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Recommendations for treatment in folliculotropic mycosis fungoides: report of the Dutch Cutaneous Lymphoma Group

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Summary

Background Folliculotropic mycosis fungoides (FMF) is an aggressive variant of mycosis fungoides (MF) and generally less responsive to standard skin-directed therapies (SDTs). Recent studies distinguished indolent (early-stage FMF) and more aggressive (advanced-stage FMF) subgroups. The optimal treatment for both subgroups remains to be defined.

Objectives To evaluate initial treatment results in patients with early- and advanced-stage FMF.

Methods A study was undertaken of 203 patients (84 early-stage, 102 advanced-stage, 17 extracutaneous FMF) included in the Dutch Cutaneous Lymphoma Registry between 1985 and 2014. Type and results of initial treatment were retrieved from the Dutch Registry. Main outcomes were complete remission (CR); sustained complete remission; partial remission (PR), > 50% improvement; and overall response (OR; CR + PR).

Results Patients with early-stage FMF were treated with nonaggressive SDTs in 67 of 84 cases resulting, respectively, in CR and OR of 28% and 83% for monotherapy topical steroids, 0% and 83% for ultraviolet B (UVB), and 30% and 88% for psoralen plus ultraviolet A (PUVA). In patients with advanced-stage FMF these SDTs were less effective (combined CR and OR 10% and 52%, respectively). In patients with advanced-stage FMF local radiotherapy (CR 63%; OR 100%), total skin electron beam irradiation (CR 59%; OR 100%) and PUVA combined with local radiotherapy (CR 5%, OR 75%) were most effective.

Conclusions The results of the present study demonstrate that not all patients with FMF should be treated aggressively. Patients with early-stage FMF may benefit very well from standard SDTs also used in early-stage classic MF and have an excellent prognosis.

What's already known about this topic?

- Folliculotropic mycosis fungoides (FMF) has a worse prognosis and is less responsive to skin-directed therapies (SDTs) compared with classic mycosis fungoides (MF).
- Recent studies distinguished indolent (early-stage FMF) and more aggressive (advanced-stage FMF) subgroups.
- The optimal treatment for both subgroups needs still to be defined.

What does this study add?

- Treatment recommendations for different subgroups of FMF are formulated.
- Treatment response of patients with early-stage FMF is superior to that of patients with advanced-stage FMF.
- Patients with early-stage FMF may benefit very well from standard SDTs also used in classic MF and have an excellent prognosis.

Folliculotropic mycosis fungoides (FMF) is a variant of mycosis fungoides (MF) with distinctive clinicopathological features.[1–7] Previous studies emphasized that FMF is generally less responsive to several first-line skin-directed therapies (SDTs) and runs a more aggressive disease course similar to that of tumour-stage classic MF and should therefore be treated accordingly.[2,3] However, more recent studies defined a subgroup of patients whose FMF showed an indolent clinical behaviour and an excellent prognosis.[8,9] These studies indicate that not every case of FMF behaves as tumour-stage disease and that early- and advanced-stage FMF may require a different therapeutic approach. Treatment results in FMF have thus far received very little attention in the medical literature, and the prevailing instructions have not been based on the most recent insights into the disease.

In the present study we evaluated the results of initial treatment in a Dutch cohort of 203 patients with FMF who participated in our previous study.[9] The main purpose of this study was to propose recommendations for optimal initial treatment in patients with early- and advanced-stage FMF.

