Radiation therapy in mycosis fungoides

Concetta Schiavone, Stefano Vagge, Filippo Grillo Ruggieri

Radiotherapy Unit, Galliera Hospital, Genoa, Italy

Abstract

Radiation therapy (RT) is administered with varying intentions, sometimes even several times in the same or in different body areas, to over 50% of patients with neoplastic conditions. Numerous techniques are available to patients in the clinical evolution of mycosis fungoides (MF), and there are several indications for radiation therapy (RT). RT as a skin-directed therapy is very widely used in these patients, either alone or in conjunction with other therapies. The application of RT, a tried-and-true therapy that improves MF patients' quality of life and treatment, can be encouraged by a multidisciplinary approach and an understanding of current methods and action mechanisms.

Introduction

Radiation therapy (RT) directed to a tumoral mass (local radiation therapy – LRT) began shortly after the discovery of X-rays in 1895. Different particles and energy and an increasing array of techniques and technologies to choose from are now in our arsenal. The fundamental mechanisms by which RT kills tumor cells are quite independent of the technique used for radiation delivery.[1]

Correspondence: Concetta Schiavone, Radiotherapy Unit, Ospedali Galliera, via Volta 6, 16128 Genoa, Italy.
Tel.: +39.0105634833.
E-mail: concetta.schiavone@galliera.it

Key words: radiation therapy; mycosis fungoides; TSEB; TSI.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Contributions: the authors contributed equally.

Conference presentation: the corresponding author presented the article's contents at the 59th ADOI Annual Meeting 2022.

Received: 11 November 2023.
Accepted: 20 November 2023.

Licensee PAGEPress, Italy
Dermatology Reports 2024; 16;(s2):9885
doi:10.4081/dr.2024.9885

In mycosis fungoides (MF), specific treatment modalities related to characteristic clinical presentation patterns are used.

In the late 1960s, many combined large fields of electron beams were used to treat whole skin surface [total skin electron beam (TSEB) RT], looking for curative intent at that time. Hoppe described the so-called Stanford Technique reporting a complete response (CR) rate of 18% with doses of TSEB less than 10 Gy, 55% with 10-20 Gy, 66% with 20-25 Gy, 75% with 25-30 Gy, 94% with 30-36 Gy. The overall survival rate was 46% at 10 years, with the major prognostic factor being the initial extent of skin involvement.[2] However, now that we know MF-cutaneous T-cell lymphoma (MF/CTCL) is chronic, TSEB must be placed in the context of the availability of multiple therapies.

In the '60s and '70s, combining specific chemotherapeutic agents with radiation was found to have synergistic anti-cancer effects in terms of results and even toxicities.

The use of chemotherapy, although relegated to the terminal stages of the disease, is difficult to reconcile with the need to preserve the host immune system for as long as possible. Molecular biology has facilitated the development of specific drugs for molecular targets involved in neoplastic processes, giving rise to targeted therapy.[3]

In 2001, the cover of The Times was earned by imatinib, an oral target therapy, for clinical results in chronic myeloid leukemia. We now have multiple agents in our armamentarium, such as brentuximab and mogamulizumab, which are more targeted with fewer immunosuppression-related and infectious adverse events overall. The reciprocity between RT and immunotherapy takes up a new task of RT in the actual therapeutic context, for the last years almost limited to a palliative intent.

These monoclonal antibodies, together with other active systemic therapies approved (bexarotene, denileukin diftitox, vorinostat, romidepsin), fill the gap between the skin-directed treatments and the traditional cytotoxic chemotherapeutic agents that were previously the only option for advanced disease.[4]

Radiation: mechanism of action and interactions with biological macromolecules

RT acts principally through DNA damage. A direct effect of DNA strand breaks and an indirect effect mediated by reactive oxygen species that oxidize proteins and lipids. Different types of DNA damage, including single-strand breaks and double-strand breaks, and different spatial patterns of these areas of DNA damage are described based on the ionization track of the incident radiation. The processes of DNA damage repair are mediated by several pathways that work in unison to repair individual DNA damages needed for cell cycle progression.

