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ORIGINAL ARTICLE

Allogeneic donor split skin grafts for treatment of refractory ulcers in cutaneous chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation—a retrospective analysis on seven patients

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Abstract

Refractory skin ulcers due to severe chronic graft-versus-host disease (cGVHD) remain to be associated with significant morbidity and mortality.

We performed an allogeneic donor skin transplantation in seven adult patients after allogeneic hematopoietic stem cell transplantation for cGVHD-associated refractory skin ulcers. While four patients received a split skin graft (SSG), in one patient, a full thickness skin graft for two small refractory ulcers of the ankle was performed, and one patient received in vitro expanded donor keratinocyte grafts derived from hair roots of the original unrelated donor. In one additional patient, a large deep fascial defect of the lower leg was covered with an autologous greater omentum free graft before coverage with an allogeneic SSG. An additional patient was treated with an autologous scrotal skin graft for a refractory ulcer associated with deep sclerosis of cGVHD after unrelated donor transplantation.

All skin grafts engrafted and resulted in permanent coverage of the grafted ulcers without any signs of immunological mediated damage. In the patient receiving in vitro expanded keratinocyte grafts, two localized ulcers were permanently covered by donor skin while this approach failed to cover extensive circular ulcers of the lower legs.

Allogeneic donor skin grafts are a valuable treatment option in refractory ulcers due to cGVHD but are restricted mainly to related donors while keratinocyte grafts from unrelated donors remain experimental. In male patients lacking a related donor, autologous scrotal skin graft may be an alternative option.

Keywords Allogeneic hematopoietic stem cell transplantation · Skin grafts · Chronic graft-versus-host disease · Cutaneous ulcers

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Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is the curative treatment of choice in a variety of hematological diseases but is associated with significant morbidity and mortality mainly due to the occurrence of acute and chronic graft-versus-host disease (GvHD) [1–3].

One of the most frequently affected organs of chronic GvHD (cGvHD) represents the cutaneous tissue which may result infrequently in refractory ulcers in regions affected by deep cutaneous sclerosis [4, 5]. Moreover, cutaneous cGvHD increases the risk for cutaneous malignancies requiring surgery which may result in large defects in areas with severely impaired wound healing capacity and the ability to perform autologous skin grafts may be impaired by the lack of unimpaired skin areas in patients with disseminated changes of cGvHD [6, 7].

It is known since the first alloHSCT that hematopoietic donor chimerism results in tolerance to allogeneic donor skin grafts [8–13]. We therefore performed skin grafting from the hematopoietic stem cell donor in seven patients with refractory cutaneous ulcers due to cutaneous cGvHD with deep sclerosis and performed a retrospective analysis on the outcome. The analysis includes one patient reported previously and one additional patient receiving an autologous split skin graft after unrelated alloHSCT [9].

Material and methods

Seven patients were evaluated retrospectively after receiving donor skin grafts for treatment of refractory ulcers due to severe cGvHD with deep cutaneous sclerosis from 2009 to 2016 at the University Hospital of Regensburg (Germany; $n = 6$) and at the Karolinska University Hospital in Stockholm (Sweden; $n = 1$). Six of these patients were treated by allogeneic split skin grafting from the original sibling donor. One patient received multiple keratinocyte transplants harvested from in vitro expanded keratinocytes derived from the hair of the original HLA-identical unrelated stem cell donor [14]. All donors were evaluated before donation according to the guidelines for blood and hematopoietic stem cell donors including screening for infectious diseases and provided informed consent for skin harvest. None of the allogeneic donors had a relevant dermatological disorder prior to or at time of donation.

In parallel recipient ulcers were conditioned by surgical debridement. In one patient, a vascularized autologous greater omentum graft was performed in general anesthesia to cover a large deep fascial defect of the lower leg 4 days before the allogeneic skin grafting. One additional patient transplanted from an unrelated donor received an autologous split skin graft (scrotal skin not affected from cGvHD) for a small refractory ulcer in the knee region. After reaching sufficient wound conditions including absence of an invasive infection, the donor and recipient were set up for the allogeneic skin transplantation in two operation theaters.

