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Original scientific paper

Treatment of patients with severe aplastic anaemia with allogeneic stem cell transplantation - single centre experience

Marija Popova-Labachevska[1*], Aleksandra Pivkova-Veljanovska[1], Sanja Trajkova[1], Lazar Chadievski[1], Borce Georgievski[1], Lidija Cevreska[1], Nevenka Ridova[1], Simona Stojanovska Jakimovska[1], Milena Grivchevska[1], Bojan Labacevski[2], Irina Panovska-Stavridis[1]

[1]*University Clinic for Hematology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Mother Thereza 47, 1000 Skopje, North Macedonia*
[2]*Institute of Preclinical and Clinical Pharmacology with Toxicology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Mother Thereza 47, 1000 Skopje, North Macedonia*

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Abstract

Aplastic anemia is a rare hematological syndrome caused by bone marrow failure and pancytopenia. It can be either inherited or acquired, the second one being more common. A variety of trigger factors have been implicated in the etiology of acquired aplastic anemia. However, in around 70% of the cases, the reason remains unknown. The two first line treatment options with competitive rate of success are immunosuppressive therapy (IST) and allogeneic stem cell transplantation (SCT). In this retrospective study we present our experience in the treatment of thirteen patients with severe acquired aplastic anemia. Six of the patients mentioned underwent matched unrelated (MUD) SCT and had all been previously treated with IST, except for one patient. The remaining seven patients included in our study underwent matched related SCT, without previous IST. Conditioning regimen, graft versus host prophylaxis, veno occlusive disease prophylaxis, antimicrobial prophylaxis and treatment, source of stem cells, as well as blood counts were taken into account, within a 7 year follow up period on average. Our findings revealed an overall survival rate of 92%. Three cases of graft versus host disease were observed, two within the MUD SCT group of patients (33%) and one within the matched related SCT group (17%). Faster engraftment was reached in patients treated with matched related SCT. One patient demanded a second allogeneic SCT. Comparable to other findings in literature, our study corroborated the favorable outcome of both allogeneic related and unrelated hematopoietic stem cell transplantation in the treatment of patients with severe aplastic anemia.

Key words: aplastic anemia, immunosuppressive therapy, stem cell transplantation

Introduction

Aplastic anemia (AA) is a rare hematological disease characterized by inability of bone marrow to produce mature blood cells leading to different degrees of peripheral blood cytopenia, without abnormal infiltrate or bone marrow fibrosis (Bacigalupo, 2017). Primarily affected are children, young adults, and those over 60 years of age (Montane et al., 2008).

Estimated incidence rate ranges from 1-2 per million population each year, and it appears to be two to three times higher in Asia than in Europe (Bacigalupo, 2017; Montane et al., 2008). AA can be classified as either

*email: marijapopova85@yahoo.com

inherited or acquired. Inherited forms of AA account 20% of all AA cases, they are group of rare genetic diseases usually associated with germ line mutations and characterized with physical anomalies, presentation usually in the first decade of life and increased risk of secondary malignancies.

Majority of acquired AA cases are idiopathic (70-80%), so diagnostic approach must include tests that will exclude other possible etiologies of AA. Bone marrow biopsy is mandatory and will show "empty" bone marrow without signs of infiltration of any kind nor fibrosis. Pathophysiology of idiopathic AA is not fully known, but many studies have shown that at the basis of the disease there is autoreactive T cell mediated destruction in combination with deteriorated bone marrow microenvironment (Young et al., 2006).

Many trigger factors have been implicated in the development of AA, including drugs, infections, chemicals etc., so careful drug or occupational exposure history should be obtained. Usually 2-6 months between drug exposure and the development of AA is needed, and any potential causative drug should be discontinued (Bacigalupo, 2017).

Clinical presentation varies depending of disease severity accessed with the use of Camitta criteria by which patients are classified as very severe, severe, or non-severe AA cases (Camitta et al., 1975). Patients usually present with symptoms of anemia, hemorrhagic syndrome and infections, although serious infections are not frequent early in the course of the disease. Symptoms vary depending of disease severity and may be severe and life-threatening or minor enough to not require transfusion support (De Zern and Churpek, 2021).

However, if left untreated, mortality rate of AA exceeds 80% in the first two years of diagnosis, and major cause of death are infections (Höchsmann et al., 2013).

Hence, early and prompt diagnosis is essential because among disease severity and patient's age and comorbidities, the interval between diagnosis and start of treatment is another strong predictor of survival (Höchsmann et al., 2013). Once the diagnosis is established, taking the patient's age into account, HLA typing is the next step that needs to be taken, since allogeneic hematopoietic stem cell transplantation (HSCT) from a HLA- matched sibling donor (MSD) is well established first line therapy with great rate of success (Valdez et al., 2011). For those patients in whom bone marrow transplant isn't an option, immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporine A (CyA) is the treatment of choice. Studies have shown similar rates of success (>80%) between these two first line therapy options (Killick et al., 2016; Valdez et al., 2011).

