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Review

Clinical results of the total skin electron irradiation of the mycosis fungoides in adults. Conventional fractionation and low dose schemes

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ABSTRACT

Background: Mycosis fungoides (MF) is a rare skin condition, effectively treated by irradiation. Since 1951, different methods of total skin irradiation have been developed. Although dose–response effect has been demonstrated in many publications, controversies about low dose treatment still exist.

Aim: The analysis of results of the total skin electron irradiation (TSEI), especially low dose TSEI in comparison with standard dose treatment is the subject of this review. Also, acute and late side effects of radiotherapy in MF are discussed.

Materials and methods: Medline search and analysis of studies published between 1995 and 2012, containing key words: mycosis fungoides, standard dose TSEI, low dose TSEI, total skin electron beam therapy (TSEBT).

Results: Detailed analysis of relevant studies demonstrated that standard dose radiotherapy 30–36 Gy is the most effective treatment used in clinical practice. Objective response rate (ORR) is high, especially for less advanced stages of disease. Complete response rate (CR), although slightly lower, is still relatively high.

For more advanced MF, TSEI serves as a very good method of palliative treatment and relief of symptoms, like pruritus, pain or desquamation.

There is no consensus regarding low dose TSEI; the method is widely accepted as a palliative treatment or in case of reirradiation.

Conclusions: Standard dose TSEI is an effective method of MF treatment for radical and palliative treatment, producing high rate of ORR and reasonably long time to progression (TTP). Acute and late side effect of treatment are mostly mild and easy to manage. Low dose TSEI is still in the phase of clinical studies.

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1. Background

Mycosis fungoides (MF) is a relatively rare disease. The etiology and natural course of the disease have been discussed in separate publications. Despite its indolent course, even at low stages of disease, patients report unpleasant symptoms: pruritus and desquamation, patches and plaques and, at more advanced stages, erythrodermia mycosis fungoides is a disease which is not easy to treat and according to the majority of sources permanent recovery is unlikely. It is possible to obtain periods of remission of different duration as well as to alleviate or even eliminate the symptoms. The patient's age, the stage of the disease with or without lymph nodes being affected, and the presence of the site of the disease other than the skin are among the prognostic factors of the disease progression.¹ Affected lymph nodes are predictors of the MF progression but do not reduce the long-term survival.² In the treatment, topical methods are used, especially at the lower stages of the disease. The method of therapy which is regarded as the most effective is total skin electron irradiation (TSEI). The present review will focus on clinical results of irradiation at different clinical stages with consideration of the total administered dose.

Irradiation of patients with MF has been in use since 1951. Total skin electron irradiation (TSEI) or total skin electron beam therapy (TSEBT) is not only an effective treatment method at early stages of the disease, but it also gives effects in palliative treatment when the disease is advanced.^{3,4}

In daily clinical practice, a number of irradiation methods – whose detailed characteristics are presented elsewhere – are employed. The most common methods are the Stanford method⁵ and the rotational method.⁶

The choice of treatment and its results depend to a large degree on the stage of the disease, categorized according to the classification: T-tumor N-node M-metastasis B-blood. On the basis of this system, in 2007 the classification of the European Organization of Research and Treatment of Cancer EORTC and International Society for Cutaneous Lymphomas was created, included also in the American Joint Committee on Cancer (AJCC).^{7–9}

Electron irradiation of the skin is recommended as initial treatment mainly for patients with thickened plaques.⁴ This method is more effective than topical therapies, like nitrogen mustard or phototherapy, in the case of thickened lesions as radiation penetrates thicker infiltrations much better than medication used topically.¹¹ However, also in the case of patients with the disease at much more advanced stage, this method is commonly accepted for palliative treatment.⁴

The remission of lesions and the reduction of symptoms occur both during the therapy and thereafter, some time following the completion of therapy. Monitoring patients with MF once they have completed radiotherapy is necessary in order to evaluate properly the response to treatment.

