Original paper

Efficacy, quality of life, and safety of methotrexate versus interferon in head-to-head treatment in advanced stages of mycosis fungoides and Sezary syndrome. Prospective trial (NCT02323659)

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Abstract

Introduction: ESMO guidelines recommend interferon (IFN) and methotrexate (MTX) as first-line systemic therapies in mycosis fungoides (MF) and Sezary syndrome (SS).
Aim: A prospective, head-to-head trial comparing the efficacy and safety of INF-α and MTX as first-line treatment in MF/SS patients.
Material and methods: Forty-three patients were enrolled in the trial. The response to treatment and side effects were assessed. Study variables included mSWAT, DLQI, and VAS scores.
Results: The response rate in stage IV including SS was significantly higher in the IFN-α group than in the MTX group (100% vs. 40%; $p = 0.03$, respectively). No significant differences were found in response rate in stage IIB and III between treatment groups. Patients treated with IFN-α had significantly shorter time to achieve response (TTR). Significantly fewer in the IFN-α group experienced adverse events (AE) in comparison to patients treated with MTX (81% vs. 45%; $p = 0.02$). There was no statistically significant difference between both groups in terms of time to progression (TTP), progression-free survival (PFS), time on treatment (ToT), and time to next treatment (TTNT). The improvement in quality of life and reduction of pruritus was comparable in both treatment groups.
Conclusions: The obtained data suggest that the efficacy of IFN-α as first-line treatment in advanced stage (IV) MF and SS is significantly better than MTX. IFN-α presented significantly better safety and tolerability and shorter TTR than MTX. However, the results should be interpreted with caution due to scarce study groups.

Key words: methotrexate, interferon, cutaneous T-cell lymphoma, efficacy.

Introduction

Cutaneous T-cell lymphomas (CTCLs) comprise a clinically heterogeneous group of extranodal non-Hodgkin lymphomas, with mycosis fungoides (MF) and Sezary syndrome (SS) as the most common types [1, 2]. MF primarily affect the skin, but ultimately also lymph nodes, blood, and visceral

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organs may become involved. SS is an aggressive variant of CTCL with poor prognosis [1, 2]. MF is an incurable disease with stage-dependent treatment. Early stages of MF are treated with skin-directed therapies such as topical steroids and phototherapy (psoralen photochemotherapy (PUVA) or narrow-band UVB radiation) [3]. SS and advanced stages of MF require systemic treatment including interferon α (IFN-α), methotrexate (MTX), retinoids, total skin electron beam therapy, extracorporeal photopheresis, stem cell transplantation, or chemotherapy [3]. MTX and IFN-α seem to be effective as first-line systemic treatment in patients who are refractory to skin-directed therapies. MF and SS are rare diseases, in which adequate and well-controlled trials are difficult to perform due to small patient populations.

There are 3 major types of IFN: IFN-α, IFN-β, and IFN-γ; however, only INF-α has been approved and is commonly used in the treatment of MF/SS [4]. INF-α has been administered in various doses and treatment regimens, usually starting with 3 million units (MIU) 3 times weekly with therapy adjustment based on clinical response [3]. The major side effects of IFN-α treatment are dose-dependent and include flu-like symptoms, elevated transaminases, myelosuppression, and depression. INF-α has proven to be effective in MF and SS treatment, both as monotherapy and in combination with oral retinoids, bexarotene, or PUVA therapy [4–12]. The few studies assessing the use of IFN-α monotherapy in CTCL demonstrated that partial response was achieved in 25% to 49% of patients [10–12]. A recent retrospective study by Wain *et al.* demonstrated that IFN-α therapy was associated with a better response and a shorter time to response (TTR) compared with MTX in MF patients [9].

