ORIGINAL ARTICLE

Treatment of Mycosis Fungoides with Total Skin Electron Beam Therapy Using Modified Stanford Technique

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ABSTRACT

A retrospective review of three patients with mycosis fungoides treated with total skin electron beam therapy , from the year 2007 to 2009 , at the Oncology department, Ziauddin University Hospital.

KEY WORDS: *Mycosis Fungoides, Primary Cutaneous T-Cell Lymphoma, Total Skin Electron Beam Therapy.*

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INTRODUCTION

Primary cutaneous lymphomas are rare malignancies, representing about 2% of all lymphomas. They are sub-divided by the WHO-EORTC according to the cell lineage into B-cell and T-cell variants, the latter comprising approximately 70% of all cases.

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma. It is caused by epidermotropic proliferation of T lymphocytes (Helper T-cells) which bear the T-cell antigen CD_4 and and frequently lack other normal T-cell antigens such as CD_7 , CD_5 or CD_2. Mycosis fungoides is indolent in nature and progresses through three clinical phases:

1. Patch or pre-mycotic phase.
2. Infiltrated plaques or mycotic phase.
3. Tumour or fungoid phase.

Diagnosis of mycosis fungoides depends upon both clinical and histologic criteria. The median duration of onset of skin lesions to the histologic diagnosis is 8-10 years and it varies with patients.

ISCL/EORTC REVISION TO THE TNM CLASSIFICATION OF MYCOSIS FUNGOIDES AND SEZARY SYNDROME*

SKIN (T):
T1: Limited patches, papules or plaques covering less than 10% of skin surface.
$T1_a$ – patch only.
$T1_b$ – patch + plaque.
T2: Patches , papules or plaques covering more than 10% of the skin surface.
$T2_a$ – patch only.
$T2_b$ – patch + plaque.
T3: One or more tumours (≥ 1 cm in diameter).
T4: Confluence of erythema covering 80% or more of body surface.
NODE (N):
N_0: No clinically abnormal lymph nodes, biopsy not required.
N_1: Clinically abnormal peripheral lymph node, histopathology Dutch grade 1
Or NCI L-No 2.
N_{1a} – clone negative.
N_{1b} – clone positive.
N_2: Clinically abnormal peripheral lymph node, histopathology Dutch grade 2
Or NCI L-No 3.
N_{2a} – clone negative.
N_{2b} – clone positive.
N_3: Clinically abnormal peripheral lymph node, histopathology Dutch grade
3-4 or NCI L-No 4 ; clone positive or negative.
N_x: Clinically abnormal peripheral lymph node, no histologic confirmation.
VISCERAL (M) :
M_0: No visceral organ involvement.
M_1: Visceral involvement (histologic confirmation).
BLOOD (B) :
B_0: No circulating atypical cells (Sezary cells). ≤ 5 % of peripheral blood lymphocytes.
B_1: Circulating atypical cells (Sezary cells). > 5 % of peripheral blood lymphocytes.
B_2: High blood tumour burden; 1000/µL Sezary cells with positive clones.

*Sezary syndrome is the aggressive leukemic, erythrodermic form of Cutaneous T-cell lymphoma, characterized by circulating, atypical,malignant T-lymphocytes with cerebriform nuclei (Sezary cells) and lymphadenopathy. They have mature memory T-cell phenotype (CD_3+ , CD_4+) with loss of CD_7 and CD_{26}.

Table 1. Clinical Stage Groups

Clinical Stage	T	N	M	B
IA	T_1	N_0	M_0	B_0 or B_1
IB	T_2	N_0	M_0	B_0 or B_1
IIA	T_1 or T_2	N_1 or N_2	M_0	B_0 or B_1
IIB	T_3	N_0-N_2	M_0	B_0 or B_1
IIIA	T_4	N_0-N_2	M_0	B_0
IIIB	T_4	N_0-N_2	M_0	B_1
IVA_1	T_1-T_4	N_0-N_2	M_0	B_2
IVA_2	T_1-T_4	N_3	M_0	B_0-B_2
IVA_3	T_1-T_4	N_0-N_3	M_1	B_0-B_2

Treatment depends upon clinical stage of mycosis fungoides. Therapy includes a variety of modalities ranging from topical and systemic chemotherapies, biologic agents and ionizing irradiation. Mycosis fungoides is a radiosensitive disease and evidence suggests that total skin electron beam therapy can be used to treat whole skin at any stage of disease. It results in superior response rates in cutaneous stage of disease and good palliation in advanced or recurrent disease.

