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Methotrexate in the treatment of mycosis fungoides – a multicenter observational study in 79 patients

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Abstract. – OBJECTIVE: The first report concerning methotrexate (MTX) in the treatment of *Mycosis fungoides* (MF) was published in 1964 by Wright. The mechanism of MTX action in the treatment of primary cutaneous T-cell lymphoma (CTCL) has been not explained in detail yet (the anti-inflammatory, immunomodulating, immunosuppressive, and cytostatic actions have been under discussion).

PATIENTS AND METHODS: This is a retrospective analysis of 79 MF patients in 4 dermatology clinical centers in Poland. Data are presented in terms of the duration, use of MTX, the effectiveness of treatment with MTX in terms of time required to achieve remission, the disease stage, route of administration, age at diagnosis and the dosage. Moreover, the occurrence of side effects depending on the route of administration and duration of therapy with MTX was analyzed.

RESULTS: The analysis has revealed that 56 patients (70,9%) had achieved remission on the MTX. The remission began in the 1st month of therapy in 20% of patients, lasted 4 to 6 months in 50% of cases. At least 12 months' remission was confirmed in 25% of patients (2-year-long only in 10% and 3-year-long in 5% of patients). The time to remission was related to the stage of disease at diagnosis as well as to minimal and maximal dose of MTX. The total therapeutic dose of MTX was found important for the course of the disease: higher total dose had prolonged the remission.

CONCLUSIONS: Despite the common use of MTX in MF patients, relatively few clinical studies have been published. The response of MF subjects to MTX seems to depend on the stage and, more importantly, the dose of MTX treatment. Methotrexate appears to be an effective treatment at every stage of MF; however, it is not devoided of side effects such as infections and elevated level of aminotransferases, which are most common.

Key Words
Mycosis fungoides, MF, Methotrexate, MTX, Treatment, CTCL.

Introduction

Methotrexate (MTX), known under the chemical name 4-amino-4-deoxy-N[10]-methylpteroylglutamic acid, is an analogue of folic acid, a derivative of aminopterin. It belongs to a group of anti-metabolic drugs. Data supporting the effectiveness of low-dose MTX in the treatment of *Mycosis fungoides* (MF) are limited, in spite of that it has been used in CTCL treatment quite long: the 1st report concerning MTX in MF was published by Wright in 1964. MTX was administered in 16 MF patients in dose between 2.5 and 10 mg per week[1]. The remission was achieved in 9 patients (56.25%), while 7 patients did not respond. Zackheim et al[2] confirmed positive results of low-dose MTX in the treatment of erythrodermic CTCL. Complete remission was achieved in 41% and partial remission in 17% of treated patients. The mean survival was 8.4 years and mean time free from relapse was 31 months[2]. McDonald and Bertino[3] demonstrated the complete remission in 7 out of 11 patients (63,63%) with MF at stage II-III.

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The mechanism of MTX action in CTCL treatment has not been explained in detail. The question whether the mechanism is mainly anti-inflammatory (inhibiting *in vitro* release of prostaglandin E2, synthesis of peroxides, and inhibiting the chemotaxis of neutrophils)[4], immunomodulating, immunosuppressive or cytostatic has been still open.

Patients and Methods

79 patients were treated with MTX because of MF in 4 dermatology clinical centers in Poland [31 women (39.2%) and 48 men (60.7%)] (retrospective observational study). The mean age of patients was almost 62 (between 27 and 89 years of age). All patients were diagnosed based on results of histopathology and clinical examination according to TNMB WHO classification updated in 2016 (stage MF I: 39; MF II: 16; MF III: 16; MF IV: 8). The affected skin surface was assessed based on the rule of nines[5]. Laboratory tests were carried out in all patients, including blood cell-count, smear analysis, blood levels of creatinine, urea, liver enzymes, and lactate dehydrogenase (LDH). Laboratory tests were repeated at monthly intervals during the treatment. All patients received MTX once a week. The weekly dose was divided into three given every 12 hours in most of the cases, but repeated weekly MTX in subcutaneous injection was also recommended in a single dose in few cases (more than half of those patients had also received an oral form of MTX (Table I). The other treatment used before MTX has been shown in Table II.