The allogeneic skin grafts were harvested from the donor thigh by using an electrical dermatome set to the common cut depth of 0.3 mm. The donor procedure was performed under local anesthesia as an outpatient intervention. The grafts were postprocessed through a skin mesher to reach a surface expansion of 1.5-fold. Subsequently, the grafts were transferred to the recipient and applied to the wound using absorbable sutures. Finally, a tie-over dressing secured a plane adaption of the skin graft to the wound ground. Depending on the individual risk of bacterial wound contamination, the first change of dressing was scheduled around the fifth postoperative day. Patients were subsequently followed in an outpatient setting in the dept. of plastic surgery until complete healing of the ulcer. Subsequently, patient follow-up was managed exclusively by the outpatient dept. of the bone marrow transplant team (median follow up 3 years; range 0.6–10 years). The patients' characteristics are shown in Table 1.

Results

All allogeneic seven skin grafts engrafted and resulted in permanent coverage of the grafted skin ulcers without any signs of immunological mediated damage of the grafts. In three patients, a second skin graft was required due to initial partial coverage of the ulcer resulting in subsequent permanent complete closure. In the patient receiving in vitro expanded keratinocyte grafts, two localized ulcers (chest and upper thigh) were permanently covered by donor skin while this approach failed to cover extensive circular ulcers of the lower legs. Closure of the ulcer was as well achieved in the patient (patient 787-8) who received the autologous split skin graft. One patient required prolonged oral antibiotic therapy due to bacterial fasciitis which was present at the time of skin transplantation. The skin donation was performed at the day of transplant in an outpatient setting without any toxicity > grade 2 (CTCAE (common terminology criteria for adverse effects)). One donor developed a superficial bacterial skin infection requiring a temporary oral antibiosis. Five of the eight patients are currently alive while three patients died due to transplantation-related mortality 0.5–2 years after skin transplantation. The details of the skin transplants and their outcome are described below and are shown in Table 2.

Patient 712/1

The 49-year-old male patient underwent allogeneic PBSCT from his HLA-identical sister for AML 4 years before the

Table 1 Patient characteristics

Center/PN/ gender	Age at time of skin Tx years	Diagnosis	Donor type Donor gender	Graft source	Conditioning regimen	Type of onset of cGvHD	Overall severity and organ grading of cGvHD	Time from onset of cGvHD to skin Tx	Platelets/nl at time of skin Tx
712/1/male	49	AML 1st CR	mVRD Female to male	PBSCT	TBI, Cyclo	De novo	Severe cGvHD (skin 3 oral 2, genital 2, eyes 2)	4 years	435
513/2/female	55	ALL 1st CR	mVRD Male to female	PBSCT	TBI, Cyclo	Quiescent	Severe cGvHD (skin 3)	17 years	514
787/3/male	34	T-NHL 2nd CR	mVRD Female to male	PBSCT	Treo, Flud	Quiescent	Severe cGvHD (skin 3, oral 1, eyes 1, fascia 2) 4.5	4.5 years	327
712/4/female	49	ALL 2nd t CR	mVRD Female to female	PBSCT	TBI, Cyclo	Quiescent	Severe cGvHD (skin 3)	2 years	429
212/5/male	33	Hodgkins disease 3 rd PR	mVRD Female to male	PBSCT	TBI, Cyclo, Flud	Quiescent	Severe cGvHD (skin 3,fascia 3, liver 1, eye 1, oral 1)	7 years	310
787/6/female	29	AML 1 st CR	mVRD Female to female	PBSCT	TBI, Cyclo, Flud	Quiescent	Severe cGvHD (skin 3, genital 3, oral 2, eye 2)	4 years	307
533/7/male	55	AML 1 st CR	mVUD Female to male	PBSCT	2 Gy TBI, Flud	Quiescent	Severe cGvHD (skin 3, oral 2, fascia 3)	3 years	284
787/8/male	23	AML 3 rd PR	mmVUD, Male to male	PBSCT (3rd allo Tx)	Thio, Flud	Quiescent	Severe cGvHD (skin 3, eye 2, oral 1, liver 1)	2.5 years	584