DNA damage repair pathway factors are known to modulate immune signaling either by sensing DNA in the cytoplasm, promoting micronuclei accumulation or by releasing fragmented self-DNA to the cytoplasm.[5,6] These self-DNA fragments and micronuclei appear as cytosolic DNA both in tumor cells and in immune cells that internalize tumor cell DNA fragments from the tumor microenvironment (TME).[7,8] For example, it has been shown that

nuclear-derived self-DNA accumulates in the cytoplasm and that triggers STING-mediated innate immune signaling in response to high-LET radiation.[9]

Recent evidence suggests that DNA damage repair pathway factors, previously thought to function only in DNA damage sensing and repair, may also control signaling pathways in the innate immune system.[5] These factors work directly or indirectly to repress cytosolic DNA sensing pathway-mediated immune signaling by masking cytosolic DNA. This negative regulation of the immune system helps to maintain the proper immune microenvironment in normal cells to prevent unnecessary or defective activation. Therefore, the immune system can modulate either tumor suppression or progression, and RT has the potential to regulate immune responses to yield antitumorigenic effects by triggering antitumor immunity.[1]

Ionizing radiation can induce immunologic changes within the immunosuppressive TME, including facilitated tumor antigen release, increased effector T-cell infiltration, and upregulated MHC-1 molecule on tumor cells.

The underlying mechanisms of immunomodulatory effects of RT are probably only partially known. In 1953, Mole described for the first-time tumor regression outside of the irradiated region.[10] The so-called abscopal effect alludes to a sporadic regression of non-irradiated metastatic lesions at sites away from the primary site of irradiation. It has been observed in many cancer types, including lymphoma. Both pre-clinical and clinical studies have supported that the regression of tumors outside of the irradiation field is mediated by the effects of radiation on the immune system. With the introduction of immunotherapy, the understanding of immune activation by radiation treatment has further strengthened the role of radiation therapy in systemic disease, as well as demonstrated how the two can work synergistically for tumor burden control. Combinations of radiotherapy appear to have an immunostimulatory effect when radiation fields are optimized to induce immunogenic cell death in tumors.[11]

Two well-known immune-mediated effects are involved in the response to RT: the "bystander effect" and the "abscopal effect." The first is characterized by molecular signals transmitted from irradiated cells through direct contact or the release of diffusible factors such as cytokines and chemokines. Cells that undergo a radiation-induced bystander effect demonstrate reduced clonogenic survival, probably due to the enhanced T-cell trafficking to primary tumors through local vascular endothelial inflammation, where macrophages are well-known players in bystander signaling.[12] The abscopal effect is a response to areas of tumor involvement far from the radiation treatment site. The radiation therapy combined with immunotherapy agents may "unmask" the tumor, making it visible to both the innate and adaptive immune systems. This combination has synergistic effects stemming from both local and systemic tumor control.[13-15]

Doses and volumes of radiation therapy: practical considerations

RT target in MF is the skin involved, usually recognized as superficial lesions, but not ever simple to treat. Critical areas and presentation are numerous, also close to organs to be protected because at risk of toxicity. With a superficial target, the choice falls on electron beams targeted by linear accelerators. Electrons cover some centimeters in depth, depending on the treatment energy, permitting the treatment of the affected skin while limiting radiation to internal tissues and organs. While MV photons exhibit a steep build-up at shallow depths of <2 cm, making treatment delivery at these depths complicated, electron beams with definite range are advantageous for treating shallow tumors. Thus, high energy electrons (4-20 MeV) permit to treat superficial lesions below 6 cm depth. A bolus can increase the dose to the surface while reducing the dose distally. In some cases, it is necessary to utilize photons of orthovoltage or megavoltage, especially for lesions involving curved surfaces and/or of great thickness.

