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CLINICAL INVESTIGATION **Lymphoma**

REVISITING LOW-DOSE TOTAL SKIN ELECTRON BEAM THERAPY IN MYCOSIS FUNGOIDES

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Purpose: Total skin electron beam therapy (TSEBT) is a highly effective treatment for mycosis fungoides (MF). The standard course consists of 30 to 36 Gy delivered over an 8- to 10-week period. This regimen is time intensive and associated with significant treatment-related toxicities including erythema, desquamation, anhydrosis, alopecia, and xerosis. The aim of this study was to identify a lower dose alternative while retaining a favorable efficacy profile.

Methods and Materials: One hundred two MF patients were identified who had been treated with an initial course of low-dose TSEBT (5–<30 Gy) between 1958 and 1995. Patients had a T stage classification of T2 (generalized patch/plaque, $n = 51$), T3 (tumor, $n = 29$), and T4 (erythrodermic, $n = 22$). Those with extracutaneous disease were excluded.

Results: Overall response (OR) rates (>50% improvement) were 90% among patients with T2 to T4 disease receiving 5 to <10 Gy ($n = 19$). In comparison, OR rates between the 10 to <20 Gy and 20 to <30 Gy subgroups were 98% and 97%, respectively. There was no significant difference in median progression free survival (PFS) in T2 and T3 patients when stratified by dose group, and PFS in each was comparable to that of the standard dose.

Conclusions: OR rates associated with low-dose TSEBT in the ranges of 10 to <20 Gy and 20 to <30 Gy are comparable to that of the standard dose (≥ 30 Gy). Efficacy measures including OS, PFS, and RFS are also favorable. Given that the efficacy profile is similar between 10 and <20 Gy and 20 and <30 Gy, the utility of TSEBT within the lower dose range of 10 to <20 Gy merits further investigation, especially in the context of combined modality treatment. © 2011 Elsevier Inc.

Cutaneous lymphomas, Mycosis fungoides, Radiotherapy, Low-dose total skin electron beam therapy, T-cell lymphoma.

INTRODUCTION

Mycosis fungoides (MF) is an extranodal non-Hodgkin's lymphoma of T-cell origin with primary cutaneous involvement (1). It is the most common primary lymphoma of the skin. It is an uncommon condition with an incidence of 6.4 per 1 million persons in the United States (2). The presentation of MF is heterogeneous. In the classic form, patients often present with cutaneous eruptions ranging from pruritic patches to plaques, tumors, or erythroderma. Prognosis is related directly to the clinical stage at diagnosis with the most predictive factors being patient age, T stage classification, and presence of extracutaneous disease (3). Staging is based on a tumor-node-metastasis-blood (TNMB) classification system initially developed by the Mycosis Fungoides Cooperative Group and National Cancer Institute, which was published in 1979 (4). This system has proven to be extremely useful, and it is the foundation for the staging and classification of patients with MF or Sézary syndrome. The criteria were revised in 2007 in a joint report from the International Society for Cutaneous Lymphomas and the European Organization of Research and Treatment of Cancer (EORTC) (5). The revised staging system has recently been adopted by the American Joint Committee on Cancer (6).

Historically, radiation therapy achieves very high response rates and remains the single most effective modality in the treatment of MF. Electron beam therapy is preferable to X-ray (photon) therapy because of its limited depth of penetration. This limits the side effect profile of the treatment (7). Total skin electron beam therapy (TSEBT) was introduced as a treatment for

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Table 1. Initial course clinical response by dose

T class or range	Response	No. of patients/total (%) per dose group			
		5–<10 Gy	10–<20 Gy	20–<30 Gy	5–<30 Gy
T2	CR	1/7 (14)	13/25 (52)	7/19 (37)	21/51 (41)
	PR	5/7 (71)	11/25 (44)	12/19 (63)	28/51 (55)
	OR	6/7 (85)	24/25 (96)	19/19 (100)	49/51 (96)
T3	CR	2/8 (25)	1/14 (7)	2/7 (29)	5/29 (17)
	PR	5/8 (63)	13/14 (93)	5/7 (71)	23/29 (79)
	OR	7/8 (88)	14/14 (100)	7/7 (100)	28/29 (96)
T4	CR	0/4 (0)	4/12 (33)	2/6 (33)	6/22 (27)
	PR	4/4 (100)	8/12 (67)	3/6 (50)	15/22 (68)
	OR	4/4 (100)	12/12 (100)	5/6 (83)	21/22 (95)
T2–T4	CR	3/19 (16)	18/51 (35)	11/32 (34)	32/102 (31)
	PR	14/19 (74)	32/51 (63)	20/32 (63)	66/102 (65)
	OR	17/19 (90)	50/51 (98)	31/32 (97)	98/102 (96)

