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JPRS: 4855

8 August 1961

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- CZECHOSLOVAKIA -

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JPRS: 4855

CSO: 1764-S

TREATMENT OF CHRONIC MYELOID LEUKEMIA WITH 1.4 DIMETHYL-SULPHOXYBUTANE (MYLERAN)

-Czechoslovakia-

/Following is the translation of an article by L. Chrobak, D. Radochova, H. Chrobakova in Prakticky lekar, Vol XLI, No 3, Prague, 5 Feb 1961, pages 123-128./

1.4-dimethylsulphoxybutan ($CH_3.SO_2.O\ (CH_2)4.O.SO_2CH_3$), originally named "GT 41" and later known by the trade mark "Myleran," was discovered by Haddow and Timmis in the investigation of aromatic derivatives of nitrogenous yperite. Experiments showed that this substance subdues not only the growth of Walker rat cancer, but also has a selectively subdual effect on granulocytopoesis, whereas the formation of lymphocytes is not affected. Myleran was applied in therapy of chronic myeloses. The mechanism of the selective effect of myleran on granulocytopoesis has not yet been uniformly explained. Probably an inhibition of mitosis is involved. The first clinical experiences with Myleran were published by Galton in 1953. Since then, many works have appeared which invariably describe Myleran as a contribution to therapy of chronic myeloses (in this country, Wiedermann, Prochazka, Novotny, Ujhazy, Winkler, Cerny, Sandor, and Chrobak. In the works just cited, experience with this medicine was usually limited. In view of the fact that our own preparation, Mylecytan, is now also used, we consider it proper to reveal our own five-year experience with 1.4-dimethylsulphoxybutan in the treatment of chronic myeloid leukemia.

Myleran proved effective only in the treatment of chronic myeloid leukemia. It is quite ineffective in acute and subacute leukemia and erythroleukemia, in chronic lymphadenitis, plasmocytomas, lymphosarcoma, melanosarcoma, and carcinomas in various location.

The medicine is a peroral preparation in the form of a 2 mg dragee. The original large-dose offensive treatment (100 to 150 mg within 1 to 6 days) was discontinued because the same therapeutic effect can be obtained with doses of 4 to 6 mg, and the danger of pith paralysis, which was frequent with the large-dose treatment, is lessened. Galton considers as an optimum dose the amount of .06 mg per kg of weight, i.e. approximately 4 mg per day. This amount is administered until a normalization

of the number of leucocytes is obtained whereupon the medicine is omitted. In cases when an insufficient effect occurs, the daily dose is increased.

The number of leucocytes usually increases when the treatment begins. The first decline of leucocytes in small doses of Myleran, 4 to 6 mg, is noted after 7 to 28 days. The speed at which the number of leucocytes decrease depends upon the size of the dose and to a great degree on the individual sensitivity of the patient. The time necessary for the reduction of leucocytes to a normal level and the quantity of the medicine used varies considerably and does not depend on the initial count of white corpuscles. After discontinuation of treatment, the number of leucocytes usually is reduced. The first to disappear are the unripe forms. In the period of remission, the blood picture is often completely normalized and the only conspicuous phenomenon may be basophilia; in a more advanced stage of the disease the unripe forms do not completely disappear. The absolute number of lymphocytes remains unchanged.

A great advantage of a successful treatment with Myleran is the modification of anemia. The increase of hemoglobin is a favorable prognostic sign, and Galton considers it a better indication of the patient's sensitivity to Myleran than the decline ofleucocytes. The increase of hemoglobin almost coincides with the decline of leucocytes. In rare cases polyglobulia may appear. A conspicuous decline of hemoglobin, in treatment with Myleran, is an unfavorable prognostic sympton.

The decline of thrombocytes is an undesirable side effect of the treatment. The decline was more frequent in high, shock doses, but it can also occur in small doses even after a longer period following discontinuation of administration of the medicine. Also here, the individual sensitivity of the patient is important. The hemorrhagic state caused by thrombocytopenia may terminate in a death by brain hemorrhage. Thrombocytopenia before the beginning of treatment is not an absolute contraindication of the treatment, for in the course of the treatment the number of thrombocytes sometimes goes up, and even from thrombocytopenic values to normal. Galton, however, observed hemorrhagic symptoms where treatment was started at a thrombocyte count less than 100,000.