Choice between these two major competing treatment options depends on several variables like patient's age, performance status, disease severity and availability of HLA –matched donors especially related (Killick et al., 2016).

The aim of this study was to evaluate the success of allogeneic related and unrelated hematopoietic stem cell transplantation in the treatment of patients with severe aplastic anemia diagnosed and treated at the University Clinic of Hematology, in Skopje, Republic of North Macedonia.

Material and methods

The study was conducted at the University Clinic of Hematology, Skopje, R. of North Macedonia and included retrospective analysis of 13 patients diagnosed with severe form of aplastic anemia and treated with allogeneic stem cell transplantation (allo-SCT), related and unrelated. Median follow up period was 7 years (2-20 years). In all patients conditioning regimen with cyclophosphamide 200 mg/kg (from day -5 to day -2) and ATG (from day -5 to -3) was used. Prophylaxis against graft versus host disease (GVHD) consisted of Cyclosporine A (CyA) and methotrexate (MTX) according to Seattle protocol; prophylaxis against veno occlusive disease was conducted with ursodeoxycholic acid and low molecular weight heparin; antibacterial, antiviral and antimycotic prophylaxis and treatment was tailored individually according to patient's status. We used bone marrow (BM) as stem source in two pts, and in other 11, peripheral stem cells. Blood parameters (hemoglobin, leucocytes, absolute neutrophil count, platelets) were analysed at diagnosis, at engraftment achievement and during follow up. Engraftment was defined by peripheral blood neutrophil count of > 500 x 10^6/L (Wolff, 2002), and platelet count of more than >20 x 10^9/L (Teltschik et al., 2016).

Results and discussion

This study included 13 patients with severe AA admitted at our clinic with various degree of pancytopenia. Definitive diagnosis of AA was established with histological analysis of bone marrow biopsy after excluding other possible causes for pancytopenia. According to Camitta criteria patients were referred as severe AA cases (neutrophils <0.5 x 10^9/L, platelets <20 x 10^9/L, reticulocytes <20 x 10^9/L, bone marrow cellularity <25%). In our study, 7 patients underwent related allogeneic SCT; in 6 pts matched unrelated SCT (MUD SCT) was performed and in three of them, the procedure was performed abroad and they were followed at our clinic afterward. Table 1 shows patient's characteristics that underwent MUD SCT.

Mean age at diagnosis was 29.5 years (17-45); Five patients were initially treated with IST consisted of ATG plus Cy A and supportive treatment with blood and platelet transfusions according to standard guidelines and one patient proceeded directly to MUD SCT; mean time from diagnosis to MUD SCT in 5 pts that were initially treated

with IST was 20 months and in the one that directly underwent MUD SCT was 2 months after diagnosis. Hemoglobin, leucocyte and platelet counts of the pts are shown in Fig. 1, 2, and 3 respectively. GVHD was observed in two pts (33%) as shown in Fig. 4.

Table 1. Patient's characteristics that underwent MUD SCT

	Age at diagnosis	Year of diagnosis	Patient gender	Initial hemoglobin g/L	Initial leucocyte count 10^9/L	Initial ANC (10^9/L)	Initial Platelets (10^9/L)
T.D	17	2014	Female	78	3.1	1.0	11
R.P	14	2019	Male	84	0.4	0.2	17
I.J	45	2017	female	62	2.9	0.9	23
M.D	39	2018	Male	51	2.8	0.8	19
S.D	31	2018	Male	93	0.8	0.1	28
I.P	31	2012	female	89	1.0	0.5	30

