Research Article / Araştırma Makalesi

The Treatment of Steroid-Refractory Severe Gastrointestinal Acute Graft-Versus-Host Disease in Children after Allogeneic Hematopoietic Stem Cell Transplantation: A Single-Center Experience

Allojeneik Hematopoietik Kök Hücre Transplantasyonu Sonrası Çocuklarda Steroide Dirençli Şiddetli Gastrointestinal Akut Graft-Versus-Host Hastalığının Tedavisi: Tek Merkez Deneyimi

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Abstract: Acute graft-versus-host disease is a common complication of allogeneic hematopoietic stem cell transplantation and is a major cause of morbidity and mortality. Systemic steroid therapy is the first-line treatment for acute graft-versus-host disease, although about half of patients will become refractory to treatment. We aimed to evaluate treatment options by reviewing available alternatives for patients with steroid-refractory acute graft-versus-host disease by comparing data from recently published studies. We retrospectively studied the safety and efficacy of treatment in 22 children with steroid-dependent/refractory acute GVHD between the years 2010 and 2023. Seven (31.8%) out of 22 patients with acute graft-versus-host disease were still alive. The seven surviving patients have been followed for an average of 1141 (±403) days. 15 non-responders with grade III/IV acute graft-versus-host disease died from causes associated with acute graft-versus-host disease and/or other conditions. Among 15 patients who died, the number of patients who received all three treatments, MSC, ECP and infliximab, was 5 (33%). The most common cause of death was infection (8 cases in 15 patients, 53.3%). Other causes of death were gastrointestinal hemorrhages (n=5, 33.3%), and intracranial hemorrhages (n=2, 13.3%). When factors causing morbidity were evaluated, it was observed that three patients developed posterior reversible encephalopathy syndrome, two patients developed hepatic veno-occlusive disease, and one patient developed hypertension. The estimated probability of survival after 1 year was 31.8%, and the median survival was 655 days. We believe that it would be crucial to show the safety and efficacy of novel treatments in comprehensive, randomized clinical trials.
Anahtar Kelimeler: Allogeneic hematopoietic stem cell transplantation, graft-versus-host disease, pediatric.

Özet: Akut graft-versus-host hastalığı, allojeneik hematopoietik kök hücre naklinin yaygın bir komplikasyonu olup önemli bir morbidite ve mortalite nedenidir. Sistemik steroid tedavisi, akut graft-versus-host hastalığı için ilk basamak tedavidir, ancak hastaların yaklaşık yarısı tedaviye direnç gösterebilmektedir. Akut graft-versus-host hastalığı için güvenli ve etkili tedavilerin keşfedilmesi, allojeneik kök hücre nakli yapılan hastaların sayısı arttıkça, özellikle durumu sistemik steroid tedavisine dirençli hale gelenler için daha önemli hale gelecektir. Yakın zamanda yayınlanmış çalışmalardan elde edilen verileri karşılaştırarak, steroide dirençli akut graft-versus-host hastalığı olan hastalar için mevcut alternatifleri gözden geçirerek tedavi seçeneklerini değerlendirmeyi amaçladık. 2010-2023 yılları arasında steroide bağımlı/refrakter akut graft-versus-host hastalığı olan 22 çocukta tedavinin güvenliğini ve etkinliğini retrospektif olarak inceledik. Akut graft-versus-host hastalığı olan 22 hastanın yedisi (%31,8) hayatta kaldı. Hayatta kalan hastaların takip gün sayısı ortalama 1141 (±403) idi. Evre III/IV akut graft-versus-host hastalığına sahip, tedaviye yanıt vermeyen 15 hasta farklı nedenlerden dolayı öldü. En sık ölüm nedeni enfeksiyondu (16 hastada 8 vaka, %53,3). Diğer ölüm nedenleri arasında mide-bağırsak kanaması (n=5, %33,3) ve kafa içi kanama (n=2, %13,3) yer aldı. Ayrıca morbiditeye neden olan faktörler değerlendirildiğinde üç hastada PRES sendromu, iki hastada hepatik veno-okluzif hastalık ve bir hastada hipertansiyon geliştiği görüldü. 1 yıl sonra tahmini hayatta kalma olasılığı %31,8 ve ortalama hayatta kalma süresi 655 gündü. Steroide dirençli akut graft-versus-host hastalığında kombinasyon tedavi yöntemlerinin etkisini retrospektif olarak değerlendirdik. Yeni tedavilerin güvenliğini ve etkinliğini kapsamlı, randomize klinik araştırmalarla göstermenin önemli olacağını düşünüyoruz
Keywords: Allojeneik Hematopoietik Kök Hücre Transplantasyonu, Akut Graft-Versus-Host Hastalığı, Pediatrik

