THERAPY OF POLYCYTHEMIA VERA WITH MYLERAN

Myleran による真性多血球血症の治療

By NIEL WALD, TAKASHI HOSHINO (星野　孝), and MARY E. SEARS

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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

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Myleran* は Haddow と Timmis による各種のスルフォン酸エステルの腫瘍抑制効果の研究の過程で開発されたものである。[1] ヒトの各種癌に対する臨床試験では効果を示さなかったが，副作用が好中球減少以外に認められなかったので，1950年に GaltonはMyleran を慢性骨髄性白血病の治療に用いた。[2] Galton が認めた本疾患の治療に対する Myleran の効用は，その後他の多くの研究者にも認められ，その報告がある。[3]

広島 ABCC において慢性骨髄性白血病に対する Myleran の使用は1953年 Moloney と藤井によって始められた。[4] 1954年 Sears を加えた3人は，白血球数増多を示す真性多血球血症2例にも使用し，白血球増多の減少をみた。[5] それ以来，著者らは主として赤血球造血系に対する効果を主目的に，白血球数とは無関係に，多血球血症再発例に Myleran を使用してきた。真性多血球血症5例に対して，9回の多血球血症増悪期に Myleran 治療を行ない，臨床的および血液学的に寛解をみた過程を検討することができた。

方　法

広島ABCCで既往症，診察所見，臨床検査成績に基づいて日本人患者5名に真性多血球血症の診断をくだ

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*最初は英国 London 市にある Royal Cancer 病院の Alexander Haddow 教授の好意によって入手したが，その後は New York 州 Tuckahoe 市にある Burroughs Wellcome 社から入手した。

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.

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 in-

した。そのうち3例については，Myleran 療法の前後に血液と骨髄の一般検査以外に Cr^{51} による血液量[6]および赤血球の寿命の測定[7]ならびに Fe^{59} による赤血球生成[8]および鉄転換の測定[9]を行なった。使用したトレーサー技法の詳細については別報[10]のとおりである。診察および臨床検査所見によって決定した服用量の Myleran（2 mg錠）を経口投与した。

結　果

5例の真性多血球血症において9回の増悪期に投与された Myleran 量を寛解期間を併記して表1に示した。完全寛解をもたらした Myleran の平均投与量は週29.4 mgでその範囲は22～40 mgであった。週14 mgと17 mgを投与した2例には部分的寛解をみた。有効な Myleran 療法を2クール以上受けた例では，その後の寛解を得るために投与量を有意に増加させる必要はなかった。

完全寛解が7回みられたが，次のような特徴が認められた。臨床症状ならびに高血圧および脾肥大を含む異常診察所見の消失と血液検査所見の改善もみられた。2回不完全寛解がみられた。その場合，臨床症状は軽快したが，血液検査では白血球数と血小板数の減少があったが，赤血球には大きな変化はなかった。

血液所見に対する Myleran の効果を表2に示した。一定の投与量に対する反応には個人差があったが，コントロールには大きな困難もなく，また治療による合併症も生じなかった。3例について治療前後に行なった放射性同位元素によるトレーサー検査の結果を表3に示した。

図1は症例2にみられた一つの典型的な臨床過程を示すものである。この患者に静脈切開手術を時折行な

Table 1. Duration of Remissions in Five Cases of Polycythemia Vera Treated with Myleran

表1　Myleran 治療を受けた真性多血球血症5例の寛解期間

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.
部分的寛解．さらに治療を行なったので，観察期間が中断

† Remission still present at time of this report.
本報作成時も寛解中

Table 2. Effect of Myleran on Blood Findings in Five Polycythemia Vera Cases

表2　真性多血球血症5例における血液所見に対する Myleran の効果

Case No.	Course of Therapy	HGB (Gm.)		RBC ($\times 10^5$)		HCRT (%)		ESR (mm./hr.)		WBC		Platelets ($\times 10^3$)	
		$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$
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			

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

$\overline{a}$ = Myleran 治療前　$\overline{P}$ = Myleran 治療後の最大変化時

* Based on hematologic data of Hiroshima control groups Band C.[14]
広島対照群C帯の血液学的資料による。[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