MTX is a cytotoxic antifolate drug used in CTCL treatment in low doses once weekly, both as monotherapy and in combination with IFN-α or bexarotene [3]. The clinical efficacy of MTX therapy has been demonstrated with reported response rates (RR) ranging from 33% to 71% [8, 13–15]. MTX is usually well tolerated and safe when the treatment is properly monitored. The most frequent side effects include liver function abnormalities, bone marrow suppression, and gastrointestinal toxicity [3]. Moreover, MTX is a teratogen, so women of childbearing potential are required to use contraception during and after MTX therapy. Even though MTX and IFN-α are commonly used in CTCL treatment, to our knowledge there are no prospective studies and only 1 retrospective study evaluating the efficacy and safety of systemic MTX vs. IFN-α in MF [8].

Aim

A head-to-head comparison of IFN-α versus MTX could provide useful information on the superiority of any of these therapies over the other in CTCL, because such conclusions have rarely been reported. Therefore, we conducted a prospective study comparing the following head to head: efficacy, safety, quality of life, and tolerance of MTX and IFN-α used as first-line treatment in MF and SS (ClinicalTrials.gov Identifier: NCT02323659). The patients were randomised in a 1 : 1 ratio.

Material and methods

Patients diagnosed with MF and SS treated at the Department of Dermatology, University of Medical Sciences in Poznan, Bydgoszcz Cancer Centre, the Department of Dermatology, Sexually Transmitted Diseases, and Immunodermatology of the Antoni Jurasz University Hospital No. 1 in Bydgoszcz between June 2014 and October 2017 were screened for the study. Forty-three consecutive patients with histologically confirmed MF in stage IIA to IV or SS, refractory to previous topical treatment or phototherapy, were enrolled. Disease stage was assessed according to the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) staging systems [16]. Eligible patients with stage IIA–IV were over 18 years old, had insufficient response to topical treatment and/or phototherapy, and were naïve to systemic therapy. Patients who did not meet the eligibility criteria and those with contraindications for MTX or IFN-α treatment were excluded. No concomitant systemic therapy was allowed during the trial period. Informed consent was obtained from all patients. The severity of disease and response to treatment were assessed with mSWAT. The quality of life and severity of pruritus were assessed with the DLQI questionnaire and VAS scale, respectively. A detailed history was recorded, and a general physical examination was performed before the start of therapy. Baseline investigations in all patients included complete blood counts, liver function tests (ALT, AST), C-reactive protein (CRP), lactate dehydrogenase (LDH), β2-microglobulin, and flow cytometry. While patients were on the treatment, blood tests, complete physical examinations, mSWAT, DLQI, and VAS scoring were repeated every month. Time to response, any adverse events, and treatment tolerability were recorded. Clinical endpoints and response criteria used in this study were adapted from the consensus guidelines of ISCL, the United States Cutaneous Lymphoma Consortium (USCLC), and EORTC [17]. The study was approved by the Bioethics Committee of Nicolaus Copernicus University functioning at Collegium Medicum in Bydgoszcz (KBE515/2014) and was conducted according to the principles of the Declaration of Helsinki.

Patients who met the eligibility criteria were randomized (1 : 1) to receive either IFN-α or MTX. IFN-α was administered subcutaneously at a dose of 3 MIU, 3 times a week. MTX was administered orally in a weekly divided dose of 20 mg, with supplementation of 15 mg folic acid on the day after administration of MTX. The study treatment was continued until disease progression, unacceptable toxicity, or the patient's withdrawal of consent.

Statistical analysis

Statistical calculations were performed using Statistica version 12.0 (StatSoft, Inc., 2015). Analyses of qualitative features were based on χ^2 test using the Pearson method or the Fisher test. Independent variables that met the assumptions for parametric tests were analysed using Student's *t*-test. Independent variables that did not meet the parametric test assumptions were analysed using non-parametric tests (ANOVA equivalents): Mann-Whitney *U*-test (a comparison of two samples) or Kruskal-Wallis test (a comparison of multiple samples). Odds ratios (ORs) with 95% confidence intervals were determined by logistic regression. A *p*-value of < 0.05 was considered statistically significant. Time to event outcomes such as time to progression and time on treatment were calculated using a Kaplan-Meier estimator, and comparison between groups was assessed by log-rank test.