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1. Introduction

For patients with hematological malignancies, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a commonly used method that often serves as the only curative therapeutic option. A key factor in eliminating malignant cells is the graft-versus-leukemia effect (GVL), which is mediated by donor lymphocytes (1). Graft-versus-host disease (GvHD), a condition where the recipient's tissue is recognized as foreign by the donor T cells, is a potentially fatal side effect (2). Despite prophylaxis, acute graft-versus-host disease (aGvHD) may still develop in HSCT recipients and primarily occurs in the skin, gastrointestinal system, and liver. The degree of involvement at each target organ determines the clinical diagnosis and overall clinical grade of aGvHD (3). In previous research (4), human leukocyte antigen disparity, which results in matched grafts having lower rates of aGvHD than HLA (human leukocyte antigen) -mismatched grafts, has been found to be one of the most significant risk factors for developing aGvHD. The age of the donor, sex mismatch, and the myeloablative regimen employed are other variables that may raise the risk of developing aGvHD. In pediatric patients, the incidence of grade II to IV acute GvHD ranges from 40% to 52% of recipients from an unrelated donor, depending on factors such as the degree of donor and recipient HLA mismatch and is approximately 27% after hematopoietic stem cell transplantation from an HLA-identical sibling (5-7). Systemic corticosteroid therapy is the standard first-line treatment option for aGvHD (8). However, for acute GvHD, it was seen that approximately one-third of pediatric patients may not respond to first-line treatment (9). Due to profound immunosuppression and long-lasting GvHD, steroid-refractory aGvHD has a significant rate of mortality even with intensive treatment with additional immunosuppressive therapy (6).

In this single-center retrospective study, we aim to evaluate the feasibility and efficacy of treatment modalities in patients with aGvHD after HSCT.

2. Materials and Methods

A total of 27 patients, under the age of 18, with steroid-refractory aGvHD, who received extracorporeal photopheresis (ECP) and/or mesenchymal stromal cells (MSCs) and/or infliximab between the years 2010 to 2023 in Acibadem Hospital were analyzed. (i). Five patients who were given insufficient treatment for any reason resulting in the effect of the treatment not being able to be evaluated; (ii). Patients diagnosed with steroid-responsive GI aGVHD; (iii). Patients diagnosed with chronic GVHD and overlap chronic GVHD were excluded from the study. All the patients had undergone allo-HSCT for malignant or non-malignant diseases and suffered from steroid-refractory aGvHD. At Acibadem Hospital Pediatric Stem Cell Unit, stem cell transplantation is performed annually on an average of 50 patients between the ages of 0-18. The total incidence of grade III-IV GI aGvHD in the clinic, during the last ten years, was 9%. The last follow-up was in November 2023. Patient data was retrospectively evaluated using patient records. Patient and transplant characteristics are shown in Table 1. The study was approved by Acibadem University Noninterventional Clinical Research Ethical Committee (Decision no: 2021/20, Date: 14.10.2021) in accordance with the Declaration of Helsinki. Informed written consent for participation in the study was obtained.

The criteria recommended by the European Society for Blood and Marrow Transplantation were followed in the grading and staging of aGvHD (10). Acute GvHD was described as GvHD that occurred 100 days after transplantation and had no signs of chronic GvHD symptoms. According to the area of involvement, (upper GI tract) anorexia, nausea, and vomiting; and (lower GI tract) diarrhea, typically green and watery; in severe cases diarrhea contained fresh blood and mucosa and was accompanied by abdominal cramps and, on occasion, clinical manifestations including paralytic ileus may have been seen. If the clinical diagnosis was unclear, a colonic biopsy was used to confirm the diagnosis of GI involvement. The

modified Glucksberg criteria were used to rate the acute GvHD severity (11). For every patient, HSCT was the event that caused GvHD. Steroid refractoriness or resistance was defined as progression of aGvHD within 3−5 days of therapy onset with ≥2 mg/kg/day of prednisone or failure to improve within 5−7 days of treatment initiation or incomplete response after more than 28 days of immunosuppressive treatment including steroids (12).

