DOI: 10.4149/BLL_2014_017

Bratisl Lek Listy 2014; 115 (2)
80 – 82

CLINICAL STUDY

Treatment difficulty with acute GVHD – frequent cause of mortality after allogeneic hematopoietic stem cell transplantation

Lukas J, Bojtarova E, Mistrik M, Bujdak J, Sopko L, Hatalova A, Martisova M

Department of Hematology and Transfusion Medicine, University Hospital, Bratislava, Slovakia.
jozef.lukas@gmail.com

Abstract: *Objective:* Acute graft-versus-host disease (aGvHD) remains a significant cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT).
Methods: In this study, we have retrospectively evaluated the major risk factors for the development of aGvHD in 100 patients who underwent allogeneic transplantation at the University Hospital in Bratislava between January 2007 and December 2011.
Results: 29 patients acquired acute GvHD (Grade I – 12 patients, G II – 5 , G III – 3, G IV – 9). We proved a higher incidence of developing aGvHD in patients with unrelated donor type, TBI conditioning and cyclosporine (CsA) replacement with mycophenolate mofetil due to CsA nephrotoxicity, while other risk factors such as older patient age, the use of peripheral blood progenitor cells and donor/recipient sex mismatch were without statistical significance. The average time of onset of aGvHD has been 57 days (range 13–260) after HSCT. Corticosteroids were used as standard initial therapy with 52 % complete response (CR) rate, althoug the likelihood of response rapidly decreased with increasing severity of disease (G IV – 100 % refracterness). The response to primary therapy also correlated with overall survival. Patients with steroid-refractory aGvHD received a different second-line therapies (antithymocyte globulin, anti-TNFα antibody, anti CD52 antibody) with response rate 45 % (CR – 18 %, PR – 27 %).
Conclusion: Outcome for the patients with steroid-refractory aGvHD was poor, disease very often returned or progressed with one year mortality rate 81 % , that represents an important therapeutic problem *(Tab. 2, Ref. 10)*. Text in PDF *www.elis.sk.*
Key words: acute GvHD, risk factors, steroid resistence.

Despite prophylactic strategies acute graft-versus-host disease (aGVHD) remains a significant cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT) either from human leukocyte antigen (HLA) identical related or unrelated donors.

GVHD is a complex disease resulting from donor T-cell recognition of genetically different recipient that is unable to reject donor cells after allogeneic HSCT. The classical 3 step process best reflects the current understanding of the development of GVHD. In the first step, total body irradiation (TBI) or other cytoreductive conditionings induce tissue damage and the release of inflammatory cytokines into the circulation that promote the activation of antigen-presenting cells (APCs) (1). In the second step, donor T cell proliferate and differentiate in response to host APCs that present major histocompatibility complex (MHC) antigens and also minor histocompatibility antigens (miHAs) to donor T cells. These activated T cells express interferon γ (IFN-γ), interleukin-2, (IL-2) and tumor necrosis factors α (TNF-α), leading to T-cell expansion. In the third step, activated donor T cells migrate to the target tissues of GvHD (skin, gut, liver) and mediate tissue destruction through both direct cytotoxic activity and the recruitment of other leukocytes. Homing process is organized by chemokines and adhesion molecules (2). In this retrospective study we have focused on the major risk factors for the development of acute GvHD (unrelated donor types, greater intensity of the transplant conditioning regimen, older patient and donor age, female donor/male recipient, the use of peripheral blood stem cells rather than bone marrow, cyclosporine withdrawal due to nephrotoxicity) (3, 4). We also evaluated treatment response to initial steroid therapy and to second line therapy. Treatment of steroid-refractory GvHD can be divided into three groups. In the first group the drugs responsible for elimination of T-lymphocytes are used (antithymocyte globulin, alemtuzumab, denileukin diftitox), in the second group the drugs influencing cytokines or their receptors are used (antibody against receptor for interleukin-2, TNFα blockade) and the third group includes cytostatics and immunosuppressive agents (cyclophosphamide, mycophenolate mofetil, pentostatin, sirolimus).