Statistical Analysis

The distributions of disease duration and the total dose of MTX were normalized through logarithmic transformation ($\log_{10}$). The variables concerning the duration of therapy and use of MTX were considered mainly in survival analyses, that does not require a normal distribution of data. The effectiveness of treatment with MTX in terms of time required to achieve remission was assessed based on the non-parametric Kaplan-Meier method. The effectiveness of MTX depending on the disease stage, route of administration, age at diagnosis and the total administered dose, the minimum dose and maximum dose was estimated using the Cox proportional hazards model. The analysis of differences between the time to remission in different stages of MF was carried out using the non-parametric Wilcoxon-Mann-Whitney test as well. Additional tests were performed using the non-parametric Kendall correlation coefficient τ_b. The power of the monotonic relation was analyzed for the difference between the maximal and minimal dose and time to remission (only subjects who achieved remission were considered). The occurrence of side effects depending on the route of administration and duration of therapy with MTX was analyzed using the logistic regression technique, which estimated the relation of specific factors with the probability of occurrence of individual adverse effects. In some cases, due to the very low occurrence of a particular adverse effect, it was impossible to design a reliable logistic regression model. The relationship between other than MTX treatment methods and disease stages was analyzed with the χ^2-test. Some therapies were rarely used, and the analyzed contingency tables were larger than 2x2. Therefore, we used the test version based on the Monte Carlo simulation, which is more resistant to the occurrence of low expected numbers $p < 0,05$ was considered statistically significant.

Table I. Routes of methotrexate administration – total distribution (n= 79).

Oral	Subcutaneous		Total
	No	Yes	
No	0	11	11
Yes	57	11	68
Total	57	22	79

Results

The descriptive statistics for analyzed variables: age, disease duration, time to remission

Table II. Other treatment methods – distribution in the study sample (n = 79).

Variable	Value	
	No	Yes
Glucocorticosteroids	0	79
Emollients	63	16
Antihistamine drugs	67	12
Prednisone	52	27
UVB	48	31
PUVA	39	40
Radiotherapy	69	10
Retinoid	63	16
Interferon	64	15
Chemotherapy	70	9
Cyclosporin A	77	2

Table III. Quantitative variables – descriptive statistics and normality of distributions.

Variable	M	SD	Sk.	Kurt.	Min.	Me	Max.	S-W	p	N
Age	61.77	12.22	-0.57	3.65	27.00	63.00	89.00	0.97	0.041	79
Age in dgn	56.77	12.84	-0.45	3.86	15.00	57.00	86.00	0.98	0.152	79
Disease duration	7.09	4.96	1.63	5.66	0.50	6.00	25.00	0.84	< 0.001	68
Duration of therapy to remission	4.67	5.60	3.19	16.51	1.00	2.00	35.00	0.64	< 0.001	56
Duration of remission	10.44	13.09	1.99	6.87	0.00	6.00	62.00	0.74	< 0.001	56
Duration of therapy with MTX	4.53	5.18	3.05	16.54	0.47	2.57	35.00	0.68	< 0.001	79
Duration of therapy with MTX to remission or end of therapy	4.59	5.09	3.18	17.52	0.70	2.80	35.00	0.67	< 0.001	79
Total dose	603.94	785.96	4.03	23.42	50.00	360.00	5600.00	0.58	< 0.001	79
Min. dose	14.24	7.47	1.03	3.08	5.00	12.50	30.00	0.84	< 0.001	79
Max. dose	19.30	7.29	1.05	5.65	5.00	20.00	50.00	0.90	< 0.001	79

M – mean; SD – standard deviation; Sk. – skewness; Kurt. – kurtosis; Min. – minimum; Me – median; Max. – maximum; S-W – statistics from the Shapiro-Wilk test for the normality of distribution; p – significance of the Shapiro-Wilk test; N – number of valid observations.

on MTX, total dose of MTX, minimal and maximal dose, and duration of MTX treatment to remission or end of therapy are presented in Table III.

The remission had occurred in 56 patients (70.9% of all patients). Even a short 3 months treatment with MTX led to remission in 50% of responders (Table IV). This ratio increased to about 75% for a 9-month therapy. However, for about 12-month therapy, this ratio decreased and was around 5-15%. The last value in the table (t = 35) should not be interpreted, as it is a single end-value possibly biased with a significant error (Figure 1).