Results

Patients

The patients were screened between June 2014 and October 2017, and 43 of them with histologically confirmed MF and SS were randomized. Twenty-one patients were included in the IFN-α group, and 22 in the MTX group. The mean age of patients was 60.05 ±11.12 years (median: 62.0; range: 34–78) in the IFN-α group and 60.64 ±13.29 years (median: 62.5; range: 32–82) in the MTX group. The groups were comparable in terms of CTCL stage. A summary of patient characteristics is shown in Table 1.

Response rate

The overall response rate for both treatment groups was 84%. The improvement rate was comparable in the IFN-α group (86%) compared to the MTX group (82%). No significant differences were observed between the IFN-α group and the MTX group in terms of number of patients achieving complete remission, partial remission, and refractory to treatment ($p > 0.05$).

The RR varied between the 2 treatment groups within different stages of disease (Table 2). The RR in stage IV was significantly better in the IFN-α group compared to the MTX group (100% vs. 40%; $p = 0.03$). The RR in the IFN-α group within stages IIB and IV was higher, although not significantly, than in stage IIIB (100% vs. 50%; $p = 0.09$). There was no significant difference in the RR in MF stage IIIB between MTX-treated patients and those receiving IFN-α (83% vs. 50%; $p = 0.33$). The RR in the MTX group was better, but not significantly, in stage III than IV (83% vs. 40%; $p = 0.2$). The RR in MF stage II did not differ between treatment groups and was equally high (100% vs. 100%).

The mean time needed to achieve disease response significantly differed between the groups (1.12 ±0.33 months; median: 1.0, and 1.7 ±0.59; median 2.0 in the INF-α and MTX groups, respectively; $p = 0.002$). Initial response was achieved earlier in the IFN-α group than in the MTX group. Significantly more patients achieved initial response during the first month of treatment in the IFN-α group (71%) than in the MTX group (27%) (OR = 6.67; 1.76–25.28; $p = 0.005$). Disease severity decreased from baseline in both groups, resulting in a reduction in mean mSWAT score in the INFα group (52.43 ±27.45) and in the MTX group (46.41 ±29.59). However, the mSWAT score change did not differ significantly between the 2 treatment groups during the therapy ($p = 0.34$).

Quality of life and pruritus assessment

No significant differences between the groups were found in terms of DLQI score ($p = 0.78$). The mean reduction in DLQI score was 11.94 ±5.24 in the IFN-α group and 12.8 ±8.08 in the MTX group. There were no significant differences in the reduction of pruritus intensity between the 2 groups ($p = 0.42$). The mean reduction in the itch severity score was 7.05 ±2.65 in the IFN-α group and 6.5 ±2.87 in the MTX group.

Adverse events and treatment tolerability

Significantly more patients in the IFN-α group did not experience any adverse events (AE) in comparison to patients treated with MTX (81% vs. 45%; OR = 4.8, 1.21–19.08, $p = 0.02$). No significant differences between the

Table 1. Patients' characteristics

Characteristic	IFN-α group (A) *n* = 21	MTX group (B) *n* = 22
Age [years] (range)	60.04 ±11.12 (34–78)	60.63 ±13.28 (32–82)
Sex:		
Male	11	10
Female	10	12
Stage at enrolment:		
IIA	1	2
II B	7	9
III A	1	0
III B	4	6
IV A1* (Sezary syndrome)	8	5
Disease characteristics:		
Baseline SWAT score, mean (median)	81.57 (85%)	78.5 (80%)
Baseline DLQI score	21.76 (21)	22.22 (20.5)
Previous therapies:		
PUVA + topical treatment	19	19
Topical treatment	2	3