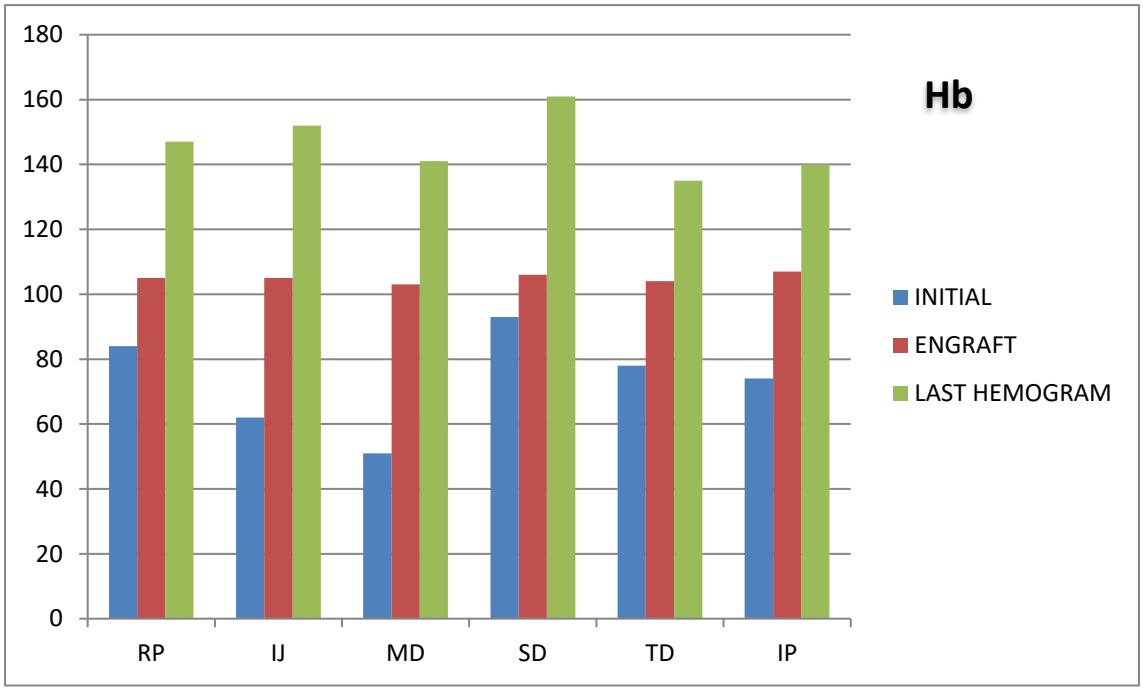

Fig. 1. Hemoglobin count (initial, engraft and last hemogram) of patients that underwent MUD SCT.

Patients' characteristics that underwent matched related SCT are shown in Table 2. Mean age at diagnosis was 18.5 years (12-28); none of the patients were treated with IST prior SCT; mean time from diagnosis to SCT was 6.5 weeks. Hemoglobin, leucocyte and platelet counts are shown in Fig. 5, 6 and 7 respectively. Of 7 pts, one patient died at day +10 of SCT and of the remaining 6, only one developed GVHD (17%) in the form of scleroderma, shown in Fig. 8.

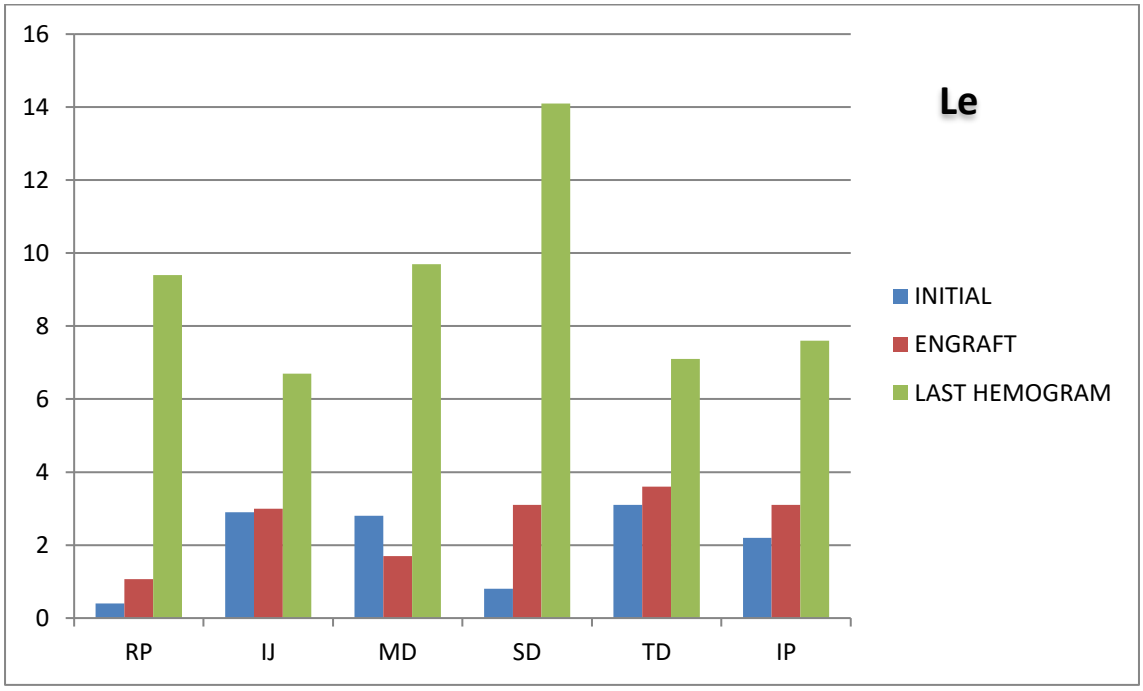

Fig. 2. Leukocyte count (initial, engraft and last hemogram) of patients that underwent MUD SCT.

