Combined total skin radiotherapy and immune checkpoint inhibitors: A promising potential treatment for mycosis fungoides and Sezary syndrome

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Summary
Radiotherapy, particularly total skin electron beam therapy (TSEB), is one of the main pillars in the strategy for treatment of cutaneous T-cell lymphoma (CTCL). Low-dose TSEB has gained considerable attention since it has a minimal toxicity profile. Low-dose TSEB has been shown to yield an overall response rate up to 95%, although the response duration is usually short. Few studies have been published on treatment outcomes after combined treatment of CTCL with TSEB and systemic therapy. Remission rates of patients who received immune checkpoint inhibitors alone ranged from 15–38% with a two-year progression-free survival of 69%. Given that TSEB results in rapid reduction of the disease burden in almost all patients, we hypothesized that TSEB followed by immune checkpoint inhibitors might be a reasonable treatment with a sustained effect for treatment-experienced patients with mycosis fungoides and Sezary syndrome.

Introduction
Mycosis fungoides (MF) and Sezary syndrome (SS) account for approximately two-thirds of cutaneous T-cell lymphoma (CTCL) cases. Monoclonal proliferation of predominantly CD4+ T-lymphocytes is characteristic of both diseases, and SS is an erythrodermic form of CTCL with blood involvement [1]. The choice of treatment strategy is based on disease stage and the latest evidence-based guidelines [2–4]. Skin-directed treatments, including radiotherapy and systemic therapy, are often used with acceptable results [5–7]. Systemic chemotherapy is used primarily for palliation [8, 9]. Immunomodulatory agents and monoclonal antibodies have gained attention recently as a means of prolonging remission in treatment-experienced patients [5, 8, 10–13]. Intra-tumoral in situ vaccination using a Toll-like receptor agonist combined with ultralow-dose (2 × 2 Gy) local radiotherapy is a practical strategy with an objective remission rate (ORR) of 35% and an acceptable toxicity profile [14]. Allogeneic hematopoietic stem cell transplantation may provide long-lasting disease improvement in patients with advanced stages of disease, but the risk of severe adverse effects is relatively high [15].

With cutaneous lymphoma, immune checkpoint inhibitors (such as PD-1 blockade) have been used to treat disease effectively while exhibiting a favorable safety profile. Some recent immunotherapy studies are summarized in Table 1.

Immune checkpoint inhibitors (ICI)
During various phases of carcinogenesis, expression of the immunosuppressive molecules programmed death-ligand 1 and 2 (PD-L1 and PD-L2) allows tumor cells to evade recognition by the immune system [16, 17]. Receptors for these molecules (such as PD-1), expressed by T-cells, suppress antitumor immunity and inhibit T-cell activation [18]. PD-L1 also protects tumor cells from lysis and can induce tumor-specific T-cell apoptosis [17–20]. PD-L1 is expressed...
Table 1: Recent trials of immunotherapy for mycosis fungoides (MF)/Sézary syndrome (SS).

| Study [ref.]         | Patients, n | Clinical stage | Drug       | Target      | ORR, % | CR, % | PFS            | Serious toxicities                           | Frequent toxicities                        |
|----------------------|-------------|----------------|------------|-------------|--------|-------|----------------|---------------------------------------------|--------------------------------------------|
| de Masson et al. 2014 [12] | MF n = 16  SS n = 23 | IIB–IV | Alemtuzumab | CD52         | 51 (MF: 25, SS: 70) | 18     |     | 3.4 mos.       | Grade 3–4 AE: 57 %, Grade 5: 5 %          | Profound lymphopenia, Infections          |
| Lesokhin et al. 2016 [22]     | MF n = 13 NA     | NA     | Nivolumab   | PD-1 receptors | 15     | 0     | 2.5 mos.       | Grade 3–4 AE: 21 %, Grade 5: 1 %           | Fatigue, pneumonitis, rash, anemia, leukopenia |
| Prince et al. 2017 [8]         | CD30+ MF n = 48 IA–IV | Brentuximab | CD30       | 65         | 10     |       | 16 mos.        | Grade 3: 29 %, No Grade 4 AE              | Peripheral neuropathy and nausea         |
| Kim et al. 2018 [10]           | MF n = 105 SS n = 81 IB–IV | Mogamulizumab | C-C chemokine receptor 4 | 28 (MF: 21, SS: 37) | 3      |       | 14 mos. (MF: 13 mos., SS: 17 mos.) | Grade 3–4 AE: 41 %, Grade 5: 2 %         | Thrombocytopenia, infusion related reactions |
| Sawas et al. 2019 [11]         | MF n = 7 NA     | NA     | AFM13       | CD30/CD16A   | 33     | 0     | NA            | Grade 3 AE: 14 %                           | Infusion related reactions, skin infection |
| Bagot et al. 2019 [13]         | MF n = 8 SS n = 35 IB–IV | IPH4102p | KIR3DL2     | 36 (SS: 43 %) | 5      |       | 12 mos. (SS: 17 mos.) | Grade 3–4 AE: 9 %, Grade 5: 2 %           | Peripheral edema, fatigue                |
| Khodadoust et al. 2019 [21]    | MF n = 9 SS n = 15 IB–IV | Pembrolizumab | PD-1/PD-L1 axis | 38         | 4      |       | 1-year PFS: 65 % (median not reached) | Grade 3–4 AE: 24 %                        | Immune-mediated skin flare reaction        |

