty in control was found, nor did any complications of therapy occur. The results of the radioisotope tracer studies in three cases before and after therapy are presented in table 3.

Figure 1 demonstrates a typical clinical course as observed in case 2. Occasional phlebotomy was ineffective in this patient, resulting in microcytosis but producing no significant fall in erythrocyte count or hemoglobin level. The dose of Myleran initially employed produced only an incomplete remission, reducing the leukocyte and platelet counts alone. The second trial of Myleran, in a higher dosage, gave a complete remission, as did the third one after a second remission ended.

DISCUSSION

The form of therapy used in this series was effective in reducing the hemoglobin, red blood cell and hematocrit levels in all instances where an adequate dosage was given. The leukocyte and platelet counts decreased significantly when originally elevated above normal. However, these elements were not markedly altered when they were within normal limits at the start, except as an occasional temporary result of over-enthusiastic treatment. The temporary reduction of red cell counts to levels somewhat below the Japanese normal was also felt to be due to moderate overtreatment resulting from early inexperience with this form of therapy. It is noteworthy that no secondary complications ensued in any case, nevertheless.

The absence of some of the typical findings of polycythemia vera in the

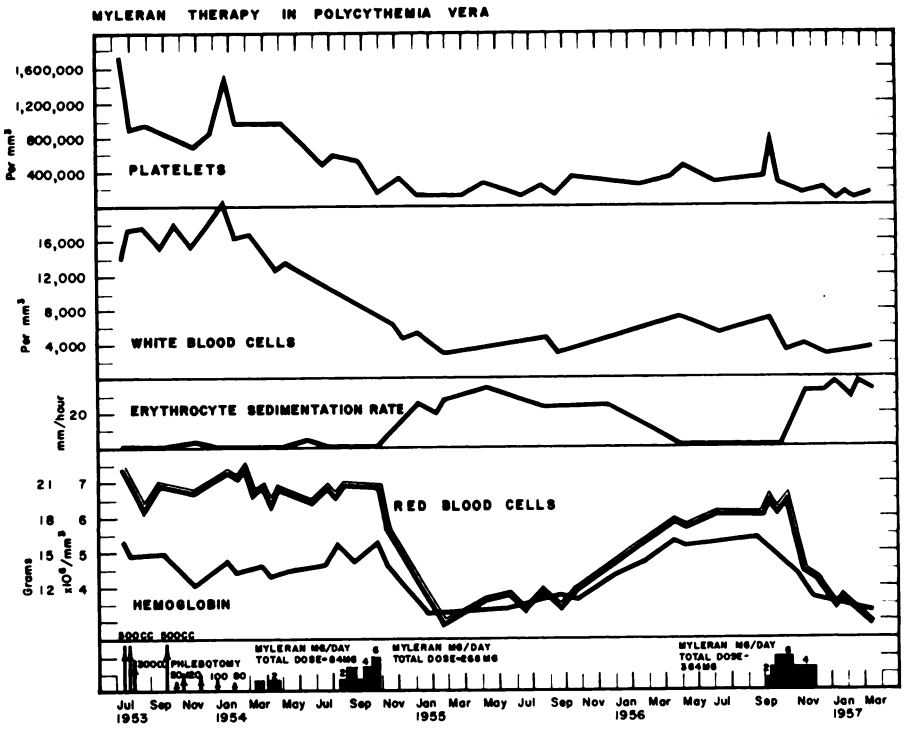

FIG. 1.—Blood changes produced by Myleran therapy during three periods of relapse in a typical case of polycythemia vera.

radioisotope studies performed prior to treatment in our small series does not rule out the presence of the disease. Even in large groups of cases such as the series of Berlin, Lawrence and Gartland[11] there was inconstancy in the occurrence of such characteristic findings as the increased hematocrit, the elevated red cell volume and the generally decreased plasma volume.

Myleran effectively reduced the red cell volume in all three cases studied by tracer methods, although other findings were not as consistently affected. However, the plasma iron turnover was reduced in two cases, and the plasma volume increased in two, after therapy. The possible contributing role of moderate overtreatment in the production of these results must be considered, but it cannot be assessed with any accuracy.

Haddow[12] has stated that Myleran produces its biologic effect through chemical alkylation of cellular protein or nucleoprotein. This property is directed preponderantly against cells in an active state of division, whether malignant or not. It is therefore quite conceivable that this agent, whose successful use against the hyperactive leukemic myeloid tissue of chronic granulocytic leukemia is generally accompanied by a secondary rise in hemoglobin and erythrocyte levels,[3] can produce depression of hyperactive erythropoiesis and, thus, a lowering of the hemoglobin and erythrocyte levels when given in the same dosage in polycythemia vera. The relatively small or absent myelodepressive effect of Myleran in polycythemia, compared with that pro-

