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Graft-versus-host disease in patients treated with allogeneic hematopoetic cell transplantation: experience from North Macedonia

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Abstract

Introduction: Graft-versus-host disease (GvHD) is the major complication arising after allogeneic hematopoietic cell transplantation (allo-HCT). It can present as acute and/or chronic GvHD. The purpose of this study was to describe the incidence of acute and chronic GvHD in patients treated with allo-HCT.

Materials and methods: This study was designed as a retrospective study, which included 65 patients treated with allogeneic transplantation from a human leukocyte antigen identical donor at the University Clinic of Hematology in Skopje, North Macedonia.

Results: Acute GvHD (aGvHD) was observed in 28 patients, with the most common localization on the skin (75%). Post-transplant phase had a significant effect on the frequency of skin aGvHD (p =0.038). Also a statistically significant difference was confirmed between patients with and without acute skin GvHD in terms of conditioning regimen (p =0.034). Chronic GvHD (cGvHD) was diagnosed in 10 patients, mostly progressing from previously acute GvHD (9.23%). Post-transplant phase had also a significant effect on the frequency of skin cGvHD (p =0.018). Patients with a higher European Society for Blood and Marrow Transplantation risk score had significantly more frequent skin cGvHD than did the others.

Conclusions: Acute and chronic GvHD are leading causes of morbidity and mortality of patients after allo-HCT. GvHD remains a major risk for patients with allo-HCT, regardless of diagnosis or type of transplantation.

Key words: allogeneic transplantation, acute and chronic GvHD, conditioning regimen, donor-recipient match, immune system

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Introduction

Graft-versus-host disease (GvHD) is the major complication arising after allogeneic hematopoietic cell transplantation (allo-HCT). GvHD is characterized by the overproduction of proinflammatory cytokines that induce target organ damage directly or indirectly by activating other effector cell populations. It can present as acute and/or chronic GvHD [1, 2].

Acute GvHD (aGvHD) continues to be an important complication following allo-HCT in the modern era [3]. In the

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early period (first 100 days) after transplantation, aGvHD develops in 25–75% of patients, and the skin, liver, and gastrointestinal tract are targeted. Acute GvHD usually occurs within the first 100 days after allogeneic transplantation and correlates with the degree of histocompatibility between donor and recipient, regardless of whether the conditioning regiment was myeloablative or non-myeloablative [4]. Other main risk factors involved in this complication are type of graft, age of patient, and gender [5]. Acute GvHD is classified by severity and number of target organs involved at grades I–IV, with grade IV resulting in the highest mortality rate [6]. Calcineurin inhibitors (cyclosporin A (CsA) and tacrolimus) are the keystone of prophylaxis, while steroids remain the mainstay of treatment [7, 8]. The most important predictor of long-term survival is the primary response to therapy of GvHD. Second-line treatments of GvHD include other immunosuppressive drugs, oral non-absorbable steroids, anti-thymocyte globulin (ATG), monoclonal antibodies, extracorporeal photopheresis, and other methods. Supportive measures are of the utmost importance. Recent improvements in non-relapse mortality and overall survival in aGvHD patients [9] certainly reflect improvements in supportive care and infection prophylaxis/treatment in transplant recipients [10, 11]. Thus, even when patients develop GvHD, they have a better chance of survival nowadays than they did 10 or 20 years ago [12, 13].

Approximately 20–50% of transplant survivors experience chronic GvHD (cGvHD), the most common late complication of allo-HCT. The onset is typically 4–6 months after transplantation. The major risk factors include human leukocyte antigen (HLA) mismatching, older age of recipient, use of peripheral blood, and female-to-male donor [14]. Chronic GvHD can be mild, requiring only topical or local interventions or short-term systemic immunosuppression, or it can be moderate to severe with the risk of poor control with available treatments causing substantial morbidity and even death [15]. A combination of CsA and prednisolone has been the standard frontline therapy for cGvHD. Salvage therapy, antimicrobial prophylaxis and supportive care are very important aspects of the treatment of these patients.

Overall, cGvHD has been associated with worse quality of life (QOL), poorer functional status, and a higher symptom burden [16, 17]. Interest in preventing and treating cGvHD has increased in recent years, with a growing recognition of the impact that this complication has on the long-term health of survivors [18–20].

The objective of our study was to analyze the incidence of acute and cGvHD in North Macedonia over the period 2000–2016 and the therapeutic measures in patients treated with allo-HCT during the first 16 years of activity of the transplant center.