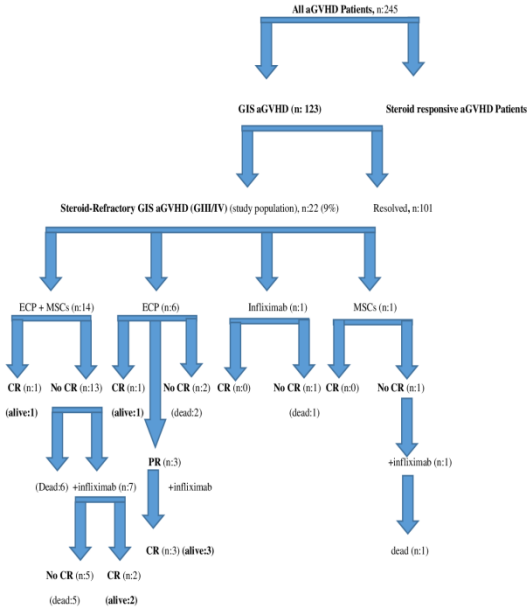

Figure 1. Outcomes of patients aGVHD patients. This figure provides a flowchart of the therapies and outcomes of 22 children with GIS aGvHD.

(*Abbreviations:* aGvHD, acute graft-versus-host disease; CR, complete remission; PR, partial remission; GIS, gastrointestinal system)

All steroid refractory GI aGvHD patients are shown in Figure 1 according to responses to treatment. ECP was performed with the UVA PIT™ Med Tech Solutions GmbH Photopheresis System (Cadolzburg, Germany). Treatment was carried out for two days in a row during one ECP cycle. The treating physicians decided whether to taper or stop ECP based on the patient's response. Patients with aGvHD were to have weekly cycles of therapy, reducing down to fortnightly phases for a duration of two to three months. During the period of ECP treatment, response in aGVHD was evaluated on day 28 and subsequently every fourth week. Complete remission (CR) was defined as complete resolution of all symptoms of aGVHD in all organs; very good partial remission (VGPR) approximated CR allowing minimal skin, liver, and gastrointestinal symptoms; partial remission (PR) entailed improvement of aGVHD stage in at least one organ affected at baseline, without worsening in any other organ; and no response (NR) meant no change in any organ or progression in stage in at least one organ.

Infliximab was given to those who did not respond to ECP+MSCs within 2-4 weeks. Patients received infliximab at a weekly dose of 10 mg/kg by intravenous infusion over four hours. Oral paracetamol at 15–20 mg/kg and intravenous chlorpheniramine at 0.1–0.2 mg/kg were administered as pre-medication. Resolution of all GI signs and symptoms was accepted as CR, while a decrease by at least one stage of GI involvement was accepted as PR. The absence of any discernible alteration or illness progression was referred to as NR (13).

MSCs were derived from the bone marrow of unrelated (second or third patient) donors with mismatched human leukocyte antigen, as previously reported (14). In accordance with good manufacturing practices, MSCs were extracted and grown using media containing

10% platelet-lysate in an authorized Acibadem University Labcells clean room. MSC therapy was initiated as soon as possible after steroid refractoriness first appeared. Within five to ten minutes, MSCs suspended in 50 milliliters of isotonic sodium chloride solution were injected intravenously. The target for each MSC infusion was $1x10^6$ cells per kg of body weight. After infusion, patients received continuous monitoring for two hours.