The pith extracts in the remission period, were found to have less cells than the extracts taken before the treatment was begun. The decrease refers primarily to the unripe elements of the granulocytic series. Erythropoesis is relatively more abundant. The first changes in the pith were noticed as early as the first and the second week of the treatment. Sometimes the pith extract became quite normalized.

Simultaneously with the improvement of the blood count, the enlargement of the spleen and liver diminishes. Even though the diminishing is somewhat slower than in X-ray treatment, the final result is the same. Even considerably large tumors may disappear.

One conspicuous phenomenon is the subjective improvement of the general condition, which the patient often announces before the decline of leucocytes. The weakness and fatigue and anorexia subside, and the patient gains weight.

The length of remission during which no Myleran need be administered vacillates from several days to several months. Afterwards, the number of leucocytes goes up and the count receives younger forms of the granulocytic series -- a relapse takes place. A repeated treatment may be started either at a fully developed relapse or at the first evident increase of the leucocyte count. The doses of Myleran necessary for preventing the leucocytes from increasing and for keeping them within normal values vary from 4 mg per week to 4 mg per day. Bernard starts preservation therapy when the number of leucocytes reaches 15,000 -- Unungur and associates at 8,000.

The Myleran treatment may be started even in patients who were previously treated by a different method. The treatment is effective even in cases where the X-ray treatment and the P_{32} treatment was ineffective. When a resistance develops, X-ray treatment or Colcemid treatment may be started.

In a myeloblast crisis, Myleran is ineffective and must be substituted by the current treatment of acute myeloses.

The preparation is tolerated very well. Dyspeptic difficulties, frequent with other cytostatic medicines and also in X-ray treatment, were not observed. Galton noticed brownish pigmentation of skin, and in women amenorrhoea occurs frequently.

The most important side effect of the medicine, apart from the state of hemorrhage resulting from thrombocytopenia, is the possiblity of pith paralysis, which especially threatened in treatment by large doses, or which may originate also in a long-term administration of the medicine without proper control of the blood picture. In small doses and with a systematic hematological control, the danger of pith paralysis is relatively small.

Proper Observation

The treatment of chronic myeloses with Myleran was begun at the end of 1954. Our records, which include twenty four patients, refer only to cases which we ourselves treated during the whole period of the disease. Those patients whose treatment was begun elsewhere or who in the course of the treatment were treated at another institute were excluded from our records. We used Myleran in treating all the patients ill with chronic myeloid leukemia without any previous selection; thus, our work makes it possible to judge to a certain degree the effect of this medicine. Out of twenty four patients, fourteen had not been previously treated and others had been treated with X-rays, TS 160. The length of the disease before the beginning of the Myleran treatment varied between one month and four years.

The treatment was begun with all patients receiving a daily dose of 4 mg (i.e. 2 dragees). When the leucocyte count decreased below 20,000, the dose was reduced to 3 and 2 mg, and when it decreased under 10,000, Myleran was discontinued. As soon as the leucocyte count increased and exceeded 10,000, the sustenance dose was administered. The sustenance dose varied between 4 to 6 mg per week and 4 mg per day. When

the leucocytes decreased below 10,000 Myleran was again discontinued. In the beginning, before we had accumulated the necessary experience, Myleran was administered to patients in bed, but later the treatment became primarily ambulatory. The patients in ambulatory treatment were in the beginning of the treatment until the remission usually contolled once in a week, in sustenance treatment, according to the size of the dose, once in two weeks, and up to once in four weeks. In control examinations, attention was given to the subjective condition of the patient, the objective finding, and in laboratory examinations, the number of red corpuscles, hemoglobin, the number of leucocytes, and the distribution and number of thrombocytes. In the sustenance treatment we were not anxious to keep the leucocyte count below 10,000, but rather we saw to it that the patient could feel well subjectively. With regard to the psychic state of the patients, we tried, whenever possible, not to control the patients more often than once a month. The sustenance dose was therefore established cautiously — somewhat lower than it should be.