Patients and methods

We studied 203 patients with FMF included in the Dutch Cutaneous Lymphoma Registry between 1985 and 2014. In all cases the diagnosis of FMF and selection of initial treatment had been made by an expert panel of dermatologists and pathologists at one of the regular meetings of the Dutch Cutaneous Lymphoma Group, and all cases met the diagnostic criteria for FMF.[1] Based on the results of our previous study, distinction was made between patients with early-stage skin-limited FMF (group A, n = 84), advanced-stage skin-limited FMF (group B, n = 102) and FMF with extracutaneous disease at first presentation (group C, n = 17) (Table 1).[9] For each patient, follow-up data including results of initial treatment had been entered yearly in the registry. Since 1985, results of initial treatment, assessed at the time of discontinuation of treatment because of (near) complete response or lack or loss of response, had been scored by means of clinical evaluation of skin lesions as complete remission (CR; complete clearance of all skin lesions), near CR (> 75% clearance of skin lesions), partial response (PR; > 50% clearance of skin lesions), stable disease (SD; < 25% increase to < 50% clearance of skin lesions) or progressive disease (PD; ≥ 25% increase in skin lesions or progression to higher stage during treatment). Overall response (OR) rate indicates the percentage of patients who obtained (near) CR or PR.[10] The term sustained complete remission (SCR) is used in case of no relapse during follow-up after initial CR.

Results

The different types and results of initial treatment in the total group of patients with FMF (n = 203) and subgroups A

Table 1 Types of skin lesions and survival rates of three subgroups of folliculotropic mycosis fungoides (FMF)

Subgroup	Skin lesions	n	5-year OS	10-year OS	5-year DSS	10-year DSS
A	Early-stage skin-limited FMF presenting with follicular papules, follicle-based, acneiform or keratosis pilaris-like lesions and/or 'early- stage' plaques[a]	84	92	72	96	93
B	Advanced-stage skin-limited FMF presenting with 'advanced-stage' plaques,[b] tumours, nodules or erythroderma	102	55	28	65	40
C	FMF with extracutaneous localizations at first presentation (stage IVA–IVB)[c]	17	23	2	23	2
Total		203	67	45	75	60

Data are presented as percentages unless otherwise stated. OS, overall survival; DSS, disease-specific survival. [a]Early-stage plaques were defined as more or less elevated or infiltrated skin lesions, histologically characterized by sparse intra- or perifollicular neoplastic infiltrates containing relatively few and mainly small neoplastic T cells.[9] [b]Advanced-stage plaques were defined as more or less elevated or infiltrated skin lesions, histologically characterized by extensive confluent or diffuse infiltrates containing many, often medium-sized to large tumour cells. Clinically, 'early-stage plaques' and 'advanced-stage plaques' can be indistinguishable.[9] [c]Extracutaneous FMF includes patients presenting with nodal, visceral and/or peripheral blood involvement.

Table 2 Type and results of initial treatment in subgroups and total group of patients with folliculotropic mycosis fungoides (FMF)

	n (%)	CR	PR	OR	SD	PD	SCR
Group A: early-stage skin-limited FMF							
Group A total	84 (100)	29	57	86	14	0	20
Topical steroids	18 (21)	28	56	83	17	0	22
UVB	6 (7)	0	83	83	17	0	0
PUVA	40 (48)	30	58	88	13	0	18
PUVA plus retinoids or IFN-α	5 (6)	0	60	60	40	0	0
PUVA plus local RT	5 (6)	60	40	100	0	0	40
Local RT	4 (5)	75	25	100	0	0	75
TSEB	1 (1)	0	100	100	0	0	0
Systemic chemotherapy	1 (1)	0	100	100	0	0	0
Miscellaneous[a]	4 (5)	25	50	75	25	0	25
Group B: advanced-stage skin-limited FMF							
Group B total	102 (100)	25	50	74	16	10	7
Topical steroids	4 (4)	0	25	25	75	0	0
UVB	5 (5)	0	20	20	80	0	0
PUVA	20 (20)	10	50	60	25	15	5
PUVA plus retinoids or IFN-α[b]	13 (13)	0	67	67	17	17	0
PUVA plus local RT	20 (20)	5	70	75	5	20	0
Local RT	16 (16)	63	37	100	0	0	19
TSEB	17 (17)	59	41	100	0	0	18
Systemic chemotherapy	5 (5)	20	40	60	20	20	0
Miscellaneous[a]	2 (2)	50	50	100	0	0	0
Group C: extracutaneous FMF							
Group C total	17 (100)	6	31	38	19	44	6
Topical steroids	–	–	–	–	–	–	–
UVB	–	–	–	–	–	–	–
PUVA	2 (12)	0	0	0	50	50	0
PUVA plus retinoids or IFN-α	–	–	–	–	–	–	–
PUVA plus local RT	2 (12)	0	50	50	0	50	0
Local RT	1 (6)	0	100	100	0	0	0
TSEB[b]	2 (12)	0	100	100	0	0	0
Systemic chemotherapy	9 (53)	11	22	33	22	44	11
Miscellaneous[a]	1 (6)	0	0	0	0	100	0
Total group							
Total group total	203 (100)	25	51	76	15	8	12
Topical steroids	22 (11)	23	50	73	27	0	18
UVB	11 (5)	0	55	55	45	0	0
PUVA	62 (31)	23	53	76	18	6	13
PUVA plus retinoids or IFN-α[b]	18 (9)	0	65	65	24	12	0
PUVA plus local RT	27 (13)	15	52	78	4	19	7
Local RT	21 (10)	62	38	100	0	0	29
TSEB[b]	20 (10)	53	47	100	0	0	15
Systemic chemotherapy	15 (7)	13	33	47	20	27	7
Miscellaneous[a]	7 (3)	29	43	71	14	14	14