**Stage IV A – T(3-4) N(0-2) M (0-1)B2 (criteria from flow cytometry) – Sezary syndrome.*

Table 2. Response and progression rates by disease stage

Variable	IFN-α group *n* = 21			MTX *n* = 22			IFN-α/MTX		
	Response, *n* (%)	TTR, mean [months]	ToT, mean [months]	Response, *n* (%)	TTR, mean [months]	ToT, mean [months]	Response, *p*	TTR, *p*	ToT, *p*
Stage:									
IIA	1/1 (100)	1.0	–	2/2 (100)	1.0	21.0	1	1	–
IIB	7/7 (100)	1.14	13.02	9/9 (100)	1.5	7.9	1	0.18	0.85
IIIA	0/1	1	4.96	–	2.2	7.45	–	0.05	0.33
IIIB	2/4 (50)			5/6 (83)			0.33		
IVA	8/8 (100)	1.14	8.77	2/5 (40)	2	3.53	0.03	0.05	0.11
Progression:		8			5		*p* = 0.27		
IIA		–			1				
IIB		3			1				
IIIA		1			–				
IIIB		2			1				
IVA		2			2				
Quality of life and mSWAT assessment:									
Change in mSWAT score, mean (median)		52.43 (59)			46.41 (59)		*p* = 0.34		
Change in DLQI score		11.94			12.8		*p* = 0.78		
Reasons for treatment discontinuation other than progressive disease:									
Consent withdrawal		5			3				
Other		1			0				

TTR – time to response, ToT – time on treatment.

2 groups were found in the severity of adverse events reported (AE1, $p = 0.72$; AE2, $p = 0.1$; AE3, $p = 0.19$). Follow-up of AEs showed that liver disorders (including abnormal liver function tests, liver toxicity, cirrhosis) were significantly more frequent than other AEs (e.g. myalgia, arthralgia, osteoporosis, visual disturbances) ($p = 0.01$). Moreover, significantly more patients in the MTX group than in the IFN-α group had elevated liver function tests (LFTs) (27% vs. 0%, respectively).

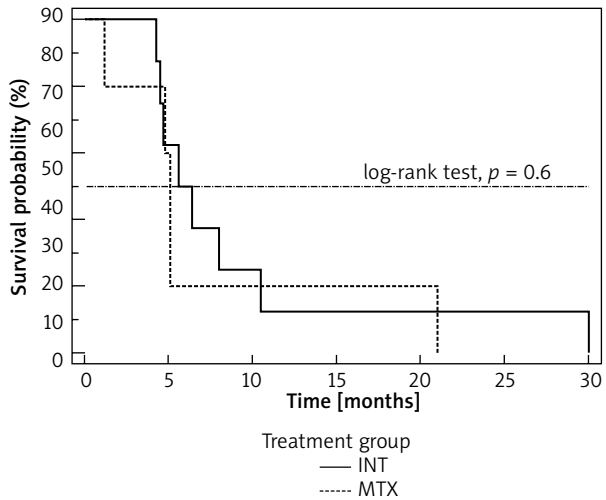

Figure 1. The Kaplan-Meier estimates of time to progression between MTX and IFN-α treatment groups. Long-rank test $p = 0.6$. Kaplan-Meier estimate suggests that response to IFNa treatment may have a long-lasting effect

Abnormal laboratory tests were present in 71% of patients treated with IFN-α and 67% of those treated with MTX. However, there were no significant differences between the groups in terms of frequency of laboratory test abnormalities other than LFTs (CRP, LDH, β2-microglobulin, complete blood counts).

There was a statistically significant difference in treatment tolerability (OR = 10.8, 2.0–58.23, $p = 0.006$); poor tolerability was noted more often in the MTX group (55%) than the IFN-α group (10%). Good tolerability of IFN-α treatment was reported by 90% of patients.

Disease progression

Disease progression was more frequent, although not significantly, in the IFN-α group compared to the MTX group; it occurred in 8 out of 21 patients (38%) and 5 out of 22 patients (23%), respectively ($p = 0.27$). Three patients in stage IIB, 3 in stage III, and 2 in stage IVA1 progressed on IFN-α treatment. In the MTX group, progression occurred in stages IIA, IIB, IIIB, and in 2 patients with stage IVA1