Owing to the fact that the toxic effect of Myleran (granulocytopenia, thrombocytopenia, or pancytopenia) may arrive even after a long period of discontinuation of the medicine, the patients were reminded to come to control with any indication of any impairment of the general condition (when afflicted with pain in throat, high temperature, or when any symptoms of skin or mucous membrane hemorrhage became apparent.

The first decrease of leucocytes was noticed after seven to twenty one days following the beginning of the treatment. Afterwards the leucocyte count sometimes went up, once even almost double the original count (from 106,000 to 192,000 — patient No 3). An increase of the leucocyte count in the first three weeks is consequently not a sign of resistance against Myleran and should not lead us to increasing the daily dose of the preparation.

The leucocyte count was normalized in 18 patients; nine out of these had only ripe granulocytes in the distribution. In four patients a conspicuous basophilia was observed (4 to 7% basophiles). In the distribution, the unripe forms of the granulocytic series were the first to disappear. In three cases, inspite of a decrease of leucocytes, the percentage of unripe granulocytes (primarily myeloblasts in the distribution) did not decrease and a myeloblastic derangement always followed. In certain patients, inspite of the normalization of the leucocyte count, an isolated occurrence of younger elements of the granulocytic series appeared. This occurred in patients who had been under treatment for a longer time, although the leucocyte count also was sometimes normal.

The quantity of Myleran necessary for obtaining the remission was different in the individual cases and depended considerably on the personal sensistivity of the patient to Myleran. For instance, in two patients with an identical initial leucocyte count (patients 2 and 13) a normal leucocyte count in the first patient was obtained after doses totaling 438 mg, and the remission, during which the patient received no Myleran, did not last a whole month; but the second patient reached the remission after doses totaling 192 mg of Myleran, and at the time

when the patient died of metastatic cancer of stomach, the remission was 13 months old. Neither of the two patients had been previously treated for leukemia, and in the case of the second patient, the disease had a longer duration previous to the beginning of the treatment.

A big advantage of the Myleran treatment is the modification of anemia. Hemoglobin and red corpuscles increased in 17 patients, in 5 patients the increase of erythrocytes and hemoglobin did not occur (in two of them, however, the blood picture, as far as the red component was concerned, had been normal before the beginning of the treatment), and in two the serious character of their condition required blood transfusions. The erythrocyte count and hemoglobin increased in the course of treatment with Myleran, but the increase usually continued even after Myleran was discontinued in the period of remission. The average increase of erythrocytes in patients was 1,000,000. Once, the increase of erythrocytes reached polyglobulic values — 6,100,000 (patient No 4). A more distinct decrease of the leucocyte count in the course of the treatment with Myleran was a very unfavorable prognostic symptom and announced, as a rule, the transition to the final stage — in most cases the approaching of acute derangement. Only one was such a decrease of erythrocytes temporarily reversed.

The favorable effect of the treatment with Myleran, apart from the decrease of the leucocyte count, was expressed also in a reduction of the spleen and the liver. In the beginning of the Myleran treatment the spleen was enlarged in 21 patients. During the treatment, the spleen was reduced in 18 patients, of which in 10 it disappeared completely, although at the time when the treatment began it frequently formed a tumor extending to the navel or even the groin. In patients treated for a long time, we sometimes noticed a gradual enlargement of the spleen, although the leucocyte count still remained normal. A rapid enlargement of the spleen was observed in the final stage in all patients who subsequently died of the basic illness.

As the spleen, also the liver was reduced as a result of successful treatment.

Sternal puncture was made in the remission period in 10 patients. In accordance with the literature the cellutarity of the pith extracts in the period of remission was, in a majority of specimens, smaller, the granulocytic series was poorer (before treatment 93.5% as an average, in the period of remission 79.2%), the younger formations decreased, and the mature formations increased. The red corpuscle series in remission was relatively more abundant (before treatment 2.8%, in remission 15.6%; in one patient even a mild relative hyperplasia of ths red series was found (35.6%).

All patients, with the exception of those who were resistent against the treatment, claimed improvement of their general condition; the weakness, fatigue, pressure under the left rib arch, and lack of appetite disappeared. The increase in weight was sometimes more than 10 kg, once as much as 25 kg.

All patients tolerated Myleran very well.