Data are presented as percentages unless otherwise stated. CR, complete remission; PR, partial remission (> 50% improvement); OR, overall response (CR + PR); SD, stable disease; PD, progressive disease during initial therapy; UVB, ultraviolet B; PUVA, psoralen plus UVA; IFN-α, interferon alpha; RT, radiotherapy; TSEB, total skin electron beam therapy. [a]Miscellaneous therapies included topical nitrogen mustard (two cases in group A), methotrexate (one case in group A) or no therapy (other four cases). [b]One missing value for therapy response.

(n = 84), B (n = 102) and C (n = 17) are presented in Table 2.

In group A, 67 of 84 patients (80%) had primarily been treated with nonaggressive SDTs, including topical steroids, topical nitrogen mustard, ultraviolet B (UVB) therapy, psoralen plus ultraviolet A (PUVA) therapy, or had received no therapy, compared with only 31 of 102 patients (30%) in group B. Combined treatment results for nonaggressive SDTs in group A showed a CR and OR, respectively, of 27% and 87% compared with 10% and 52% in group B ($P < 0{\cdot}01$). The latter group had been treated most frequently with radiotherapy-based treatment modalities, including local radiotherapy, total skin electron beam irradiation (TSEBI) and PUVA therapy combined with local radiotherapy (53 of 102; 52%),