Irradiating the total area of skin even by means of non-penetrating radiation which stops at the dermis still causes some side effects. Although in the majority of cases these side effects are not severe, they commonly include soreness and redness of the skin, desquamation, the separation of fingernails from their nail bed (onycholysis) or hair loss.¹¹

Taking into consideration the dose received by the skin, which for the conventional TSEI is 30–36 Gy,⁵ repeated course of TSEI is very rarely used for fear of intensified late radiation effects such as skin necrosis and bone marrow suppression.¹² Therefore, in some medical centers the possibility of irradiating the total area of the skin with doses lower than 30 Gy is being tested although early studies concerning MF radiotherapy indicate a strong dose–response effect.⁵ The aim of this review was to analyze available publication regarding low dose TSEBT in terms of feasibility of this method in clinical practice. To adequately assess feasibility of low dose TSEBT, results of this approach were discussed together with standard dose TSEBT, in terms of both: outcome and side effects. Moreover, special clinical indications for low dose TSEBT were presented.

2. Method

In order to review treatment results in the published studies an analysis of literature was undertaken using PubMed. Medline browsers.

The key words used were the following: mycosis fungoides, total skin electron irradiation (TSEI), total skin electron beam therapy (TSEBT), low dose TSEBT, mycosis fungoides reirradiation.

Due to the indolent course of the disease with relatively long median survival, studies from the years 1995–2012 were included in the review. Both retrospective and prospective studies which were published in English and which evaluated among their end-points the objective response (OR) and the rate of complete response (CR) were taken into account. Since MF is a relatively rare disease, studies on small numbers of patients were not disqualified. Duplicate studies which discussed the results of the same groups of patients were excluded from the review. The references of the studies incorporated in the review were analyzed and relevant further studies were subsequently added.

3. Results

Medline search identified 158 publications describing TSEI in the treatment of MF. 11 studies were eligible for analysis of treatment results, presenting analysis of long-term follow-up.

3.1. Standard dose TSEI

Table 1 presents the results of studies which resorted to TSEI using various dose. Generally, the doses amounted to 30–36 Gy. Most studies report very good results of the treatment of initial stages of MF, the response rate is 70–100% for all the stages, whereas for T1-2 N0 it reaches 97–100%. Together with the progression of the disease and the occurrence of extracutaneous lesions, the response rate drops, complete remission is achieved for a smaller group of patients and it lasts for a shorter time. 10-year disease-free survival rate is 50% for the IA stage, it drops to 20–10% for the IB stage,^{18,21} and below 10% for the IIB stage. The results of irradiation for patients with stage III disease differ depending on blood involvement. In the case of patients with erythrodermia, the rate of remission is 75%, but 5-year progression free survival (PFS) is only 25%. For

Table 1 – Results of treatment of MF with TSEI, standard (high) dose and low dose.