The second point of reference in the analysis of the effectiveness of MTX therapy was the duration of remission (Table V). In 20% of responders, the remission began in the 1st month of therapy and in about 50% of cases remission lasted 4 to 6 months. Remission lasted for 12 months or longer was observed in about 25% of patients. Remission longer than 2 years was achieved in only 10% of patients, and 3-year-long in 5% of patients. A graphic representation of results is provided in Figure 2.

The time to remission on MTX was significantly related to the stage of disease at diagnosis, minimal dose and maximal dose of the drug

Table IV. Effectiveness of MTX – time to remission (n = 79).

Months	Patients without remission before t_i	Remissions at t_i	Survival function	95% confidence interval
1.0	77	12	0.84	0.77-0.93
1.5	64	2	0.82	0.74-0.91
2.0	59	15	0.61	0.51-0.73
2.5	43	1	0.60	0.49-0.72
3.0	39	8	0.47	0.37-0.61
4.0	26	1	0.46	0.35-0.59
5.0	23	1	0.44	0.33-0.57
6.0	21	2	0.39	0.29-0.53
7.0	17	1	0.37	0.27-0.51
8.0	16	4	0.28	0.18-0.43
9.0	12	1	0.25	0.16-0.41
11.0	10	3	0.18	0.10-0.33
12.0	6	1	0.15	0.07-0.30
13.0	5	1	0.12	0.05-0.27
14.0	4	2	0.06	0.02-0.22
35.0	1	1	0.00	–

Months – number of months from the beginning of treatment with MTX; Patients without remission before t_i – number of patients without remission before a given number of months; Remissions at t_i – number of remissions exactly after a given number of months; Survival function – estimated value of survival function for a given number of months, i.e. the ratio of patients without remission at the moment of t_i or earlier; 95% confidence interval refers to the estimated value of survival function.

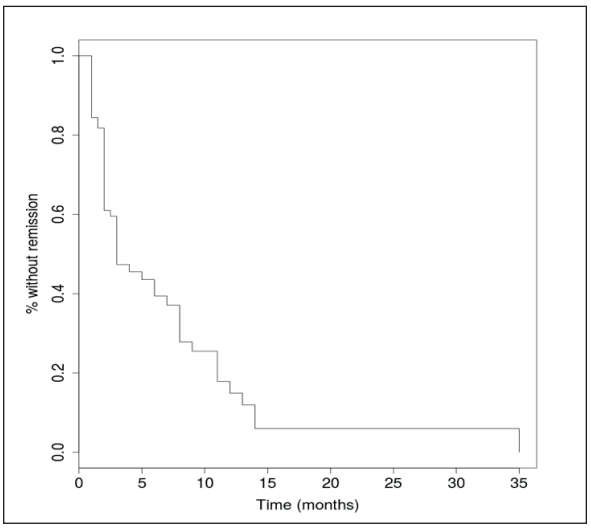

Figure 1. Survival curve (Kaplan-Meier method) for the duration of treatment with MTX and time to remission.

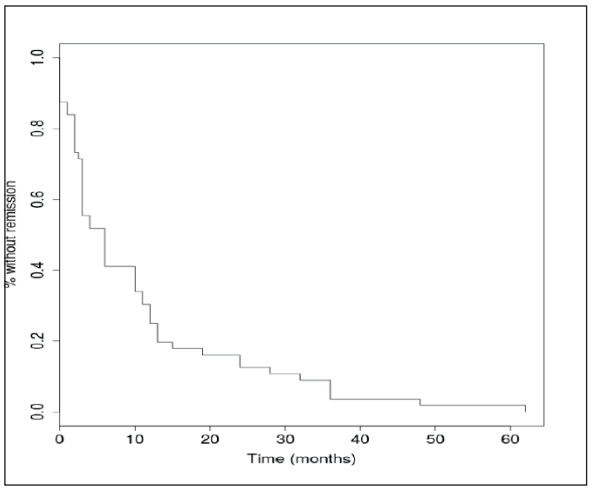

Figure 2. Survival curve (Kaplan-Meier method) for the duration of remission after therapy with MTX.

(Table VI). The conditions for the proportional hazards1 model were met both at the level of each individual predictor and globally for the whole model.

Stages MF II-IV were associated with a higher mean likelihood of remission than stage I (which was a point of reference here). For stage II, the likelihood of remission and hazard ratio was on average about 1.85-fold greater than in the group of patients with stage I2. For stages III and IV, the respective hazard ratio was on average about 2.85-fold higher. It should be emphasized that the result for stage II was not statistically significant, so the random bias cannot be ruled out. The result for stage IV was also close to the level of significance. An additional test was done to verify if stages II-IV as one group are associated with a

Table V. The effectiveness of methotrexate – duration of remission (n = 56).