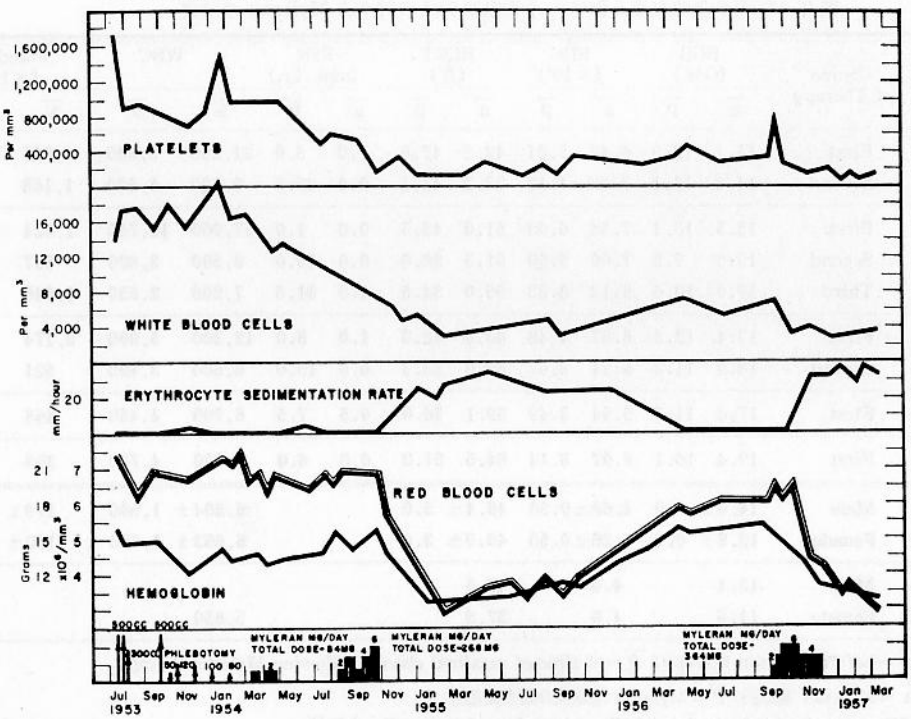
表3　真性多血球血症3例における血液量，赤血球量，血漿量，赤血球寿命期間および血漿鉄転換に対するMyleranの効果

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)	
		$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$	$\overline{a}$	$\overline{p}$
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.
当所で検出した健康な日本人成人9名の所見による。

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

図1　真性多血球血症の典型的1例において3回の再発期間中Myleran療法によって生じた血液変化



effective in this patient, resulting in microcytosis but producing no significant fall in erythrocyte count or hemoglobin level. The dose of Myleran initially employed only an incomplete remission, reducing the leukocyte and platelet counts alone. The second trial of Myleran, 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 radioisotope studies performed prior to treatment in our small series dose 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 an accuracy.

ったが，小赤血球症を生じ，赤血球数と血色素量に大きな低下はみられず，効果はなかった。Myleranの第1クールでは，白血球数と血小板数のみに減少がみられ，不完全寛解にとどまった。増量した第2クールでは完全寛解が得られ，引き続いて第3クールでも同様な結果が得られた。

考　察

投与量がじゅうぶんであれば全例において血色素量，赤血球数およびヘマトクリット量の減少に効果があった。白血球数と血小板数はそれらが正常より増加していた場合には，有意に減少したが，それらが正常範囲内にあった場合には，過度の治療による一時的な結果としてその減少が時折みられた以外，著しく変動することはなかった。赤血球数が日本人の正常値以下に一時減少したことは，この治療方法に対する経験不足に基づく中等度の過度治療によるものと考えられる。それにもかかわらず，いずれの患者にも二次合併症が起こらなかったのは注目に値する。

これらの少数の患者の治療に先だって行なった放射性同位元素検査において真性多血球血症の特有の所見が認められなかったことは，この疾患の存在を除外するものではない。Berlin, Lawrence, Gartland[11]が取り扱った多数の例においてもヘマトクリットの増加，赤血球量増加，血漿量の全般的減少などのような特有の所見に一貫性はなかった。

トレーサー技法で調べた3例に，Myleranの赤血球量減少効果が認められたが，他の所見にはそれほど一貫した変化はなかった。しかしながら，治療後，血漿鉄転換は2例で減少し，血漿量は2例で，増加した。これらの結果を生ずるうえで，中等度の過度治療がどのような役割を果たすかは考慮すべきであるが，この点については正確には評価できない。

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 produced 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

Haddow[12]は，Myleranは細胞蛋白または核蛋白の化学的アルキル化によってその生物学的効果を生ずると述べている。この性質は，悪性，良性のいかんにかかわらず，主として分裂中の細胞に対して有効である。したがって，慢性骨髄性白血病の過形成性白血病性骨髄組織に対して有効に使用した場合，一般的に血色素および赤血球数の二次的な増加を伴うが，真性多血球血症に同じ量を投与すれば，過度の赤血球形成を抑制し，血色素量および赤血球数[3]を低下させることができると考えられる。多血球血症に対するMyleranの骨髄抑制作用が，白血病に対してほぼ同量投与した場合の作用に較べて，比較的小さくまたは全くないことは，Galton[3]がはじめて指摘したように，白血病骨髄組織の感受性が強いためであろうと思われる。

