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Advantages and implications of high dose rate (HDR) total skin electron irradiation (TSEI) for the management of Mycosis Fungoides. Indian experience

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ABSTRACT

Background: Mycosis Fungoides (MF) is an indolent lymphoproliferative disorder affecting dermis caused by abnormal proliferation of CD4+ T-cells. Radiation therapy is the most effective modality of treatment for MF which offers cure in limited stage disease and desirable palliation in advance stage disease. Treating entire skin having many curved surfaces and folds with radiation is the real challenge for the radiation oncologist. Many techniques, dose schedules and modifications in total skin electron irradiation (TSEI) have been tried since 1950s. TSEI treatment is a very time consuming, inconvenient and physically challenging to both patient as well as oncologist.

Aim: At our center TSEI was performed since 1983 with conventional linear accelerator where the treatment time was prolonged beyond two hours, which was very difficult or the patient, oncologist, technical officer and eating away the machine time hampering the treatment of other patients. From 1998 we shifted to high dose rate (HDR) mode, in order to bring down the treatment time of a single patient every day from two and half hour to 15 min. The reduction of treatment time increases patient compliance and at the same time saved machine time.

Materials and methods: Between 1998 and 2003, eleven pathological diagnosed MF patients were treated using HDR TSEI. All the patients were male between 40 and 70 years of age, who had the history of having the disease for 7–22 months. Four patients had T2 and seven patients had T3 stage disease with more than 90% skin surface involvement. TSEI was performed with 4 MeV electrons with a daily fraction size of 120 cGy to a total dose of 36 Gy. At the end of 36 Gy, boost dose of 10 Gy was delivered to self shielding regions like sole, scalp and perineum. Considering the treatment related toxicities and consequent treatment interruptions, in the first seven patients, the last four patients were treated using similar HDR

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TSEI technique with modified treatment schedule, where the treatment was given on an alternate day basis following 2nd week of initiation of treatment.

Results: The patients were followed over a period of 144 months with a median of 72 months. Nine patients are alive without any evidence of disease, one patient relapsed and one died due to progression of disease. The most common radiation related morbidities are erythema, skin blisters, various degree of desquamations, swelling of joints (specially small joints) etc. which are controlled by treatment interruptions and conservative measures. By modifying the treatment schedule, the incidence of toxicity as well as treatment interruptions were brought down.

Conclusions: We can conclude that HDR-TSEI is an excellent and safe therapeutic modality for the patients with MF both curative as well as palliative without any added toxicity profile, provided patient positioning is done properly.

1. Background

Mycosis Fungoides is a low grade chronic lymhoproliferative disorder of T-lymphocytes arising out of skin, usually having an indolent course, caused by abnormal proliferation of CD4+ T cells.[1] MF itself is often an epidermotropic disorder characterized by evolution of patches into plaques and tumors composed of small- to medium-sized skin-homing T cells, some (or, rarely all) of which have convoluted, cerebriform nuclei. Individuals affected are usually in their 50s or 60s. Children are rarely affected. According to the Leukemia and Lymphoma Society in the United States, there are about 1500 new cases of cutaneous T-cell lymphoma every year. The overall incidence of MF is about 4 per 100,000.[2,3] In India there are no accurate statistics regarding the incidence of MF. The frequency of occurrence of cutaneous lymphomas was found to be 0.7 per 100 biopsy specimens. In another Indian study, the frequency of occurrence of MF to be 73% of all lymphomas.[4] Over the past three decades the incidence rate of MF is showing an increasing trend, may be because of improved diagnostic tools and techniques. However the exact incidence may still be underreported because of difficulty in diagnosis or misdiagnosis.

The principal prognostic factors are the (1) extent and phase of disease; (2) lymphadenopathy and visceral involvement and (3) presence of lymphoma cells in the peripheral circulation.[5] In the early stage of disease, the prognosis has also been independently associated with pathobiological findings like depth of cutaneous infiltration, total contiguous and non-contiguous infiltrative cell density, the proportion of reactive CD8+ cells and dermal infiltrate. However the prognosis is generally poor in advanced stage of the disease. Transformation of MF cells to large-cell lymphoma also implies a poor prognosis.[6–9]

