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Research Article

The Dilemma of Transplanting Wiskott-Aldrich Syndrome Patients to Transplant or not to Transplant

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ABSTRACT

Wiskott-Aldrich syndrome (WAS) is an X-linked primary immune deficiency disorder, It represents almost 3-5% of all our Primary Immune Deficiency Disease (PIDD) patients while Severe Combined Immune Deficiency (SCID) represents over 60% of all PIDD since the autosomal recessive takes the lead due to high rate of consanguinity in marriages.

In this study we report 29 patients presented to our center and recorded in our database. Two families were excluded because of suspected Wiskott-Aldrich Interacting Protein (WIP) rather than WAS mutation.

Twenty confirmed WAS patients have stem cell transplant, 14 patients received transplant from HLA-identical matched related donors while 6 patients received HLA- matched unrelated cord blood stem cells. We did not perform any MUDD or T-cell depleted haploidentical stem cell transplant in our center on any of our WAS patients.

The overall survival of the transplanted patients was 89.5%, with 100% survival in the HLA-matched related stem cell recipients and 66.6 % survival in the matched –unrelated Cord blood stem cell recipients. Survival among non-transplanted patients was only 60% till the end of the study with very poor quality of life.

According to our findings we highly recommend Hematopoietic stem cell transplantation in patients with WAS as early as possible if a full-matched related donor available, for those with no such donor, Cord blood hematopoietic stem cell represent a good alterative in these patients especially those with severe disease.

Keywords: Wiskott-Aldrich Syndrome (WAS), Primary Immune Deficiency Disease (PIDD), Hematopoietic stem cell transplantation (HSCT)

Introduction

Wiskott-Aldrich syndrome is an X-linked disorder caused by mutations in the gene that encodes the Wiskott-Aldrich syndrome protein (WASp). The classic features of WAS include 1) immune deficiency due to both innate & adaptive immune defects & thus increased susceptibility to infections, 2) micro thrombocytopenia, and eczema [1,2]. WAS is not as common in the Middle East as it is in the western world since the autosomal recessive types of Primary Immune Deficiency Diseases (PIDD) takes the lead in our region due to high rate of consanguinity in marriages. WAS cases represents only 3-5 % from all PIDD in our population, while Severe Combined Immune Deficiency (SCID) represents more than 60% of PIDD cases [3-5].

Mutations of the *WAS* gene on the X chromosome are responsible not only for classic WAS, but also for X-linked thrombocytopenia (XLT) and in rare instances, congenital X-linked neutropenia (XLN) [6,7].

Thrombocytopenia with small sized platelets is the most consistent feature of the disease. It is caused by ineffective thrombocytopoiesis [8], reduced platelet survival due to intrinsic platelet abnormalities, or immune-mediated mechanisms [9,10]. Hemorrhage occurs in greater than 80% of patients. Severe bleeding episodes (intestinal & intracranial hemorrhages) are common (20%- 30%) and cause death in 4% to 10 % of patients [11,12].

Several immunologic abnormalities may play a significant pathogenic mechanism in WAS patients leading to recurrent and sever infections. WAS protein plays a crucial role in actin cytoskeleton remodeling [13]. Thus,WAS patients have defective migration and homing of several cell lineages. In the myeloid lineage cells exhibit impaired phagocytosis and chemotaxis [8,14] predisposing WAS patients to bacterial infections like; otitis media, skin abscesses, pneumonia, sepsis, meningitis.

Many T cell abnormalities has been described in WAS patients leading to increase susceptibility to viral infections especially herpes simplex & cytomegalovirus which are common and sever in patients with WAS.

Defective T cell function in WAS patients is due to impaired migration, adhesion and insufficient interaction with other cells due to abnormal synapse formation. The declining numbers of lymphocytes over time in WAS patients is due to accelerated cell death. In addition proliferation of T cells to specific antigens and to anti-CD3 is reduced [15].

Serum levels of IgA and IgE may be increased in WAS patients while IgM levels are usually decreased. Antibody responses to T cell-independent antigens such as bacterial polysaccharide antigens and certain T cell-dependent protein antigens may be impaired [16].

Circulating NK cell numbers are normal or increased, but cytotoxicity of WASP-deficient NK cells is defective [17,18] and this also contribute to increased frequency of viral infections.

The incidence of autoimmune manifestations like autoimmune hemolytic anemia, vasculitis, arthritis, nephropathy, inflammatory bowel diseases & autoimmune thrombocytopenia is markedly increased among WAS patients.