Materials and methods

Study design

This was a retrospective study conducted at the University Clinic of Hematology in Skopje, North Macedonia. The studied patients were transplanted between 2000 and 2016 i.e. from the start of the availability of allo-HCT in North Macedonia. This study was approved by the Ethics Committee for Human Research, Medical Faculty in Skopje.

Patient population and selection criteria

The study included a group of 65 patients aged 16 to 65, of whom 33 were women and 32 were men. Transplantations were performed for the treatment of hematological malignancies or non-malignant diseases. All patients received stem cells from HLA-identical sibling donors.

Stem cell transplantation procedure

All patients included in the study were treated with allo-HCT. All patients received an appropriate conditioning regimen that was applied depending on the underlying disease and the numerous prognostic parameters that were analyzed in advance. A central venous catheter was routinely implanted prior to the beginning of conditioning. Day 0 was designated as the day of graft infusion. Supportive care, including antimicrobial prophylaxis, was applied after transplantation. All transfused blood products were filtered and irradiated. In the first 100 days after transplantation, patients were screened for cytomegalovirus reactivation in order to initiate pre-emptive therapy with gancyclovir, if necessary.

EMBT risk score

Earlier analyses on outcome after HCT for other diseases indicate that age, disease stage, time from diagnosis to transplantation, donor type, and donor-recipient gender combinations all influence survival, non-relapse mortality, and relapse risk. The risk score for this analysis used the same five pre-transplant risk factors as initially defined, with 0, 1 or 2 points awarded for each factor [21].

Graft-versus-host disease prophylaxis and therapy

The majority of patients received cyclosporine A in combination with methotrexate for prophylaxis. GvHD was defined in accordance with the Seattle criteria for diagnosis and GvHD setting. Both acute and cGvHD were diagnosed on the basis of clinical symptoms and/or biopsy from the skin, liver, gastrointestinal tract or oral mucositis. Acute GvHD was diagnosed clinically and evaluated by attending physicians from grade 0 to grade IV, and cGvHD was defined as mild versus moderate to severe disease according to the appropriate criteria for diagnosis and therapy [22].

Supportive care

Prophylaxis against infection included parenteral and oral antibiotics, antifungals and antivirals during the phase of neutropenia. Appropriate doses of immunoglobulins were given to all patients during the post-transplant period on the basis of a threshold value of 0.4 g/dL.

Statistical analysis

Statistical analysis of the obtained data was performed in the statistical program SPSS for Windows 17.0. The obtained data was represented by distributions, quantitative data was represented by mean ±standard deviation (SD). To determine the significant predictive factors for fatal outcome, multivariate logistic regression analysis was used, with determination of the exposure probability ratio (OR, odds ratio). The statistical accuracy of OR was obtained by calculating the confidence limits around the estimated values — confidence intervals (CI); values of p <0.05 were taken as statistically significant.

Results

Demographics

With respect to the European Society for Blood and Marrow Transplantation (EBMT) score: one patient had an EBMT score of 5, two patients had a score of 4, eight patients had a score of 3, 22 patients had a score of 2, 29 patients had a score of 1, and three patients had a score of 0. Acute GvHD was reported in 28 (43.08%) patients. Overall, 24 patients had aGvHD ≥2nd grade, including 8 patients with aGvHD ≥3th grade. Chronic GvHD was reported in 10 (15.4%) patients (six mild, three moderate and one severe).

The most common localization of aGvHD was skin, in 21 (75%) patients, followed by gastro-intestinal tract (GIT) in 15 (53.6%) patients. The frequency of skin aGvHD was higher in patients transplanted with active disease than in patients transplanted in remission (p =0.038), and higher in patients after busulfan +cyclophosphamide (Bu–Cy) conditioning compared to other types of conditioning regimens (p =0.034). The gender of the patient was not associated with the occurrence of aGvHD (p =0.9). Acute GvHD was reported in 43.75% (14/18) of male patients and in 42.42% (14/19) of female patients. Patients with aGvHD had an average age of 34.8 ±12.4 years while patients without aGvHD had an average age of 32.4 ±12.6 years (p =0.43). No significant differences were found with respect to donor-recipient relationship. Two patients (one male, one female) had steroid refractory GvHD; both were diagnosed with acute myeloid leukemia (AML), and transplantation was made in remission of the disease.