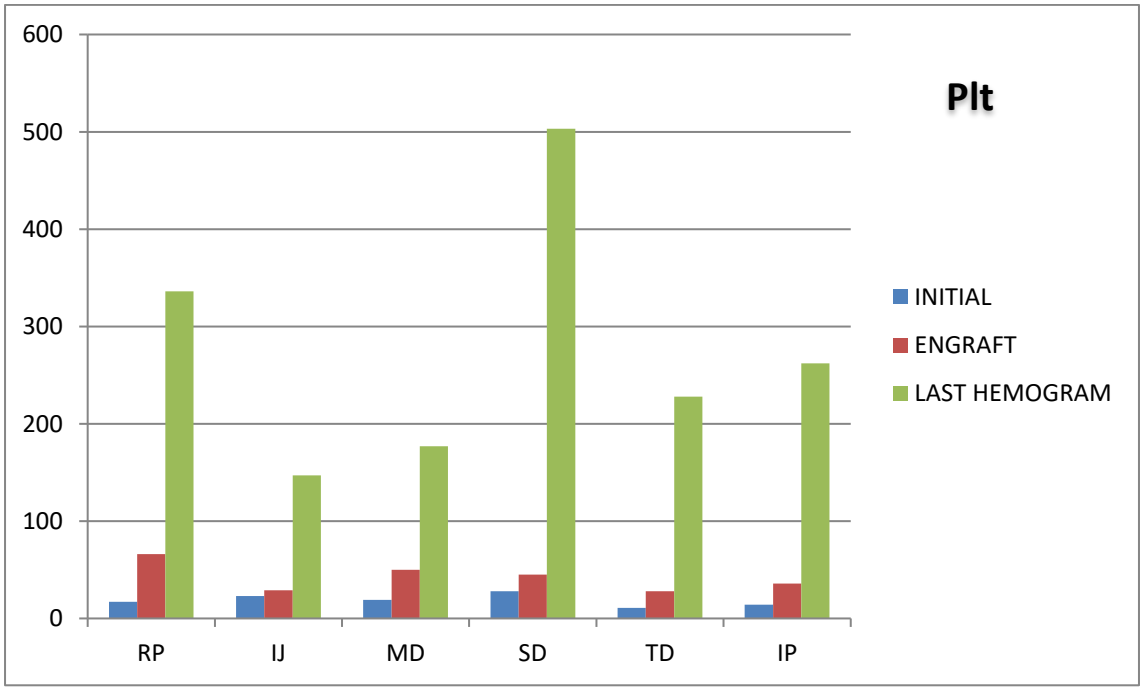

Fig. 3. Platelet count (initial, engraft and last hemogram) of patients that underwent MUD SCT.

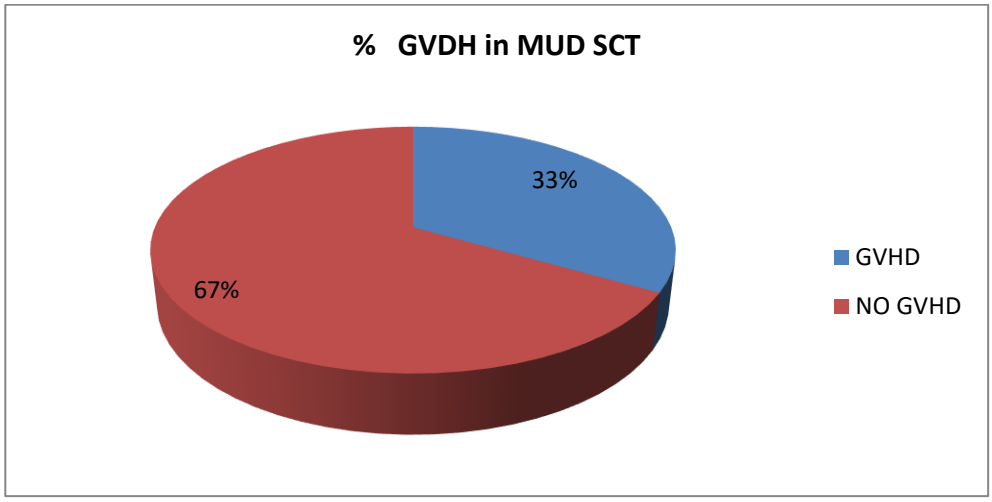

Fig. 4. GVHD % in MUD SCT.