Malignancies predominantly lymphoma, leukemia & myelodysplasia have been reported in up to 22% of patients in two series [14]. Malignancies in patients with WAS are usually fatal if they did not undergo HSCT or gene therapy.

Life expectancy of patients with classic WAS is reduced if they did not receive HSCT with bleeding being the leading cause of death. Other causes of death in WAS patients are infections, autoimmune disease and malignancies [16].

Treatment modalities include prophylactic antibiotics and immunoglobulins replacement therapy but the curative treatment is hematopoietic stem cell transplantation.

Hematopoietic Stem Cell Transplantation (HSCT) represents the curative treatment in WAS patients with replacement of the defective hematopoietic cells with normal donor cells.

In many previous reports, HSCT accomplished has a high rate of success in a majority of patients, if treatment was done at young age. Best results reported by using HLA-matched donors [19-22].

In patients lacking such a donor, Cord blood hematopoietic stem cell represents an alternative option with reasonable rate of success. Other types of hematopoietic stem cell transplantation also improved survival for WAS patients but has less satisfactory results [18].

In this study, we report the analysis of 20 transplanted WAS patients out of total 29 WAS patients referred to our tertiary center and recorded in our data base. We also compare our transplant results for WAS patients to similar results reported from other centers.

Patients and Methods

We retrospectively analyzed our experience with of hematopoietic stem cell transplantation in patients with WAS recorded in our data base till August 2014 at our tertiary center.The number of patients recorded who had WAS phenotype was 38 patients, we enrolled in this study only 29 patients, 7 patients from 2 families with a high number of affected females were excluded because of suspected WIP rather than WASP mutation. WIP was confirmed in one family of 5 patients and yet to be confirmed in the other family of 2 patients. We also excluded 2 patients who received MUDD hematopoietic stem cell transplantation before outside our center and both expired post transplantation abroad.

Out of the 29 patients analyzed in the study 14 patients received transplant from HLA-identical matched related donors & 6 patients received HLA- matched unrelated cord blood stem cells. (Patient characteristics are summarized in Table 1 and 2).

Clinical, molecular & laboratory data were collected from medical records and from our ICIS system before & after stem cell transplantation & recorded in a specific data collection sheet.

Informed consent was taken from the parents of all children& study was approved by the ethical committee in the hospital.

Hematopoietic stem cell transplantation

HCT was performed according to the hospital protocols, Transplantation was done using HLA- full matched related donors (FMRD) or matched unrelated cord blood stem cells (MUCBT). Cord blood stem cells were obtained from New York city USA before 2010 but after that 80% of cod blood stem cells came from our national cord blood bank.

Table 1: Characteristic and outcome of transplanted patients.

PT	Gender	WAS score	Age at trans-plant	Transplant	Engraftment	Last STR post	Time till platelets engraftment	Platelet transfusion after transplant	Outcome/ complications	Spleene-ctomy	Comments	Current age
1	M	?	50 M	FM sibling	engrafted	engrafted	?	No recent available data	Cured, no infection	NO	first case 1984	38
2	M	?	27 M	FM sister	Engrafted	100 % L&M	?	No platelet transfusion for long time	Cured, no infection, Thyroid adenoma, left hemithyroidectomy with follicle atypia 2012, he developed (thyroid cancer recently)	Yes	Normal platelets count	29
3	M	?	17 M	FM sibling	engrafted	engrafted	?	No recent available data	Cured, no infection	No	Normal platelets count	25
4	M	2	55M	FM sister	engrafted	L : 100 % M: 85 %	?	No platelet transfusion for long time	Cured, no infection	No	Normal platelets count	25
5	M	2	22 M	FM sister	100% L&M	100% L&M	?	No platelet transfusion for long time	Cured, no infection, growth delay, s/p growth hormone theapy	No	Normal platelets count	18
6	M	5	32 M	CBT	L: 97% M: 96.6%	L: 97% M: 96.4%	52 days	Expired	Expired	No	Expired due to sever Adenovirus infection	Deceased
7	M	2	9M	CBT RIC	L: 46.4% M: 23.4%	L: 94% M:17%	28 days	No platelet transfusion for long time	Cured/Seizure BCGitis GVHD skin	Yes	Pre transplant ICH, Normal platelets count	13
8	M	2	11 M	FM sister	L: 84.3 % M: 4.7 %	L: 54% M:19%	poor platlet engrafment	No platelet transfusion for long time	No bleeding plat count 31-51x109 No infection	No	refused 2nd transplant	20
9	M	3-4	19 M	FM sister	99.8 % L&M	100 % L&M	30 days	No platelet transfusion for long time	Cured Sepsis,C. difficle infection	No	Normal platelets count	18
10	M	2	94 M	FM sister	100 % L&M	100 % L&M	20 days	No platelet transfusion for long time	CMV infection Neutropenia	No	Normal platelets count	14
11	M	2	91 M	FM brother	L : 100 % M: 100 %	L :93.4 % M: 81 %	18 days	No platelet transfusion for long time	Molluscum infection HRT	No	Normal platelets count	20
12	M	5	31 M	CBT	No	No	-	Expired	Expired after 6 days from CBT from ICH	No	Expired after 6 days from CBT from ICH	Deceased
13	M	2	23 M	FM brother	L :96.9 % M: 100 %	L : 100 % M: 100 %	27 days	No platelet transfusion for long time	Resolved CMV infection ICH pre transplant	Yes	Normal platelets count	13