Extreme radiosensitivity of tumoral cells in MF permits low-dose treatments that can achieve a high level of response rate.[16] Radiotherapy remains an important treatment option in the management of these patients either for those with limited stage or those with advanced stage disease.[17]

Local radiation therapy

The RT technique, fractionation, and total dose mainly depend on irradiation volume, presentation site and extent, nearby critical organs, skin condition, intent, and if any prior RT. LRT is given as monotherapy with curative intent for initially localized disease at a 24-30 Gy dose with conventional fractionation (1.8-2 Gy per day for five days a week). Historically, the total prescribed dose has been divided into several small fractions to preserve substantial amounts of normal tissue within the treatment field. This approach is advisable for radiosensitive tumors as lymphomas extended to large treatment areas. If the aim of radiotherapy is palliative, LRT can be delivered to the tumor in a few fractions and a low total dose to reduce the patient's inconvenience and optimize resources.

Of note, there is an emerging, only experimental, technique called ultra-high dose rate (FLASH)-RT that involves the ultra-fast delivery of a large single dose of radiation (10-20 Gy) at a mean dose rate above 40 Gy per second.[18] Linear accelerators used in radiation therapy treatments usually provide the capability of irradiating with different dose rates, and the relative biological effectiveness of radiation therapy varies with this physical parameter. Only specific experimental linear accelerators can deliver a dose rate above 40 Gy per second, which is several orders of magnitude greater than what is currently used in routine clinical practice. Several recent studies have demonstrated that FLASH therapy induces fewer toxicities in normal tissue than conventional RT.[19-21] The first human receiving FLASH-RT was a 75-year-old patient presented with a CD30+ T-cell cutaneous lymphoma disseminated throughout the whole skin surface.[20] Localized skin RT was previously used over 110 times for various ulcerative or painful cutaneous lesions progressing despite systemic treatments. The patient was treated on the limb with a 6 MeV ultra-high dose-rate (UHDR) electron beam, and the tumor response was rapid, complete, and durable with a short follow-up of 5 months. At three weeks, limited and transient toxicity was observed. Clinical examination was consistent with the optical coherence tomography showing no decrease in the thickness of the epidermis and no disruption at the basal membrane with a limited increase of the vascularization. Superficial skin lesions are potential candidates for UHDR high-energy electron RT, given a clinical rationale and expected clinical benefit that could justify using FLASH-RT.[22]

Total skin irradiation

Multiple approaches for total skin irradiation (TSI) exist in treatment techniques. In TSEB radiotherapy, almost the entire skin surface is treated with electron beams delivered by a linear accelerator. Certain radiation sensible areas, such as conjunctiva, or when necessary, such as previously high-dose irradiated areas and lesions with granulation tissue, are protected from the radiation

with dedicated shields. There are two principal treatment methodologies to deliver planned doses of radiation in TSEB RT, depending on the treatment cancer center experience and equipment.

At our institution, the TSEB RT was introduced into clinical practice over thirty years ago by Grillo Ruggieri and implemented by the medical physics team.[23,24] The technique followed the original techniques seen in use at Stanford University, as also described by Page.[25] In the Stanford technique, the patient will be positioned in a series of poses, while in the platform technique, he will stand still on a spinning platform. In both techniques, the patient had to maintain an upright position.

TSEB treatment cycles are generally constituted by 12 daily fractions. Two or more weeks of intervals between consecutive cycles are necessary. At the end of TSEB cycles, thicker tumoral lesions, suboptimal response areas, and some affected skin areas in the shade of RT fields, like the soles of the feet, the palm of the hands, the intergluteal sulcus, the perineum, the skin folds in upright standing position, and the inframammary folds may be treated as separate volumes. TSI can be performed with photons using helical tomotherapy, a linear accelerator with a ring shaped gantry suitable for treating highly conformal radiation doses of long and complex targets, but the dose in depth is not negligible using photons, with a high percentage of transient hematopoietic damage. TSEB is a highly effective therapy for CTCL; however, the duration of the response may not be long, especially for patients with advanced-stage disease. Maintenance therapy after TSEB therapy has been proposed as a promising approach for patients with CTCL.