disease. Detailed information on patients with progression is summarized in Table 2. CRP and white blood count were the most common abnormalities that accompanied progression in the IFN group. Overall medium TTP (for both treatment groups) was 5.1 months (95% confidence interval, CI for median: 4.5 – 8). Median TTP for the IFN-α group was 5.6 months (95% CI for median: 4.3 to 10.5). Median TTP for the MTX-group was 5.1 months (95% CI for median: 1.2 to 21) There was no statistically significant difference between both groups in terms of TTP in log-rank test; $p = 0.6$. The Kaplan- Meier estimate of the TTP is presented in Figure 1. Median ToT for the IFN-α group was 8.93 months vs. 10.52 months for the MTX group. There was no statistically significant difference between both groups in terms of progression-free survival (PFS) in log-rank test; $p = 0.76$. There was also no statistically significant difference in time to next treatment data (Table 3). The second most frequent cause for discontinuation (after disease progression) in both the MTX and IFN-α groups was consent withdrawal, and further causes of discontinuation included adverse events, side effects, and death. There were no cases of treatment-related deaths. One patient treated with IFN-α died during the clinical trial due to cardiac failure. Four patients (1 in the IFN-α group and 3 in the MTX group) died during post-treatment follow-up. All deceased patients treated with MTX did not achieve treatment response, and 2 of them had disease progression. The patient in the IFN-α group achieved an initial response to the treatment, but later discontinued treatment due to disease progression and died.

Table 3. Time to next treatment data

Parameter	All patients (both arms, all stages)	
Mean	9.209	
SE	1.178	
95% CI for the mean	6.901 to 11.518	
Median	11	
95% CI for the median	5.000 to 12.000	
Parameter	**IFN-α (all stages)**	**MTX (all stages)**
Mean	9	12.273
SE	1.348	1.379
95% CI for the mean	6.357 to 11.643	9.570 to 14.976
Median	11	15
95% CI for the median	5.000 to 12.000	–
P-value	0.9037	
Parameter	**IFN-α (stage II)**	**MTX (stage II)**
Mean	11.5	13.636
SE	0.5	1.839
95% CI for the mean	10.520 to 12.480	10.032 to 17.240
Median	12	15
95% CI for the median	–	–
P-value	0.6619	
Parameter	**IFN-α (stage III)**	**MTX (stage III)**
Mean	5.1	0
SE	2.475	0
95% CI for the mean	0.250 to 9.950	0.000 to 0.000
Median	6	–
95% CI for the median	0.000 to 11.000	–
P-value	0.5442	
Parameter	**IFN-α (stage IV)**	**MTX (stage IV)**
Mean	9.188	0
SE	4.431	0
95% CI for the mean	0.503 to 17.872	0.000 to 0.000
Median	5	–
95% CI for the median	0.000 to 16.000	–
P-value	0.3691	

Discussion

MF and SS treatment is challenging because there is no simple algorithm of therapeutic strategies. According to current ESMO Clinical Practice Guidelines [18], IFN-α seems to be preferred over MTX in MF/SS treatment. IFN-α has been recommended for MF treatment ranging from stage IA to stage III, especially when skin lesions are more extensive or refractory to skin-directed therapies, while low-dose MTX is usually administered in more advanced stages, particularly in stage III [18]. Both IFN-α and MTX are recommended as first-line treatment of SS [18]. Many therapies suggested by the guidelines, including histone deacetylase inhibitors, monoclonal antibodies, retinoids, skin-directed therapies, as well as novel agents, are unavailable or access to them is limited in many countries. Both MTX and IFN-α are widely available because they are relatively inexpensive and commonly used in many other diseases. However, there is a lack of clinical trials comparing the efficacy and safety of those agents in CTCL treatment. Most of the treatment recommendations are based on retrospective studies and expert opinions; therefore, every clinical trial can contribute to the determination of rational treatment strategies for lymphomas.

In our study, we analysed head to head 2 frequently used systemic therapies in MF and SS as first-line treatment. Due to the small population size, cautious interpretation of the data is required. We found that both IFN-α and MTX were effective in MF and SS treatment, with a slightly better response in the IFN-α group (86% vs. 82%, respectively). This is consistent with a number of studies reporting on the beneficial effects of IFN-α in the treatment of CTCL. The RR to IFN-α varied between 33% and 87%, depending on the study [8, 13, 19]. IFN seems to be efficient not only as a systemic but also as a topical

therapy. A recent study by Hu *et al.* showed successful management of MF lesions with intralesional injections of low-dose recombinant IFN-α2, which was free of generalised side effects [20]. Topical MTX also turned out to be efficient in early-stage MF, indicating that systemic drugs may represent new therapeutic options for topical treatment [21, 22].