Since early 1950s various treatment techniques have been used.[1,2,3]

A low energy electron beam (3-4 Mev) is used with patient treated at long source to skin distance. Some techniques have involved scanning the patient through the beam on a moving couch or rotating the patient on a rotisserie but most current techniques treat the patient using multiple stationary fields (moss rad.onco, 7th ed). Current standard is the modified Stanford technique using a conventional LINAC in HDR electron mode to deliver matched dual fields at a distance of 3.5-4.5 meters. Aim of the treatment is to deliver the dose uniformly to entire surface of body. (red book)

The average thickness of normal skin is 2-3 mm. cellular infiltrates of CTCL with tumour formation may extend upto a depth of 15 mm. In previous studies the treatment depth for electrons was taken from several millimeters to one centimeter.[4,5] For this purpose electron energy of 4 MeV -6 MeV can be used. Delivering TSEBT is complicated because variation in shape, orientation and size of the body makes it difficult to obtain uniformity of dose.[6] Hence it requires expertise of radiation oncologist, physicist and the technicians. The recommended dose according to the EORTC recommendation is 30-36 Gy.(pg429, haematological malignancies)

METHODOLOGY

Three patients with histologically proven mycosis fungoides, with involvement of extensive body surface, from the year 2007 to 2009, treated with total skin electron body therapy using modified Stanford technique at the department of oncology, Dr. Ziauddin university hospital, Karachi.

Total skin electron beam was set up using 5 MeV electron beam with Siemens Primus (model: MID energy) with a gantry angle of 265^{o} and 285^{o}. The position and distance was anterior, posterior and oblique, 306 cm from the accelerator source. The field direction for the first day wasone anterior and two posterior oblique. For the second day, the field direction was set for one posterior and two anterior oblique. Single field was employed for soles, vertex and perineum on both day 1 and day 2.

For Dosimetry a 3 mm thick plastic sheet placed at 56 cm from the target was used as scatterer. The degraded energy measured at the treatment distance of 306 cm was 3.5 MeV. The dose evaluation was carried out by using a Markus chamber Model PTW (34045) in conjunction with a UNIDOSE PTW electrometer. All the six treatment fields (90X90 cm) were scanned at the extended SSD with the help of a mini-phantom fabricated locally with a Perspex sheet and utilizing D_{max} of the degraded energy. At the central axis of the treatment plane, the dose was found higher than the periphery. The machine was operated at higher dose rate mode (900 cGy/min) and for calculated MUs for 180 cGy/ Fr, for all the treatment fields AP and PA and left and right oblique fields. The in-situ measurements were simulated by placing the mini-phantom at various center points of the subject. Total dose prescribed was 36 Gy over – weeks. Tumours of thickness of ≥ 1.5 – 2 cm were treated with local electron fields before start of TSEBT (15 Gy in 5 Fr). It was required for only one patient.

All patients tolerated the treatment well, with minimal side effects which included temporary erythema, grade 2 nail changes, and dry skin. The clinical response to treatment was determined by physical examination. The treatment schedule is shown in Table 2 and 3.

RESULTS

All patients achieved a complete response clinically (defined as complete clinical regression of all skin lesions). One patient was lost to follow-up after 10 months of treatment. Among the other two patients, one had no clinical evidence of disease for three years post

irradiation, while the other developed recurrence of skin lesions after 6 years of treatment.

Table 1. Treatment Schedule for Day 1

Patient Position	1st Week		2 Week		3rd Week		4th Week	
DAY-1	Tue	Fri	Mon	Wed	Wed	Fri	Mon	Wed
AP Front Upper Position	1892	1640	1664	1678	1700	1700	1700	1700
AP Front Lower Position	1932	2245	1926	1792	605	1700	1700	1700
Lt-Post Oblique Upper Position	1932	2723	3079	1909	752	752	752	1700
Lt-Post Oblique Lower Position	2923	3716	2007	1775	480	500	510	1700
Rt-Post Oblique Upper Position	1892	1969	1723	1601	1315	1700	1700	1700
Rt-Post Oblique Lower Position	2363	2069	2109	1713	946	1000	1700	1700
Scalp		162	162	108	108	108	108	108
Soles of feet		300	300	200	200	200	200	200
Perinem		117	117	78	78	78	78	78

