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BLOCKADE OF ACUTE GRADE IV SKIN AND EYE GRAFT – VERSUS – HOST DISEASE BY ANTI – INTERLEUKIN – 2 RECEPTOR MONOCLONAL ANTIBODY IN GENOIDENTICAL BONE MARROW TRANSPLANTATION SETTING*

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A six-year-old boy with homozygous β-thalassemia in the favorable class 1 risk group received a bone marrow transplant, from his histocompatible sister. He developed grade IV skin and eye graft-versus-host disease (GVHD) following varicella zoster reactivation. Despite the appropriate prophylactic use of cyclosporin A (CsA), methotrexate (MTX), and prompt treatment with high-dose steroids, GVHD progressed resulting in total body epidermal necrolysis. Anti-IL-2 receptor monoclonal antibodies (anti-IL-2R moAb) in combination with steroids were administered to selectively block the activated T cells. After 27 days of daily administration, followed by 17 doses of alternate-day therapy with anti-IL-2R moAb, the severe skin and eye GVHD resolved. The patient, at two years post-transplant, has full engraftment and immune reconstitution without chronic GVHD (cGVHD). In conclusion, we suggest that in the HLA-genoidentical bone marrow transplantation setting, very severe and steroid-resistant GVHD can be controlled through the use of anti-IL-2 receptor antibodies which specifically block the activated IL-2 receptor expressing T cells. *Key words: acute GVHD, skin, eye, anti-IL-2R, monoclonal antibodies.*

Acute grade IV graft-versus-host disease (aGVHD) is not commonly observed in the younger low-risk (class I) patients with homozygous β-thalassemia following genotypically identical sibling bone marrow transplantation (BMT) compared to the higher-risk groups[1]. Class 1 patients have a very high probability of cure, with low early and late morbidity and mortality rates. The prognosis of acute grade IV GVHD in any BMT setting despite prompt and aggressive treatment with steroids and cyclosporin A (CsA) is very poor[2,3]. Severe aGVHD is usually steroid-resistant. In this report, we present a six-year-old boy with homozygous β-thalassemia in the low-risk group who, despite CsA and methotrexate (MTX)

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prophylaxis, developed skin and eye GVHD following varicella zoster reactivation after an HLA-genotypically identical sibling BMT. Under high-dose steroids GVHD progressed, including the conjunctivae. Under the additional use of anti-IL-2 receptor monoclonal antibodies (anti-IL-2R moAb)[4,5] the GVHD resolved after two months with no relapse at two years post BMT.

Case Report

A six-year-old boy with homozygous β-thalassemia, under a well-controlled transfusion and chelation regimen without portal fibrosis or hepatomegaly (class 1 risk group)[1], was bone-marrow transplanted from his genotypically identical sister. The HLA types of the recipient and the donor were as follows: A2/3, B18/Bw6, DRB1.1301-1.11/DRB3.0101-DRB 3.02. Because of the genoidentity, cytotoxic T-lymphocyte precursor assay and mixed lymphocyte cultures were omitted. The patient was prepared for BMT with busulfan (14 mg/kg total dose) and cyclophosphamide (200 mg/kg total dose). GVHD prophylaxis consisted of CsA (10 mg/kg on day 0 and thereafter adjusted to obtain serum levels of 400-600 µg/L in the polyclonal assay) and MTX (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6 and 11). He received 2.4×10^8 nucleated cells/kg body weight. The first 15 days post BMT were unremarkable with hematopoietic recovery (> 0.5×10^9 granulocytes/L on day 15. On day 16, vesicular eruptions appeared on the trunk for which acyclovir (1500 mg/m^2) was immediately started. Electron microscopic examination of the vesicular fluid showed presence of herpesviruses. The lesions began to regress on day 25. A maculopapular rash appeared on day 29, covering all of the trunk and extremities, spreading to the face. Skin biopsy on day 30 showed no evidence of virus. The patient, still under acyclovir, was started on steroids at first at a dose of 2 mg/kg/day and subsequently at 5 mg/kg/day i.v. Between days 31 and 34 (Table I), there was continuous bullae formation covering the whole body, including ears, hands, feet, penis and mucosa of the eyelids. The liver and the gastrointestinal tract were not involved. On day 36 there was complete involvement of the skin with bullae, desquamation and rupture along the epidermal-dermal border resembling toxic epidermal necrolysis. The eye became extremely photosensitive. On this day, anti-IL-2R moAb (BB-10, BT 563, Leucotac, Biotest, Othmarsingen, Switzerland) were started at 0.4 mg/kg/day i.v.[4,5]. On day 40, as the skin manifestations seemed to be stabilized, the eye findings reached their summit with edema and shedding of the mucosa of the upper and lower eyelids with ulcerations. There were no signs of other organ involvement. On day 55 the lesions started to regress with the beginning of epithelial regeneration. Anti-IL-2R moAb treatment was discontinued after 19 days of daily administration. Steroids were continued at 2 mg/kg/day i.v. Three days after the moAb were stopped, the rash reappeared. The soluble IL-2 receptor levels are shown in