3. Results

Median age of patients was 7.1 years (range, 1–16 years). Patients' diagnoses were acute myeloblastic leukemia (AML) (n=5, 22.7%), acute lymphoblastic leukemia (ALL) (n=4, 18.1%), beta thalassemia major (TM) (n=4, 18.1%), myelodysplastic syndrome (MDS) (n=2, 9%), juvenile myelomonocytic leukemia (JMML) (n=2, 9%) and others (n=5, 22.7%). HSCT was performed with peripheral blood stem cells (n=16, 72.7%) or the bone marrow (n=6, 27.3%) of 9/10 HLA-matched donors (n=11, 50%), 10/10 HLA-matched (n=9, 41%), or haploidentical donors (n=2, 9%) after myeloablative (n=19, 86.3%) or a reduced intensive condition regimen (n=3, %13.7).

In all patients, aGvHD typically developed while using preventive immunosuppressive medication. Of the 22 aGvHD patients, 11 (50%) and 11 (50%) had grade IV and III aGvHD respectively, with involvement of the skin and the GI tract or the GI tract only. In accordance with protocols, all patients with aGvHD received calcineurin inhibitor (CNI) medication (cyclosporin A or tacrolimus) together with prednisone at a dose of 2 mg/kg daily. 12 patients also received mycophenolate mofetil (MMF). Anti-thymocyte globulin (ATG) was given to 16 patients as serotherapy. Additionally, sirolimus and ruxolitinib were given to three patients each. The median time between transplantation and diagnosis of aGvHD was 30.68 days (range, 5–78 days). Anorexia, nausea, vomiting, diarrhea, and abdominal pain were among the clinical signs of GI aGvHD that all patients showed.

After diagnosis, ECP administration was started for 20 patients for a median of 16 cycles (range 4-28). A total of 310 ECP procedures were performed in all patient groups. No patient experienced side effects. Catheter removal was performed in only one patient due to obstruction. No problems were observed with vascular access leading to reduced processing of whole blood. On day 28, following the start of ECP, 7 out of 22 patients had responded [complete remission (CR), (very good partial remission) VGPR, or partial remission (PR)]. 12 patients received infliximab treatment in the study. 11 of 12 patients who received infliximab treatment also received it together with MSC and/or ECP treatment. The complete remission rate in patients receiving infliximab in addition to ECP and or MSC was 46% (5 in 11 patients). MSCs were given to 15 patients (68.1%). Each patient received a median of 3.6 infusions (range, 1–4 infusions). One patient received one MSC infusion, and 14 patients received two or more MSC infusions.

All surviving patients with aGvHD had their steroid medication stopped six months after the completion of the ECP (seven of 22 patients with steroid-resistant severe aGvHD). All immunosuppressive treatment was stopped in the patients (Patients 1, 2, 5, 6, 7, 8 and 11). No adverse effects were experienced by any of the patients during the infliximab infusion.

As of November 2023, seven (31.8%) out of 22 patients with aGvHD were still alive. At different stages of treatment, 15 non-responders with grade III/IV aGvHD died from causes associated with aGvHD and/or other conditions. The seven surviving patients have been followed for an average of 1141 (±403) days. The most common cause of death was infection (8 cases in 15 patients, 53.3%). Other causes of death were gastrointestinal hemorrhage (n=5, 33.3%), and intracranial hemorrhage (n=2, 13.3%). In addition, when factors causing morbidity were evaluated, it was observed that three patients developed posterior reversible encephalopathy syndrome, two patients developed veno-occlusive disease, and one patient developed hypertension. The estimated probability of survival after 1 year was 31.8%, and the median survival was 655 days.

Table 1. Patient characteristics.

