Cutaneous Lymphoma; Total Skin Electron Therapy

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INTRODUCTION

• Heterogenous group of B & T cell lymphocytes
• Cut T-Cell Lymphoma (CTCL) arise from T lymphocytes of helper T phenotype having affinity for skin and epidermis
• Mycosis Fungoides - most common CTCL
• Incidence as low as 0.4 /1 lakh
<table>
<thead>
<tr>
<th>Lymphomas Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis / Sezary</td>
<td>82.3%</td>
</tr>
<tr>
<td>Lymphatoid Papulosis</td>
<td>12.6%</td>
</tr>
<tr>
<td>B cell Lymphoma</td>
<td>4.5%</td>
</tr>
<tr>
<td>Peripheral T cell lymphomas</td>
<td>2.9%</td>
</tr>
<tr>
<td>CD30+ anaplastic large cell lymphomas</td>
<td>0.9%</td>
</tr>
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Mycosis fungoides

- Rare often indolent T cell lymphoma
- About 1000 new cases in US/year
- Average age at diagnosis 50-60 yrs
- Children and adolescents not spared
- Median duration between onset of skin lesions and diagnosis 8-10 yrs
- Lesions can occur anywhere in body -- predilection for body folds
PHASES OF MF

- Patch or premycotic phase
- Plaque phase
- Tumor phase
- Sezary syndrome
- Erythroderma
Patch Phase

- Thin, non-palpable, erythematous & eczematous lesions
- Histologic features - diagnosis of MF
- DD: psoriasis, eczema, fungal infections, pityriasis rosea, drug eruptions
- Pruritus: most common symptom
Plaque Phase

Clinically perceptible palpable lesion
Tumor Phase

- Neoplastic infiltrate extends below the upper dermis.
- Cutaneous ulceration
- Secondary infection
Erythroderma
Stage I: Limited to skin. No Tum, ulcer, adenopathy or visc involvement
Stage Ia: Limited skin invol < 25%
Stage Ib: Invol. of more than 25%
Stage II: Skin Tum or Bx proven LN
Stage III: Invol skin with Bx proven LN or Spleen
No other visc invol
Stage IV: Cut and extracut MF with documented visc invol
TNM(B) Classification

T1- Limited patch/plaque (<10% of skin surface involved)
T2- Generalized patch/plaque (>=10% of skin surface involved)
T3- Cutaneous tumors (one or more)
T4- Generalized erythroderma (± patch, plaque or tumors)

N0- LN clinically uninvolved
N1- LN clinically enlarged, histologically uninvolved
N2- LN clinically unenlarged, histologically involved
N3- LN clinically enlarged and histologically involved

M0- No visceral disease
M1- Visceral disease present

B0- No circulating atypical cells (<1000 Sezary cells[CD4+CD7-]/ml)
B1- Circulating atypical cells (>=1000 Sezary cells/ml)
### Stage classification of MF

<table>
<thead>
<tr>
<th>IA</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1-2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3</td>
<td>N0-1</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T1-4</td>
<td>N2-3</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T1-4</td>
<td>N0-3</td>
<td>M1</td>
</tr>
</tbody>
</table>

The B classification does not alter clinical stage.
Prognostic factors

- Age
- Stage
- Lymph node involvement
- Visceral involvement
DIAGNOSTIC WORK UP

- General
  - History (attn to pace of evolution)
  - Derma eval and proper lesion charting
  - Routine physical exam – LN, liver, spleen etc

- Imaging studies
  - CXR
  - CT Scan Chest, Abd & Pelvis
Diagnostic workup contd.