Table 2. Patient's characteristics that underwent matched related SCT

	Age at diagnosis	Year of diagnosis	Patient gender	Initial hemoglobin g/L	Initial leucocyte count 10^9/L	Initial ANC (10^9/L)	Initial Platelets (10^9/L)
A.S	15	2020	female	33	3.6	0.8	18
A.K	28	2016	female	113	5.4	1.0	36
E.F	19	2018	male	63	2.8	0.7	13
A.P	16	2016	female	101	1.3	0.5	60
S.D	21	2012	male	85	2.0	0.5	9
D.M	?	2002	male	90	3.0	0.5	20
A.S	12	2012	female	90	2.0	0.6	5

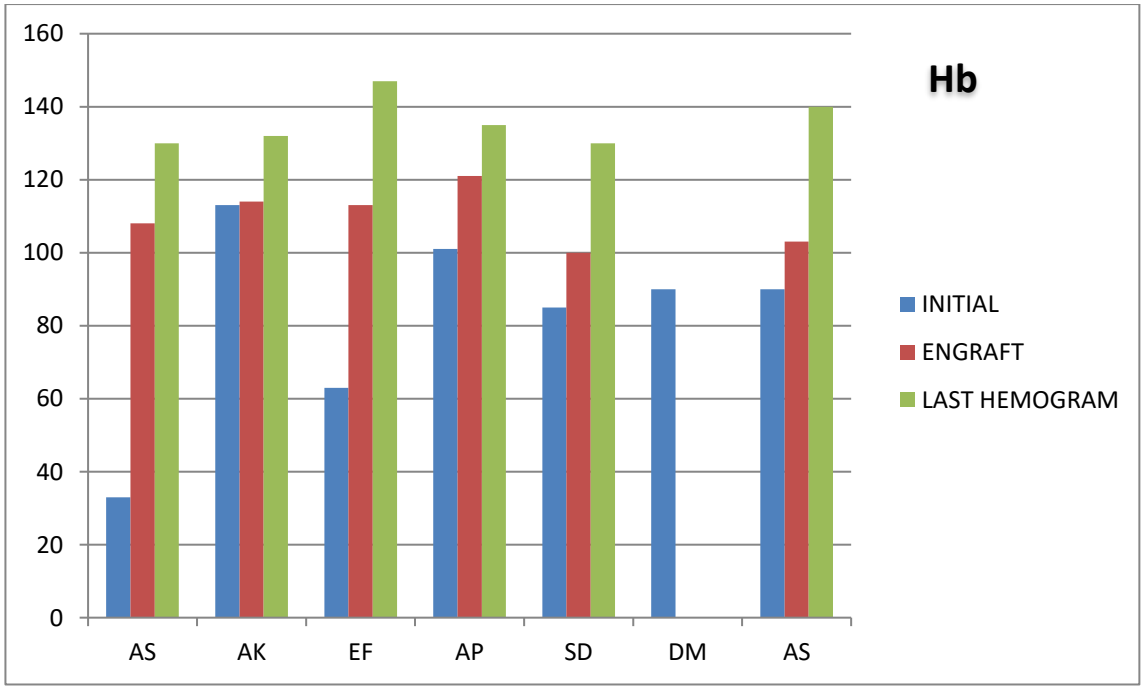

Fig. 5. Hemoglobin count (initial, engraft and last hemogram) of patients that underwent matched related SCT.