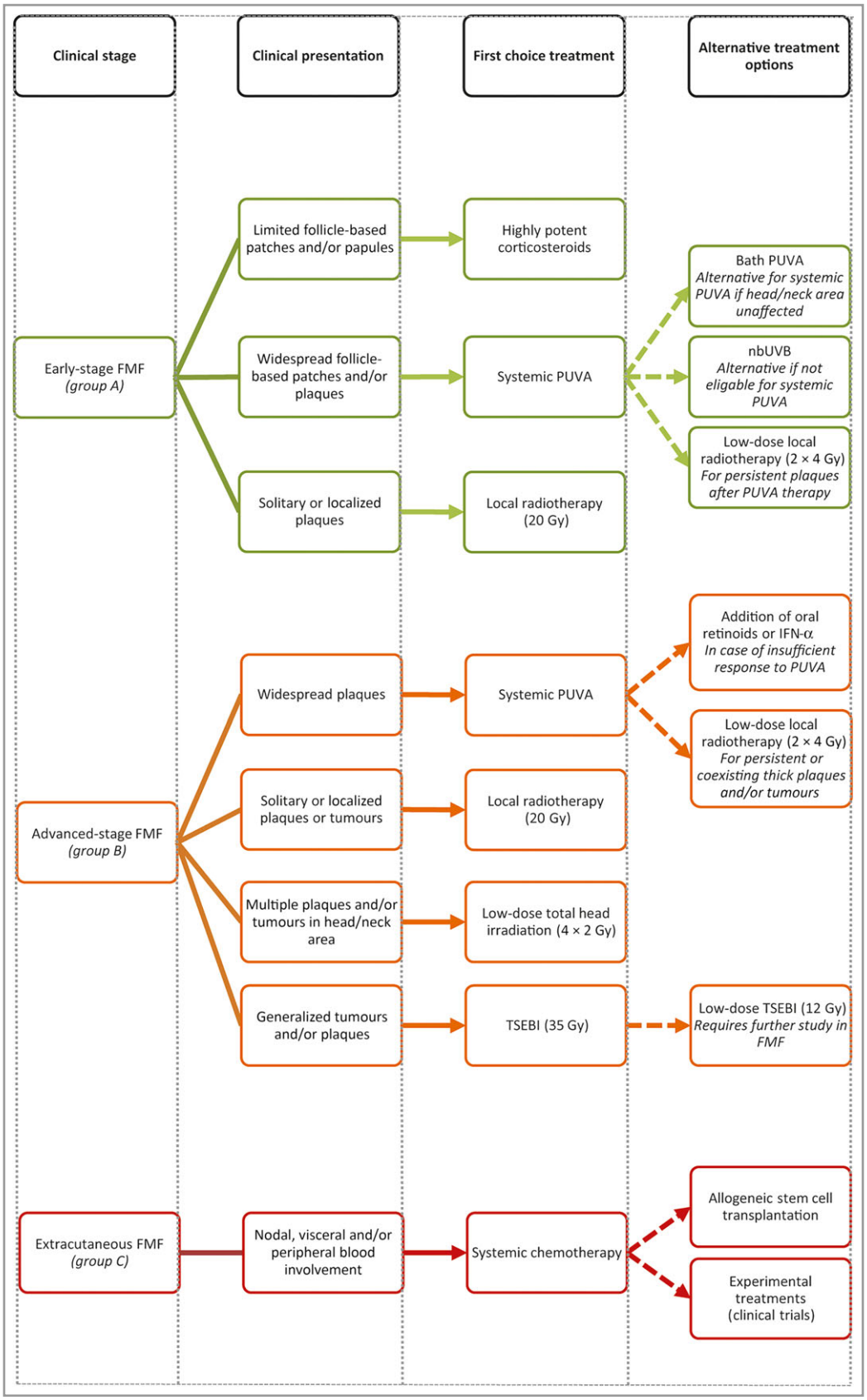

Fig 1. Recommendations for initial treatment in patients with folliculotropic mycosis fungoides (FMF). PUVA, psoralen plus ultraviolet A; nbUVB, narrowband UVB; IFN-α, interferon alpha; TSEBI, total skin electron beam irradiation.

or with PUVA therapy combined with acitretin, interferon (IFN)-α or methotrexate (13 of 102; 13%). In group C, nine of 17 patients (53%) had been treated with chemotherapy.

Discussion

The present study showed that patients with early-stage FMF can benefit very well from nonaggressive SDTs and that not all patients with FMF should be treated similarly to patients with tumour-stage classic MF, as suggested previously.[2,3] Based on the results of this study and few available reports in the literature, recommendations for effective initial treatment for different stages and clinical manifestations of FMF were formulated and consensus was reached after discussions at the regular quarterly meetings of the Dutch Cutaneous Lymphoma Group in 2015 and 2016 (Fig. 1). Treatment recommendations for patients with FMF with extracutaneous disease (group C) have never been different from those for patients with classic MF with extracutaneous disease[11] and will therefore not be further discussed.