- Laboratory studies
  - CBC, blood chemistry, LDH
  - Peripheral Blood smear for Sezary cells
  - Flow cytometry of peripheral blood
  - Biopsy
    - Punch biopsy of lesion
    - Biopsy of palpable LN
    - Bone marrow biopsy
Treatment modalities

Skin- directed therapy
- Localized EBRT
- Topical chemotherapy (NM, BCNU)
- Topical retinoids (Bexarotene)
- Total skin electron beam therapy (TSET) - Most effective
- Phototherapy

Biologic response modifier
- Extracorporeal photopheresis
- Interferon alpha
- Systemic retinoids
- Recombinant fusion protein (e.g. denileukin difitox)
- Vorinostat

Systemic chemotherapy (CHOP, COPP)
Combined modality therapy
Denileukin Dieitox
HDAC Inhibition on Cancer Cells With Vorinostat

Anticancer Effects of Vorinostat

TREATMENT BY STAGE

Stage Ia

- generalized *topical HN2*
- Unable to tolerate topical HN2 – *PUVA, Re-PUVA, topical BCNU*
- Progression/refractory to trt – TSET, *PUVA with Interferon alpha*
Stage Ib /IИa

- Chronic dis - topical HN2 or PUVA
- Rapidly prog disease with thick plaques
  - TSET with optional follow up therapy - topical HN2, PUVA, Photopheresis to maintain remission
  - Refractory to these trt - systemic drugs exa- Interferon alpha, retinoid, or single agent CT exa- MTX
Stage IIb:

*TSET* with boost to tum with optional follow-up topical trt/photopheresis to maintain response

- *sequential topical therapies* for refractory lesions
- Disease progression – *photopheresis*
- No response - *systemic therapy*
Stage III

- Photopheresis

- Progression or unresponsive – add MTX to photopheresis

- Progression - palliative PUVA, palliative topical HN2, interferon, syst CT, retinoids, exp protocols exa-fludarabine, MAB or BMT
Stage IVa

- *Individualized palliative trt*
  - Interferon-alpha, syst CT
  - local radiation to sympt dis
  - Photopheresis
  - Retinoids
  - exp protocols
Stage IVb

- *Individualized palliative trt*
  - Syst CT
  - Interferon, retinoids, exp protocols
Radiation Therapy Technique

Skin thickness
- Average : 2-3 mm
- min (eyelid) : 0.5 mm
- Max (back) : 5 mm

Cellular infiltration in MF
- Mainly superficial portion of skin
- Often extend in deeper tissue exa- hair follicle
- Tumor formation : 15 mm
RT Techniques used in MF

- β-rays from Sr$^{90}$
  - superficial lesion
- Superficial irradiation (80-140 KV)
  - Infiltrated plaque
- Orthovoltage irradiation
- TSET
Conventional Radiation Therapy

- Markedly infiltrated plaques & tumors
  - High energy ortho-voltage (200-280 KV) or local-field electron beam irradiation (10-15 MeV)

- Discrete lesion
  - 10-20 Gy / 3-4#/ 3-4 days OR
    20-30 Gy /10-15# / 2-3 weeks
  - Generous portals
  - Document the treated area (photograph, portal drawing or tattooing)
  - Possible need of subsequent irradiation
Conventional Radiation Therapy

Cotter et al. (IJROBP 1983;9:1477)
- 20 patients (110 lesions)
- RT for cutaneous MF
- Superficial X-ray, Co60, electron beam
- Plaque (50%), tumor <3 cm (20%), tumor >3 cm (27%)

<table>
<thead>
<tr>
<th></th>
<th>10 Gy</th>
<th>10-20 Gy</th>
<th>20-30 Gy</th>
<th>30-40 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesion</td>
<td>27</td>
<td>46</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Complete response</td>
<td>26 (96%)</td>
<td>41 (89%)</td>
<td>28 (100%)</td>
<td>9(!)%</td>
</tr>
<tr>
<td>Partial response</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Recurrence after CR</td>
<td>11/26 (42%)</td>
<td>13/41 (32%)</td>
<td>6/28 (21%)</td>
<td>0/9</td>
</tr>
<tr>
<td>Mean time to recurrence</td>
<td>5 mon</td>
<td>10 mon</td>
<td>16 mon</td>
<td>No fail.</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>12/27 (44%)</td>
<td>18/46 (39%)</td>
<td>6/28 (21%)</td>
<td>0/9</td>
</tr>
</tbody>
</table>
Conventional Radiation Therapy