The gender of patients had no significant effect on the occurrence of cGvHD (p =0.96). Chronic GvHD was equally present in male and female patients (15.63% vs. 15.15%, respectively). No significant differences were found for age of patients with/without cGvHD (32.30 ±11.3 vs. 33.67 ±12.7; p =0.75). There was no statistically significant difference between patients with and without cGvHD depending on the donor-recipient relationship (p =0.51). Skin was the most common localization of cGvHD, as manifested in 7/10 patients. Psoralen ultra-violet A (PUVA) radiation was administered in 4/7 patients. The second localization by frequency of cGvHD was GIT. No differences

Table I. Patient and donor characteristics

Variable	Value
Number	65
Age (range):	
• <20	9
• 20–30	22
• 30–50	22
• >50	12
Underlying disease:	
• acute myeloid leukemia (AML)	36
• acute lymphoblastic leukemia (ALL)	10
• chronic myelogenous leukemia (CML)	5
• primary myelofibrosis (PMF)	5
• severe aplastic anemia (SAA)	5
• myelodysplastic syndrome (MDS)	2
• Hodgkin lymphoma (HL)	1
• multiple myeloma (MM)	1
Stage of underlying disease:	
• in remission	57
• active disease	8
Comorbidities:	
• with comorbidities	55
• without comorbidities	10
Donor/recipient sex:	
• male to male (M→M)	19
• male to female (M→F)	22
• female to male (F→M)	14
• female to female (F→F)	10
Type of conditioning regimen:	
• busulfan +cyclophosphamide (Bu–Cy)	25
• busulfan +cyclophosphamide +melphalan (Bu–Cy–Mel)	31
• cyclophosphamide +ATG	5
• BEAM	2
• FLAG–Ida	2

ATG — anti-thymocyte globulin; BEAM — carmustine, etoposide, cytarabine, melphalan; FLAG–Ida — fludarabine +cytarabine +granulocyte colony-stimulating factor (G-CSF) +idarubicin

Table II. Relapse after allogeneic hematopoietic cell transplantation

Characteristics		N	Relapse		*P* value
			No	Yes	
Gender	Male	32 (49.2)	23 (71.88)	9 (28.13)	0.52
	Female	33 (50.8)	26 (78.79)	7 (21.21)	
Diagnosis	ALL	10 (15.4)	5 (50)	5 (50)	
	SAA	5 (7.7)	4 (80)	1 (20)	
	AML	36 (55.4)	28 (77.78)	8 (22.22)	
	PMF	5 (7.7)	5 (100)	0	
	MDS	2 (3.1)	2 (100)	0	
	NHL	1 (1.5)	0	1 (100)	
	CML	5 (7.7)	4 (80)	1 (20)	
	MM	1 (1.5)	1 (100)	0	
Donor→recipient	M→M	19 (29.2)	14 (73.68)	5 (26.32)	0.78
	M→F	22 (33.8)	16 (72.73)	6 (27.27)	
	F→M	14 (21.5)	10 (71.43)	4 (28.57)	
	F→F	10 (15.4)	9 (90)	1 (10)	
Disease stage	In remission	57 (87.7)	44 (77.19)	13 (22.81)	0.39
	Active disease	8 (12.3)	5 (62.5)	3 (37.5)	
EBMT risk score	0	3 (4.6)	2 (66.67)	1 (33.33)	0.44
	1	29 (44.6)	22 (75.86)	7 (24.14)	
	2	22 (33.8)	17 (77.27)	5 (22.73)	
	3	8 (12.3)	7 (87.5)	1 (12.5)	
	4	2 (3.1)	1 (50)	1 (50)	
	5	1 (1.5)	0	1 (100)	
Conditionig regimen	Bu–Cy	25 (38.5)	22 (88)	3 (12)	0.047
	Bu–Cy–Mel	31 (47.7)	22 (70.97)	9 (29.03)	
	Cyclophosphamide +ATG	5 (7.7)	4 (80)	1 (20)	
	BEAM	2 (3.1)	0	2 (100)	
	FLAG–Ida	2 (3.1)	1 (50)	1 (50)	