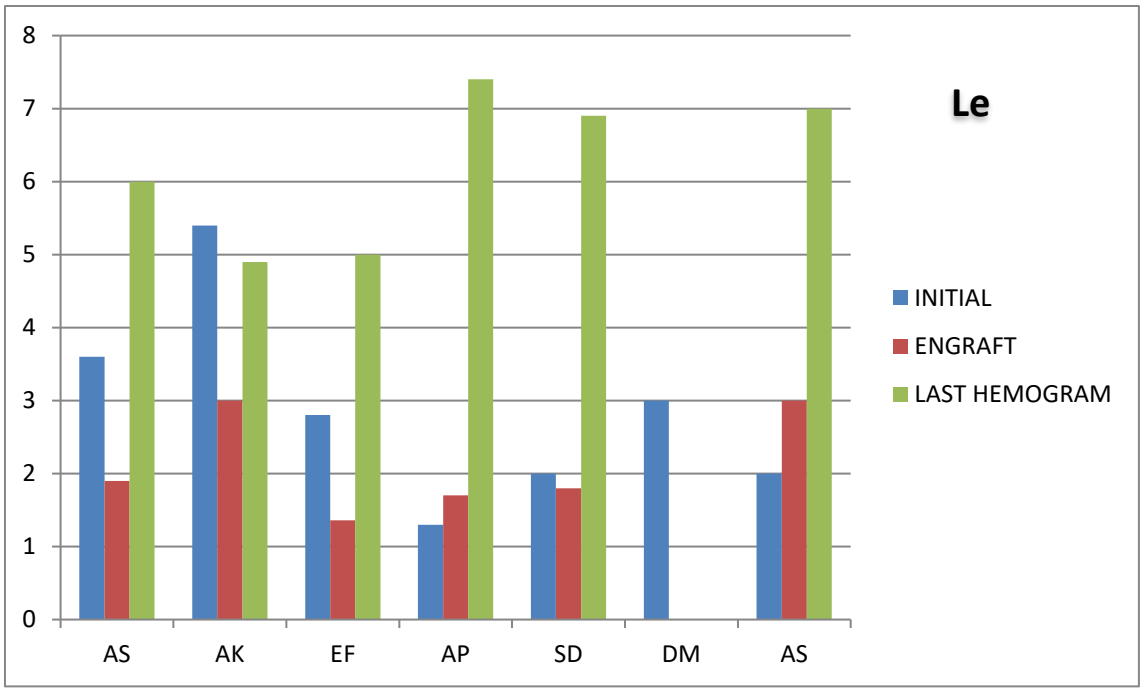

Fig. 6. Leukocyte count (initial, engraft and last hemogram) of patients that underwent matched related SCT.

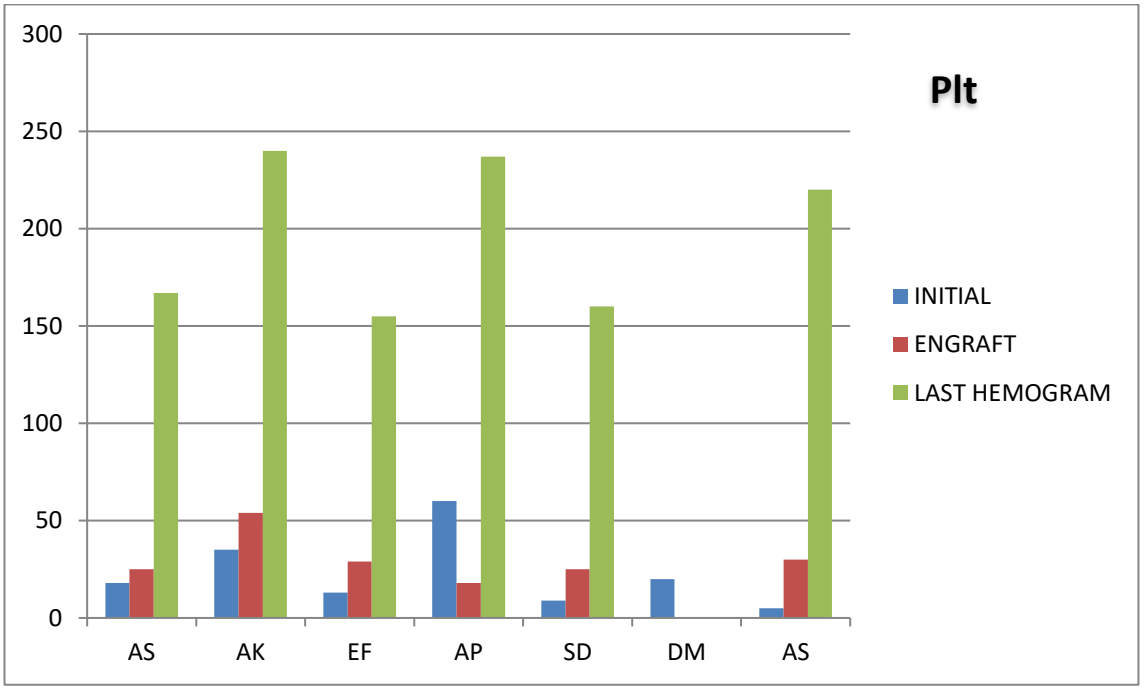

Fig. 7. Platelet count (initial, engraft and last hemogram) of patients that underwent matched related SCT.