Concerning systemic MTX, our trial showed that RR was much higher (82%) than reported in other trials with low-dose MTX, ranging from 33 to 58% [8, 14, 19, 23]. An even higher response to treatment was observed in the study by Aviles *et al.*, in which combination therapy with both MTX and IFN-α was associated with a complete RR of 74% [23]. Concerning RR, it should be stressed that both study groups were relatively small, which might be the reason for such high RR in both therapies.

Zackheim *et al.* demonstrated that MTX-treated patients with erythrodermic MF had a better RR compared to patch/plaque MF (58% vs. 33%) [14]. We also observed differences in MF and SS response to MTX and IFN-α within the different stages of the disease. Our results indicate that both MTX and IFN-α are equally efficient in tumour stage IIB. Moreover, MTX appears to be a slightly better treatment option than IFN-α in the erythrodermic stage of MF, which is consistent with the study by Zackheim *et al.* [14]. Because of a lack of statistical difference, none of the therapies can be unreservedly treated as a better treatment option than the other in the erythrodermic stage of MF. On the other hand, patients with advanced MF stage IV and SS treated with IFN-α presented significantly better RR than those in the MTX group (100% vs. 40%). This suggests that IFN-α is more effective in the advanced stage of MF compared to MTX; however, the obtained data should be interpreted with caution due to scarce study groups. It would be of great value to perform studies including larger and more diverse study groups.

We also did not observe any difference in the overall reduction in mSWAT score between the 2 groups, perhaps due to the relatively small study groups. There was no statistically significant difference between both groups in terms of TTP, PFS, ToT, and TTNT. Interestingly, the TTR was significantly shorter in the IFN-α group than in the MTX group (1 month vs. 2 months). Responses to both IFN-α and MTX were achieved 1 month earlier compared to the results published by Wain *et al.* [9]. The reasons for differences in TTR and RR between our trial and the Wain *et al.* study are unclear [9]. Interestingly, 90% of our patients were previously treated with topical agents and psoralen plus ultraviolet A (PUVA) therapy, albeit without success. It is possible that photochemotherapy, by its immunosuppressive and apoptotic effects, had facilitated subsequent IFN-α and MTX activity.

Adverse events were more frequent in the MTX group than in the IFN-α group, which is contrary to the results of Wain *et al.* However, only 1 patient treated with MTX discontinued treatment due to symptoms of cirrhosis. Laboratory test abnormalities were slightly more frequent in the IFN-α group than in the MTX group, but they did not influence patient tolerability assessments. Overall, the tolerability of IFN-α was much better compared to MTX. Our results are comparable to those of Wain *et al*., suggesting that side effects of MTX impair treatment evaluation to a greater extent than in the case of IFN-α [9]. The improvement in quality of life (DLQI score) was similar in both groups during our trial. Moreover, both drugs similarly reduced itching.

To our best knowledge, this is the first prospective randomized study comparing the efficacy of MTX and IFN-α in MF and SS as first-line treatment. The majority of our observations are supported by the results of the retrospective study by Wain *et al.* [9]. In conclusion, despite the limitations of a small sample size, the presented data indicate that IFN-α seems to be superior to MTX in terms of safety, tolerability, and time to achieve response to treatment. Considering RR, the efficacy of the 2 drugs is comparable in tumour stage MF and significantly better for IFN-α in advanced stage IV of MF/SS. MTX is a cost-effective and relatively efficient drug, and it should be considered as a second-line treatment or a first choice in cases of contraindication to IFN-α therapy. Due to various side effects and the TTR, both drugs should be used after considering the patient's comorbidities, medication, and individual needs.

Conflict of interest

The authors declare no conflict of interest.

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