The most serious of the side effects of Myleran is the pith

paralysis, which may even present itself in a patient who has been under close control. The peripheral picture of pancytopenia was noticed in the course of the treatment with Myleran in two patients. In one patient, this announced the acute myeloblastic derangement (patient No 12), in another (patient No 7) the periperal picture of pancytopenia was accompanied with a conspicuous fatigue, loss of appetite, and nose bleeding. He was the only patient to whom we administered, even when the leucocyte count was under 10,000, small doses of Myleran (54 mg in seven months, i.e. approximately 2 mg per week). The red corpuscles went down from 4,210,000 to 2,460,000, leucocytes to 3000 with a normal distribution: Seg 67, Bazo 1, Mono 6, Ly 26, thrombocytes 52,800. In the pith there was a relative hyperplasia of the red series (35.6%). The blood picture normalized after three months without any blood transfusion (Ery 4,000,000, Hb 80%, leuco 6400, Seg 82, Bazo 1, Mo 2, Ly 15). After two months the patient died of a myeloblastic derangement.

In patient No 16, five months after discontinuing Myleran leucopenia appeared; this reached the lowest value of 2300 leucocytes six months after the last dose of the preparation (total amount 190 mg). In the distribution there was neutrophilia: Seg 81, Eo 1, Ly 18; symptoms of agranulocytosis were not present, the patient felt well and is today — after almost 3 years — subjectively and objectively in good condition. Further treatment with Myleran did not cause more leucopenia.

In two patients (No 1 and 11), thrombocytemia arose in the Myleran treatment. In one (No 1), thrombocytemia was accompanied with thrombophlebitis of the right shank which, after injection treatment with butylpyrin, disappeared within a week. In one case (patient No 19) treatment of the patient was begun when the thrombocyte values were thrombocytemic, but no complications were produced.

Out of 11 women of our combination, eight were in menopause; in the remaining three, permanent amenorhoea developed.

In two patients (No 2 and 15) dark brown pigmentation of skin was observed; in the first also symptoms of peripheral neuritis occurred in both lower members (this was a patient to whom it almost always was necessary to administer permanently high doses of Myleran; over a period of 11 months the patient received total 1300 mg of Myleran).

In another patient (No 17) uncommon changes of plasma and nuclei of neutrophilic granulocytes were noticed during the Myleran treatment. In the plasma of certain neutrophiles both the azurophilic and the specific granulation disappeared, and the plasma received a pink hue. At the same time, the structure of the nucleus became very thin, as if the nucleus was dissolved. The changes were more prominent in the specimens from the pith than in specimens from peripheral blood. However, these changes of plasma have been described in leukemia so that an accidental time coincidence with the Myleran treatment may account for it.

With two patients, resistance against Myleran was noticed. It was noticed in the first (No 20), who had not been treated before, that the number of leucocytes in the treatment with Myleran went down over a period of four weeks from 320,700 to 49,800 and then began to go up again.

The patient was afterward very sensitive to X-ray therapy. Resistance against Myleran remained even after this irradiation, whereas a repeated X-ray irradiation for relapse was successful even the second time. In the second patient (No 22), who was sent to us because of resistance against X-ray irradiation, at first we noticed the reverse — an increased sensitivity to Myleran. The leucocyte count went down from 64,900 to 4,000 within 14 days after a total amount of 56 mg, but immediately afterwards the number of leucocytes began to increase very vigorously and Myleran proved to be completely ineffective. After another three months a myeloblastic derangement occurred.

The results of the treatment are considered as successful in 19 patients, partly successful in two, and unsuccessful in three, of which two of the last group were unsuccessful owing to the patients' resistance against Myleran. When evaluating the success or failure of the treatment of our patients it is necessary to note that in some patients the treatment was begun at an advanced stage of the disease when X-ray treatment would have been unsuitable (patients 6, 17, and 18). The partial success of the treatment in two patients and the one failure occurred only among these patients. Out of the 24 patients 9 died, 15 lived and 8 of the latter have been under treatment to the present from 37 to 47 months.

