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SHORT COMMUNICATION

Denileukin Diftitox plus Total Skin Electron Beam Radiation in Patients with Treatment-refractory Cutaneous T-cell Lymphoma (Mycosis Fungoides): Report of Four Cases

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Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL) (1). Most patients initially respond well to standard therapy, but advanced MF is often treatment refractory. Thus, a combination of the available treatment options is an important strategy. Total skin electron beam radiation (TSEB) is effective in MF, with a complete remission rate of up to 90% in the early stages. However, in patients with more advanced stages, remission rates are considerably lower (2, 3). Denileukin diftitox (DD) (Ontak®) is a recombinant fusion protein of the receptor-binding domain of interleukin (IL)-2 and the enzymatic and translocation domains of diphtheria toxin (4). It targets the alpha-subunit of the IL-2-receptor (CD25). There are no reports on this combination therapy in MF.

CASE REPORTS

Four patients with treatment-refractory MF were treated with 2 cycles of DD (9 μg/kg/day for 5 days) combined with simplified TSEB (sequential half-body radiation, 9×2 Gy, cumulative dose 18 Gy). *In vivo* dosimetry was performed, but no supplemental patch irradiation fields for underdosed areas were used. One patient received boosts to most prominent tumours. Patients had disease durations of 2–9 years and multiple comorbidities (Table I).

Case 1. As reported (5), patient 1 had tumour-stage MF with CD30 transformation and lymphadenopathy. During the first course he developed intermittent fever and arterial hypotension. Otherwise, the treatment was well tolerated. After 5 weeks clinical response was seen in the upper body. During the second cycle of DD he developed intermittent fever and arterial hypotension and, 4 days later, self-limiting maculopapular exanthema. Lower-body radiation was started 1 week after the last DD infusion. Then tumours on both legs had improved already. Complete remission lasted for 7 months until his general status deteriorated and he died aged 89 years. At the time of death, the patient's skin remained free of signs of MF.

Case 2. Patient 2 had erythrodermic MF including lymphadenopathy. The first cycle of DD was well tolerated and followed by radiation of the lower body and both hands. Due to erosive dermatitis only 16 Gy were applied to these areas. After 4 weeks she received a second DD cycle without further irradiation. She had arterial hypotension despite intravenous (i.v.) fluids. The patient's skin condition and pruritus improved substantially, but she still had infiltrated plaques on the trunk; 2 weeks after the second DD cycle pruritus increased again. A third cycle of DD was given, combined with upper-body radiation. DD infusions were well tolerated. Due to radiation dermatitis, only 7 fractions (14 Gy) were given. The patient showed limited response, with regression of some plaques and slightly improved pruritus.

Case 3. Patient 3 had plaques involving 70% of the body surface area, and severe pruritus (Fig. 1a). Initially, treatment was well tolerated, but after 5 days the patient was readmitted due to severe dermatitis and lobar pneumonia. After antibiotic and topical treatment she recovered completely. Before application of the second cycle of DD, her skin had improved, with only hyperpigmented residues. DD was stopped after 3 days due to diarrhoea and fever; after successful antibiotic treatment DD was continued. TSEB of the lower body was postponed by 2 weeks, and then administered with no adverse effects. Complete remission was achieved, with some hyperpigmentation left on the trunk (Fig. 1b). After 7 months the patient died of cholangiosepsis without recurrence of MF.

Case 4. Patient 4 had erythrodermic MF with severe pruritus, tumours on the eyebrows with CD30 transformation, and 30%

Table I. *Patient's characteristics, prior treatment, response and duration of response after denileukin diftitox plus total skin electron beam radiation*

Pat. no.	Sex/age, years	Disease duration, months	Stage/TNM	Prior treatment	Medical history/internal diseases	Response (duration)
1	M/89	20	IIB T3NxM0B0	Local XRT, MTX, Bex, lip doxo, HDACI, anti-CD4-ab	Atrial fibrillation, coronary artery disease, art HTN, DM2, PVD, CKD	Complete remission (7 months†)
2	F/82	31	IVA T4N2bM0B0	MTX, oPUVA, Bex, HDACI, anti-CD4-ab	art HTN, DM2, CKD, s/p spondylodiscitis/ psoas-abscess	No major response
3	F/78	56	IIA T2N1M0B0	MTX, Bex, oPUVA+Bex, Local XRT, lip doxo, HDACI, anti-CD52-ab	B-CLL, peripheral neuropathy, dyslipidaemia, s/p endometrial cancer	Complete remission (7 months†)
4	M/72	104	IVA T4N0M0B2	oPUVA+ INF-α-2, Bex, HDACI, lip doxo	art HTN, PVD, s/p aortic aneurysm, s/p apoplexia, dyslipidaemia	Partial remission (4 weeks)

†Patients died without disease progression.

oPUVA: oral psoralen plus ultraviolet A; MTX: methotrexate; Bex: bexarotene; XRT: radiotherapy; lip doxo: liposomal doxorubicin; HDACI: histone deacetylase inhibitors; anti-CD4-ab: zanolimumab; anti-CD52-ab: alemtuzumab; art HTN: arterial hypertension; DM2: diabetes mellitus type 2; CKD: chronic kidney disease; PVD: peripheral vascular disease; s/p: status post; TNM: tumour node metastasis.