Clinically, patients with early-stage skin-limited FMF (group A) present with localized or more extensive follicular papules or follicle-based patches, often associated with hair loss, keratosis pilaris-like and acneiform lesions or plaques with histologically sparse peri- and intrafollicular infiltrates. This group has an excellent prognosis with a 5-year OS of 92–94%.[8,9] We have noted that patients with only limited follicle-based patches (T1) respond very well to monotherapy with potent topical steroids, with CR and OR rates of 83% and 100%, respectively. Some of these patients even achieved durable SCR and may be considered cured. However, this has not been found effective in patients with plaques. In the case of more widespread skin lesions, narrowband (nb)UVB may produce PR in patients with only follicle-based patches, in particular localized outside the head/neck area, but it too has been found ineffective in patients with plaques. PUVA treatment proves much more effective, both in patients with patches and patients with plaques, with CR and OR rates of 30% and 88%, respectively, and sustained CR in 18% of cases. PUVA proved effective irrespective of localization and degree of extension (T1 or T2) of skin lesions. Because of the preferential localization of FMF to the head and neck area and the presumed superior efficacy, we normally advise oral rather than bath PUVA. However, one study reported high efficacy of bath PUVA in 14 early-stage FMF cases with superficial or keratosis pilaris-like skin lesions that were mainly localized outside the face, resulting in CR and OR rates of 71% and 100%, respectively.[12] Taken together, nonaggressive SDTs had been used as initial treatment in 80% of early-stage FMF patients and were sufficient in most cases, with CR and OR rates of 27% and 87%, respectively. In the case of residual lesions after SDTs, low-dose radiotherapy (2 × 4 Gy) proves highly effective.[13] In rare cases presenting with a solitary skin lesion, local radiotherapy (20 Gy) had resulted in CR in all cases.

Patients with advanced-stage skin-limited FMF (group B) present with infiltrated plaques, histologically characterized by extensive confluent or diffuse infiltrates containing many, often medium-sized to large T cells, tumours, nodules or in rare cases erythroderma, and have a less favourable prognosis with a 5-year OS of 55%.[9] Treatment with potent topical steroids or nbUVB had been ineffective in this group. PUVA monotherapy was found to be less effective than in group A, but the OR rate was still 60%. In patients with plaques this treatment can therefore be attempted first. When treatment fails or when patients present with very thick plaques or tumours, several options may be considered: (i) PUVA therapy combined with local radiotherapy for most infiltrated lesions; (ii) TSEBI; and (iii) PUVA therapy combined with IFN-α or retinoids. In patients with widespread skin lesions we often prefer PUVA with additional low-dose radiotherapy for (persistent) thick plaques or tumours. This approach is very patient- and department friendly (needing only two irradiations), has no side-effects other than temporary hair loss in some patients, and is highly effective.[13] As patients with FMF may typically present with skin lesions on the head, total head irradiation with the same technique as used for TSEBI, but with a dose of 4 × 2 Gy and shielding of nonfacial skin when appropriate, was found a very useful approach for extensive and infiltrated lesions. Concurrent less infiltrated skin lesions on trunk and extremities can be treated with PUVA. For patients presenting with a solitary or few localized plaques or tumours, local radiotherapy is highly effective, may give durable CR and is the preferred mode of treatment.[2,14,15]

In patients presenting with widespread thick plaques and/or tumours, TSEBI with a standard dose of 35 Gy proved an effective initial treatment, with high CR and OR rates. In three of 19 cases durable complete remissions were observed, but in most patients response to treatment was short lived. Repeated use of TSEBI with a dose of 35 Gy is limited due to cumulative toxicity. Recent studies reported favourable responses of low-dose TSEBI (10–12 Gy) in classic MF, although the CR rates are lower than with conventional TSEBI (> 30 Gy). An advantage of low-dose TSEBI, which is intended as palliative treatment, is that it can be used multiple times.[16,17] However, efficacy of low-dose TSEBI in FMF needs further study. PUVA combined with retinoids or IFN-α has been suggested as first-line therapy in patients with early-stage FMF, with OR rates of 61% and 50%, respectively.[3] The results of the present study, in which these combinations were particularly used in patients with advanced-stage skin-limited FMF (group B), showed an OR rate of 65% but CR was not achieved. After a good initial response, disease can often be controlled effectively by continued treatment with retinoids or IFN-α, without further PUVA therapy. While several studies describe efficacy of bexarotene monotherapy in patients with FMF, results on bexarotene as initial treatment have not been reported.[5,18]

In conclusion, the present study demonstrates that not all patients with FMF require aggressive initial treatment. Patients with early-stage FMF have an indolent disease course and may benefit very well from nonaggressive SDTs.

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