14	M	2	9M	CBT	L : 86.6 % M: 95.5 %	L : 100 % M: 100 %	45 days	No platelet transfusion for long time	post CBT AIHA Skin GVHD 2, depressed palatogenesis s/p transplant	Yes	Normal platelets count	14
15	M	2	18 M	CBT	L : 80.9 % M: 82 %	L : 100 % M: 100 %	31 days	No platelet transfusion for long time	Cured/GVHD skin	No	Normal platelets count	13
16	M	?	28 M	CBT	100 % L&M	100 % L&M	39 days	No platelet transfusion for long time	Cured	No	Normal platelets count	10
17	M	2	4 M	FM brother	L : 76.5 % M: 100 %	L : 87.5 % M: 100 %	36 days	No platelet transfusion for long time	Cured	No	Normal platelets count	6.5
18	M	2	24 M	FM sister	L : 96 % M: 100 %	L : 100 % M: 100	24 days	No platelet transfusion for long time	Cured / CMV infection	No	Normal platelets count	8
19	M	2	44 M	FM brother	100% L&M	100% L&M	22 days	No platelet transfusion for long time	Cured/GVHD skin	No	Normal platelets count	8
20	M	2	17 Y	FM brother	L : 100 % M: 91%	L : 100 % M: 100	25 days	No platelet transfusion for long time	Cured, No infection	NO	Normal platelets count	21

Table 2: Characteristic and outcome of non-transplanted patients.

PATIENT	GENDER	WAS SCORE	Platelet transfusion	Comment	CURRENT AGE
1	M	2	No data available	No data available	14 Y
2	M	4	Deceased	Deceased	Deceased
3	M	2	Frequent improved after splenectomy	On IV IG every 4 weeks, recurrent pneumococcal infection, resolved meningitis, dental abscesses, amputated fingers secondary phalangists	21 Y
4	M	3	Deceased	Deceased	Deceased
5	M	2	No data available	No data available	15 Y
6	M	2	Deceased	Deceased	Deceased
7	M	5	Frequent improved after splenectomy at age of 7 years	On IV IG every 4 weeks, recurrent febrile illness and pneumonia	9 Y
8	M	2	Deceased	Deceased	Deceased
9	M	2	Deceased	Deceased (lymphoma)	Deceased

Donor and recipient HLA typing was performed by serology or by molecular DNA typing.

Patients underwent either myeloablative or reduced-intensity conditioning. Busulfan (4-5 mg/kg) and cyclophosphamide (200 mg/kg) were used as myeloablative regimen in FMRD while busulfan, cyclophosphamide & ATG (120 mg/kg) were used when Cord blood stem cells were used.

In reduced-intensity conditioning Melphalan (140 mg/m²) in combination with Fludarabine at (160 mg/m²) and ATG (rabbit ATG at a dose of 20 mg/kg) were used for both MUCBT & FMRD. Methotrexate (30 mg/m²), cyclosporine A (3 mg/kg IV) or both were used for GVHD prophylaxis.

Engraftment of all hematopoietic cell line was monitored closely SCT and recorded in specific tables. Platelets engraftment was defined as the first of three consecutive days with Platelets count > 20 x 10⁹ without transfusions for at least seven days).

Engraftment and chimerism analysis

Engraftment of all hematopoietic cell line was monitored closely post SCT and recorded in specific tables. Platelets engraftment was defined as the first of three consecutive days with Platelets count > 20 x 10⁹ without transfusions for at least seven days.

Donor cell chimerism was analyzed post SCT using different methods such as red cell typing, FISH, VNT& STR.

