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Bone marrow transplant for recessive dystrophic epidermolysis bullosa

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ABSTRACT

Recessive dystrophic epidermolysis bullosa is an incurable, often fatal mucocutaneous blistering disease. A 2yr -old girl, presented with generalized bullous lesions since birth. She underwent matched sibling donor haemotopoietic stem cell transplant from her sister. Skin lesions reduced and healing improved. Allogeneic bone marrow transplant can partially improve skin and mucosal integrity in patients with recessive dystrophic EB.

Epidermolysis bullosa (EB) is characterized by loss of skin integrity that leads to spontaneous as well as trauma-induced blisters and erosions. It is a heterogeneous group of more than 20 inherited blistering diseases with highly variable clinical severity [1]. Recessive dystrophic epidermolysis bullosa (EB) is the most severe form and is caused by loss-of-function mutations in the collagen type VII (C7) gene (*COL7A1*) [2,3]. These mutations result in severely diminished expression of C7, a collagen localized at the dermal–epidermal junction. C7 is the major component of the anchoring fibrils that tether the epidermal basement membrane to the dermal matrix. In the absence of normal C7 expression, these fibrils do not form properly, and epidermal-dermal adherence is lost beneath the lamina densa of the basement membrane. From birth onwards, children with recessive dystrophic epidermolysis bullosa can have painful erosions and blisters on mucosal membranes and skin, often resulting in esophageal strictures, mutilating scars, local and systemic infections, joint contractures, fusion of fingers and toes, and aggressive squamous-cell carcinomas [4,5]. Allogeneic marrow contains stem cells capable of ameliorating the manifestations of recessive dystrophic epidermolysis bullosa in humans. Donor blood and bone marrow (sources that contain both haemopoietic and non-haemopoietic stem cells) home towards the gradient of stress signals or proinflammatory factors secreted systemically from active wounds. Once integrated in these so-called docking stations, donor cells secrete C7 chains that homopolymerise in the extracellular matrix and, as they reach the barrier of the basement membrane zone, form anchoring fibrils, resulting in increased skin stability [6]. We report here our experience of allogeneic haematopoietic stem cell transplant (HSCT) in one patient with recessive dystrophic epidermolysis bullosa.

A 2-year-old girl from Iraq a case of recessive dystrophic epidermolysis bullosa with COL7A1 mutation was admitted for matched sibling donor HSCT. She had history of bullous lesions on the skin 2–3 hour post birth. Lesions initially appeared on the trunk and limbs and later involved the entire body. She also had history of bullous lesions following trauma. On admission she had bullous lesions all over body (Fig. 1) and multiple ulcers in the mouth causing difficulty in swallowing food. There was no family history of such disease. Rest of the systemic examination was normal. Written consent of parents was taken before transplant. Pretransplant work up done for donor and patient was normal. Conditioning chemotherapy was started after inserting hickman catheter and Percutaneous endoscopic gastrostomy (PEG) tube. PEG was inserted for proper nutrition and to minimize vomiting because pretransplantation evaluation showed extensive mucosal involvement in addition to cutaneous disease and also there was history of esophageal dilation in past because of stricture which is a known complication in such type of patients. We followed the same immunomyeloablative conditioning regimen as used by Wagner et al. [9] who have done maximum number of HSCT for EB so far. It

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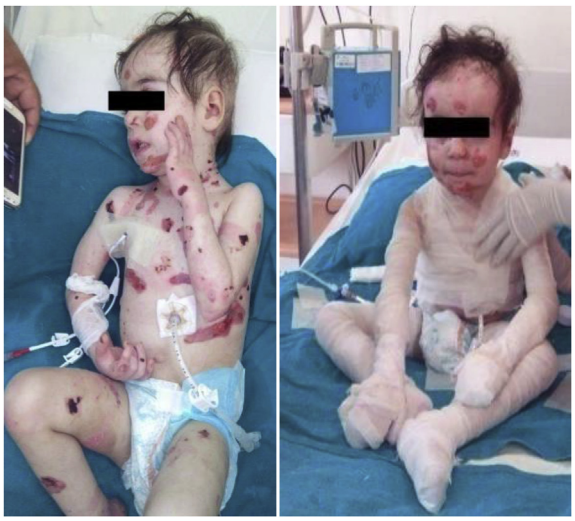

Fig. 1. Picture before Bone marrow transplant showing multiple bullous lesions and surface area of skin covered with dressing.

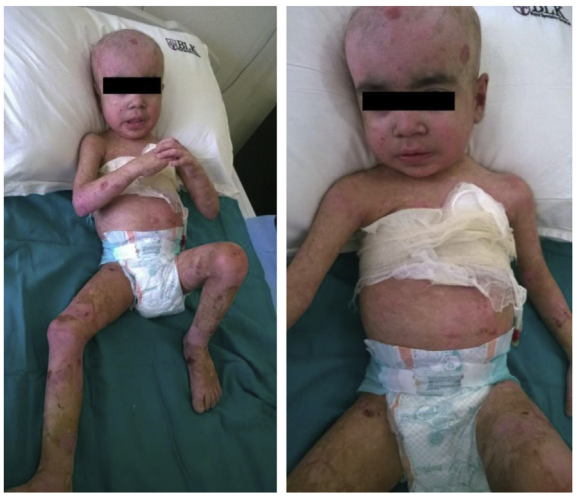

Fig. 2. Picture day +100 post HSCT showing decreased number of skin lesions and decreased surface area of dressing.