- Micailey et al. (*IJROBP* 1998;9:475)
  - 18 patients with unilesional MF
  - *Local* electron beam irradiation only
    - Median dose 30.6 Gy
    - 10 Yr relapse free SR = 86.2%
    - 10 Yr overall SR = 100%

- TSET is not indicated for unilesional MF
Total Skin Electron Beam Therapy

- Only in major radiotherapy centers
- Aims to irradiate the patient’s whole skin
  - Radiation dose by proper choice of electron energy
  - Dose to epidermis and upper dermis
  - Sparing deep dermis & subcutaneous tissues
- First used by Trump et al.* using a van de Graaff generator
- Stanford technique**

**Page et al. Radiology. 1970:94;635
Various TSET Techniques
Modified Stanford technique

- Six field
- Two beams (15 degree above & below horizontal)
- 1st day- Ant, RPO & LPO
- 2nd day- Post, RAO & LAO
- Dose – 30-40 Gy / 8-10 wks – one wk gap at 18-20 Gy, 1.5-2Gy/#.
- 3 fields /day
- Boost - 15-20Gy ; 1-2Gy/# to soles, scalp perineum and inframammary

Page et al. Radiology 1970; 94:635-41
Shielding

- Eye
- Finger Nails
- Toe nails
TSET Applicator
Pretreatment Evaluation

- Detailed history
- Clinical examination
- Cutaneous lesions charting
- Haemogram, LFT, RFT
- Peripheral blood smear
- Bone marrow examination
- X-ray chest and USG abdomen and pelvis
LPO
BOOST TO SCALP
Reclined patient position

• For pts who cannot stand
• Pt lies reclined on a low couch close to the floor
• Two symm 48 deg electron arc fields
• Field uniformity of 5%
• 6 positions - Ant, Post & 4 obliques, over a 2 day period
• Disadv - More time consuming (because of low electron dose rate)

Rotational total skin electron irradiation

• Improved surf dose homogeneity
• Simplify pt positioning
• Pt stands on rotational platform - dist 285 cm
• 6 MeV electron  HDR mode
• Trt time reduced < 10 min
• Skin dose homogenous - within +10% to -20%

AIIMS PROTOCOL

- Modified Stanford tech
- Machine used CI 20/2300CD, SL 20/Precise
- 6 trt positions – Ant, Post, RAO, LAO, RPO, LPO
- All 6 fields trtd every day; 120cGy/day
- 5 days/week
- Trt dist - 10 feet from isocenter
AIIMS PROTOCOL cont.

- 4 MeV/6MeV electron (with beam spoiler)
- LDR (500 cGy/min) in the initial years
- Now HDR mode (2500-3000 cGy/min)
- Dose - 36 Gy/30 #
- Boost to scalp, perineum, sole & residual tum
- Nails, eyes shielded
Rationale of treating with 6 fields

- Better dose uniformity
- Entire body surface get better exposure
- Self shielding regions are better irradiated
Radiation accompaniments

- **Acute**
  - generalized erythema, itching
  - edema
  - moist desquamation
  - Alopecia

- **Late**
  - hyperpigmentation
  - telangiectasia
  - dry skin
  - Necrosis of nails
ACUTE RADIATION ACCOMPANIMENTS
LATE SEQUEL

RADIATION DERMATITIS
Recurrence and re-irradiation

- Frequent in MF

- Relapse with diffuse cut inv not amenable to other topical modalities may be offered a second course of TSEI

Criteria for re-irradiation

- Long gap following first course of TSEI
- Diffuse cut invol
- Failure of other adj modalities
Review of literature

  Suggested a technique for large field electron therapy

  Increasing the no of fields improves dose homogeneity
A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides

- N=103
- Randomized: 3000 cGy of electron-beam + CT (n = 52) or seq topical trt (n = 51)
- Comb therapy produced considerable toxicity
- Comb therapy pts-- sig higher rate of CR than conserv therapy (38% vs. 18% P = 0.032)
- FU 75 mo-- no sig diff between the trt groups in DFS or OS