治療後，寛解中であった3例についてCr^{51}により赤血球生存期間を調べたが，全例とも短縮していたのは興味深い。そのうち2例では，赤血球生存期間が治療前の正常範囲よりやや長く，後に正常または正常以下に減少した。Myleranは赤血球生成の低下のみならず，赤血球形成の質的変化をも生じさせる可能性がある。これが赤血球の生存期間の減少として現われ，真性多血球血症の赤血球量減少にはいっそう有効である。他に考えられる説明としては，赤血球寿命が明らかに短縮されるのは，血球からのCr^{51}溶出が増大するためであるか，または標識血球が急速に内臓にプールされ，以後徐々に放出されるためである。

今後Myleran療法を続けて，その効果がはっきり確認されれば，この治療法にはいくつかの明確な利点がある。P^{32}やX線による放射線照射をする必要がなく，したがって，ある条件のもとでは白血病を誘発することの知られている放射線[15,16]を，すでに白血病の発生がふえている疾患の治療に使用することを避けることができる。Myleranは安価で，主治医が容易に投与することができ，毎週1～2回の通常血球数検査を必要とする以外は特殊治療，訓練，認可，相談など

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.

を必要としない。最後に，Myleranは安全であり，副作用のないことは注目に値する。このことは，われわれの少数の治療例のみならず慢性骨髄性白血病でMyleran療法を受けている多数例[3]についても認められたのである。

要 約

真性多血球血症患者5名において，9回の増悪期にMyleranを使用した。臨床検診，血液検査および3例については治療前後の放射性同位元素トレーサー検査で，この治療法の有効性，安全性および簡易性が認められた。真性多血球血症にMyleran療法を試みる必要があると思われる。

REFERENCES
参 考 文 献

1. Haddow, A. and Timmis, G. M.: Chemical constitution and biological action. Lancet *1*:207, 1953.
2. Galton, D. A. G.: Myleran in chronic myeloid leukaemia. Result of treatment. Lancet *1*:208, 1953.
3. ——: Advances in Cancer Research. New York, Academic Press, Inc., 1956, vol. 4, p. 73.
4. Moloney, W. C. and Fujii, T.: The use of Myleran in the treatment of chronic myelogenous leukemia in atomic bomb survivors. Acta Haemat. Japonica *17*:120, 1954.
5. Atomic Bomb Casualty Commission Semi-Annual Report Covering Period January 1, 1954 through June 30, 1954. Part I. Research, U.S.A.E.C., Tech. Info. Ext., Oak Ridge, Tenn., 1956, NYO-4475, 9.
6. Gray, S. J. and Sterling, L.: Determination of circulating red cell volume by radioactive chromium. Science *112*:179, 1950.
7. Ebaugh, F. G. Jr., Emerson, C. P. and Ross, J. F,: The use of radioactive chromium 51 as an erythrocyte tagging agent for the determination of red cell survival *in vivo*. J. Clin. Invest. *32*:1260, 1953.
8. Huff, R. L., Tobias, C. A. and Lawrence, J. H.: A test for red cell production. Acta Haemat. *7*:129, 1952.
9. ——, Elmlinger, P. J., Garcia, J. F., Oda, J. M., Cockrell, M. C. and Lawrence, J. H.: Ferrokinetics in normal persons and in patients having various erythropoietic disorders. J. Clin. Invest. *30*:1512, 1951.
10. Wald, N., Hoshino, T. and Driscoll, D.: Determination of blood production and destruction using radioactive iron-59 and chromium-51. Acta Haemat. Japonica *19*:207, 1956.
11. Masouredis, S. P. and Lawrence, J. H.: The problem of leukemia in polycythemia vera. Am. J. M. Sc. *233*:268, 1957.
12. Haddow, A.: Discussion on the chemotherapy of the reticuloses. Proc. Roy. Soc. Med. *46*:692, 1953.
13. Miyasaka, G.: Normal blood picture of the Japanese (1955-1957). Acta Haemat Japonica *20*: (3), Suppl., 98, 1957.
14. Wald, N.: Blood picture of Hiroshima A-bomb survivors. Am. J. M. Sc. *233*:152, 1957.
15. Court-Brown, W. M. and Doll, R.: Leukaemia and aplastic anemia in patients irradiated for ankylosing spondylitis. Med. Research Council, Special Report Series No. 295. London, H. M. Stationery Office, 1956.
16. Wald, N.: Leukemia in Hiroshima City atomic bomb survivors. Science *127*:699, 1958.