The classical MF progresses through five distinct phases; premycotic, patch, plaque, tumor and erythroderma. The symptoms vary according to the stage of the disease and degree of skin involvement. Patients with stage 1A and 1B disease (patch and plaque stage only) account for about 75% of all new patients. Therefore, early-stage disease that is mostly localized in the skin has an excellent chance of cure with skin-directed therapies alone. Radiation therapy remains most effective form of curative as well as palliative form of treatment. The cutaneous lesions are extremely radioresponsive and a dose–response relationship has been demonstrated.[10–13] The complete remission rates with this therapy may be as high as 90–100% in localized lesions. Cotter et al. have even demonstrated 100% remission with a radiation dose in excess of 30 Gy.[14] Wilson et al. have reported a remission rate of 97% with external beam radiotherapy.[15] Therefore it is extremely important to deliver a total dose of 36–40 Gy of radiation over a period of 10–11 weeks, not having too many treatment interruptions in-between because of the treatment related toxicities.

Between 1985 and 1998 we had treated 14 patients of MF. TESI was carried out using a high-energy Linear Accelerator (Clinac 20) with 6 MeV electrons in conventional method. The patients were made to stand on a stationary platform with the legs wide apart behind a polystyrene screen, which was used for reducing the beam energy from 6 MeV to 4 MeV at a distance of 10 feet from the iso-center of the accelerator. Two large overlapping fields were used to irradiate the whole length of the body. The central axis of the fields pointed 15° upwards and downwards from the horizontal plane to minimize photon contamination, as described in the Stanford technique. All the patients were treated in six positions (anterior, posterior, left anterior oblique, left posterior oblique, right anterior oblique and right posterior oblique). All The 12 fields (6 upper half and 6 lower half of body) were treated every day. The total dose of radiation varied from 8 to 36 Gy with a daily fraction size of 120 cGy, given over 5 days in a week. Since beginning of TSEI the eyes and nails were shielded with a 3 mm-thick lead. A supplementary boost dose of 10 Gy was given to self-shielding areas like the scalp, perineum and soles.[16]

Problems encountered with conventional TSEI: The patient positioning behind polystyrene screen remained too much complicated and as the dose rate of the Clinac 20 was less, the total treatment time for each patient was taking more than two hours every day. For the patient standing eyes blinded for two long hours was the real challenge, therefore ending up with less patient compliance.

2. HDR TSEI: materials and methods (Indian experience)

Between 1998 and 2004 eleven patients were treated with TSEI using Electa (SL-20) dual energy linear accelerator having a special attachment which delivers electron at a very high dose rate (30 Gy/min) at the iso-centere.[17] The high dose rate mode delivered 4 MeV electron beam with acceptable beam uniformity, adequate depth dose while maintaining a low-level of X-ray contamination. All the patients were male between 40 and 70 years of age, who had the history of having the disease for 7–22 months. Four patients had T2 and 7 patients had T3 stage disease with more than 90% skin surface involvement. In three patients the lesions were confluent, ulcerated and bleeding on manipulation. Extra-cutaneous sites were not involved in any of the patients. The treatment technique remained same as in conventional TSEI except no polysterene screen was used. All patients were administrated a total dose of 36 Gy over 9–14 weeks with a daily fraction of 120 cGy, with a booster dose of 10 Gy to scalp, perineum and sole. Thermo luminescent dosimeter (TLD) measurements of the prescribed skin dose were obtained at the lateral margins, dorsum of the foot, perineum and scalp to see if there are certain hot spots over any skin curvatures. The patients were evaluated according to a fixed schedule, given hydration before treatment and advised to take high calorie diet throughout the treatment. All the routine investigations except the chest X-ray were performed biweekly throughout the treatment period.

Advantages of HDR TSEI: The use of the polystyrene screen was not required. The treatment time for each individual patient drastically came down to 15 min only from more than two hours in conventional method, thereby increasing compliance and comfort of the patient, oncologist and technologist. Reducing treatment time also keeps the machine free to be used for other patients.

Problems encountered with HDR TSEI: But there were treatment interruptions for various duration in all the patients because of radiation-associated morbidities such as decrease in hemoglobin and total leucocytes count, development of cutaneous blisters, moist desquamation of the skin (grade II-3, grade III-2) and the poor general condition of the patients. The period of treatment interruptions ranged from 5 to 11 days and occurred in batches of 2–3 during the entire treatment.

As the end-response to radiation therapy in MF is dependant on the total radiation dose and duration of treatment, prolonged overall treatment duration can spare the tumor cells and lower the chance of cure, where as delivering the total dose over a shorter duration provides greater radiobiological benefit and offers better tumor control.[10,11] Hence, it is very important not to have many treatment interruptions.