Out of the nine patients who died, seven died as a result of myeloblastic derangement (patients 2, 3, 6, 7, 12, 14, 17); in one patient (No 5), there appeared in the final stage of the disease a considerable effeteness with onset of high temperatures, which we ascribed to the otherwise negative discovery to the basic disease. In the last patient (No 13), the development was interesting because along with chronic myelosis a carcinoma of the stomach was discovered for which the stomach was resected. After the operation we started the Myleran treatment. The remission (owing to numerous metastases at the time of the death) was 13 months old. The pith punctuate and the peripheral picture, apart from anemia, were normal.

In the myeloblastic derangement, Myleran proved to be unsuccessful. For that reason we discontinued it and started a treatment common in acute myelosis, i.e. with Puri-Nethol and steroids. At present, we concentrate on the problem of when to begin the treatment with Puri-Nethol and steroids, or if in the initial period of the myeloblastic derangement a combination treatment with Myleran and Puri-Nethol is suitable.

In the end we would like to try to answer several questions in connection with the treatment of chronic myeloses with 1.4-dimethylsulphoxybutan, using our own experience and that presented in the literature.

When to begin with the treatment? The treatment should not be begun as long as the patient is untroubled. The treatment should not be postponed until the patient complains of any subjective difficulties such as weakness, fatigue, or if the spleen is somewhat conspicuously enlarged.

What with doses to start the treatment? The shock treatment with large doses is no longer used, since small doses, up to 4-6 mg, are

A	B	C	D	E	F	G	H	I	J	K
1.	JB	32♂	1	37	38	0	3 480	5 140	43 600	5 300
2.	MF	56♀	3	11	14	0	4 310	4 300	219 000	8 100
3.	MF	61♀	24	5	29	RTG: 54 55	2 900	3 960	106 900	7 800
4.	FH	65♂	48	46	94	TS 160; 1951	4 120	6 100	73 000	6 400
5.	LH	47♀	35	16	51	RTG: 53, 54, 55	3 560	4 200	179 000	7 000
6.	LH	56♀	24	2	26	0	1 900	transf.	468 000	58 900
7.	VJ	63♂	42	24	66	RTG: 51, 52 TS: 51	3 500	5 000	139 100	3 900
8.	OK	44♂	10	36	46	0	4 000	4 820	138 600	7 900
9.	BK	39♀	44	45	89	RTG: 52, 2× 53, 54	3 100	4 000	243 000	8 300
10.	MK	33♀	6	47	53	RTG: 55	4 000	4 800	58 400	6 400
11.	JN	23♂	5	36	41	0	3 300	4 900	73 300	5 800
12.	MN	21♂	1	26	27	0	4 500	5 200	121 000	9 100
13.	AP	51♂	10	14	24	0	3 320	4 000	202 100	4 000
14.	AS	55♀	43	11	54	RTG: 52, 53, 54, 55	3 200	4 200	23 200	10 900
15.	MŠ	33♀	8	44	52	RTG: 55	4 560	4 500	16 600	6 700
16.	AV	56♀	10	43	53	0	3 850	4 450	100 400	2 300
17.	JD	48♀	0	3	6	0	3 450	3 470	102 100	34 800
18.	AČ	67♀	1	8	9	0	3 150	3 400	447 300	28 100
19.	AP	49♀	10	17	27	0	3 560	4 000	25 900	5 100
20.	VS	24♂	2,5	4	37	RTG: 58	1 870	transf.	320 700	49 800
21.	JŠ	35♂	2	8,5	10,5	0	3 100	4 730	321 500	5 500
22.	OŠ	48♂	18	3	24	RTG: 58, 59 regist.	3 960	4 150	64 900	4 000
23.	JM	43♂	11	4	15	0	3 910	4 880	112 300	5 400
24.	MN	57♀	3	6	9	0	4 100	4 690	275 000	11 100

Legend: A - Number; B - Name; C - Age; D - Length of disease before Myleran treatment was begun; E - Myleran treatment in months; F - Total length of disease; G - Previous treatment; H - Erythrocytes before treatment; I - Erythrocytes in remission; J - Leucocytes before treatment; K - Leucocytes in remission;