Department of Hematology and Transfusion Medicine, University Hospital, Bratislava, Slovakia

Address for correspondence: J. Lukas, MD, Deparment of Hematology and Transfusion Medicine, St. Cyril and Method University Hospital, Antolska 11, SK-851 07 Bratislava, Slovakia.
Phone: +421.2.6867 2634

Patients and methods

We retrospectively evaluated incidence and major risk factors of developing acute GvHD in 100 patients who underwent

allogeneic transplantation at the University Hospital in Bratislava between January 2007 and December 2011. GvHD prophylaxis consisted of cyclosporine (CsA) with therapeutic plasma levels 200–400 ng/mL started on day-1 in combination with methotrexate (15mg/m^2 D+1, 10mg/m^2 +3,+6+11). In 15 cases cyclosporine had to be discontinued due to its nephrotoxicity and replaced by mycophenolate mofetil (2x1g/day). Staging and grading of acute GvHD were classified according to modified Glucksberg kriteria (5). Biopsy confirmation of GvHD was not required, but we used capsule endoscopy 3 times to define the extent of bowel involvement. Patients in whom acute GvHD developed continued cyclosporine treatment and received methylprednisolone 2 mg/kg per day in divided doses as initial therapy. In patients with prominent intestinal manifestation of GvHD we added budesonide (6–12 mg/d) and mesalazine (3x2 g/d) . Steroid-resistant acute GVHD was defined as progression of acute GVHD after 4 days of treatment or no improvement of acute GVHD after 7 days of treatment with methylprednisolone. We considered these patients as nonresponders to steroids and they were eligible for second-line therapy. In 7 cases we used antithymocyte globulin (rATG, 3 mg/kg/per day every other day for a total of 6 doses) for non-specific elimination of T-lymfocytes, in 2 cases we used alemtuzumab (30 mg per day for 3 consequent days repeating every 21 days with a median of 2 cycles) in combination with inhibitor of tumor necrosis factor (infliximab, 10 mg/kg/d once a week with a median of 3.5 doses). In 2 last cases we fortified immunosuppressive therapy by adding mycophenolate mofetil to cyclosporine. Steroids were not discontinued during second line therapy despite the well-know side effects. Complete response (CR) was defined as complete resolution of all signs of acute GvHD, partial response (PR) as reduction of GvHD to a less severe grading, progressive disease (PD) as progression of GvHD to a more severe grading. All patients received antifungal and antibacterial prophylaxis and were monitored for cytomegalovirus (CMV).

Results

Characteristics of patient who underwent allogeneic transplantation at the University Hospital in Bratislava between January 2007 and December 2011 for hematologic malignancies are summarized in Table 1. 58 patients recieved graft from HLA identical related donors and 42 from unrelated donors. Median donor and also recipient age was 36 years. The most frequent diagnosis indicated for allo-HSCT was acute myelogenous leukemia (n=39). We used peripheral blood stem cell grafts much more often than bone marrow (92 vs 8). Myeloid engraftment (ANC >0,5x10^9/l) occured with a median of 20 days after transplantation. 29 % of patients who underwent allo-HSCT developed acute GvHD. Unrelated transplantation, conditioning with TBI and replacement of cyclosporine prophylaxis with mycophenolate mofetil due to elevated serum creatinine level proofed to be the high risk factors responsible for developing acute GvHD. Other evaluated prognostic risk factors such as older donor or recipient age, sex mismatch (female donor/male recipient), early engraftment , incompatibility in AB0 system and the use of peripheral blood stem cells didn‘t reach statistical significance. As the Table 2 shows 17 patients with acute GvHD (59 %) were considered to be responders to first-line treatment with methylprednisolone (2 mg/kg/d). Nonresponders (41 %) had higher grades of GvHD (grade II–IV) and recieved a second-line therapy with response rate 45 % (CR –18 %, PR –27 %). However the outcome for the patients with steroid-refractory aGvHD was poor with one year mortality rate 81 %. Capsule endoscopy that we used in 3 cases showed characteristic mucosal damage including loss or shaven villi, mucosal hemorrhages, ulcerations, inflammatory exudates, scalloped folds and aphthous lesions.

Tab. 1. Clinical characteristics of patients who underwent aloTx between January 2007 – December 2011 according to risk factors for developing aGvHD.

	Total	aGvHD	
N. of aloTx	100	29	
Donor type			
HLA identical sibling	58	10 (17%)	
Unrelated	42	19 (45%)	P=0.0035
Median donor age, y. (range)	36 (15–61)	38 (23–61)	
Median recipient age, y. (range)	36 (19–63)	36 (19–61)	
Female donor / male recipient, no.	19	2	
Diagnosis			
AML	39	6	
ALL	27	14	
MDS	10	5	
AA	9	1	
CML	4	1	
PNH	3	1	
OMF	3	1	
HL	1	0	
Conditioning with TBI, no.	27	14 (51%)	P=0.0054
Day of engrafment (range)	20 (13–38)	16 (13–27)	
Source of stem cells			
Bone marrow, no.	8	2 (25%)	
Peripheral blood	92	27 (29%)	P=1
Incompatibility in ABO system, no.	40	15 (37%)	
Interval from Tx to GvHD, d. (range)	–	57 (13–260)	
Cydosporine withdrawal in patient who aquired aGvHD (G:II–IV)	15	8(53%)	P=0.033

AML – acute myelogenous leukemia, ALL – acute lymphocytic leukemia, MDS – myelosplatic syndrome, AA – aplastic anemia, CML – chronic myelogenous leukemia, PNH – paroxysmal nocturnal hemoglobinuria, OMF – osteomyelofibrosis, HL – Hodgkin lymphoma, TBI – total body irradiation

Tab. 2. grades and treatment of aGvHD.