ALL — acute lymphoblastic leukemia; SAA — severe aplastic anemia; AML — acute myeloid leukemia; PMF — primary myelofibrosis; MDS — myelodysplastic syndrome; NHL — non-Hodgkin lymphoma; CML — chronic myelogenous leukemia; MM — multiple myeloma; M — male; F — female; EBMT — European Society for Blood and Marrow Transplantation; Bu — busulfan; Cy — cyclophosphamide; Mel — melphalan; ATG — anti-thymocyte globulin; BEAM — carmustine, etoposide, cytarabine, melphalan; FLAG–Ida — fludarabine +cytarabine +granulocyte colony-stimulating factor (G-CSF) +idarubicin

were found in time from diagnosis of the disease to transplantation between patients with cutaneous cGvHD compared to others (p =0.3). Disease phase had a significant effect on the frequency of cGvHD on the skin (p =0.018). Frequently more skin rash was associated in patients who were transplanted in active disease compared to patients transplanted in remission. Patients with a higher EMBT risk score had significantly more frequent skin cGvHD than did the others. Comorbidities had no significant impact on the presence of cutaneous cGvHD in our cohort. In 6/10 cases, chronic GvHD developed from previously acute GvHD.

In 16 (24.61%) patients with allo-HSCT, there was a relapse of the underlying disease, including five acute lymphoblastic leukemia (ALL), one aplastic anemia (AA), eight AML, one chronic myelogenous leukemia (CML), and one non-Hodgkin lymphoma (NHL). The type of conditioning was significantly different in patients with and without relapse (p =0.047) (Table II).

Deaths after HCT occurred in 19 patients (27.7%), including 10 men and nine women. The most common reason for death in our cohort was relapse of the underlying disease and GvHD. A statistically significant difference was confirmed between patients with and without a fatal outcome depending on the donor-recipient match (p =0.029). Significantly more patients with a female donor and a male recipient — 57.14% (8/14) — had a fatal outcome, while lower mortality was registered in the group with a male donor and a male recipient — 10.53% (2/19). For p =0.046,

Table III. Deaths after allogeneic transplantation

Characteristics		N [%]	Deaths		*P* value
			No	Yes	
aGvHD	No	37 (56.9)	30 (81.08)	7 (18.92)	0.069
	Yes	28 (43.1)	17 (60.71)	11 (39.29)	
cGvHD	No	55 (84.6)	40 (72.73)	15 (27.27)	1.0
	Yes	10 15.4)	7 (70)	3 (30)	
Relapse	No	49 (75.4)	38 (77.55)	11 (22.45)	0.12
	Yes	16 (24.6)	9 (56.25)	7 (43.75)	
Donor→recipient	M→M	19 (29.2)	17 (89.47)	2 (10.53)	0.029
	M→F	22 (33.8)	17 (77.27)	5 (22.73)	
	F→M	14 (21.5)	6 (42.86)	8 (57.14)	
	F→F	10 (15.4)	7 (70)	3 (30)	
Disease stage	In remission	57 (87.7)	43 (75.44)	14 (24.56)	0.2
	Active disease	8 (12.3)	4 (50)	4 (50)	
EBMT risk score	0	3 (4.6)	3 (100)	0	0.046
	1	29 (44.6)	24 (82.76)	5 (17.24)	
	2	22 (33.8)	16 (72.73)	6 (27.27)	
	3	8 (12.3)	3 (37.5)	5 (62.5)	
	4	2 (3.1)	1 (50)	1 (50)	
	5	1 (1.5)	0	1 (100)	

aGvHD — acute graft-versus-host disease; cGvHD — chronic graft-versus-host disease; M — male; F — female; EBMT — European Society for Blood and Marrow Transplantation

a statistically significant difference was found between deceased and surviving patients in terms of EBMT risk score. There were no deaths among patients with an EBMT risk of 0, while patients with a higher EBMT risk score had frequently more deaths (Table III).

Discussion

Long-term survival and/or cure after allogeneic transplantation leads to an increased risk of complications. Post-transplant complications, especially acute and chronic GvHD, are a significant factor in additional mortality and morbidity in patients treated with allo-HCT. North Macedonia is a country of Balkan region, with a population of 2.02 million people. HCT activity in our country began in the year 2000, and the only transplant center is located in Skopje, the capital and the largest city with 0.5 million inhabitants. As the number of allogeneic transplantations in our country started to grow, so also grew the need to create an effective therapeutic strategy for GvHD with defined recommendations in correlation with the other currently registered retrospective and prospective clinical studies that deal with this problem. Our study was the first analysis of acute and chronic GvHD in our Transplant Center at the University Clinic of Hematology in North Macedonia.