	L	M	N	O	P	Q	R
1.	852	NE	NE	–	–	++	Thrombocytemia, thrombophlebitis.
2.	1300	R	R	Periph. neuritis	pigm.	++	High doses of Myleran, d. AD
3.	440	R	R	–	–	+	d. AD
4.	826	R	R	–	–	+++	
5.	656	NR	NR	–	–	++	Death at high temperature proper to basic illness.
6.	834	R	R	–	–	–	d. AD
7.	862	R	R	Pancytopenia	–	+++	d. AD
8.	602	R	R	–	–	+++	
9.	1230	R	R	–	amenorrhoea	+++	
10.	1708	R	R	–	amenorrhoea	+++	
11.	1	R	R	–	–	+++	Thrombocytemia
12.	476	R	R	Pancytopenia	–	++	d. AD
13.	192	R	R	–	–	+++	d. of metastasis of stomach cancer preceded by 13-mo. remission.
14.	722	R	R	–	–	+	d. AD
15.	2378	NE	NE	–	amenorrh. pigm.	+++	
16.	824	R	R	Leucopenia	–	+++	
17.	374	NR	R	–	–	temporary +	No remission; d. AD
18.	812	R	R	–	–	+	No remission; beginning of AD
19.	572	R	R	–	–	+++	Thrombocytemia before treatment.
20.	344	R	NR	–	–	–	Resistance to Myleran; responds well to X-ray therapy (2 times).
21.	436	R	R	–	–	+++	
22.	228	NE	NE	–	–	–	Short-time remission (one wk) with subsequent resistance
23.	182	NE	NE	–	–	+++	
24.	284	R	R	–	–	++	

(continued) L - Quantity of Myleran in mg; M - Liver; N - Spleen;
O - Toxic symptoms; P - Side symptoms; Q - Success of treatment;
R - Comments.

Abbreviations in table: E - Enlarged; NE - Not enlarged; R - Reduced;
NR - Not reduced; d. - Died; AD - Acute derangement.

equally effective and the danger of pith paralysis is, with the small doses, less, as it appears from the literature. We ourselves ever exceeded a daily dose of 4 mg. A certain patience is required in the beginning of the treatment when the leucocyte count may even go up in the first 3 to 4 weeks. Increasing the doses of the medicine because of a reduced sensitivity to the preparation would be erroneous.

A question arises whether to transfer the patient to a sustenance treatment or to await a complete relapse, and then begin with treatment again. All but one patient were treated with sustenance doses in a way that we have already mentioned. We think that the sustenance treatment has, above all, the advantage that a patient is kept in a subjectively good condition and often can even perform his work. He can become accustomed to the regular checkup, which is, as a rule, practiced not more often than once a month and which does not present any psychic involvement. The fears that, in the sustenance treatment, higher doses are needed and that therefore a theoretical possibility exists that a resistance against the medicine will develop, do not seem justified to us, because the appearance of resistance is not caused by the quantities of the administered preparation alone. In two of our patients resistant to Myleran, the resistance occurred after administering small doses (108 mg and 56 mg), whereas there are patients who were under treatment for almost 4 years who had been administered amounts which by far exceed the above, but no resistance occurred.

For the time being we are unable to answer the question of whether Myleran extends the lifetime of patients afflicted with chronic myelosis in comparison with other methods of treatment as in the X-ray method. The very good results obtained in some of our patients (patients 4 and 9), who have been treated with Myleran for almost 4 years and whose disease is 7 to 8 years old, indicate that the method in question represents a very valuable contribution to the treatment of chronic myeloses. The Myleran treatments may be applied even in cases where other methods failed, or where for other reasons they are not suitable. The treatment does not call for a stay of the patient in a hospital, is inexpensive, keeps the patient in a good condition, and in a number of cases, makes it possible for the patient to continue his employment. The treatment is not accompanied by the unfavorable side effects which occur in the X-ray treatment. The danger of pith paralysis is, with appropriate control of the patient, small.

Summary

The report deals with experiences gathered over a period of several years and which relate to the treatment with 1.4-dimethylsulphoxybutan (Myleran) of chronic myeloid leukemia in 24 patients. Myleran is a valuable contribution to the treatment of chronic myeloses. The preparation is tolerated very well and its administration may be ambulatory. The danger of pith paralysis is, with an appropriate control of the patient, small.

-END-