Radiotherapy Approach in the Treatment of Mycosis Fungoides: Principles and Recommendations

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Abstract

Background: Mycosis fungoides (T-cell non-Hodgkin’s lymphoma) is a quite rare neoplasia, which follows an indolent course, characterized by presenting epidermotropism in spite that there is a possibility of compromise of structures like lymph nodes and visceral organs. Its incidence increases starting from the fourth decade of life with posterior drop after more or less the age of 80, having preference among black men [2-4].

Following an indolent course, the disease is characterized by presenting epidermotropism, in spite that there is a possibility of compromise of structures like lymph nodes and visceral organs [5,6]. Its etiology still remains uncertain and there is no real proof of the cause-effect relation with the following risk factors: cytomegalovirus infection and HTLV-1 (Human T-lymphotropic virus type I) infection, smoking, alcoholism and pesticide exposure and radiation [7-9]. The main prognostic factor is the disease staging (Table 1), [10] mainly in what refers to extent and type of involvement in the skin and the presence or absence of extracutaneous disease.

This study has the objective of demonstrating the role of radiotherapy in the therapeutic approach of patients with diagnosis of mycosis fungoides.

Recommendations of Treatment in Accordance with Staging

Stage I

The treatment options for stage I patients are topical chemotherapy (nitrogenated mustard or Carmustine), [11] phototherapy, [12] topical corticotherapy, [13] local radiation (X-ray or electrons), [14] and topical retinoids [15].

MF is extremely sensitive to radiation. Low energy x-ray (100 kvp) can be applied in the treatment of isolated lesions although its use may be limited as a consequence of acute and late toxicity. Electron radiotherapy technique is the standard for the approach of these lesions. It presents complete response rate of 40 to 98%. The treatment margin is 2 cm with total dose of 15 to 25 Gy administered in 3 weeks. Generally it is indicated after treatment failure with nitrogenated mustard and topical corticoid [15].

Stage IB/IIA/IIB

For stages IB – IIB patients there are innumerous treatment forms that vary from radiotherapy of the entire skin with electrons (total skin irradiation – TSI), topical chemotherapy (nitrogenated mustard or Carmustine), phototherapy (PUVA or UVB), topical corticoid up to systemic retinoids, interferon and systemic chemotherapy [16,17].

TSI has complete response rate of 80 – 97%. It can be employed as initial therapy in the presence of thick lesions for presenting greater therapeutic effect than topical chemotherapy and phototherapy. Normally it is used in patients with history of rapid disease progression or under the effect of treatment failure after initial topical approach [18-20].

Goujon et al. [21] in a retrospective study with 68 initial stage patients (30 stages T1; 38 stages T2) assessed the efficacy of TSI. The average time of treatment was six weeks and after three months from the end of therapy, 97% of patients had complete response. The global survival rates in five and 10 years were 86% and 71%, respectively. Thirty-nine patients (57.4%) had relapse with average disease free interval of 1.8 years. The disease-free survival was 41% and 31% for five and 10 years respectively, being greater when TSI was employed earlier (P = 0.003). After 21 years of follow-up, only one patient developed cutaneous neoplasm (basocellular carcinoma).

Ysebaert et al. [22] in a retrospective study included 141 stages T1 and T2 patients with MF that were treated with TSI. Of these, 25 patients received topical therapy prior to radiotherapy. Energy of 6 MeV was used with daily dose of 2 Gy (4 days/week) and total dose of...
palmo-plantar hyperkeratosis and diffuse lymph node access. Patients suffering from SS have worse prognosis.

Syndrome (SS). SS is a leukemic variant of the disease, which, generally, is manifested since its start with erythroderma and goes through usually with diffuse alopecia,

Note:

Stage IIIA/IIIB/IV be considered as maintenance therapy.

phototherapy or topical chemotherapy with nitrogenated mustard can
toxicity.

alopecia and secondary squamoproliferative skin neoplasias. Due to
the most common: erythema, peeling skin with or with no ulceration,
in men and epistaxis were already described. In long-term there can
inflammation, and gastrointestinal and hematological toxicity.

After three months from the conclusion of TSI, execution of
phototherapy or topical chemotherapy with nitrogenated mustard can
be considered as maintenance therapy.

Stage IIIA/IIIB/IV

In patients with advanced disease, introduction of more aggressive
therapeutic measures becomes necessary. The treatment options
topical or systemic corticotherapy, topical or systemic chemotherapy,
topical or systemic retinoids, phototherapy, chemotherapy, vorinostat,
denileukin diftitox, bone marrow transplantation, TSI) vary depending
on the characteristics of the presented lesions and on previously
employed treatments [18].