All of the patients who were included in this analysis were treated with allo-HCT, and this shows the growing experience of the transplant team in this field, one that is complex and challenging. GvHD can lead to a fatal outcome as a direct complication or in association with an immune deficiency that increases susceptibility to infection. A number of variables related to patient characteristics or transplantation [21], such as age of patient, type and duration of underlying disease or conditioning regimen (aGvHD on the skin for p =0.034), and administration of immunosuppressive drugs, may have an effect on acute and chronic GvHD [1]. Our study found that disease phase had a significant effect on the frequency of aGvHD on the skin (p =0.038) and cGvHD on the skin (p =0.018). Despite advances in supportive treatment, the incidence of these complications is still relatively high.

Treatment of aGVHD remains challenging, despite several decades of studies and many immunosuppressive/immunomodulatory tested agents [6, 8]. There are difficulties not only in treatment, but also with the overall assessment of the disease and the involved organs, with several possible options for assessing grade, and variability according to the individual assessor [5, 9, 13].

Despite the differences in assessment and the difficulty in grading GvHD [22], it is recognized that mortality

increases with increasing severity of GvHD [3, 7]. Our study is an example of the impact of aGvHD evaluation on the outcome of allogeneic transplants and, on the other hand, the lack of effective treatment when the disease is higher than grade III. It is reasonable to try to prevent the progression of aGvHD. This can be achieved if the aGvHD is treated at a very early stage (at the earliest with grade I, or with a skin rash involving <50% of body surface area). We found a strong association of early GvHD with GvHD severity and survival. Patients who developed grade I GvHD during the first 20 days after transplant were more likely to develop grade III/IV GvHD compared to other patients and had a higher risk of fatal outcome (p =0.069) [10].

A remaining challenge with allogeneic HCT is to eliminate toxicity and severe GvHD and to support the effect of graft-versus-lymphoma (GvL) [2, 23]. However, the best prophylaxis for GvHD remains the subject of debate [24, 25]. Since the results of the transplantation also depend on the patient's age, donor type, risk of disease and transplant status, in order to assess more precisely the impact of GvHD prophylaxis on transplant outcomes, our study was limited to a homogeneous patient population analysis with an HLA-identical donor.

GvHD remains a major risk for patients with allo-HCT regardless of diagnosis and/or transplantation [16]. Chronic GvHD is a serious complication of allogeneic HSCT [17, 19]. In addition to increasing the risk of death, moderate or severe cGvHD also impairs the quality of life [15, 18].

We also found that sex-mismatched transplants, especially female → male HCT, were an important factor influencing survival, the occurrence of GvHD, and fatal outcome (p =0.029). In our cohort, sex-disagreement with an increased risk of aGvHD was observed in the group with myeloablative conditioning. Many factors can potentially contribute to the onset of aGvHD, such as differences in conditioning intensity (p =0.034), the use of prophylactic immunosuppression, and/or immunological reconstitution. These can all contribute to the timing and onset of aGvHD [20]. We found increased incidence of aGvHD in male (M)→female (F) and M→M transplants compared to F→F and F→M transplants, whereas the occurrence of cGvHD showed no difference in all donor sex combinations. It can be concluded that male recipients have a better outcome with male donors in terms of cGvHD incidence, quality of life, and fatal outcome.

The majority of patients respond to immune suppression with GvHD. All patients who developed GvHD after immunosuppression were treated with steroids with or without restarting low-dose sirolimus or tacrolimus. In all patients surviving GvHD, therapy significantly improved the symptoms of GvHD.

Our results should be interpreted with caution because the protocols for transplantation, and the treatment of complications and monitoring, were not identical among all patients in our group. Transplantation techniques have changed over the two decades since our first patient, and thus the prevention of some complications after transplantation, such as acute GvHD, has improved [11]. In addition, transplantation is now more often used in elderly patients and in patients in whom donors are not HLA identical siblings [26]. Chronic GvHD remains the biggest challenge [16, 17, 26].

The rapidly growing population of all-transplant patients creates an obligation to educate patients, their families and doctors. Monitoring of the post-transplant period and clinical follow-up of the registered complications will enabled the creation, standardization and acceptance of uniform criteria in the approach to each patient treated with this intervention [26].

Authors' contributions

IM — writing manuscript; all authors — study design and final approval.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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