Center EBMT center code, *PN* patient number, *mVRD* matched voluntary related donor, *mVUD* matched voluntary unrelated donor, *mmVUD* mismatched voluntary unrelated donor, *PBSCT* peripheral blood stem cell transplantation, *TBI* total body irradiation, *Cyclo* cyclophosphamide, *Flud* fludarabine, *Treo* treosulfan, *Thio* thiotepa, *Tx* transplantation

Table 2 Skin transplant characteristics and outcome

Center/ PN	Donor	IS at time of skin Tx	Graft type	Days inpatient	Size of the defect	Outcome of the graft and complications	Follow-up
712/1	Sister	ECP, steroids	SSG	12 days	28 cm circumferent lower leg	Progression of preexisting bacterial fasciitis requiring prolonged oral antibiosis	Alive, 3 years after skin graft doing well on ECP and ruxolitinib
513/2	Brother	None, 15 years before skin Tx end of IS	SSG followed by a full thickness graft	7 days	15 × 25 cm	Partial response with a remaining small ulcer, re Tx with a small full thickness skin graft (1.5 × 1.5 cm) after 6 months from the same donor resulting in closure of the ulcer (pressure point of the ankle). superficial bacterial infection after skin harvest responding to oral antibiosis as outpatient	Alive, 3 years after skin graft doing well
787/3	Sister	Tacro, MMF ECP, steroids	Full thickness	outpatient	1 × 1 cm 1 × 1 cm	Complete coverage of original ulcers by subsequent new ulcers at other sides due to progression of cGvHD responding to tocilizumab	Died 18 months after skin transplant due to rectal cancer
712/4	Sister	Steroids,rituximab	Autologous omentum majus and allo SSG	32 days followed 16 days 3 months later	20 × 5 cm deep fascial defect	Remaining defect required a 2nd transfer 3 months after the initial transplant which resulted in complete coverage of the defect.	Died 6 months after skin transplantation due to sudden cardiac arrest
212/5	Sister	Steroids, CsA	SSG	8 days	Multiple small ulcers (two in the palms; three on the soles)	Hyperproliferation of allogeneic skin grafts, remaining uncovered ulcers	Alive 2 years after skin transplant current treatment of cGvHD with in vitro expanded donor regulatory T cells
787/6	Sister	Steroids, MMF, MTX	SSG	25 days	12 × 17 cm	Initial skin graft engrafted successfully on 50% of surface, 3 months after initial grafting 2nd transfer was performed resulting in permanent coverage	Alive, 10 years after skin transplant, off immunosuppression
533/7	Unrelated donor	Steroids, MMF, rituximab, ECP	In vitro expanded keratinocytes	27 days 40 days	4 × 1 cm chest 5 × 1.5 cm upper leg Multiple circumferent ulcers lower leg	Coverage of the chest ulcer and ulcer on upper leg Failure to engraft due to relapsing pseudomonas infection	Died 2 years after skin transplant due to sepsis from remaining ulcers of the lower leg
787/8	Autologous scrotal tissue	Steroids, ruxolitinib	Autologous SSG scrotal skin	7 days	2 × 2 cm knee (resulting from a puncture of the knee in an area of severe sclerosis)	Coverage of the ulcer	Alive, 3 years after skin transplant. cGvHD controlled on ruxolitinib

IS immunosuppression, *Tacro* tacrolimus, *CsA* cyclosporine, *SSG* split skin graft