Months	Patients without remission before t_i	Remissions at t_i	Survival function	95% confidence interval
0.0	56	7	0.88	0.79-0.97
1.0	49	2	0.84	0.75-0.94
2.0	47	6	0.73	0.62-0.86
2.5	41	1	0.71	0.60-0.84
3.0	40	9	0.55	0.44-0.70
4.0	31	2	0.52	0.40-0.67
6.0	29	6	0.41	0.30-0.56
10.0	23	4	0.34	0.24-0.49
11.0	19	2	0.30	0.20-0.45
12.0	17	3	0.25	0.16-0.39
13.0	14	3	0.20	0.12-0.33
15.0	11	1	0.18	0.10-0.31
19.0	10	1	0.16	0.09-0.29
24.0	9	2	0.13	0.06-0.25
28.0	7	1	0.11	0.05-0.23
32.0	6	1	0.09	0.04-0.21
36.0	5	3	0.04	0.01-0.14
48.0	2	1	0.02	0.00-0.13
62.0	1	1	0.00	–

Months – number of months to achieve remission; Patients with remission before t_i – number of patients still in remission before a given number of months; Remissions at t_i– number of remissions that ended exactly after a given number of months; Survival function – estimated value of survival function for a given number of months, i.e. the ratio of patients still in remission at the moment of t_i or earlier; 95% confidence interval refers to the estimated value of survival function.

Table VI. The effectiveness of methotrexate – duration of remission (n = 56).

	b	exp(b)	s_b	z	*p*
Stage II	0.62	1.85	0.37	1.68	0.093
Stage III	1.05	2.85	0.42	2.51	0.012
Stage IV	1.05	2.87	0.54	1.94	0.053
Min. dose	0.07	1.07	0.03	2.27	0.023
Max. dose	-0.07	0.93	0.04	-1.93	0.054
R^2 Cox-Snell	0.16				
Goodness of fit	0.65				
Odds ratio test	χ^2 (5) = 13.35; p = 0.020				

b – coefficient for a given predictor; exp(b) – odds ratio for a unit increase in the predictor compared to odds before increase; s_b – standard deviation for the coefficient b; z – standard value of the coefficient; *p* – significance of the coefficient (two-sided). R^2 Cox-Snell – pseudo R^2 indicating model quality; Goodness of fit – ratio of pairs for which a unit with a higher predictor of remission had remission before the unit with a lower predictor (this is another measure of model quality); Odds ratio test – tests significance as a whole (verifies its superiority over the model without any predictors).

higher hazard of remission than stage I. A suitably designed Wald test was carried out. Test results were close to the level of statistical significance, which suggested it was indeed likely, but it could not be confirmed based on the collected data with the assumed certainty ($\chi^2(3)$; p = 0.054) (Figure 3). The non-parametric Wilcoxon-Mann-Whitney test has revealed that, despite large differences between the observed statistics in groups, the collected data did not clearly indicate if this was caused by relevant differences at the population level. The differences observed between the groups were not statistically significant.

The analysis of doses showed that each unit increase in the minimal dose was on average associated with a 1.07-fold increase in the likelihood of remission, and the correlation was negative (a 0.93 decrease) for the maximal dose. In addition, the result in case of the maximal dose was not statistically significant although it was very close to the established level of $\alpha = 0.05$. Results obtained for maximal and minimal doses have suggested the concurrent minimization of the maximal dose and maximization of the minimal dose, what finally implies that doses should be maintained at an intermediate level with minimal variation and difference between the minimal and maximal dose. The non-parametric Kendall correlation coefficient τ_b was performed, and the power of the monotonic relationship was analyzed for the difference between the maximal and minimal MTX dose and time to remission (only subjects who achieved remission were considered). The analysis clearly confirmed previous findings (τ_b = 0.34; p = 0.001). The coefficient value indicated that in about 67.2% of cases, if in a randomly chosen pair of individuals difference between the maximal and minimal dose is higher for subject A than for subject B, time to remission will be longer for subject A. The final limited model demonstrated that the total dose (in $\log_{10}$ scale) and the minimal and maximal dose had a significant influence on the duration of remission after therapy with MTX (Table VII).