Modification of the TSEI schedule: In order to reduce HDR-TSEI related toxicities and treatment interruptions, last four patients were treated with a modified fractionation schedule.[18] The treatment was carried out using a HDR mode delivering 4 MeV electron at a dose rate of 30 Gy/min at isocenter. In this protocol the patients were treated with similar Stanford Technique, 120 cGy/field/day, to a total dose of 36 Gy. Both halves of body received treatment at each session. But the treatment delivery days were modified. The treatment is delivered 5 days/week for first two weeks and then on alternate days until completion of total radiation dose. At the end of the treatment, a booster dose of 10 Gy was delivered to self shielding areas such as sole, scalp and perineum. Rest of the evaluation and follow up protocols were similar to previous group of patients.

Advantages of modifying the treatment schedule: there were absolutely no treatment interruptions and therefore the total radiation dose could be delivered within 9–10 weeks which helped in obtaining better tumor control (Table 1).

3. Results

The patients were followed up at an interval of every 6 weeks in the first year, every 3 months during the second year and every 6 months there after following TSEI over a period of 144 months with a median of 72 months. Nine out of eleven patients had complete remission both clinically and histopathologically following TSEI (Table 2). In the other two patients the lesions healed with a few ulcers. In one patient the lesions relapsed on the trunk after 10 months and in the other patient who did not received the boost treatment, the lesions relapsed over the eyelid and the perineum after 4 months. He was treated with 10 Gy of radiation dose to these regions. Out of these two, one patient subsequently progressed, lost to follow up and the other one died. The most common radiation related morbidities are erythema, skin blisters, various degree of desquamations, swelling of joints (specially small joints) etc. which are controlled by treatment interruptions and conservative measures. One patient developed pericardial effusion leading to generalized edema; who was managed for cardiac disease and treated like other patients. At the end of 12 years (1998–2010), all nine patients were alive without any evidence of disease.

The modification in the treatment protocol resulted in much less occurrence of radiation associated toxicities like wet desquamation, swelling of joints etc. with no treatment interruptions. The toxicities were limited to small blisters and mild swelling and pain of small joints. All the patients could complete the radiation treatment of total dose of 36 Gy within 10 weeks, compared to 14 weeks by conventional method.

4. Discussions

Although radiation as a therapy was used for the treatment of localized/limited lesions of MF in 1902, large areas of skin or the entire skin with low-energy X-rays or electrons could not be treated due to lack of equipment and technical shortcomings. TSEI is still a technically and practically challenging procedure. Hence, not many centers around the world use it. The set-up for performing TSEI requires a proper infrastructure, and the optimum management of MF patients requires a close collaborative efforts amongst the radiation oncologist, medical physicist and dermatologist. A variety of technical and clinical issues related to TSEI and its effects were reviewed by Reavely et al.[19] A model of TSEI treatment using the 'Six dual field' technique was reviewed by Faz D et al.[20] In a study by Hoppe et al, the initial complete response ranged from 86% in early-stage diseases to 44% in the tumor stage. Kuten et al.

Table 1 – Comparison of treatment schedules.

	HDR TSEI	Modified alternate day HDRTSEI
Total radiation dose, Gy	36	36
Total treatment duration, wks	14	10
Treatment schedule	5 fractions/wk until completion of total dose On alternate days until completion of total dose	5 fractions/wk for 2 wks, then 3 fractions/wk
Treatment-related toxicity		
Mucositis	++	+
Desquamation	++	+
Blisters	+++	+
Edema of the limbs	++	+
Treatment interruptions	2–3	Nil

have reported a cure rate of 95–100% with TSEI.[21] Ysebeart et al. have described that TSEI produces excellent results in T1, T2 stage of MF.[22] The probability of complete remission is high with TSEI it and offers good palliation in advanced diseases.[23] Regardless of the technique used, the most important factors to get the best results in TSEI remain the electron energy, which should be 4 MeV and the total dose which should be more than 30 Gy.[16,17,24] The procedure has been modified several times during the process of developing the TSEI program at Stanford University to make it more technically refined and clinician as well as patient friendly, which was widely accepted by many centers and at the same time many centers tried to improve upon the dose-schedule of the technique.