In the palliative perspective where there is extensive or recurrent
cutaneous and extra cutaneous disease after the first course of TSI there
is possibility of repeat irradiation with new TSI plan with substantial
benefits and acceptable toxicity rate.

Funk et al. [23] analyzed the efficacy of palliative TSI in 18 patients
with advanced stage (stages IIb – V) cutaneous T-cell non-Hodgkin’s
lymphoma refractory to previous treatments. The average applied total
dose was 25 Gy with average follow-up of 11 months. Fifty percent of
patients had complete response, 39%, partial response. The progression
free survival in one year was 24% and the global survival in 1 year was
48%. All patients had acute side effects of mild to moderate intensity.

In a study conducted at Yale University (USA), [24] 14 patients
received two courses of TSI while five patients, three courses. The
median dose used in the first and second course was 36 Gy and 18 Gy
respectively. Of the 5 patients who received a total of 3 courses, three
received 12 Gy, one received 16 Gy and one received 30 Gy. After the
first course of TSI, 93% had complete response; after the second, 86%,
after the third, 60%. The median disease free interval after the first
course of therapy for those with complete remission was 20 months and
11.5 months after the second course. All patients presented skin-
related side effects, with an acceptable risk profile.

Table 1: Classification system for mycosis fungoides (TNMB) and Clinical staging system for mycosis fungoides.

| T (skin) | T1 | Limited patch/plaque/papules (< 10 percent of total skin surface) |
| T2 | Generalized patch/plaque/papules (>10 percent of total skin surface) |
| T3 | Tumors (≥ 1 cm diameter) |
| T4 | Generalized erythroderma (confluence of erythema covering ≥ 80 percent body surface area) |

| N (nodes) | N0 | Lymph nodes clinically ≤1.5 cm (biopsy not required) |
| N1 | Lymph nodes enlarged clinically, but not involved by histology (includes "reactive" and "dermatopathic" nodes) |
| N2 | Lymph nodes enlarged clinically and abnormal cells are present on histology but they do not efface the nodal architecture. |
| N3 | Lymph nodes enlarged clinically. On histology, there is partial or complete effacement of the nodal architecture by abnormal cells. |

| M (vissers) | M0 | No visceral involvement |
| M1 | Visceral involvement (histologically confirmed) |

| B (blood) | B0 | No circulating atypical (Sezary) cells (<5 percent of lymphocytes) |
| B1 | Circulating atypical (Sezary) cells (≥5 percent of lymphocytes) |
| B2 | High blood tumor burden: ≥1000/microL Sezary cells with positive clone |

Clinical stage

| Clinical stage | T | N | M | B |
|---------------|---|---|---|---|
| IA | T1 | N0 | M0 | B0 or B1 |
| IB | T2 | N0 | M0 | B0 or B1 |
| IA | T1 or T2 | N1 or N2 | M0 | B0 or B1 |
| IB | T3 | N0 to N2 | M0 | B0 or B1 |
| IIA | T4 | N0 to N2 | M0 | B0 |
| IIIB | T4 | N0 to N2 | M0 | B1 |
| IVA1 | T1 to T4 | N0 to N2 | M0 | B2 |
| IVA2 | T1 to T4 | N3 | M0 | B0 to B2 |
| IVB | T1 to T4 | N0 to N3 | M1 | B0 to B2 |

Note: Sézary cells are atypical mononuclear cells with cerebriform nuclei. Their presence in more than 5% in peripheral circulation is used for diagnostic criterion of Sézary’s Syndrome (SS). SS is a leukemic variant of the disease, which, generally, is manifested since its start with erythroderma and goes through usually with diffuse alopecia, palmo-plantar hyperkeratosis and diffuse lymph node access. Patients suffering from SS have worse prognosis.

Table 1:

30 Gy. Three months after completion of treatment, 87.5% (T1) and
84.8% (T2) had complete response. Treatment failure in one year was
54.4%. From all those that had relapse (31 patients), 18 were submitted
to a second course of TSI (24 Gy in 12 fractions) while the remaining
13, to other combined therapies. Local control in five years was greater
in the group that received the second course of TSI (70% vs. 39%).
For the entire group, the global survival in five, 10 and 15 years was
90%, 65% and 42%, respectively. In univariate analysis, T1 (P = 0.03),
complete response after the first course of TSI (P = 0.04) and age under
60 years old (P < 0.001) were prognostic factors for global survival. In
multivariate analysis, only patients with age under 60 years old had
association with the increase of survival (P = 0.001).

Normally patient submitted to TSI tolerate well the treatment.
Meanwhile, the large majority presents some type of side effect, being
the most common: erythema, peeling skin with or with no ulceration,
itch, alopecia, fall of nails, alteration in transpiration with hypohydrosis,
edema of hands and feet. In spite that it is rare, cases of gynecomastia
in men and epistaxis were already described. In long-term there can
be appearance of telangiectasia, permanent dystrophy of nails, partial
alopecia and secondary squamoproliferative skin neoplasias. Due to
low electron penetration, there is no gastrointestinal and hematological
Toxicty.