The analysis of model parameters has clearly indicated the positive effect of the total dose. The value of exp(b) for $\log_{10}$(total dose) indicated that on average each 10-fold increase in the $\log_{10}$(total dose) reduced the risk of relapse to the level of 28% of that before taking a higher dose of MTX. At the same time, the results for the minimal and maximal doses, although oscillating within the

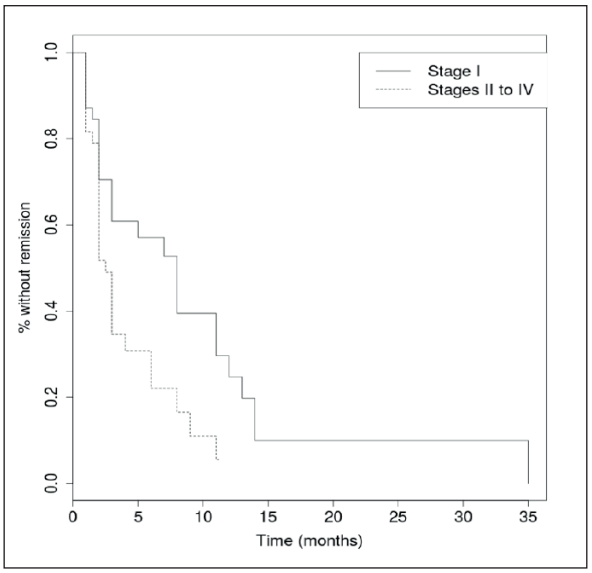

Figure 3. Survival curve (Kaplan-Meier method) for time to remission in groups with stage I and stages II-IV.

Table VII. Duration of remission versus total dose (log10 scale) and minimum and maximum doses – proportional hazards model (n = 56).

	b	exp(b)	s_b	z	p
$\log_{10}$ (total dose)	-1.27	0.28	0.46	-2.77	0.005
Min. dose	0.05	1.05	0.03	1.71	0.088
Max. dose	0.06	1.06	0.03	1.83	0.068
R^2 Cox-Snell	0.37				
Goodness of fit	0.70				
Odds ratio test	χ^2 (3) = 26.25; $p < 0.001$				

b – coefficient for a given predictor; exp(b) – odds ratio for a unit increase in the predictor compared to odds before increase; s_b – standard deviation for the coefficient b; z – standard value of the coefficient; *p* – significance of the coefficient (two-sided). R^2 Cox-Snell – pseudo R^2 indicating model quality; Goodness of fit – ratio of pairs for which a unit with a higher predictor of remission had remission before the unit with a lower predictor (this is another measure of model quality); Odds ratio test – tests significance as a whole (verifies its superiority over the model without any predictors).

limits of statistical significance, have suggested that a unit increase in the maximal or minimal dose was each time associated with a 5-6% mean increase in the risk of relapse. Therefore, two conclusions can be made based on these findings: a higher total dose of MTX taken during the therapy has a positive effect on the duration of remission, but it is probably best if MTX is given in a higher number of lower doses. Apart from that, it appears again that the variation in dosage and difference between the maximal and minimal dose has a negative effect on the duration of remission. The difference between the maximal and minimal dose has been positively correlated with the duration of remission (τ_b = 0.24; *p* = 0.018); this suggests that in the case of the duration of remission some variation in dosage is recommended.