Study/years conducted	No. of Pts (sex: M/W)	Stage TNM (patients)	Median age (range)	TSEI Dose – Gy (patients)	FU median (months)	ORR%	CR % (stage TNM)	OS% (years)	TTP (months)
Navi D Stanford, 1970–2007 ¹³	180	T2 (103) T3 (77)	NA	30–40	77	100	60 all 75 (T2) 47 (T3)	59 (5) 40 (10)	NA
Maignon Dijon, 1975–1995 ¹⁴	45 (34/11)	T3, T4	61 (27–87)	24–30 [photon/electron]	85 (18–244)	75	24 all 67 (T3) 28 (T4) 64 (N1) 41 (N3)	(5y OS) 37 [T3] 44 [T4] 63 [N1] 32 [N3]	NA
Kamstrup MR Copenhagen, 2002–2006 ¹⁵	10 (6/4)	T2 (7) T3 (3) N1 (1) N0 (9)	68.7 (55–82)	4	NA	80	2	NA	2.7
Lindahl LM Aarhus, 2001–2008 ¹⁰	35	T1 (2) T2 (14) T3 (17) T4 (2)	66 (41–85)	30 (25) 4 (10)	7.6 [3d-3,7y]	100	68 [HD] 10 [LD] 66.7 (T2) 78.6 (T3)	NA	4
Shouman T Cairo, 1997–2002 ¹⁶	40	T1, T2 (34) T3 (6)	50 (24–63)	35	19.5 (6–48)	100	87.5	NA	10.5
Funk A Heidelberg, 1993–2004 ⁴	18 (15/3)	IIB (1) IVA (10) IVB (7)	59 (34–78)	>25 (12) <25 (6)	11	89	50	NA	NA
Kamstrup MR Copenhagen Aarhus, 2009–2010 ¹⁷	10 (8/2)	T2 (6) T3 (2) T4 (2)	62 (48–84)	10	NA	90	70	NA	4.2
Harrison C Stanford, 1958–1995 ⁷	102 (68/34)	T2 (51) T3 (29) T4 (22)	59 (21–90)	5–<10 10–<20 20–<30	NA	96	16 [<10 Gy] 35 [<20 Gy] 34 [<30 Gy]	NA	NA
Jones GJ Ontario, 1977–1992 ¹⁸	146	T1 (44%) T2 (34%)	55	30 (25) 35 (121)	60	82	NA	100 (10) [for 35 Gy]	NA
Quiros PA Yale, 1974–1993 ¹⁹	114	T1 (39) T2 (75)	58 (20–88)	36	62 (3–179)	NA	97 (T1) 87 (T2)	(5y OS): 85 [all] 100 [PUVA+] 82 [PUVA-]	NA
Ysebaert L Dijon, 1975–2001 ²⁰	141	T1 (24) T2 (33)	61 (19–84)	30	114 (14–300)	97.4	87.5 (T1) 84.8 (T2)	90 (5) 65 (10)	NA

two-thirds of the group of patients with the B0 feature disease-free survival is 10 years,¹⁸ in contrast to patients with the B1 feature whose survival is only 15%. Patients with identified stages IVA and IVB can undergo effective palliative treatment, the complete remission rate is 70% and in some cases long-term remissions are obtained. Post-treatment survival for IV B stage rarely reaches 5 years. However, TSEI improves the quality of life and reduces the unpleasant symptoms.¹⁸

3.2. Low dose TSEBT

Published results of research on low-dose TSEI are scarce, which impedes drawing definite conclusions concerning the outcomes of low-dose therapy. The study conducted in the Department of Dermatology in Copenhagen showed that doses as low as 4 Gy delivered in 4 fractions administered to the skin in the process of total skin irradiation may induce partial remission in the case of early stage mycosis fungoides MF – IB-II; however, it is a short-term remission.^{10,15} Despite discouraging results of low-dose irradiation with doses of 4 Gy, attempts have been made to use this method and irradiate the skin using the dose of 10 Gy.¹⁷ Kamstrup obtained satisfactory results of both clinical response and remission time, particularly in patients with complete remission.

3.3. Palliative treatment

TSEI is also applied in strictly palliative treatment: in the MF resistant to psoralen ultra violet A and chemotherapy at stage IIB–IV. In his research, Funk presented encouraging results of TSEI irradiation with the dose of >29 Gy: in 50% of patients a complete remission was noted which continued for 1–18 months. The actuarial one-year progression free survival was 24%.⁴ 89% of patients experienced the reduction of symptoms such as itch, pain, bleeding or ulcers, which, however, was accompanied by the occurrence of temporary side effects of the treatment.

3.4. Side effects

An acute radiation – induced reaction mainly includes drying and desquamation of the skin, erythema, edema, particularly on the limbs, overpigmentation and hair loss. Existing skin ulcers due to infiltration of the skin might lead to temporary epitheliolysis or bacterial superinfection.⁴

These symptoms are nearly always temporary and mostly subside after ca. 2–3 weeks.¹⁴ Acute reaction is intensified around the second week of the treatment. Moreover, leuconychia and dystrophy occur during the stage of acute reaction and persist for a longer period.²² Due to the presence of the symptoms and need for supportive care, patients treated with TSEI are hospitalized.