No	Age (yr)	Gender	Diagnosis	Donor, HLA match, stem cell source	Condition Regimen	Serotherapy	GVHD prophylaxis	Onset of GI GVHD post-transplant	Organs involved by aGVHD (stage), overall grade	Inital GVHD therapy	ECP	infliximab	MSCs	Outcome	Cure time (days)	Follow-up (days)	Causes of death
1	4	M	T-ALL	MUD, 9/10, PBSC	Bu+Eto+Cy	ATG	CsA+MTX+MMF	Day+42	GI (4), skin (2), IV	CNI, MMF	12	4	4	Alive	64	1231	
2	12	F	AML-M0	MUD, 10/10, PBSC	Bu+Cy	ATG	CsA	Day+37	GI (4), V	CNI, MMF	28	4		Alive	493	1289	
3	9	F	MDS	MSD, 10/10, BM	Bu+Flu+TT		CsA	Day+37	GI (4), skin (1), IV	CNI, MMF, Ruxolitinib	26		4	Exitus		299	Infection
4	15	M	AML-M0	MUD, 9/10, PBSC	Bu+Cy+Mel	ATG	CsA+MTX+MMF	Day+17	GI (3), III	CNI, MMF, Ruxolitinib ,sirolimus	18		4	Exitus		121	Infection
5	3	M	BTM	MUD, 9/10, PBSC	Bu+Flu+Cy		CsA	Day+18	GI (3), skin (1), III	CNI, MMF	4	4		Alive	142	1162	
6	10	M	T-ALL	MFD, 10/10, PBSC	Bu+Eto		CsA	Day+18	GI (4), IV	CNI	12			Alive	252	1510	
7	5	M	BTM	MUD, 9/10, PBSC	Bu+Flu+Cy	ATG	CsA	Day+25	GI (4), IV	CNI	26	4		Alive	54	1200	
8	16	F	BTM	MFD, 10/10, BM	Treo+Flu+TT	ATG	CsA+MTX	Day+62	GI (3), skin (2), III	CNI, MMF	14	4	4	Alive	124	1420	
9	6	F	SCA	MUD, 9/10, BM	Bu+Flu+Cy	ATG	CsA	Day+14	GI (4), skin (1), IV	CNI	24		4	Exitus		595	IC Hemorrhage
10	7	M	CA	MUD, 10/10, BM	Bu+Cy	ATG	CsA	Day+59	GI (3), skin (2), III	CNI, MMF	18	4	3	Exitus	140		GIS hemorrhage

11	5	M	BTM	MUD, 9/10, PBSC	Bu+Flu+ Cy+TT	ATG	CsA+MTX	Day+5	GI (3), skin (1), III	CNI, MMF	18		4	Alive	61	2318	
12	5	M	AML	MUD, 10/10, BM	Bu+Cy+ Eto		CsA	Day+18	GI (3), III	CNI		4		Exitus		46	GIS Hemorrhage
13	6	F	HLH	MFD, 10/10, PBSC	Bu+Flu		Mtx	Day+25	GI (3), III	CNI	26		4	Exitus		214	IC Hemorrhage
14	2	F	DBA	MFD, 10/10, PBSC	Treo+Flu+ TT		CsA+MTX	Day+13	GI (4), IV	CNI, MMF, sirolimus		4	4	Exitus		51	Infection
15	4	M	JMML	MUD, 9/10, PBSC	Bu+Cy+ Mel	ATG	CsA+MTX	Day+24	GI (3), III	CNI, MMF	12	4	1	Exitus		88	GIS hemorrhage
16	12	M	B-ALL	MFD, 7/10, BM	Bu+Flu+ TT	ATG	CsA+MTX	Day+18	GI (4), skin (2), IV	CNI, MMF, Ruxolitinib	4	3	4	Exitus		120	Infection
17	7	F	B-ALL	MUD, 9/10, PBSC	Bu+Cy+ Eto	ATG	CsA+MTX+ MMF	Day+35	GI (3), skin (2), IV	CNI	8		4	Exitus		112	GIS hemorrhage
18	4	F	JMML	MUD, 6/10, PBSC	Bu+Flu+ TT	ATG	CsA+MMF	Day+69	GI (4), skin (1), IV	CNI, sirolimus	4		2	Exitus		392	Infection
19	10	M	AML-M1	MUD, 9/10, PBSC	Bu+Cy	ATG	CsA+MTX	Day+24	GI (4),IV	CNI	16			Exitus		362	GIS hemorrhage
20	10	M	AA	MUD, 10/10, PBSC	Bu+Cy	ATG	CsA+MTX	Day+23	GI (3), skin (1), III	CNI	12			Exitus		933	Infection
21	1	M	MDS	MUD, 9/10, PBSC	Treo+Flu+ TT	ATG	CsA+MTX	Day+14	GI (3), skin (1), III	CNI, MMF	12	4	4	Exitus		195	Infection
22	3	M	AML-M1	MUD, 9/10, PBSC	Bu+Cy	ATG	CsA+MMF	Day+78	GI (4), skin (2), IV	CNI	16	4	4	Exitus		114	Infection