Ultimate results of radiation therapy for T1-T2 mycosis fungoides (including reirradiation)

- 1975 - 2001; n=14
- 3 mo after TSET OR - 94.7%
- CR - 87.5% of T1 and 84.8% of T2
- 31(54.4%) had a skin failure (8 with T1 and 23 with T2) within 1 year
- 18/31 received a reirradiation
- For the whole group, 5-year DFS was 50%
- 5/10/15-year OS were 90%/65%/42%
- TSET is highly effective in early-stage MF without adjuvant therapy
- Second TSET is feasible, time-saving, and cost-effective

Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides

- T2 and T3
- TSET +/- topical HN2 Vs HN2 alone
- TSET +/- HN2 : higher CR rates than HN2 alone for T2 and T3
  - 76% vs 39%, p = 0.03 for T2
  - 44% vs 8%, p < 0.05 for T3

Local superficial radiotherapy in MF

- Local superficial RT studied in early stage IA MF
- Failure is unusual
- Pt should receive a min surface dose of 20 Gy
- Sequela -- minimal

Our publications


Pharmacology and therapeutics

Cutaneous T-cell lymphoma treated with electron beam irradiation in Indian patients

Dillip K. Parida, MD, Kaushal K. Verma, MD, Subhash Chander, MD, R. C. Joshi, MSc, Dip RP and Goura K. Rath, MD

Abstract
Background Cutaneous T-cell lymphoma (CTCL) is a rare occurrence in India. Total skin electron irradiation (TSEI) is a well-accepted therapeutic modality for the treatment of CTCL throughout the world. The aim of this study was to retrospectively analyze the treatment outcome of TSEI in Indian patients with CTCL and to determine the different parameters affecting the disease-free survival in these patients.

Methods Fourteen male patients between 27 and 82 years of age with CTCL (duration of disease, 4 months to 2 years) were treated with TSEI between 1985 and 1998. Seven patients had early stage disease, while the other seven had advanced disease. Two patients had lymph node involvement at the time of presentation. The TSEI was performed according to the Stanford technique delivering a total dose in the range 8–36 Gy.

Results Of the 14 patients, 10 showed complete remission following TSEI. The total follow-up period was 4–110 months (median, 52 months). Five patients were disease free at the end of 5 years. Two patients died due to rapid progression of the disease, while the cutaneous lesions relapsed in three patients after 2–27 months and one patient developed visceral metastasis.

Conclusions TSEI was an effective therapeutic modality for the treatment of CTCL in this group of patients, both as a curative and palliative measure, although the long-term prognosis is poor.
## Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>14</td>
</tr>
<tr>
<td>Complete remission</td>
<td>10</td>
</tr>
<tr>
<td>NED at 5 years</td>
<td>5</td>
</tr>
<tr>
<td>Relapsed skin lesions</td>
<td>3</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>1</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
</tr>
</tbody>
</table>

Follow-up period 4-110 months (mean 52 months)
Total skin electron irradiation therapy in mycosis fungoides using high-dose rate mode: a preliminary experience.

Parida DK, Verma KK, Chander S, Joshi RC, Rath GK

Department of Radiation Oncology and Dermatology*, All India Institute of Medical Sciences, New Delhi -110029, India

Results

- Total no. of patients: 7
- MFU: 9 Mo
- Complete remission: 6
- NED at 2 years: 4
- Relapsed skin lesions: 2
- Mortality: 1
Total skin electron irradiation treatment for mycosis fungoides with a new alternate daily treatment schedule to minimize radiation-associated toxicity: a preliminary experience.

Parida DK, Verma KK, Rath GK

Department of Radiation Oncology and Dermatology*, All India Institute of Medical Sciences, New Delhi -110029, India

Results

N : 4
T2 : 1
T3 : 3
RT Dose : 5 days/week X 2 wks followed by treatment on alternate days to deliver a total dose of 36 Gy.

Follow up Period : 60-84 months
All without any evidence of disease at FU
Minimal toxicity, less OTT, good clinical remission and prolonged DFS
Thank you