In the '70s, Hoppe reported that employing adjuvant topical treatment as mechlorethamine after electron beam therapy in the treatment of patients with MF has demonstrated better relapse-free survivals.[26] Many agents, such as ultraviolet therapy, have been studied since then. Maintenance therapy after TSEB has been assessed in a consistent number of studies; however, these studies were largely from the late 1990s to early 2000s, had small patient numbers, and reported mixed outcomes. In 2020, Kudelka reported that among the patients with CTCL who had received TSEB therapy,[27] ultraviolet-based maintenance therapy improved PFS for all patients and improved both PFS and OS in a subset of patients. On multivariate analysis for PFS, administration of maintenance therapy (HR, 0.55; 95% CI, 0.34-0.90; P=.018) and a CR to TSEB (HR, 0.32; 95% CI, 0.19-0.54; P<.001) were significantly associated with increased PFS. Very encouraging data suggest following TSEB RT with systemic therapies to maintain response and concomitant use of bexarotene. Memorial Sloan Kettering Cancer Center is conducting a phase Ib trial combining bexarotene with ultra-low dose TSEB radiotherapy to treat diffuse CTCL.[28] Despite the limited safety data for the use of TSEB RT in different combinations with systemic retinoids, histone deacetylase inhibitors (such as romidepsin or vorinostat), or mogamulizumab, these approaches appear very promising. An early low-dose TSEB is increasingly the therapy's linchpin in the case of extensive skin involvement. The intent of the treatment of MF may be to improve and maintain disease control and quality of life. TSEB RT keeps its promise of reducing and controlling symptoms. The goal is now to reduce the dose of radiotherapy useful for obtaining a remission of the disease while conserving therapeutic space for subsequent treatments that should be necessary.

TSEB is a particularly safe and potentially effective treatment strategy in CTCL patients treated with allogeneic hematopoietic cell transplant, both to induce remission prior to allo-HSCT and to rescue early post-transplant relapse occurring before immunosuppression withdrawal. TSEB is used as a bridge to transplant strategy in these last cases.[29]

TSEB toxicities (alopecia, nail dystrophy, *etc.*) have a few impacts on the quality of life of the patients when compared to the positive effects, including the remission of itching. The use of low doses and the superficial distribution of doses are encouraging from a hematological point of view.

Conclusions

The availability of multiple techniques and the personalization of treatment make RT a versatile weapon in the therapeutic strategy of patients suffering from MF with its complex clinical presentations. Due to the extreme radiosensitivity of most histological variants and subtypes, re-treatment in the same areas and with different clinical intent is also possible. Therefore, therapeutic interventions must be guided by a multidisciplinary approach with due attention to the patient's quality of life.

All radiotherapy centers in Italy, mostly equipped with linear accelerators, have all the technology for local treatments, there are a few centers where the patient may be a candidate for TSEB RT, considered a special radiation technique.

References

1. Kumari S, Mukherjee S, Sinha D, et al. Immunomodulatory effects of radiotherapy. Int J Mol Sci 2020; 21:8151.
2. Hoppe RT, Cox RS, Fuks Z, et al. Electron-beam therapy for mycosis fungoides: the Stanford University experience. Cancer Treat Rep 1979;63:691-700.
3. Lin SH, Ye R, Wang Y. Preclinical Strategies for Testing of Targeted Radiosensitizers. In: Willers, H., Eke, I. (eds.) Molecular targeted radiosensitizers. Cancer Drug Discovery and Development. Humana, Cham; 2020.
4. Kim E. Mogamulizumab for CTCL: targeted therapy and immunotherapy crossing paths. Dermatol World Insights Inquiries 2020;2.
5. Mukherjee S, Abdisalaam S, Bhattacharya S, et al. Mechanistic link between DNA damage sensing, repairing and signaling factors and immune signaling. Adv Protein Chem Struct Biol 2019;115:297-324.
6. Abdisalaam S, Bhattacharya S, Mukherjee S, et al. Dysfunctional telomeres trigger cellular senescence mediated by cyclic GMP-AMP synthase. J Biol Chem 2020;295:11144-60.
7. Deng L, Liang H, Xu M, et al. STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. Immunity 2014;41:843-52.
8. Vanpouille-Box C, Alard A, Aryankalayil MJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 2017;8:15618.
9. Bhattacharya S, Srinivasan K, Abdisalaam S, Su, et al. RAD51 interconnects between DNA replication, DNA repair and immunity. Nucleic Acids Res 2017;45:4590-605.
10. Mole RH. Whole body irradiation-radiobiology or medicine? Br J Radiol 1953;26:234-41.
11. Nabrinsky W, Macklis J, Bitran J. A review of the abscopal effect in the era of immunotherapy. Cureus 2022;14:e29620.
12. Daguenet E, Louati S, Wozny AS, et al. Radiation-induced bystander and abscopal effects: important lessons from preclinical models. Br J Cancer 2020;123:339-48.
13. Son CH, Fleming GF, Moroney JW. Potential role of radiation therapy in augmenting the activity of immunotherapy for gynecologic cancers. Cancer Manag Res 217;9:553-63.