General symptoms which occur in a number of patients especially in the case of more advanced stages are myelosuppression and fatigue. Late radiotherapy-induced reactions such as hyper- and depigmentation as well as hyperkeratosis occur a few years after treatment completion. Another frequently observed symptom is hipohidrosis caused by sweat gland atrophy.⁴

Some authors report the occurrence of rare symptoms such as benign secondary neoplasms, i.e. diffuse lipoma or eccrine poroma.²³

4. Discussion

TSEI is one of more efficient, widely accepted methods of treating MF which is also recommended by EORTC guidelines. Although, as numerous authors emphasize, TSEI is not a radical treatment for MF, the rate and long period of obtained complete remissions of MF at less advanced stages as well as a satisfactory palliative effect in the case of the advanced disease, make radiotherapy the basic method of MF treatment. The results of treatment presented in available publications are consistent for both more and less advanced stages. Likewise, prognostic factors such as age, stage or involvement of lymph nodes do not raise controversy.

Discrepancies in outcomes of treating T2 and T3 stages, which can be found in literature stem, according to various authors, derive from the difficulty in defining these MF stages histopathologically and clinically. Authors indicate that similar problems occur in the case of assessing lymph nodes involvement which may cause differences in the evaluation of treatment results.

The focus of the current studies is on prolonging remission and reducing the recurrence rate particularly at stage IB. The proposed strategies are chiefly targeted at an adjuvant and concurrent therapy including PUVA¹⁹ administration of topical drugs such as bexarotene or systemic treatment like methotrexate, gemcytabine or liposomal doxorubicin. Administering mechlorethamine (nitrogen mustard) concomitantly with TSEI was not satisfactory both in terms of complete remission rate and overall survival.³

It was demonstrated that without adjuvant therapies for stage IB, 10-year-cause-specific survival is 96%, and median overall survival is 15–20 years, and half of deaths are caused by MF.¹⁸ Since adjuvant treatment with high-dose cytostatic drugs and bone marrow transplant has not provided to deliver the expected satisfactory results, administering cytostatics and delivering TSEI at the same time has been proposed²¹ as well as including total nodal irradiation.²⁴

Historic papers on radiotherapy of MF show dose levels evolved and increased from low doses of 8 Gy to higher doses of 30–36 Gy, which was the result of finding a dose-response relation. This was the reason for abandoning treatment with low doses of 4–10 Gy, which as several publications confirm, have not proved to be sufficiently effective. However, recently, the return to low-dose TSEI in MF and attempts at finding application for this kind of radiotherapy have been observed. Treatment results are inconsistent: some papers present a favorable toxicity profile and emphasize a similar complete remission rate with the use of low doses.¹⁵

An undeniable advantage of such a treatment scheme is the fact that it may be repeated without fearing severe radiation-induced reactions, both early and late, while the length of remission is the main disadvantage of low-dose techniques. The group of patients treated with low-dose TSEI is still small, which does not allow to draw a valid conclusion. Some authors propose introducing low-dose TSEI schemes in the case of

frequent MF recurrences, which makes it possible to repeat radiotherapy.⁷ Lower total doses in these cases allow repeated total skin electron therapy without severe late symptoms, such as skin necrosis or chronic, refractory radiodermatitis. On the basis of available publications, it appears that total skin electron beam therapy will be applicable in the case of carefully selected group of patients receiving primary treatment or suffering from recurrence as well as those receiving palliative treatment.²⁵ In the future, low-dose TSEI may be applied in a concomitant therapy with radiosensitizers such as cytostatics or targeted therapy.

The assessment of treatment results, beside standard end-points such as complete remission or disease-free survival, should also take into account the quality of life of the patient receiving treatment^{26,27} and be regarded as one of the most important end-points of the study, especially in case of disease which has a relatively long natural history and troublesome symptoms such as itch and desquamation.

Conflict of interest

None declared.

Financial disclosure

None declared.

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