Abbreviations: M;male, F;female, AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, MDS; myelodisplastic syndome, BTM; Beta-Thalassemia Major, SCA; sickle cell anemia, HLH; hemophagocytic lymphohistiocytosis, CA; congenital neutropenia, DBA; Diamond–Blackfan anemia, AA;aplastic anemia, MUD;matches unrelated donor, MFD;matched family donor, Bu;busulfan, Cy;cyclofosfamid, Eto;etoposit, Flu; fludarabin, Tre;treosulfan, Mel;melphalan, PBSC; peripheral blood stem cell, Csa; sandimmun, MTX; methotrexate, TT;thiotepa, GI; gastrointestinal, CNI; calcineurin inhibitors, MMF; mycophenolate mofetil, IC; intracranial.

4. Discussion

Acute graft-versus-host disease is a common complication after allo-HSCT. Steroid refractory aGvHD frequently has a poor response rate and increases the risk of treatment sequelae such as life-threatening infections, hyperglycemia, hypertension, and growth retardation. The prognosis is dismal and there is currently no proven second-line therapy for patients who do not respond to corticosteroid therapy (15). Several immunosuppressive agents such as MMF, methotrexate, antitumor necrosis factor (anti-TNF) or anti-TNF receptor antibodies (etanercept and infliximab), extracorporeal photopheresis, and MSCs are commonly used in treatment (16). The positive effects of MSCs and ECP, as well as infliximab, on treatment outcomes in steroid-resistant GI aGVHD, have been shown in many studies in the literature (7,8,15,16).

MSCs are pluripotent cells found in bone marrow that differentiate into muscle, adipose tissue, cartilage, and bone. MSCs can be found in a variety of tissues, including the bone marrow, placenta, umbilical cord, tooth pulp, and adipose tissue. These cells can be effectively generated in vitro following plastic adhesion and density centrifugation. They play a crucial role in the healing of tissue injury and the control of inflammation, both of which are necessary for the therapy of aGvHD. The production of various growth factors and the expression of adhesion molecules for cell-to-cell contacts are the mechanisms via which MSCs affect immunomodulation (17). Numerous research studies have indicated that MSCs may be helpful in treating aGvHD that is steroid-refractory without presenting any safety issues (18).

In the therapeutic procedure known as extracorporeal photopheresis (ECP), buffy coat cells are isolated via centrifugation and then sensitized using 8-methoxypsoralen. After being exposed to UVA light, 8MOP is photoactivated, which causes DNA cross-linking and rapid cell death 72 hours later (19). For both acute and chronic GvHD patients, the use of ECP has been demonstrated to be a promising therapy approach (19,20).

A chimeric (human-murine) monoclonal IgG1-kappa anti-TNF-α antibody, infliximab has been shown to be clinically effective against a number of autoimmune diseases, such as inflammatory bowel disease and juvenile idiopathic arthritis. Previous studies have demonstrated that infliximab sucsessful treatment option for steroid-refractory aGVHD (21,22). It is well tolerated medicine and appears effective in children with steroid-refractory or dependent GI aGVHD. Similarly, in our study, it was observed that the CR rate was high (46%) in patients in which infliximab treatment was combined with ECP and/or MSC.

The occurrence of grade II-IV aGVHD in pediatric patients varies depending on many factors, including donor type [HLA-matched sibling donor (MSD), HLA-matched family donor (MFD) or HLA-matched unrelated donor (MUD)] and HLA incompatibility. The incidence of grade II-IV aGVHD ranges between 40 and 85% from an unrelated donor and averages approximately 27% after hematopoietic stem cell transplantation from an HLA-identical sibling (5-7).