14. Frey B, Rückert M, Deloch L, et al. Immunomodulation by ionizing radiation-impact for design of radioimmunotherapies and for treatment of inflammatory diseases. Immunol Rev 2017;280:231-48.
15. Jiang W, Chan CK, Weissman IL, et al. Immune priming of the tumor microenvironment by radiation. Trends Cancer 2016;2:638-45.
16. Trowell OA. The sensitivity of lymphocytes to ionizing radiation. J Pathol Bacteriol 1952;64:687-704.
17. Mazzeo E, Rubino L, Buglione M, et al. The current management of mycosis fungoides and Sézary syndrome and the role of radiotherapy: Principles and indications. Rep Pract Oncol Radiother 2013;19:77-91.
18. Montay-Gruel P, Bouchet A, Jaccard M, et al. X-rays can trigger the FLASH effect: ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice. Radiother Oncol 2018;129:582-8.
19. Bourhis J, Montay-Gruel P, Jorge PG, et al. Clinical translation of FLASH radiotherapy: Why and how? Radiother Oncol 2019;139:11-7.
20. Bourhis J, Sozzi WJ, Jorge PG, et al. Treatment of a first patient with FLASH-radiotherapy. Radiother Oncol 2019;139:18-22.
21. Favaudon V, Caplier L, Monceau V, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med 2014;6.
22. Rahman M, Trigilio A, Franciosini G, et al. FLASH radiotherapy treatment planning and models for electron beams. Radiother Oncol 2022;175:210-21.
23. Scielzo G, Grillo Ruggieri F, Brunelli B, et al Physico-technical aspect of total skin irradiation with high intensity dose electrons. Radiol Med 1990;80:147-50.
24. Schiapparelli P, Zefiro D, Massone F, Taccini G. Total skin electron therapy (TSET): a reimplementation using radiochromic films and IAEA TSR-398 code of practice. Med Phys 2010;37.
25. Page V, Gardner A, Karzmark CJ. Patient dosimetry in the electron treatment of large superficial lesions. Radiology 1970;94:635-41.
26. Price NM, Hoppe RT, Constantine VS, et al. The treatment of mycosis fungoides: adjuvant topical mechlorethamine after electron beam therapy. Cancer 1977;40:2851-3.
27. Kudelka MR, Switchenko JM, Lechowicz MJ, et al. Maintenance therapy for cutaneous T-cell lymphoma after total skin electron irradiation: evidence for improved overall survival with ultraviolet therapy. Clin Lymphoma Myeloma Leuk 2020;20:757-67.
28. Memorial Sloan Kettering Cancer Center. Protocol: 21-501. Available from: https://www.mskcc.org/cancer-care/clinical-trials/21-501
29. Valli VB, Grillo Ruggieri F, Saporiti G, et al. Total skin electron beam therapy in patients with advanced cutaneous T cell lymphoma undergoing allogeneic stem cell transplantation: a single centre experience. Blood 2019;134:2042.