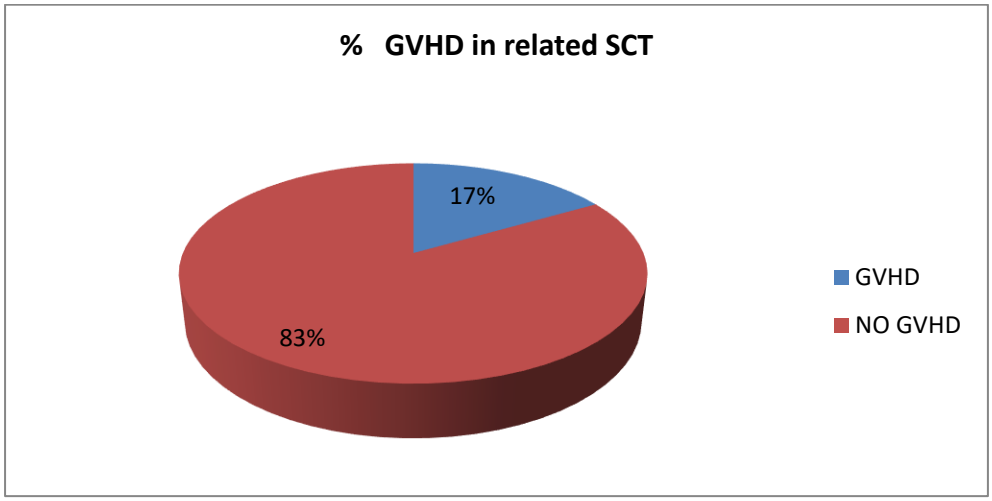

Fig. 8. GVHD % in matched related SCT.

Our study observed that engraftment was achieved faster in pts with related allogeneic SCT (mean time to engraftment at day +13) then in those with MUD SCT (at day +20.5) ($p<0.05$) (Fig. 9).

Overall survival in our cohort was 92% i.e. of total of 13 pts only one died at Day +10 of the procedure relapse was observed in one patient and second allogeneic related SCT was performed and this patient is free of disease at the moment (Fig. 10).

Discussion

Allogeneic SCT and IST are two first line treatment options with similar success rates, with the first being preferred in younger patients, especially in those <40 years (Killick et al., 2016, Marsch et al., 2009). In older patients, preference is given to IST because of the higher incidence of graft failure and GVHD, with exceptions in selected cases with good performance status and severe AA where SCT should be carefully considered (Bacigalupo et al., 2000, De Zern et al., 2020). Although data from several studies show superior outcomes with BM stem cell source compared with peripheral stem cells, our experience shows no difference in terms of GVHD development or overall survival (Bacigalupo et al., 2000). Prevention of bleeding and infective complications before start of treatment was also of great significance that contributed to the high rate of overall survival in our group of patients. Our results in terms of overall survival are consistent with data from literature, showing that early and prompt diagnosis, and treatment of AA cases is essential in order to achieve long and sustainable remission of the disease.

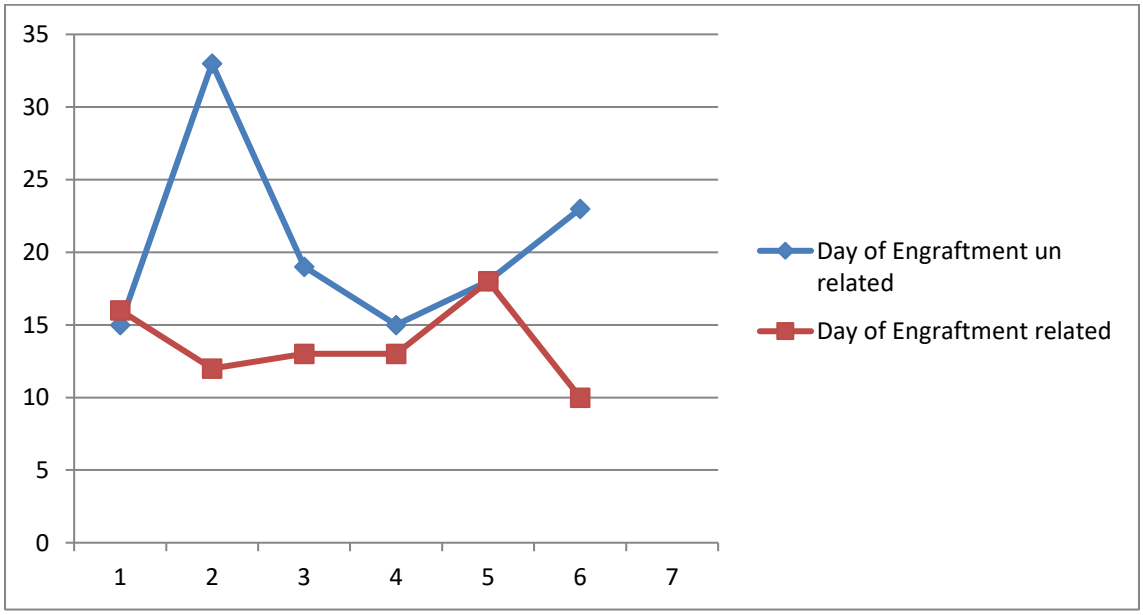

Fig. 9. Day of engraftment in patients that went MUD SCT and matched related SCT.