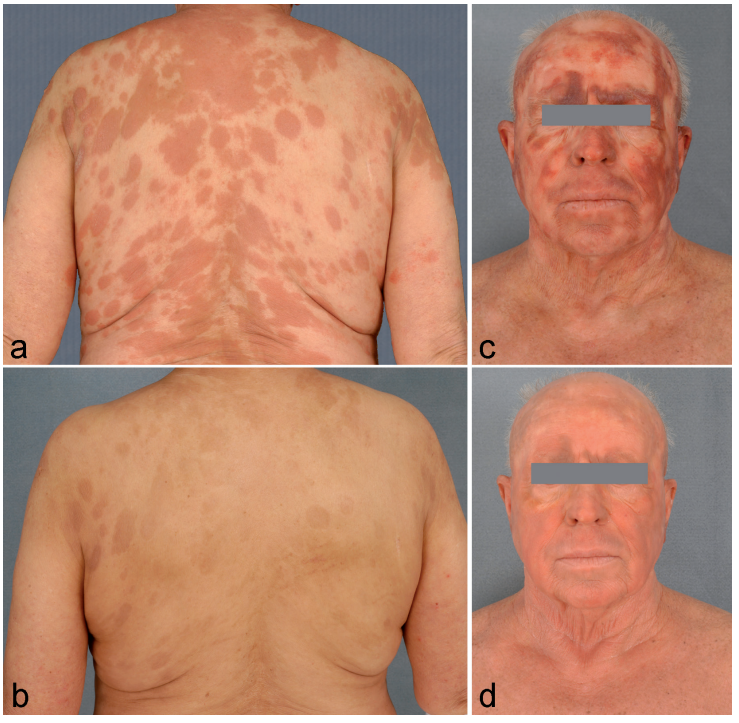

Fig. 1. Patients 3 (a, b) and 4 (c, d) before therapy and after 2 cycles of denileukin diftitox plus total skin electron beam radiation.

atypical T-lymphocytes (> 1,000/µl) in the peripheral blood (Fig. 1c). His upper body was irradiated, followed by DD. Three days later he developed fever due to catheter sepsis (*Staphylococcus aureus*), which was treated successfully with flucloxacillin. After 3 weeks his skin condition had improved remarkably. The proportion of atypical T-lymphocytes among peripheral blood lymphocytes was reduced to 15%. The second cycle of DD in combination with lower body radiation was well tolerated. Partial remission was achieved with some residues (Fig. 1d). This status lasted 4 weeks. The patient was subsequently started on thalidomide. During further treatment he reported hypohydrosis and skin dryness, which was treated with topical moisturizers.

DISCUSSION

Complete remission was achieved in 2 out of 4 patients. The duration of complete remission lasted at least 7 months, since both patients died of other causes without reoccurrence of MF; 1 patient showed partial remission. Adverse effects included fever (3/4), hypotension (2/4) and infectious complications (3/4) that could be treated successfully. Advanced-stage MF is associated with substantial immunosuppression, bearing an increased risk of infections. No patient developed vascular leak syndrome. Two of 4 patients developed moderate-to-severe radiation dermatitis, which is extremely unusual at the low dose used on the skin. Despite inhomogeneous irradiation doses, with underdosing of intertriginous skin, no remaining manifestations of MF or disease progression were seen in these areas.

Disease progression to advanced stages occurs in approximately 20% of patients with MF (6). There is no curative treatment for advanced MF; the treatment goal is to achieve durable remission. Radiation therapy is widely used. In early MF the remission rate with TSEB is as high as 96%, but when applied in the advanced stages only 36–60% of patients experience complete remission (3). Approximately 30% of patients showed progression-free survival after 5 years (4). PUVA or extracorporeal photopheresis (ECP) after successful TSEB may lead to prolonged remission (7).

DD specifically binds to the IL-2 receptor, which is expressed mainly on activated T-cells and CTCL cells. It inhibits protein synthesis by ADP ribosylation of elongation factor 2, resulting in cell death. DD has the potential to induce long-lasting complete remission, with an overall response rate of 30% in MF (2, 5, 8). However, in advanced-stage MF, doses of 9 µg/kg daily over 5 days may induce complete remission in only 10% of patients (2, 9). IL-2 receptor status ($CD25^{+/-}$) does not correlate with outcome (10, 11), and therefore was not performed in our patients.

Combination treatment can improve response, but potentially increases toxicity. DD and TSEB both show pro-apoptotic effects with different toxicity profiles. However, in 2 patients severe radiation dermatitis was seen, despite only doses of 16–18 Gy being applied. This might be caused by a radiosensitizing effect of DD.

Taking the age and comorbidities of our patients into account, combination treatment was well tolerated. Our cases demonstrate that a combination of 9 µg/kg DD and TSEB (18 Gy) is an effective treatment option for refractory, intermediate stage MF, with limited toxicity.

Conflicts of interest. KB and PAM received an educational grant from Teva-Cephalon. GB, SU and EBB declare no conflicts of interest. JCB is the consultant and member of speaker's bureau for Teva-Cephalon.

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