Abbreviations: CR = complete response (clinical resolution of all cutaneous lesions); PR = partial response (>50% resolution of cutaneous lesions defined by the physicians global assessment); OR = Overall response (PR plus CR).

patients with MF in 1952 (8). Early patients were treated with total doses as low as 8 Gy. Excellent responses were recorded at this dose, with minimal associated toxicity. Relapses eventually occurred, and doses were gradually increased. By the mid 1970s, the standard dose had increased to 36 Gy, administered over an 8- to 10-week period (9).

Although the likelihood of a CR increases with the standard dose, it is associated with greater toxicity (10). The most common acute complications of standard dose TSEBT are erythema and dry desquamation. Intermediate and long-term side effects include partial alopecia and temporary loss of fingernails and toenails (11). Most patients report the inability to sweat properly for 6 to 12 months following therapy and complain of xerosis (12, 13). Because of the risk for skin atrophy and potential necrosis, there has been reluctance to administer more than two conventional courses of TSEBT in a patient's lifetime (14). Since most patients will have recurrent disease with the standard dose, this limitation restricts the use of this effective therapy.

There has been recent interest in revisiting the effectiveness of lower dose TSEBT in the management of patients with MF (15). In comparison with the standard 8- to 10- week course of 30 to 36 Gy, lower dose treatment has several advantages. It may limit radiation-related toxicities, expand options for combination or sequential therapies, and permit the administration of multiple treatment courses. A shorter regimen would also improve access to this treatment modality.

In this study, we retrospectively reviewed the Stanford University experience treating patients with stage T2 to T4 MF, using an initial course of low-dose TSEBT (5–<30 Gy). We also reviewed the outcomes of those who received subsequent courses of TSEBT following the initial low-dose course. Our goal was to identify a low-dose range of TSEBT with a favorable efficacy profile.

METHODS AND MATERIALS

Patients

We used the comprehensive database of the Stanford Multidisciplinary Cutaneous Lymphoma Program to identify patients with MF who received low-dose TSEBT (5–<30 Gy) in the Department of Radiation Oncology from 1958 to 1996. The majority of patients receiving the lower dose did so prior to widespread adoption of the 30 to 36 Gy standard regimen. All patients had a diagnosis of MF confirmed in the Cutaneous Lymphoma Clinic at Stanford. For classification and staging, patients underwent a thorough physical examination, complete blood cell count assay with examination for Sézary cells, general chemistry panel, and chest radiography. When indicated, additional studies including bone marrow biopsy or lymph node biopsy or other imaging studies were used to evaluate for extracutaneous involvement. A lymph node biopsy or fine needle aspiration was performed in those patients with palpable lymphadenopathy suspicious for involvement by MF. Suspected involvement of any visceral sites was confirmed by biopsy whenever possible. All patients were staged according to the TNMB classification system (4, 5).

Study design

We limited this analysis to patients with stage T2–4 N0–1 M0B0 disease at the time of TSEBT initiation. Only patients receiving their first course of TSEBT at doses ranging from 5 to <30 Gy were included. Patients did not receive systemic therapy during the TSEBT course, and they remained off therapy unless their disease worsened significantly during the follow-up period. For the purpose of comparison, data were also analyzed for a cohort of patients with T2–4 N0–1 M0B0 disease who were treated with standard doses (≥30 Gy) of TSEBT from 1970 to 2007.

We also identified a cohort of patients who were retreated with low-dose TSEBT. Patients were given the additional course upon disease worsening or relapse following the initial low-dose treatment. Only those with stage T2–4 N0–1 M0B0 disease were included, and the outcomes from these additional courses were analyzed separately. All aspects of the study design and analysis were reviewed and approved by the Stanford Institutional Review Board.

Response criteria

Initial clinical responses were determined using a global assessment of response. This was performed approximately 4 to 6 weeks after completing TSEBT, when the acute skin reactions associated with radiotherapy had subsided. Complete response (CR) was defined as clinical resolution of all cutaneous MF lesions, and partial response (PR) was defined as greater than a 50% clearing of