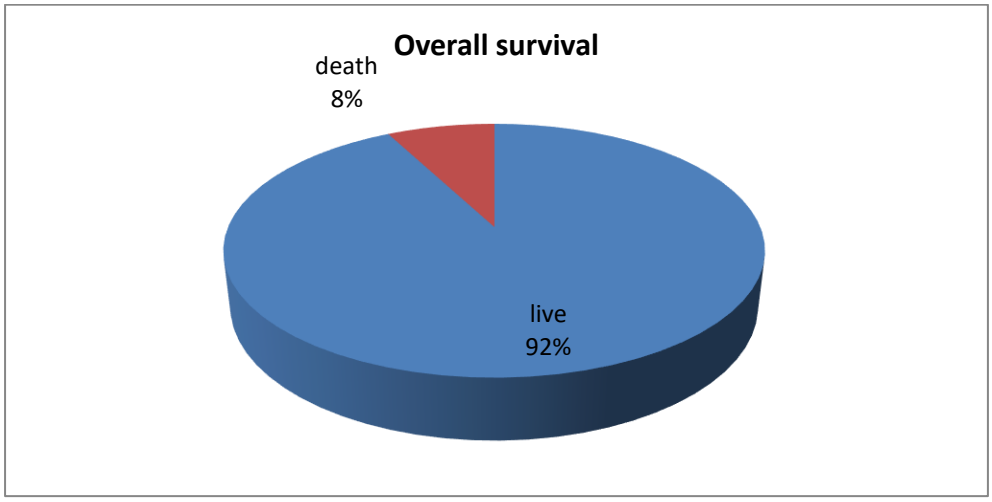

Fig. 10. Overall survival rate in the cohort.

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Резиме

Третман на пациенти со тешка апластична анемија со алогена трансплантација на хематопоетски матични клетки - наши искуства

Марија Попова-Лабачевска[1], Александра Пивкова-Вељановска[1], Сања Трајкова[1], Лазар Чадиевски[1], Борче Георгиевски[1], Лидија Чевреска[1], Невенка Ридова[1], Симона Стојановска Јакимовска[1], Милена Гривчевска[1], Бојан Лабачевски[2], Ирина Пановска-Ставридис[1]

[1]Универзитетска клиника за хематологија, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Мајка Тереза 47, 1000 Скопје, Р. Северна Македонија
[2]Институт за претклиничка и клиничка фармакологија и токсикологија, Универзитет „Св. Кирил и Методиј“, Мајка Тереза 47, 1000 Скопје, Р. Северна Македонија

Клучни зборови: апластична анемија, имуносупресивна терапија, трансплантација на хематопоетски матични клетки

Апластичната анемија е редок хематолошки синдром кој се карактеризира со неспособност на коскената срцевина за продукција на крвни елементи и последователна панцитопенија. Може да биде вродена или стекната, со поголема инциденца на второспоменатата форма. Широк спектар на етиолошки фактори се поврзуваат со појавата на апластична анемија, но кај околу 70% од случаите етиологијата останува непозната. Доколку остане нелекувана, стапката на морталитет надминува 80% во првите две години од дијагноза. Поради тоа, навремено поставување дијагноза и почнување терапија е од основно значење. Прва линија на третман за оваа болест се имуносупресивна терапија и алогена трансплантација на хематопоетски матични клетки, со слична стапка за успех. Во оваа ретроспективна студија го прикажуваме нашето искуство со третман на 13 пациенти со тешка форма на апластична анемија со алогена трансплантација, сордна и несродна. Кај шест од овие пациенти беше спроведена алогена несродна трансплантација на хематопоетски матични клетки, по претходно ординирана имуносупресивна терапија (со исклучок на еден пациент кај кој директно е спроведена алогена несродна трансплантација на хематопоетски матични клетки). Кај останатите седум пациенти спроведена беше алогена сродна трансплантација на хематопоетски матични клетки, без претходно истите да бидат поставени на имуносупресивна терапија. Просечен период на следење на пациентите изнесува седум години, и беа следени хематолошките параметри во моментот на поставување дијагноза, во периодот на прифаќање на графтот како и последните хематолошки вредности, и појава на калем против домаќин болест.Стапката на преживување согласно резултатите добиени во нашата студија изнесува 92%. Нотирани беа три случаи на болест калем против домаќин, и тоа кај двајца пациенти третирани со несродна (33%) и еден пациент (17%) третиран со сродна алогена трансплантација на хематопоетски матични клетки. Забележано беше побрзо прифаќање на графтот кај пациентите третирани со сродна алогена трансплантација на хематопоетски матични клетки и потреба од втора алогена трансплантација на хематопоетски матични клетки имаше кај еден пациент и истиот е без знаци за болест во моментот. Согласно претходните податоци и сознанија во литературата, нашата студија потврдува дека алогената трансплатација на хематопоетски матични клетки, сродна и несродна, се успешна прволиниска тераписка метода кај пациентите со тешка форма на апластична анемија.