skin grafting procedure. Two years after transplantation, severe de novo cGvHD occurred with severe oral mucosa and moderate genital involvement with subsequent progression to deep cutaneous sclerosis of the lower legs resulting in multiple ulcers from the proximal third over a length of 28 cm to the distal third of the right lower leg being affected over the entire circumference despite multiple systemic treatment lines with steroids, extracorporeal photopheresis (ECP), everolimus, cyclosporine (CsA), and mycophenolate mofetil (MMF). In addition, signs of bacterial infection of fascia were present. Of note, deep venous thrombosis of the involved leg was treated 3 years before skin grafting resulting in mild venous insufficiency as predisposing factor. As a single surgical procedure, a surgical debridement using a hydrosurgery device (Versajet®, Smith & Nephew) as well as allogeneic split skin transplantation from his original stem cell donor was performed. The postoperatively applied negative pressure wound dressing had to be removed shortly after the procedure due to occurrence of local infection with *Pseudomonas aeruginosa* most likely due to the preexisting fascial infection. A topic antiseptic treatment improved the situation resulting in a stable skin graft healing in the proximal part of the ulcer. Subsequently, a new distal ulcer was detected due to a relapse of the bacterial fasciitis resulting in a partial loss of one skin graft in the distal circumferential part of the ulcer. After a prolonged application of broad spectrum antibiotics, the infection resolved and all remaining skin grafts were integrated.

Patient 513/2

A 53-year-old female who received an alloHSCT 17 years before the skin grafting procedure was referred to our transplant center for treatment of a refractory ulcer on her right lower leg which occurred in an area of prior cutaneous cGvHD with deep sclerosis. Immunosuppression had already been terminated years before the referral. Vascular cofactors were absent. The ulcer extended to the entire circumference of the ankle joint with a diameter of 15 cm resulting in a total size of 15 × 25 cm and was treated unsuccessfully twice with autologous skin grafts. A surgical debridement was performed by hydrosurgery followed by an allogeneic split skin transplantation from brother during a single surgical procedure. Afterwards, a negative pressure wound therapy was applied for 7 days. This strategy led to stable wound conditions and the patient was discharged at that time. Since a small circumscript ulcer at the lateral malleolus remained, the patient received a small second full thickness skin graft from the donor 6 months after the initial transplantation resulting in permanent complete remission of the ulcer during the further course.

Patient 787/3

A 34-year-old male underwent autologous followed by alloHSCT from his HLA-identical sister for peripheral T cell lymphoma which had progressed on first-line treatment. On day 180, he developed quiescent onset cGvHD of the skin and liver after an episode of steroid responsive acute GVHD. Subsequent treatment of cGvHD with steroids, tacrolimus, everolimus, rituximab, MMF, mesenchymal stem cells (MSC's), total nodal irradiation, and ECP failed to control cGvHD which progressed to diffuse deep sclerosis over 4 years resulting in severe contractions of all large joints and the neck and two refractory skin ulcers of the left lower leg (each 1 × 1 × 1 cm) on the medial malleolus of the left lower leg developing during treatment with everolimus in the absence of vascular cofactors. In a single stage procedure, a surgical debridement and allogeneic skin transplantation from the original donor was performed. The full-thickness skin graft was fixed in place using a tie-over dressing for 5 days resulting in successful engraftment. Unfortunately, the patient developed new ulcers due to further progression of cGvHD which finally responded to tocilizumab. This also resulted in healing of the ulcers by the support of conservative strategies. Sadly, 18 months after successful skin grafting, he developed a secondary rectum carcinoma and died due to pneumonia following surgery.

Patient 712/4

A 49-year-old female was transplanted from her HLA-identical sister for high risk ALL in second remission. She developed severe quiescent onset cGvHD after an episode of steroid sensitive acute GvHD involving the skin with deep sclerosis which failed to respond to sirolimus, steroids, ECP, methotrexate (MTX), and MMF. Two years after alloHSCT, she was referred for second opinion to our GVHD center and presented with a 20 × 5 cm ulcer on the volar aspect of her right lower leg in the absence of vascular cofactors. The tendon of the musculus tibialis anterior was visible on the surface and thus soft tissue transplantation was required to cover the defect. Faced to the risk of GvHD-associated wound healing disturbance after harvesting a tissue-transplant from the body surface, we performed a free greater omentum flap transfer obtained by laparoscopy. The right gastroepiploic artery was connected to the anterior tibial artery (Fig. 1a). Four days after the transfer (see picture 1), the omentum was covered with an allogeneic split-skin graft (Fig. 1b). The patient was discharged on day 28 postoperatively after primary wound healing. Due to the typical initial secretion of the transplanted