included busulfan (0.8 mg/kg intravenously every 6 hours on days −9 to −6), Fludarabine (25 mg/m^2/day, given intravenously on days −5 to −3), and cyclophosphamide (50 mg/kg/day, given intravenously on days −5 to −2). Graft versus host disease (GVHD) prophylaxis consisted of cyclosporine (targeting trough levels of 200–300 μg per liter on day 3 before transplantation to day 100 after transplantation, with the dose tapered by 10% each week thereafter) and Mycophenolate Mofetil 10 mg/kg/dose three times day on day −3 to day 45 after transplantation. Donor was her elder sister and bone marrow was used as a graft source. She received Bone Marrow harvested stem cells from her sister with Mononuclear Cell Count/kg body weight of the recipient 1.5×10^8/kg/L and Calculated Absolute CD34 positive cells dose 2.32×10^6/Kg/L. Her transplant course was very stormy which was complicated by Acinetobacter sepsis during neutropenic phase and grade II mucositis on Day+8 which recovered by day +14. Her skin swabs showed positivity for Methicillin resistant staph aureus (MRSA). All these required prolonged antibiotic course. Polymorphonuclear cell and platelet engraftment were seen on D+17 and D+19 respectively. She required intensive skin dressings every 3rd day and her nutrition was supported by PEG tube feeding regularly. She was discharged on day +26 with stable vitals on oral medications. She was followed up as outpatient with strict monitoring for Cytomegalovirus (CMV) reactivation and GVHD. Her disease status was assessed by detailed clinical examination at regular interval and number of bandages used per week for dressing. She had increased wound healing and decreased mucocutaneous blistering by day +40. The percentage of body surface area affected was reduced according to parents and by clinical observation (Fig. 2), with more objective evidence provided by documented reductions in bandage use. Her whole blood chimerism on day +21 and day +50 showed 99.35% and 98.86% of donor cells respectively. However she had Grade II gut GVHD on day +68 which was managed with intravenous methylprednisolone. After day+100 her improvement in skin lesions was static. Presently, she is day+700 post transplant not completely cured but the frequency of eruption of bullous lesion has decreased and healing of these lesions had significantly improved. No skin-biopsy was done to assess response as patient had significant clinical improvement.

In the past the care of patients with recessive dystrophic EB included only intensive treatment of individual wounds [7,8]. Allogeneic HSCT can partially correct the C7 deficiency and improve skin and mucosal integrity in patients with recessive dystrophic EB. Allogeneic marrow contains stem cells capable of ameliorating the manifestations of recessive dystrophic EB in humans. The rates of recovery and ultimate outcomes varied among the surviving patients. To date there is only one published study to assess the role of allogeneic HSCT in EB by Wagner et al. [9] They treated 7 children who had recessive dystrophic EB with Immunomyeloablative chemotherapy and allogeneic HSCT. One patient died of cardiomyopathy before transplantation. Of the remaining 6 patients, one had severe regimen-related cutaneous toxicity, with all having improved wound healing and a reduction in blister formation between 30 and 130 days after transplantation. Five recipients were alive 130–799 days after transplantation; one died at 183 days as a consequence of graft rejection and infection. Our present report also showed that Allogeneic HSCT can partially correct the C7 deficiency and improve skin and mucosal integrity in patients with recessive dystrophic EB. The unique skin and mucosal membrane defects of this disease pose a particular challenge to any bone marrow transplantation program. Clearly, much remains to be learned regarding the mechanism of the apparent functional correction as well as the long term risks and benefits of this therapeutic approach.

Funding source

None.

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from the patient's parents in this study.

Declaration of competing interest

None.

References

[1] Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the third international consensus meeting on diagnosis and classification of EB. J Am Acad Dermatol 2008;58:931–50.

[2] Dang N, Murrell DF. Mutation analysis and characterization of COL7A1 mutations in dystrophic epidermolysis bullosa. Exp Dermatol 2008;17:553–68.

[3] Woodley DT, Hou Y, Martin S, Li W, Chen M. Characterization of molecular mechanisms underlying mutations in dystrophic epidermolysis bullosa using site-directed mutagenesis. J Biol Chem 2008;283:17838–45.

[4] Pillay E. Epidermolysis bullosa. 1. Causes, presentation and complications. Br J Nurs 2008;17. 292– 6. Erratum, Br J Nurs 2008; 17:413.

[5] Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life threatening cancers: the National EB Registry experience, 1986-2006. J Am Acad Dermatol 2009;60:203–11.

[6] Tolar J, Wagner JE. Allogeneic blood and bone marrow cells for the treatment of severe epidermolysis bullosa: repair of the extracellular matrix. Lancet 2013;382(9899):1214–23. https://doi.org/10.1016/S0140-6736(13)61897-8.

[7] Mellerio JE, Weiner M, Denyer JE, et al. Medical management of epidermolysis bullosa: proceedings of the IInd international symposium on epidermolysis bullosa, Santiago, Chile, 2005. Int J Dermatol 2007;46:795–800.

[8] Ly L, Su JC. Dressings used in epidermolysis bullosa blister wounds: a review. J Wound Care 2008;17:482. 484–6, 488.

[9] Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med 2010;363:629–39.