Table I. Anti-IL-2R moAb were restarted at 0.25 mg/kg/day and steroids increased to 4 mg/kg/day i.v. On day 64, skin manifestations improved. However, conjunctivae were once again severely involved. After eight days of daily administration, anti-IL-2R moAb were continued every other day at the same dose together with 2 mg/kg steroid administration. On day 69, the patient developed septic shock, due to Acinetobacter baumannii, with anuria, disseminated intravascular coagulopathy, liver failure; he was intubated and needed intesive care for eight days. He was treated with ceftazidime and ciprofloxacin. during this period, GVHD treatment was continued. Thereafter, the skin and eye manifestations regressed continuously with complete recovery at day 91. The soluble IL-2-receptor level was 82 U/ml. The anti-IL-2R moAb were then stopped. Under anti-IL-2 moAb treatment, a slow but consistent increase in the CD4 and CD8 cell counts could be observed, so that at the time of discharge, the absolute CD4 cell count was 0.32×10^9/L with a normal poliferation to phytohemagglutinin stimulation. The patient was discharged on day 116 with no signs of acute or chronic GVHD and no scar formation. He had received a total of 27 doses daily and 17 doses on alternating days of anti-IL-2 moAb. At present, two years post BMT, the patient is well with full engraftment (as shown by variable number of tandem repeat analyses of bone marrow cells), immune reconstitution and no signs of cGVHD.

Table I: Evolution of the T-lymphocyte Subsets and Soluble IL-2 Receptor Levels During the Course of Graft-Versus-Host Disease Following Bone Marrow Transplantation

Days post-BMT	31-34	40	55	62	69	91	116
Clinical Signs of GVHD	Grade IV Skin GVHD	Grade IV Skin and Eye GVHD	Repression of Skin and Eye Findings		Grade II Skin and Eye GVHD; Septicemia	Complete Recovery	Discharge from Hospital
CD4*	80	70	70	110	140	250	320
CD4 + DR*	30	20	20	30	20	150	90
CD8*	120	70	90	150	140	170	100
CD8 + DR*	40	20	30	60	20	70	30
CD25*	100	1	2	10	1	0	230
sIL-2R**	1821	ND	ND	27	438	82	ND
Treatment							
Steroids	+	+	+	+	+	+	–
anti-IL-2R moAb	–	+	–	+	–	+	–

BMT : bone marrow transplantation; GVHD : graft-versus-host disease; CD4 : helper T-lymphocytes; DR : stimulated (HLA-DR expressing) lymphocytes; CD8 : cytotoxic T-lymphocytes; CD25 : IL-2 receptor expressing lymphocytes; sIL-2R : soluble IL-2 receptor (normal range = 0-477 U/ml); anti-IL-2R moAb : anti-IL-2 receptor monoclonal antibody.

* number/µl.

** U/ml.

Discussion

Our patient was in the low-risk thalassemia group in terms of morbidity related to HLA-genoidentical BMT[1]. The evolution of the symptoms suggests that the varicella zoster infection was probably responsible for the development of severe GVHD, although the causal relationship is usually inverse, i.e., the aGVHD precedes the reactivation of varicella zoster infection[6]. The prognosis of grade IV aGVHD, which is mostly steroid-resistant, is usually very poor with an almost 100 percent mortality rate[2,3]. Anti-thymocyte immunoglobulins or various anti-pan-T moAb have been used as second-line therapy[7,8]. We decided not to use anti-thymocyte immunoglobulins because of their nonselective elimination of all T cells leading to a significant delay in immune reconstitution. Since the binding of IL-2 to its receptor stimulates clonal expansion of T cells reactive with specific antigens, the anti-IL-2R moAb are theoretically able to inhibit this response by blocking the transplanted T-helper cells directing the immune reaction against recipient tissue antigens and the cytotoxic cells mediating the tissue damage during the early phase of aGVHD[4,5]. Anti-IL-2R moAb have successfully been used with good tolerance of long-term administration[4,9]. The anti-IL2 moAb do not seem to influence the overall cellular immune reconstitution, as evidenced by our case, in which a steady increase was seen in the mature T-cell population with a normal proliferation to mitogen stimulation. Racadot et al.[10] recently reported a combined treatment directed against IL2 and TNFα. The sequential combination of moAb seems to be more effective compared to anti-IL-2R moAb alone. However, the recovery in our patient with severe but probably limited GVHD was due to the genoidentical nature of the transplantation, and thus, anti-IL-2R moAb alone sufficed to specifically block the activated T cells. To our knowledge, there are no published reports regarding the evolution of severe eye involvement. In conclusion, this case suggests that steroid-resistant acute grade IV skin and severe eye GVHD in HLA-genoidentical BMT can be effectively treated using anti-IL-2R moAb without relapse and with full immune reconstitution.

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