The occurrence of side effects related to MTX treatment occurred as follows: the most frequent adverse effects included infections (58.7% of cases), elevated level of aminotransferases (33.3%), nausea (18.5%), disturbances in lipid metabolism (24.7%), and abnormal blood counts (leukopenia, neutropenia, thrombocytopenia). Gastrointestinal ulceration, gastrointestinal bleeding (2.5%), dizziness, kidney failure, and other disorders of the nervous system (1.2%) were less frequent. In some cases, due to the very low occurrence of a particular adverse effect, it was impossible to design a reliable logistic regression model, except datas on leukopenia were insufficient to design a model considering the route of administration. Therefore, only descriptive statistics are presented, and they allow for speculation that leukopenia can be related to a longer therapy with MTX. That was also confirmed using the Wilcoxon-Mann-Whitney test, which showed that the mean duration of therapy with MTX was longer in patients with leukopenia (W = 262.5; *p* = 0.028). Cases of neutropenia were also too rare to allow for the design of logistic regression models. The Wilcoxon-Mann-Whitney test revealed a comparable duration of therapy with MTX in both groups – with and without neutropenia (W = 221; *p* = 0.148). The duration of therapy with MTX was comparable in a group with thrombocytopenia and without (W = 166.5; *p* = 0.716). The route of administration was not correlated with the frequency of both (neutropenia: oral: $X^2(1) = 0.00$; *p* = 1.00; subcutaneous: $X^2(1) = 0.63$; *p* = 0.427; thrombocytopenia: oral: $X^2(1) = 0.00$; *p* = 1.00; subcutaneous: $X^2(1) = 0.00$; *p* = 1.00). A comparable duration of MTX therapy was observed in a group with elevated levels of aminotransferases and without (W = 695.5; *p* = 0.950). The test also demonstrated a significant correlation between the elevated levels of aminotransferase and oral administration of MTX (it occurred only in subjects on oral MTX) ($X^2(1) = 4.66$; *p* = 0.031). Despite the clearly longer use of MTX in the group of patients with somnolescence (also rare), available data were insufficient, and the Wilcoxon-Mann-Whitney test showed no significant differences between the groups (W = 42; *p* = 0.066). But the test revealed a strong and significant correlation between somnolescence and route of MTX administration, since somnolescence occurred only in subjects on subcutaneous MTX ($X^2(1) = 4.78$; *p* = 0.029). The route of administration was not correlated with the frequency of anorexia as well. Statistical analysis showed a comparable duration of therapy with MTX in both groups (W = 233; *p* = 0.337). Similar observations were made in fever (W = 159.5; *p* = 0.840) and blurred vision (W = 94; *p* = 0.605). Patients without arthralgia used MTX for a longer time (W = 282.5; *p* = 0.050). In the case

Table VIII. Other treatment methods versus disease stage at diagnosis.

Variable	Value	Stage				χ^2	df	p
		I	II	III	IV			
Emollients	No	28	13	14	8	4.18	3	0.240
	Yes	11	3	2	0	4.18	3	
Folic acid	No	10	4	10	3	7.61	3	0.061
	Yes	29	12	6	5	7.61	3	
Retinoid	No	30	14	12	7	1.31	3	0.774
	Yes	9	2	4	1	1.31	3	
Prednisone	No	26	10	10	6	0.47	3	0.931
	Yes	13	6	6	2	0.47	3	
Interferon	No	35	14	8	7	12.59	3	0.006
	Yes	4	2	8	1	12.59	3	
Chemotherapy	No	36	13	15	6	3.27	3	0.390
	Yes	1	3	3	2	3,27	3	
Antihistamine drugs	No	31	12	16	8	6.35	3	0.084
	Yes	8	4	0	0	6.35	3	
Radiotherapy	No	33	12	16	8	5.94	3	0.089
	Yes	6	4	0	0	5.94	3	
Cyclosporin A	No	38	16	16	7	4.05	3	0.266
	Yes	1	0	0	1	4.05	3	
UVB	No	18	10	13	7	8.73	3	0.034
	Yes	21	6	3	1	8.73	3	
PUVA	No	21	7	5	6	4.72	3	0.208
	Yes	18	9	11	2	4,72	3	

UVB - phototherapy with UVB light, PUVA – psoralens plus phototherapy with UVA light.
The analysis demonstrated that interferon was used significantly more often at stage III, and UVB at stage I, which conforms with Polish and international therapeutic recommendations.
ght, PUVA – psoralens plus phototherapy with UVA light.

of disturbances in lipids metabolism, none of the predictors had a significant effect, and the overall model did not allow for any prediction significantly better than the one based on the distribution of elevated cholesterol and triglyceride levels in the whole study sample (as indicated by the likelihood ratio test). Therefore, there were no significant correlation between this adverse effect and route of administration or duration of therapy with MTX ($X^2(3) = 3.34$; $p = 0.343$). The question is that this side effect can be not related to treatment at all.

The mean duration of therapy with MTX was shorter in patients with elevated LDH (W = 556; $p = 0.035$). In addition, the occurrence of elevated LDH in subjects on subcutaneous MTX was significantly higher than that implied by the distribution of data in the whole study group ($X^2(1) = 18.55$; $p < 0.001$).