Grade	n	responders to glucocorticoids	second-line treatment	response	mortality
	29	59%	41%		
I	12	12	–		0
II	5	3	2xATG	2xCR	0
III	3	2	–	–	1
IV	9	0	5xATG	2x PR with early relaps 3xPD	9
			2x anti-TNF+anti CD52 antibody	1x PR with early relaps 1xPD	
			2xMMF	2xPD	

ATG – antihymocyte globulin, MMF – mycophenolate mofetil, CsA – cyclosporine, CR – complete response, PR – partial response, PD – progressive disease

Discussion

Acute GvHD, despite of in vivo prophylaxis remains a major cause of sickness and death. It develops according to published data in approximately 30 % of patients after allogeneic HSCT that correlates with our data (29 %). We are not able to eliminate the majority of risk factors such as unrelated donors or TBI conditionig. Controversial remains the question what type of GvHD prophylaxis agents should be used instead of cyclosporine that in some situations has to be discontinuated due to its nephrotoxicity. Mycophenolate mofetil seems to be insufficient. 47 % of patients who developed acute GvHD grade II–IV didn't have cyclosporine in the therapy because of elevated serum creatinine level. Another calcineurin inhibitor - tacrolimus that is considered to be equal to cyclosporine is also known for its nephrotoxicity. The initial management of acute GvHD ussually consists of adding corticosteroids (prednisone or methylprednisolone 1 to 2 mg/kg/d) while continuing prophylaxis with cyclosporine. While some published data suggest that the response rate of GvHD may increase with increasing dose of methylprednisolone, there is no data to show that long-term survival is improved (6). Complete responses occur in 25 % to 40 % of patients (in our group in 52 % of cases) and correlate with better survival. However, the likelihood of response decreases with increasing severity of the disease. Steroid-resistant acute GvHD is extremely difficult to manage and is associated with death in more than 70 % (in our group even in 81 % of patients) (7). Patients with steroid-resistant acute GvHD are severely immunocompromised with high incidence of opportunistic infections. Despite variety of treatment options their efficacy is basicaly similar (8). Considerable experiences are with antithymocyte globuline (ATG) used to treat visceral GvHD and with TNFa blockade in patients with gastrointestinal involvement (9, 10). Although these agents are able to achieve complete remissions also in the cases of high grades of aGVHD, we are still waiting for more effective reagents.

References

1. Shlomchik WD, Couzens MS, Tang CB et al. Prevention of graft versus host disease by inactivation of host antigen-presenting cells. Science 1999; 285: 412–415.

2. Socié G, Blazar BR. Acute graft-versus-host disease: from the bench to the bedside. Blood 2009; 114: 4327–4336.

3. Gale RP, Bortin MM, van Bekkum DW et al. Risk factors for acute graft-versus-host disease. Br J Haematol 1987; 67: 397–406.

4. Przepiorka D, Smith TL, Folloder J et al. Risk factors for acute graft-versus-host disease after allogeneic blood stem cell transplantation. Blood 1999; 94: 1465–1470.

5. Przepiorka D, Weisdorf D, Martin P et al. Consensus conference on acute GVHD grading. Bone Marrow Transplant 1995; 15: 825–828.

6. Van Lint MT, Uderzo C, Locasciulli A et al. Early treatment of acute graft-versus-host disease with high-or low-dose 6 methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. Blood 1998; 92: 2288–2293.

7. Weisdorf D, Haake R, Blazar B et al. Treatment of moderate/severe acute graft-versus-host disease: secondary treatment. Blood 1990; 75: 1024–1030.

8. Mayer J, Cetkovský P, Krejčí M. Steroid-refractory acute graft-versus-host disease (GVHD). Trans Hemat dnes 2007; 13: 192–199.

9. MacMillan ML, Weisdorf DJ, Davies SM et al. Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease. Biol Blood Marrow Transplant 2002; 8: 40–46.

10. Couriel D, Saliba R, Hicks K et al.Tumor necrosis factor-α blockade for the treatment of acute GVHD. Blood 2004; 104: 649–654.

Received June 8, 2012.
Accepted October 27, 2013.