Table 2. Treatment Schedule for Day 2

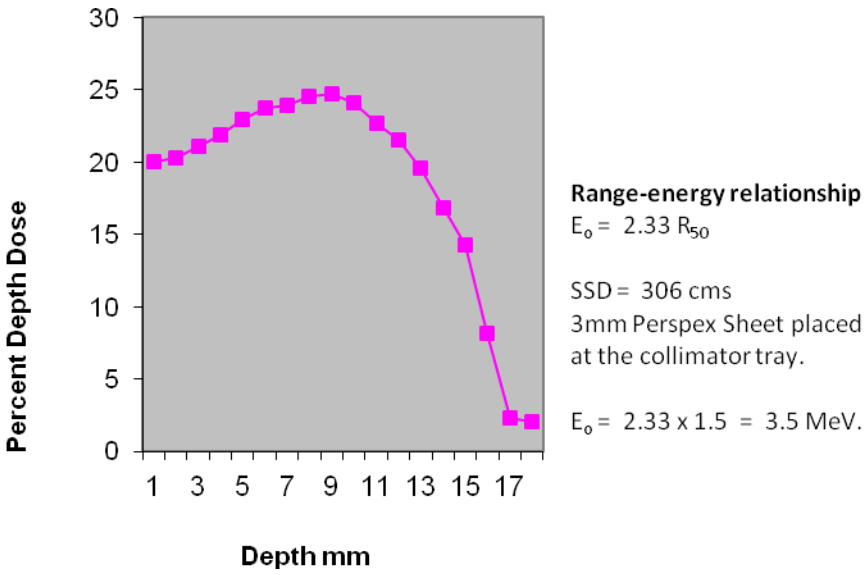
Patient Position	1st Week		2 Week		3rd Week		4th Week	
DAY-2	Wed	Sat	Tue	Thr	Thr	Sat	Tues	Thr
PA Front Upper Position	1749	1867	1484	1670	1700	1700	1700	1700
PA Front Lower Position	2309	1798	1000	1700	1700	1700	1700	1700
Lt-Ant Oblique Upper Position	2670	2519	…… ….	1700	1700	1700	1700	1700
Lt-Ant Oblique Lower Position	2808	2145	200	1700	1700	1700	1700	1700
Rt-Ant Oblique Upper Position	2043	2005	1052	1700	1700	1700	1700	1700
Rt-Ant Oblique Lower Position	2473	1915	712	1700	1700	1700	1700	1700
Scalp		162	162	108	108	108	108	108
Soles of feet		300	300	200	200	200	200	200
Perineum		117	117	78	78	78	78	78

Table 4. Figure Skin Dose Distribution

Area	Anterior	Right or Medial	Left or Lateral	Posterior
Head	96±1	97±2	96±3	96±1
Neck	91±6	93±2	91±1	95±4
Abdomen	102±2	93±3	90±3	101±2
Elbow	-------	87±15	93±4	-------

Palm	85±1	-------	-------	85±2
Knee	90±1	90±4	81±10	93±1
Foot	88 ± 2	80 ± 6	80 ±6	87±1
Single Measurement				
Scalp vertex	46 ± 13			
Perineum	61±15			
Sole	Nil			

Figure 1. 5 Mev Electron PDD Graph and Range Energy Relationship



DISCUSSION

TSEBT can be used to treat any stage of mycosis fungoides. For generalized erythroderma presentation as well as for advanced or recurrent disease TSEBT is an appropriate therapy.[7]

MF is very sensitive to irradiation and TSEBT presents complete response rates of 40-98% in early stages. In advanced disease, introduction of more aggressive measures may be required. However for palliation for extensive and recurrent disease, there is possibility of a repeat TSI with substantial benefit and acceptable toxicity.[8]

The efficacy of TSEBT has been demonstrated in various studies.[9,10,11,12.13]

There are diverse techniques for irradiation in order to obtain adequate dose distribution in the entire treatment area and different techniques have been described by AAPM[14]. One of the most clinically used technique is the Modified Stanford technique (Ballerina's technique) which uses six dual fields[15] and this is the current standard[16]. TSEBT depends upon the availability of equipment and limitation imposed by treatment room design[17]. 5-10 MeV energy electrons have been used in most centers. The degraded energy varied from 3.5 to 7 MeV at the position of the patient with large nominal SSD 300-500 cm[18]. Beam uniformity was achieved from hands to feet by multiple fields delivering dose to upper and lower halves separately[19].

Entire thickness of the infiltrated skin is the cornerstone of the treatment. The infiltration is mainly localized to the superficial portion of the skin (2-4 mm). in some cases it often extends upto the deeper regions e.g. hair follicles, subcutaneous tissues, at the depth of 15 mm or

more. This may result in inhomogeneous dose distribution[20].

The x-ray contamination resulting from large electron fields is not uncommon. At our center, the total x-ray contamination was about ± 5 % which is quite acceptable.

Dosimetry and calibration of the radiation beams of the radiotherapy units is carried out with the system routinely calibrated by the Secondary Standard Dosimetry Laboratory (SSDL) of Pakistan Atomic Energy Commission, according to the Pakistan Nuclear Regulatory Authority's (PNRA) directives[21]. The daily, weekly, monthly quality assurance/ quality control program is followed as per AAPM guidelines[22,23,24]. The radiological safety program of the hospital is reviewed by the hospital radiation safety committee periodically and endorsed by yearly inspection of PNRA.

The main limitations that presented during the study pertained to few number of patients (only 3), non-availability of TLDs, absence of human body phantom, the amount of time consumed for dosimetry and wide fluctuations in main supply affecting environmental parameters.

CONCLUSION

Although therapy of MF includes a variety of modalities including topical and systemic chemotherapies, biologic agents and total skin irradiation[25], the most beneficial therapies which offer long term disease control have been TSEBT, PUVA and nitrogen mustard[26,27,28,29].

Modified Stanford technique was implemented for TSEBT in the treatment of mycosis fungoides. SSD was limited due to treatment room geometry. The treatment energy and dose uniformity was achieved by using scatterer-degrader. The uniformity of dose was found comparable to that achieved by TSEBT protocols elsewhere. TSEBT showed to provide excellent clinical outcomes in this study. Even with limited resources the TSEBT can be applied at other centers of the country.

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