The duration of therapy was comparable in groups with and without nausea (W = 461.5; $p = 0.821$), with and without gastrointestinal bleeding (W = 122; $p = 0.163$), and with and without abdominal pain (W = 493.5; $p = 0.091$). Also, the mean duration of therapy with MTX was longer in patients without headache (W = 640; $p = 0.001$) and in patients with haematuria (W = 645; $p < 0.001$). The route of administration did not correlate with the frequency of all mentioned side effects.

There was only one case of dizziness and one of renal failure, so it was impossible to analyze the correlation of this adverse effect with other

variables. The same concerns other disorders of the nervous system.

The analyses of other than MTX treatment methods have revealed the correlation of INFa and UVB with disease stages. UVB was mainly ordered in patients at stages I and II while INFa at stages I and III (Table VIII). The analyses demonstrated that INF-α was used significantly more often at stage III, and UVB at stage I (as it is recommended in Polish And International Therapeutic Guidelines).

Discussion

There are limited numbers of reports on the effectiveness of MTX in patients with MF. MTX is usually administered in the oral dose form as the second-line drug according to EORTC and WHO recommendations for stages IA-IIB. MTX should be given in a dose of 20 to 75 mg per week, usually divided in three doses every 12 hours weekly. MTX can also be combined with glucocorticoids, PUVA or INF-α[3,5-7].

Remission was achieved in 70% of our patients (higher response rate than in Wright and Zackheim studies)[1,2], 1/5 of our responders' answer for the treatment in the 1st month, ½: in 3 months. When treatment was prolonged to 9 months, remission was observed in 75% of responders, but up to 2-year remission was observed only in 10%.

In a study with low-dose MTX treatment of 69 patients in stage T2 MF, Zackheim et al[8] observed a complete remission in 12% and partial remission in 22% of patients[8]. In a group of 7 patients with nodular MF, only one responded to treatment. The remission was achieved in 6 out of 8 patients with nodular MF in our study. Also, the effectiveness of therapy with MTX have appeared to be dependent on the weekly dose of the drug – MTX appeared to be most effective when taken in an intermediate dose divided into three smaller doses with the minimal variation in doses. The total therapeutic dose of MTX was also important: the higher total dose caused, the longer remission duration. But the adverse events can be related to higher doses.

Recently developed competitive inhibitor of folate metabolism – pralatrexate (PDX) – might be an alternative for MTX in MF. However, in comparison to MTX, side effects of PDX tend to be more severe and common, including mucositis, fatigue, nausea, anorexia, skin toxicity, epistaxis, and anemia[9]. Due to its adverse effects, PDX use is rather limited to advanced stages of MF/SS and other aggressive types of CTCLs[9].

When it comes to MTX, the most frequently reported adverse effects of therapy include gastritis, leukopenia, infections, fatigue, interstitial pneumonia, hepatitis, ileitis, and inflammation of other internal organs[10]. It is suspected that stomatitis can occurr more frequently in patients with MF than in those with psoriasis (0.8%), also taking MTX[11], but we did not observe stomatitis at all in our group. The most common adverse effects in our study had been infections in 58.7% of cases and elevated level of aminotransferases in 33.3%. The least common were gastrointestinal bleeding (2.5%) and disorders of the nervous system other than fatigue and headache (1.2%). Despite the high occurrence of infections, no significant correlations were found between the route of MTX administration and duration of therapy. It is known that CTCL itself promotes the development of infections and, thus, despite the lack of correlation between infection, dose and duration of therapy, the risk of severe infections related to treatment ordered in MF has to be continuously analyzed. Our study had also revealed that leukopenia could be related to longer therapy with MTX, that is also observed in patients with inflammatory dermatoses treated with MTX, e.g., psoriasis, but not to the route of administration. Elevated levels of aminotransferases had occurred only in case of oral MTX treatment, but the somnolescence and LDH – only in cases of subcutaneous route. Most likely, LDH (LDH4 and LDH5) is released not only from the liver but also from muscles – what can be a reason. It seems, therefore, that the subcutaneous administration of the drug causes more adverse effects compared to oral treatment, but the evaluated sample is relatively small, and analysis of a larger group of patients is necessary to formulate firm conclusions.

For ethical reasons, the group of patients with MF treated with MTX cannot be compared against a group of patients with MF receiving no medication.

Conclusions

MTX appears to be effective at every stage of MF, but because of the increased risk of infection, it should be ordered when all other available

topical methods and phototherapy have failed or cannot be applied.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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