For the entire group, the global survival in five, 10 and 15 years was
90%, 65% and 42%, respectively. Of the 5 patients who received a total of 3 courses, three
received 12 Gy, one received 16 Gy and one received 30 Gy. After the
first course of TSI, 93% had complete response; after the second, 86%,
after the third, 60%. The median disease free interval after the first
course of therapy for those with complete remission was 20 months and
11.5 months after the second course. All patients presented skin-
related side effects, with an acceptable risk profile.
Becker et al. [25] in a retrospective analysis studied 15 patients that received second course of TSI. The average dose employed in the first treatment was 32.6 Gy; in the second, 23.4 Gy; the complete and partial response rates after the second course were 40% and 60%, respectively. The observed late toxicity was restricted to drying of skin, telangelactasia, alteration of cutaneous pigmentation and alopecia.

The criteria used for indication of repeat irradiation include the observed clinical response and the disease free interval after the first course of TSI, the area of cutaneous affection and the prior failure of other therapeutic modes. Patients with nodal and/or visceral involvement are often benefited with course of palliative TSI with total dose of 20 to 30 Gy (2 to 3 Gy/fraction).

Technical Aspects of Radiotherapy

There are diverse irradiation techniques in order to obtain an adequate dose distribution in the entire area to be treated. It is important to emphasize that in all of them dosimetry calculations are complex. Most services employ focus-skin distance (FSD) of approximately three to four meters. Habitually, the maximum distance that is achieved between the beam focus and the treatment table is lesser than two meters. Thus, it becomes necessary to use beams directed towards the lateral walls of the room in order to obtain an irradiation field of the order of 120 x 120 cm² on the treatment plane which allows coverage of large body surface area simultaneously. The extensive air layer to be crossed must be considered, since the beam energy spectrum is broadened, which can alter its penetration. Moreover, not all radiotherapy rooms were built with necessary minimum dimensions, since it is desirable for the patient to be at a distance of at least 1 meter from the wall to avoid possible backscatter contributions of the beam. It is important to stress that in these techniques, the patient stays standing up for a long period of time, being this, often, a limiting factor to its employment. One of the most classically used techniques is the “ballerina’s” technique (modified Stanford technique) [19] where six incidences of beams are used in the upper part and another six in the lower part of the body (separated by the bellybutton) making a total of twelve incidences. The patient is positioned on a rotating base that suffers rotations at every 60º.

As alternative, technique that uses lower FSDs (100 to 140 cm) so as to suppress the difficulties listed above. That is, in spite that, fields of area of the order of 30 x 30 cm² are used and, consequently, there is an increase of number of necessary incidences to cover the entire body surface, the treatment is performed with the patient lying down during the entire application not having any restrictions with respect to the dimensions of the room. Dose distribution in this technique is homogeneous as demonstrated by Martins [26] in a master's degree dissertation of the Instituto de Física da Universidade de São Paulo.

The total prescription dose in the first course of treatment varies from 30 – 36 Gy with possibility of dose complement (boost) at medical criterion in the areas of subdosing and/or with tumor lesions. The patient is treated four days a week (two applications in the anterior region and two applications in the posterior region) with dose/fraction day of 200 cGy uninterrupted. The duration of the treatment is from 10 to 11 weeks (36 sessions) in the first phase; if there is need of boost, this is executed in five to 10 more sessions on a daily basis (five times a week). The average period of every session is 60 minutes. In case there is need of repeat irradiation, the first is done with total dose of 20 Gy and the second, with 12 Gy using the same technique described above.

Conclusions

Radiotherapy is indicated to patients suffering from MF in all stages especially when the disease affects more than 50% of the body surface. Starting from stage IB, TSI is employed with dose of 30 to 36 Gy with boost at medical criterion. Consider phototherapy or topical chemotherapy with nitrogenated mustard as maintenance therapy after three months of TSI. Repeat irradiation is viable, however with treatment doses lower than those employed in the first therapeutic cycle.

Comprehensive Summary

- Indications for radiotherapy: Patients at all stages particularly when the disease affects more than 50% of body surface.
- Technical issue: Fields with direct energy of 6 MeV (electrons).
- Area of treatment: From stage IB, the entire body surface.
- Dose: 200 cGy on each side of the body 1000 cGy totaling in 10 days of treatment. Total dose of 3000 to 3600 cGy. Boost the physician’s criteria.
- Consider phototherapy or topical chemotherapy with nitrogen mustard after 3 months of TSI to maintenance therapy.

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