TABLE 2.—*Effect of Myleran on Blood Findings in Five Polycythemia Vera Cases*

Case No.	Course of Therapy	HGB (Gm.)		RBC (x 10^5)		HCRT (%)		ESR (mm./hr.)		WBC		Platelets (x 10^3)	
		$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$
1	First	11.1	12.9	6.42	5.01	42.2	47.0	1.0	5.0	21,200	6,800	4,025	901
	Second	14.5	13.1	7.08	4.12	52.2	43.1	0.0	25.5	9,100	5,500	1,168	688
2	First	13.5	13.1	7.54	6.08	51.0	48.5	0.0	1.0	17,000	12,760	1,024	966
	Second	15.0	9.2	7.00	3.00	51.5	29.0	0.0	19.0	8,500	3,800	597	198
	Third	17.0	10.6	6.12	3.53	56.0	34.5	1.0	31.5	7,200	2,550	1,046	201
3	First	17.4	12.8	6.67	4.48	60.0	42.5	1.0	8.0	12,300	5,900	2,174	434
	Second	18.9	11.3	6.21	3.67	59.0	33.5	0.0	15.0	6,600	3,100	521	469
4	First	17.6	11.5	5.94	3.49	59.1	36.0	0.5	7.5	6,700	4,450	466	265
5	First	19.4	16.1	6.07	5.14	64.5	51.0	0.0	6.0	8,700	4,750	358	247
Japanese Normal[13]	Male	14.0 ± 0.9		4.62 ± 0.50		46.4 ± 3.0				6,604 ± 1,500		179 ± 7.0	
	Female	12.8 ± 0.9		4.26 ± 0.50		40.9 ± 3.0				6,653 ± 1,500		180 ± 7.0	
ABCC Normal*	Male	13.4		4.5		43.6							
	Female	11.6		4.0		37.8				5,850			

$\bar{a}$ = before Myleran therapy; $\bar{p}$ = at time of maximal change following Myleran therapy.

* Based on hematologic data of Hiroshima control groups Band C.[14]

TABLE 3.—*Effect of Myleran on Blood, Red Cell and Plasma Volume; Red Cell Survival; and Plasma Iron Turnover in Three Polycythemia Vera Cases*

Case No.	Course of Therapy	Blood Volume (ml./Kg.)		Red Cell Volume (ml./Kg.)		Plasma Volume (ml./Kg.)		Plasma Fe Turnover (mg./Kg./day)		Red Cell Cr^{51} Half-Life (days)	
		$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$	$\bar{a}$	$\bar{p}$
2	Third	88.8	60.9	46.0	18.9	42.8	42.0	2.17	0.39	32	24
3	Second	52.3	58.1	27.0	20.5	25.2	37.6	1.01	0.36	25	20
4	First	62.8	63.1	34.7	24.9	28.1	38.2	0.62	0.68	34	28
Japanese Normal Average ± S.E.*		62.0 ± 2.9		26.4 ± 1.6		35.4 ± 1.6		0.47 ± 0.05		28.8 ± 1.8	
Normal Range*		52.0 to 78.9		21.0 to 37.3		29.0 to 43.0		0.22 to 0.69		20.0 to 36.0	

*Based on findings in 9 healthy Japanese adults studied in our laboratory.

duced by similar dosage in leukemia, is probably due to the greater sensitivity of leukemic myeloid tissue which was first noted by Galton.[3]

It is of interest that the chromium-51 survival half-time of the red cells was shortened following therapy in all three cases studied during remission. In two of these the initial survival time was somewhat beyond the normal range and subsequently fell to normal or below. The possibility exists that Myleran produces not only a reduction in erythropoiesis but also a qualitative alteration in red cell formation, which is manifested by decreased erythrocyte longevity and is therefore of additional benefit in reducing the red cell volume in polycythemia vera. Other possible explanations are that this apparent shortening of erythrocyte life-span is really due to an increased elution of chromium-51 from the cells, or to a rapid pooling of tagged cells in internal organs, with subsequent gradual release.

Provided that the apparent efficacy of Myleran therapy is confirmed by further use, there are several distinct advantages to this form of treatment. It obviates the need for radiation, either by P^{32} or by x-ray, and thus avoids the use of an agent which, under some circumstances, is known to be leukemogenic,[15,16] in treating a disease in which there already is an increased incidence of leukemia.[11] It is inexpensive and easily administered by the patient's own physician, requiring no special treatment, training, authorization or consultation other than that needed for the performance of routine blood counts at biweekly or weekly intervals. Finally, it is noteworthy for its safety and freedom from side effects. This is true not only in our small series but also in the much larger number of cases receiving Myleran for chronic granulocytic leukemia.[3]

SUMMARY

Myleran was used in the therapy of nine relapses of polycythemia vera in five patients. Clinical examinations, blood studies, and, in three instances, radioisotope tracer tests before and after treatment demonstrated the effectiveness, safety and simplicity of the treatment. Further trial of Myleran therapy in polycythemia vera seems warranted.

SUMMARIO IN INTERLINGUA

Myleran esseva usate in le therapia de 9 recidivas de polycythemia ver in 5 patientes. Examines clinic, studios del sanguine, e — in tres casos — tests a traciatores radioisotopic ante e post le tractamento demonstrava le efficacia, innocentia, e simplicitate del tractamento. Essayos additional con le uso de Myleran in le therapia de polycythemia ver pare esser justificate.

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