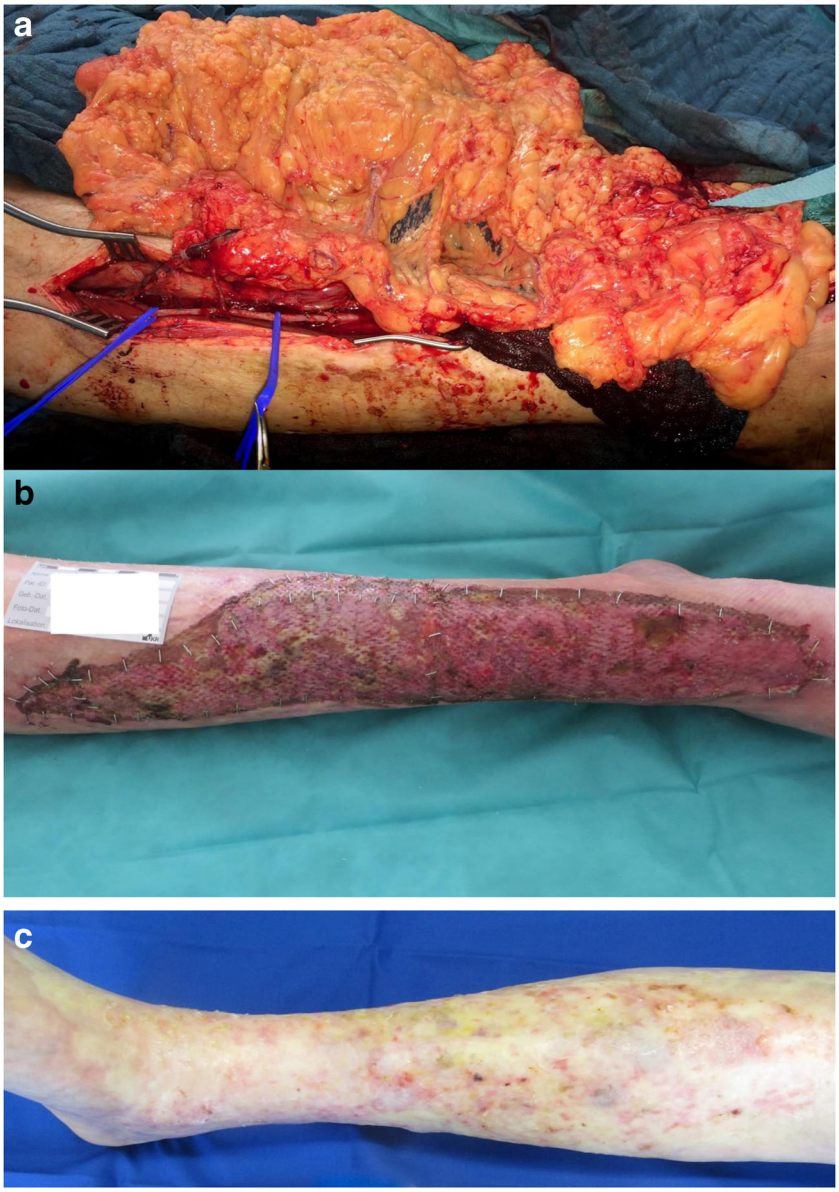

Fig. 1 **a**–**c** Greater omentum transplantation to lower leg of patient 712/4: **a** right gastroepiploic artery connected to anterior tibial artery via end-to-side anastomosis, **b** 14 days after greater omentum and split skin transplantation, **c** 3 months after surgery

greater omentum, a part of the skin graft failed and a further skin transplantation was performed 2 months later resulting in complete stable coverage of the ulcer (Fig. 1c). The patient died 6 months after the initial skin transplant due to sudden cardiac arrest unrelated to cGvHD.