*Abbr.: CR, complete response; PFS, progression-free survival; mos., months; ORR, objective response rate; EFS, event-free survival; NA, not available.*
by CTCL cells and is more frequently expressed in patients with advanced tumor stages and large-cell transformation than in patients with early stages of disease (100 % vs. 80 %) [20]. Therefore, PD-L1 blockade is expected to enhance the production of tumor-specific T-cells, particularly in patients with advanced disease. In contrast, PD-1 is more commonly expressed in the early stages of MF than in advanced stages (70 % vs. 50 %), which implies that PD-1 inhibitors may have more therapeutic potential at early stages [20].

Several PD-1 axis agents are currently used to treat adults with solid and hematologic tumors (e.g. Hodgkin or non-Hodgkin lymphoma) [16]. In hematologic malignancies, PD-1 blockade is effective and has a favorable safety profile. With respect to relapsed or refractory MF/SS, pembrolizumab was associated with an ORR of 38 % (complete response: 4 %) and a two-year progression-free survival of 69 % [21]. The ORR associated with the immune checkpoint inhibitor nivolumab was 15 % [22]. Specific immune-mediated adverse effects include skin flare (more common in SS: 40 %), and toxicity of grade 3 or higher (up to 24 % of patients) [21, 22]. Currently, a phase II trial of anti-PD-L1 atezolizumab is ongoing in patients with MF/SS who have previously completed another treatment (ClinicalTrials.gov NCT03357224).

Radiotherapy

Conventional radiotherapy doses (≥ 30 Gy) have been used to treat CTCL for decades; however, the toxicity rates have been very high [23]. Thus, lower doses (10–12 Gy) are gaining more attention as radiation oncologists work to reduce the risk of acute and late adverse effects [24–26].

Local radiotherapy

Radiotherapy is very effective for MF patients, yielding ORRs in the range of 90–100 % [5]. Local radiotherapy alone may be administered to patients presenting with T1 MF lesions (patch/plaque < 10 % total skin surface), clustered T2 lesions (generalized patch/plaque > 10 % of total skin surface), or T3 lesions (tumor ≥ 1 cm diameter). Total skin electron beam therapy (TSEB) is indicated for patients with diffuse T2 lesions or T4 skin lesions (erythema ≥ 80 % body surface area).

TSEB therapy

TSEB is a feasible option for MF patients with T2–T4 lesions and SS. Recently, low-dose TSEB schedules (10–12 Gy) have demonstrated acceptable disease control with markedly lower toxicity than conventional-dose TSEB [5, 27]. Following 12 Gy TSEB, ORRs up to 95 % (complete response rate 33 %) have been reached (Table 2). However, response
durations are usually short (≤ 12 months) [4, 24–26]. Although TSEB with maintenance therapy may be associated with improved survival [28, 29, 36], prospective studies of post-TSEB maintenance therapy for MF/SS are lacking. Meanwhile, TSEB seems to improve peripheral blood burden in patients with SS [30].

Combination therapy

Conceptually, it is reasonable to consider combination therapy for various stages of MF and SS. Although radiotherapy is a very effective treatment for local forms of disease, the finding that most patients who are treated locally experience a relapse outside the radiation field argues in favor of systemic therapy to prevent relapse or progression [5–7]. Moreover, abscopal responses in non-irradiated lesions have been observed in 36–50 % of patients who received ICI after local radiotherapy [14, 16], and this combination therapy has demonstrated both safety and tolerance in small patient cohorts [16]. In advanced stages of disease, adding induction TSEB to ICI seems to enhance the antitumor immune response, which is critical to reducing the risk of disease progression [5, 16], 31]. Interestingly, radiotherapy prior to PD-L1 inhibitor treatment improves progression-free survival and overall survival in patients with solid tumors [32, 33].

Given that TSEB results in rapid reduction of disease burden in almost all cases of MF and SS [5], we hypothesize that TSEB followed by sequential (adjuvant or maintenance) PD-1 or PDL-1 blockade may provide lasting benefits in treatment-experienced patients. Radiotherapy may prime and modulate the tumor immune response, and subsequent maintenance ICI may sustain the immune response via development of immunologic memory, thereby generating a durable remission [16]. Following radiotherapy, expression of PD-L1 and MHC class I is upregulated on tumor cells [34, 35]. A combination of radiotherapy and PD-L1 pathway inhibition may therefore induce long-term immune-mediated antitumor activity [34]. In addition, high PD-L1 expression represents a potential biomarker for response to PD-1-based ICI [16]. Three clinical trials (Table 3) are currently underway to evaluate the safety and efficacy of combined modality for the treatment of MF/SS.

Conclusions

TSEB is a very effective treatment modality that can reduce MF and SS disease burden rapidly, and this reduction is followed by short-term remission. TSEB followed by sequential checkpoint inhibitors may be a reasonable treatment strategy for providing long-term effects in patients with MF and SS. Two prospective TSEB plus ICI combination studies are ongoing.

Conflict of interest
None.

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