We have been using this therapeutic modality in MF patients since 1985, and in our experience TSEI is an excellent treatment modality in both early and advance diseases. The total treatment time taken for an individual setting was about 2 h when the patient is being treated with conventional way but such prolonged treatment time many times become a hindrance for proper execution of TSEI, particularly in case of elderly patients they cannot stand for such a long time with eyes closed and also maintain proper posture and position. This difficulty was being addressed when treatment is executed by high dose rate (HDR) mode and the treatment time for an individual patient is drastically reduced to only about 15 min, which is significantly shorter than delivering TSEI by conventional mode, while retaining proper functioning of the accelator dosimetry systems and interlocks. A dose of 4 MeV is usually used to treat epidermal and dermal lesions homogeneously. As most of the dose (80%) is delivered at a depth of 1 cm and less than 5% beyond 2 cm, structures below the deep dermis are spared. Shadowed regions like the scalp, perineum, sole and other skin folds are boosted later with local electron fields.

It is acknowledged that any TSEI program development is heavily dependent on the specific technique chosen, the particular equipment on which it is carried out and the facility where it will be implemented. The techniques themselves are often complex with concomitant hazards and most are time consuming to develop and carry out on a routine basis. A rigorous quality assurance program should be an integral part of especially HDR TSEI, because of high electron dose rates at isocenter are usually employed to minimize treatment time may produce undesirable side effects if patient set up is not done properly.

Table 2 – Results of HDRTSEI ($n = 11$).

Response	No. of patients
Complete remission	9
Recurrence	2
Progressive disease	1
Death	1

The skin of patients treated with TSEB irradiation at doses >10 Gy usually develops mild erythema and dry desquamation that may become uncomfortably symptomatic. Lesions frequently become more erythematous than clinically normal areas during the early phase of treatment and may later become hyperpigmented. At higher doses (>25 Gy), some patients experience transient swelling of the hands, edema of the ankles, and occasionally large blisters that may necessitate local shielding or temporary discontinuation of therapy. Unless hair and nails are shielded, loss of these skin appendages invariably occurs by the end of treatment, but they regenerate within 4–6 months. In our treatment schedule, the eyes and nails were shielded from day one of the treatment. Chronic cutaneous damage from TSEI irradiation is unusual at doses of <10 Gy and is acceptably mild through 25 Gy. Superficial atrophy with wrinkling, telangiectases, xerosis, and uneven pigmentation are the most common changes. With higher total doses, frank poikiloderma, permanent alopecia, skin fragility, and subcutaneous fibrosis are more likely to occur but are uncommon. In general, the nature and severity of acute and chronic radiation effects are a function of technique, fractionation scheme, total dose, concomitant use of topical or systemic cytotoxic drugs, previous treatments, and the condition of the skin before irradiation. In order to avoid these toxicities, the patients have to be informed and explained properly regarding the maintenance of correct positions particularly when treated with HDR mode.

Many modifications to the technique and dose fractionation have been done to obtain better results, which have been documented in many studies.[25–28] In 1971, Fuks and Bagshaw presented therapeutic results in 107 patients treated with 2.5-MeV electrons at Stanford University. They increased the total dose to 30 Gy and presented evidence indicating that increasing the total dose also have an impact on post treatment disease-free intervals, thereby justified a more aggressive therapeutic approach than that used previously.

In a study by Rosenblatt et al. analyzed the influence of total skin dose and dose-fractionation schedules on the response

rate, survival and skin toxicity of patients with MF treated with TSEI found that a reduction of the total dose and dose-per-fraction resulted in an acceptable CR rate and a significantly lower toxicity. But in our experience it was noticed that when the patients were treated with a dose less than 30 Gy, the disease control rate was not good. Disease control and late skin toxicity is directly related to the dose–fractionation schedule. We have demonstrated that HDR TSEI increases patient compliance with reduced treatment time and modification of treatment schedule decreases treatment related toxicities allowing to deliver total radiation dose above 30 Gy and obtaining better disease free interval.

5. Conclusions

As a conclusion, we can submit that TSEI is an excellent therapeutic modality for the patients with MF both curative as well as palliative. HDRTSEI reduces treatment time considerably making it more users friendly. As the treatment is delivered over a short period of time, stress must be given on proper patient positioning in order to avoid hot spots due to overlapping of radiation fields. The severity of acute toxicity can be minimized by proper dose-fractionation schedules.

Conflict of interest

None declared.

Financial disclosure

None declared.

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