Patient 212/5

A 33-year-old male presented 7 years after alloHSCT with refractory cGvHD with severe skin and fascial, mild oral, ocular, gastrointestinal, and hepatic involvement after alloHSCT from his HLA-identical sister performed for relapsed Hodgkin's disease after autologous HSCT. cGvHD progressed despite multiple treatment lines including cyclosporin, steroids, MSC's, ECP, MTX, rituximab, MMF, interleukin 2, and ruxolitinib and caused widespread deep sclerosis with extensive contractures and multiple ulcers involving the palms of both hands, the sole of the left foot, and the heel of the right foot in the absence of any vascular cofactors. Since he had basically no skin area not involved in cGvHD, an allogeneic split skin graft from his donor was performed covering two ulcers in his palms and three ulcers (maximum 3 × 3 cm size) under his feet after surgical debridement. Moreover, a full thickness graft was performed at the scalp region after resection of a metatypic basal cell carcinoma. The skin transplants resulted in coverage of the transplanted ulcers and decrease of inflammation but did not had any effect on the subsequent course of cGvHD. Interestingly, the grafts showed signs of hyperproliferation of keratinocytes in the absence of inflammation as shown in

figure 2 (suppl.). Due to further progression of cGvHD, the patient was treated 18 months later with in vitro expanded regulatory T cells from the donor within the TREG 003 trial (EudraCT No 2016-003947-12).

Patient 787/6

Patient 787-6 was reported previously and remains in remission of the ulcer off immunosuppression 10 years after the skin transplantation working fulltime [9].

Patient 533/7

A 55-year-old male patient presented for second opinion for treatment of refractory cGvHD progressing on CsA, MMF, steroids, tacrolimus, rituximab, everolimus, and ECP, which developed after HLA-matched unrelated donor alloHSCT for AML. At that time of presentation, deep sclerosis already affected almost the entire integument including multiple ulcers with a mean size of 2 cm of the lower legs. Additional, multiple erosions at other locations with additional involvement of the eyes and oral mucosa existed. In addition, he already developed a spinocellular carcinoma in the sternoclavicular region which required resection but the resulting wound 4.1 × 1.0 cm size did not show any signs of healing due to deep sclerosis. Another ulcer, which spontaneously occurred 6 months before on the right medial thigh, measured 5.0 × 1.5 cm. Since the patient did not have any areas of healthy skin, the donor center was contacted after informed consent of the patient as well as the donor and the original donor donated hairs which were sent to Euroderm® for tissue-engineering of epidermis-equivalent sheets from outer root sheath (ORS) keratinocytes (figure 3a–b; suppl.). Four weeks after hair donation, the engineered sheets were transplanted resulting in sufficient epithelialization of the ulcer of the right medial thigh and the defect resulting from resection of the skin carcinoma (figure 3c; suppl.). One year later, another surgical debridement and transplantation of donor keratinocytes was performed using remaining keratinocyte sheets due to progression of preexisting multiple confluent superinfected ulcers on the left lower leg which did not result in epithelialization due to recurrent infections of the skin and the large size of the confluent ulcers. The patient died 2 years after the first transplant procedure from a fulminant invasive bacterial infection of the ulcers with corresponding septic shock syndrome.

Patient 787/8

A 26-year-old patient suffering from severe cGvHD after 3rd alloHSCT from an unrelated donor for second relapse of AML involving the skin with large areas of deep sclerosis of the legs and arms and additional mild oral and eye involvement presented to our clinic with a refractory 2.0 × 2.0 cm ulcer in the left knee region developing after diagnostic puncture for diagnosis of a spontaneous bacterial infection of the knee joint. Due to the location of the ulcer being close to the knee joint, an urgent coverage of the ulcer was required. Since the patient was transplanted from an unrelated donor, the ulcer was covered by an autologous split skin graft from the unaffected scrotum after water-jet debridement of the recipient site. Afterwards a negative pressure wound therapy was applied for 5 days and the patient was discharged with stable wound conditions and stable healing of the ulcer was achieved during the following 2 months.