The major cause of GvHD is mismatches between major and/or minor histocompatibility antigens between the donor and recipient, which lead to donor T cells reacting to recipient tissue antigens. One potential risk factor for GvHD has been the effect of donor and recipient polymorphisms in cytokine genes that play important roles in the characteristic "cytokine storm" of GvHD (23). Numerous polymorphic genes, such as variations of interferon-γ (IFN γ), interleukin 10 (IL-10), and tumor TNF-α, have been linked to GvHD (24). The monoclonal antibody infliximab inhibits the connection between TNF-α and its receptors, hence preventing TNF- α's subsequent actions. No clear evidence exists to support the claim that a particular second-line medication helps these patients achieve better results. Currently, steroid-refractoriness is the only circumstance in which second-line therapy is employed. Previous research has investigated the function of infliximab in the context of

steroid-refractory or dependent aGvHD (13). Treatment outcomes for aGvHD with infliximab have been inconsistent. The majority of these studies have demonstrated infliximab's effectiveness in treating steroid-refractory aGvHD. In the study conducted by Yang et al., in 10 children diagnosed with leukemia and thalassemia who underwent HSCT, infliximab was found to be well tolerated and effective in the treatment of steroid-refractory or dependent GI aGvHD (25). In a retrospective study with 68 patients with grade III/IV aGvHD, 41 patients (60%) showed a response to infliximab therapy. However, 61 patients (90%) experienced infections, and 17 patients (33%) died as a result of infections (8). In our study, in 5 out of the 12 (41.6%) patients receiving infliximab treatment (with additional salvage treatments), aGvHD regressed and a cure was achieved. The most common cause of death was infection, similar to the literature (five patients, 71.4%).

MSCs have been studied in numerous clinical trials as a potential cellular treatment for aGvHD over the past 20 years. A substantial number of clinical trials, with varying success rates, verified the safety of MSCs in pediatric patients with steroid-refractory aGvHD (26,27). On the other hand, compared to adults, children revealed a tendency toward better CR (28). Recently, the results of a multicenter study conducted by Bader et al. with 60 pediatric and adult patients with steroid-resistant aGvHD and concomitant multiple immunosuppressive therapy were published. In the study, which included patients diagnosed with Grade III (36%) and IV (59%) aGvHD, the average MSCs dose was 1.4×10^6 MSCs/kg. On average, a total of 3 doses were administered. The cumulative incidence of non-relapse mortality was estimated to be 27% at six months (29). In this case series, 15 patients received an average of 3.6 doses of MSCs (with additional infliximab and/or ECP). The cure was achieved in three (20%) of the patients. Study results that are not consistent may be due to variations in the pharmacological quality of MSCs brought on by the absence of a uniform approach for MSC creation, dosage, and inter-donor heterogeneity (27).

ECP has a low side effect profile and has shown to be effective in treating both aGvHD and cGvHD (chronic graft-versus-host disease), even in patients unresponsive to conventional immunosuppressive treatments, especially in skin involvement (30). In our study, ECP was applied to all patients except 2 for a number of cycles ranging from 4 to 28. Apart from tenderness of the eye and central venous catheter obstruction in a limited number of cases, no serious side effects were observed. An efficacy evaluation could not be made for ECP alone, as it was given together with multiple salvage immunosuppressive therapy with infliximab and MSCs. However, among patients on immunosuppressive therapy, the mean time to achieve CR for seven surviving patients was 170 (±158.4) days. In a retrospective study, Winther-Jørgensen et al. evaluated the feasibility, safety, and efficacy of ECP in 15 children with steroid-dependent/refractory acute or chronic GvHD who received ECP treatment. Although only a few mild side effects were observed, six of nine patients with Grade II-III aGvHD responded to treatment on day 28, and CR was achieved in all patients after the last ECP treatment[7].

5. Conclusion

In this retrospective study, we showed the effect of a combination treatment of steroid-refractory aGvHD. But even with differences in immune systems and baseline transplant characteristics between pediatric and adult patients, aGvHD remains a leading cause of mortality and morbidity following aHSCT. It will be crucial to show the safety and efficacy of novel treatments in comprehensive, randomized clinical trials, particularly for those who become refractory to systemic steroid medication, as the number of patients undergoing this procedure rises. Determining new targets will continue to depend on our understanding of the GvHD's etiology.

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Ethics

Ethics Committee Approval: The study was approved by Acibadem University Noninterventional Clinical Research Ethical Committee (Decision no: 2021-20/06, Date: 14.10.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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