SHORT COMMUNICATION

Allogeneic Haematopoietic Cell Transplantation for Epidermolysis Bullosa: the Dutch Experience

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Efforts to find a cure for the devastating inherited blistering disease, epidermolysis bullosa (EB), have received much attention in recent years. The extremely poor long-term prognosis of EB has motivated many patients and clinicians to pursue high-risk experimental therapies (1–6). One such therapeutic strategy is allogeneic haematopoietic cell transplantation (HCT) in recessive dystrophic epidermolysis bullosa, generalized severe, (RDEB-gen-sev) patients (1), who completely or partially lack type VII collagen (Col7) at the dermo–epidermal junction (DEJ).

Based on encouraging results in mice (7, 8) and humans (1), we designed a study in the Netherlands. We aimed to treat 11 RDEB-gen-sev patients using a previously described HCT protocol (9, 10) (Fig. S1[1]).

Between May 2014 and October 2017, 2 RDEB-gen-sev patients were enrolled and treated following the study protocol. Unfortunately, both patients died due to transplantation-related complications after 50 and 283 days after cord blood transplantation (CBT), respectively. We wish to report detailed results of this trial which has now been prematurely closed.

CASE REPORTS

The first patient (#1; EB109-01) was a 13-year-old girl with an extensive RDEB-gen-sev phenotype due to homozygous mutation in intron 20 of *COL7A1* gene (NM_000094.3); c.[2710+1G>A];[2710+1G>A] with no Col7 expression in immunofluorescence antigen mapping (IFM; monoclonal antibody LH7:2, Sigma-Aldrich, Poole, UK). Minimal toxicity was noticed with conditioning and the skin condition slightly improved with reduced blistering and inflammation. Unfortunately, the 4/6 cord blood graft (6/10 matched on high resolution molecular typing; NC/kg=6.4×10^7/kg) was rejected (bone marrow aspirate confirmed day +25, 85% patient chimerism) with the course being further complicated by very early cytomegalovirus reactivation (day +2), prolonged neutropaenia without autologous recovery, followed by multiple bacterial- and therapy-resistant aspergillus infections, resulting in her death (day +50). The study was put on hold and the treatment protocol was adjusted to improve safety by adding: cryopreservation of an autologous back-up graft (for rescue in case of non-engraftment), targeting the pre-HCT ATG to high exposure >80 AU*d/l (while assuring low post-HCT exposure <10 AU*d/l) to reduce the probability of donor-graft rejection and anti-fungal prophylaxis with liposomal amphotericin B instead of fluconazole.

The second child (#2; EB402-01), was an 8-month-old boy, with a homozygous large deletion starting in intron 12 and ending in exon 24 of the *COL7A1* gene; c.[1637-240_3252del4061],[1637-240_3252del4061] resulting in no Col7 expression on IFM (Fig. S2[1]). At baseline, he had minimal cutaneous involvement, severe mucosal (oral and ocular) erosions and nail dystrophy (Fig. S2[1]). The conditioning was well tolerated and he engrafted quickly (day +17) with a 5/6 unrelated cord blood unit (matched 7/10 on high-resolution molecular typing; NC/kg=15.1×10^7/kg). However, the treatment course was complicated with several transplantation-related toxicities, requiring resuscitation and multiple intensive care admissions. These included refractory grade III skin graft vs. host disease (GvHD), acute oesophageal bleeding, gastric paresis, capillary leak syndrome, pneumothorax and severe respiratory insufficiency. Several switches in immunosuppression were necessary due to medication-induced transplantation-related microangiopathy and kidney toxicity. Acute GvHD was controlled with 3 additional mesenchymal stromal cell infusions (outside the treatment protocol) and basiliximab. Gastroenteral GvHD was suspected, but never proven, despite extensive endoscopic evaluation. Similar to patient 1, patient 2 also developed cytomegalovirus reactivation, even before transplant, which was treated pre-emptively. The load waxed and waned over the disease course, but was never higher than log3 IU/ml. He also had multiple bacterial infections, which were well-controlled. The respiratory problems, however, persisted and required ventilation (4 separate episodes) and oxygen support, leading to progressive decline in lung function and ultimately death (day +283). We are unable to fully explain whether all these complications were related to the immunological phenomena of a CBT or EB.

In addition to the multiple life-threatening complications in patient 2, there was clear lack of clinical or biological evidence of efficacy in ameliorating the EB disease course, despite >97% donor peripheral blood chimerism and 9 months' follow-up. Mucosal blistering flared up and persisted throughout the treatment period. Cutaneous blistering was seen during hospital admission, largely explained by iatrogenic trauma. The mini-skin rub test was persistently positive (day +180) (11). Neither Col7, nor its main constituent anchoring fibrils were detected at the various time-points, including post-mortem (day +283) (Fig. S2[1]). Unfortunately, we could not assess dermal chimerism (with X-Y FISH), as the donor and recipient were the same sex.

DISCUSSION

The first HCT trial in 2010, described treatment of 6 RDEB-gen-sev patients, with transplantation-related mortality in one patient and clinical improvement in the remaining 5 patients, including presence of donor cells in the injured skin and increased Col7 deposition at the DEJ

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(1). Later, in another HCT trial, 2 RDEB-gen-sev patients survived the treatment, showed dermal chimerism and exhibited some short-lived clinical benefit; however, no Col7 was re-instituted after HCT (12). A report from an international EB meeting in 2017 stated that no individual has been cured after HCT, but mortality rates have improved and several patients showed a marked reduction in blister formation with major improvement in quality of life (13).

Although, we also observed some temporary beneficial effects from the treatment in both of our patients, their dramatic course of treatment did bring to light many issues. Firstly, could the clinical improvement observed after HCT, with or without Col7 expression or anchoring fibril formation (1, 12), be attributed to the wound-healing properties of immunosuppressive medications, particularly corticosteroids (14), used during HCT treatment protocols?

Secondly, it is important to understand whether haematopoietic stem cells (HSC) that migrated to the skin are capable of producing Col7 at the DEJ. It is well known that Col7 at the DEJ is contributed by both keratinocytes and fibroblasts. The differentiation capabilities of these migrated HSCs are not yet clearly understood, with some studies suggesting that HSCs might not be capable of trans-differentiation into keratinocytes, while others suggest that the HSCs might convert into dermal fibroblasts, particularly at wound sites where remodelling is occurring, contributing to the reported increase in Col7 expression (1, 4, 5, 7, 15, 16).

Finally, the most important question that arises is what qualifies for success attributable to HCT in EB? Although, clinical improvement has been reported, it is difficult to speculate if such an effect is temporary, as the long-term benefit of haematological engraftment remains to be shown. If HCT promises mostly symptomatic alleviation with no or limited biological correction of disease, i.e. reconstitution of Col7 and/or anchoring fibrils, other safer therapeutic options should be considered. Taken together, our study team, in accordance with the safety monitoring board recommendation, suspended and subsequently closed the trial. HCT for severe forms of dystrophic EB remains a high-risk therapeutic option of undetermined clinical benefit.

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