Discussion

Refractory skin ulcers in cGvHD patients remain a therapeutic challenge and are the result of a long lasting inflammation with subsequent tissue fibrosis including vascular damage resulting in impaired microcirculation [15, 16]. Moreover, any inflammatory condition bears the risk for recruitment of alloreactive immune-cells perpetuating the ongoing inflammation with corresponding impaired healing of skin ulcers [17, 18]. Thereby, skin defects in areas of deep sclerosis are difficult to treat by the use of standard therapeutic strategies.

With his renowned experiments on guinea-pigs, Nobel prize laureate Peter B Medawar showed that successful skin transplantation is a reliable indicator to prove immune-tolerance between recipient leucocytes and donor skin [19]. Thus, in case of complete hematopoietic donor cell chimerism, tolerance against skin transplants from the stem cell donor can be expected excluding any alloreactivity against donor skin grafts. Several case reports already proved this theory [8–13, 20].

After a first successful treatment of a cGvHD-associated ulcer using a skin transplant from the stem cell donor, we subsequently pursued this therapeutic strategy in a small series of six additional cases [9].

In all six cases grafting with split skin grafts or full thickness skin grafts, a permanent complete wound coverage of the grafted region was accomplished. One patient even achieved a full remission of cGvHD after failing multiple treatment lines. Treatment failed in only one patient who suffered from graft loss of grafted keratinocyte sheets due to relapse of a long lasting bacterial infection of the grafted skin region. Later, the patient died due to an invasive infection from ulcers, which emphasizes the urgent need to intervene and cover ulcers before refractory infections occur. Furthermore, frequent antibiotic treatments lead to emergence of multidrug-resistant bacteria. Moreover, keratinocyte sheets in contrast to split- or full thickness skin grafts may be more vulnerable to graft loss caused by infectious complications due to the lack of a dermal layer.

For a successful integration of skin transplants, a reasonable vascular supply of the recipient wound bed is mandatory. In one case, a soft tissue transplantation was required to achieve suitable wound conditions, as low vascularized tissue, such as tendon and bone tissue, was exposed. To avoid the induction of further donor site complications, the greater omentum was transferred to cover all exposed tendon and bone structures prior to split skin grafting [21, 22].

One crucial prerequisite for successful engraftment is the absence of invasive infections as indicated by two cases with one developing a new ulcer which resolved after successful treatment of bacterial fasciitis and in the other case by graft loss.

Overall, split skin transplantation from the stem cell donor appears to be an efficient, well-tolerable method for the immunosuppressed patient. Unfortunately, this technique remains reserved to related transplant donors only. In case of unrelated unavailable donors, autologous scrotal skin grafts may be an alternative option, particularly considering the fact that scrotal skin is rarely affected by cGvHD. Furthermore, due to its skin laxity, wound healing disturbance after split skin harvest in this area is unlikely. Another potential option would be the transfer of in vitro–derived donor keratinocytes from hair routes of the stem cell donor [5, 23]. These cultured epidermal sheets from plucked hair follicles can directly be transferred to the wound without harming a skin donor region. However, both scrotal skin grafting and donor derived epidermis sheets are limited to small ulcers only.

In terms of pathophysiology, the successful treatment of therapy refractory ulcers with stem cell donor skin underlines the importance of alloreactivity of cutaneous damage in cGvHD while autoreactivity seems to be less relevant [18, 24]. Moreover, the successful donor allografting after failure of autologous skin grafts in patient 513/2 suggests that even in inactive cGvHD, areas of ulcers may show graft-specific alloreactivity. The same applies to cGvHD-associated ulcers with vascular cofactors as indicated by patients 712/1.

Overall, the small case series showed that split skin grafting from the stem cell donor can lead to successful coverage of otherwise therapy refractory cGvHD-associated ulcers. In cases lacking suitable skin donors, scrotal skin grafting or cultured allogeneic epidermal sheets from plucked hair follicles may be a potential option. For patients lacking a related donor, the use of a bilayered third party donor (neonatal foreskin) skin graft (APLIGRAF) may be an additional option [25].

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Compliance with ethical standards

Conflict of interest DW and EH received honoraria from Novartis and Mallinckrodt. None of the others authors indicated a conflict of interest.

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