Results

In this study we report the analysis of 29 WASP patients presented to our center & recorded in our database till August 2014.

38 WAS- phenotype patients were recorded in our data base, 7 patients from 2 families excluded. The first family with five members confirmed to have WIP mutation. The second family of 2 patients suspected to have WIP mutation was excluded from the study. Two more patients who had MUDD hematopoietic stem cell transplantation abroad were also excluded.

Data of 29 patients from 16 families was available for analysis (all were males). Some families had one affected member, others had multiple affected members. Most patients were either grade 2 to 4 by WASP with severe eczema & sever recurrent infections. Three patients had score of 5 due to severe autoimmunity and intractable thrombocytopenia and 2 of our patients had malignancy, 1 transplanted and one not [26,27].

Out of the 29 WAS patients 9 patients did not undergo HSCT for different reasons while 20 patients received HSCT from different sources. The mean age for transplant for WASP patients was 82.1 months (range from 4 to 204 months).

Fourteen patients received HSCT from HLA-identical matched related donors, all from full matched siblings. The mean age for transplant in this group was 108.2 months (range from 4 to 204 months). Six out of the 20 transplanted WASP patient received HLA-matched unrelated cord blood stem cells transplantation, the mean age for Cord blood transplant was 21.6 month (range from 9 to 32 months).

Only 4 of our transplanted patients had splenectomy prior to transplantation and all are surviving.

From the recorded data 13 of the 14 patients who received full matched stem cell from a sibling had myeloabliative conditioning in the form of Busulfan (4-5 mg/kg) and cyclophosphamide (200 mg/kg). 1 patient received reduced intensity conditioning (RIC) due to severe infection in the form of Melphalan (140 mg/m²) in combination with Fludarabine (150 mg/m²) & ATG (rabbit ATG at a dose of 20 mg/kg).

For cord blood stem cell recipients 5 out of 6 patients received myeloabliative conditioning in the form of. Busulfan (4-5 mg/kg), cyclophosphamide (200 mg/kg) & ATG (rabbit ATG at a total dose of 20 mg/kg). 1 patient received RIC due to recent Intra Cranial Hemorrhage; he received Melphalan (140 mg/m²) in combination with fludarabine (150 mg/m²) & ATG (rabbit ATG at a total dose of 20 mg/kg).

For GVHD prophylaxis, Methotrexate (30 mg/m²), cyclosporine A (3 mg/kg IV) or both were used.

All patients who received HSCT from full matched sibling had more than 90% lymphocyte engraftment by STR except one patient who had only 54% lymphocyte engraftment with suboptimal platelets engraftment (platelets count range 30- 50 x10⁶) but patient is not platelet transfusion dependent. All the patients had stable donor cell chimerism of both lymphoid and myeloid cell lineage. There was no significant difference observed between FMRD and MUCBT recipient in the percentage or stability of chimerism measured by STR in either lymphoid or myeloid lineage.

Platelets engraftment time (defined as the first of three consecutive days with Platelets count > 20 x 10⁹ without transfusions for at least seven days) was assessed in 15patients. The overall median time for platelets engraftment was 29 days, range from 18 to 52 days (Table1 and Figure 1).

It was observed that platelets engraftment occurred earlier in FMRD recipients (median 24 days, range 18 to 36 days) than MUCBT recipients (median 39 days, range 28 to 52 days). All surviving patients had normal platelets numbers except the previously mentioned patient.

All patients experienced myeloid engraftment (defined as the first day that the absolute neutrophil count (ANC) was greater than 0.5 x 10⁹/ L for three consecutive days or Leucocytes count greater than 1.0 x 10⁹/ L.) The neutrophil engraftment records for only 14 patients were available (median 14.5 days, range 10-36 days). There was no significant difference in FMRD and MUCBT recipient in myeloid engraftment.

The overall survival rate of the transplanted patients was 89.5 %, with 100% survival in the HLA-matched related stem cell recipients and 66.6% survival in the matched –unrelated Cord blood stem cell recipients with a mean follow up time of 13.5 years (Figure 2).

Transplantation was tolerated well in the majority of patients. There was little immediate regimen-related toxicity in this series except one patient who developed hypertension and mucositis. No patient developed Veno-Occlusive disease (VOD), four out of 20 patients developed acute GVHD, all were grade I-II and resolved with corticosteroid treatment; there were no cases of a GVHD of grade III or above.

Of the 18 patients who survived past day 100, none developed chronic GVHD and no deaths were attributed to GVHD regardless of stem cell source.
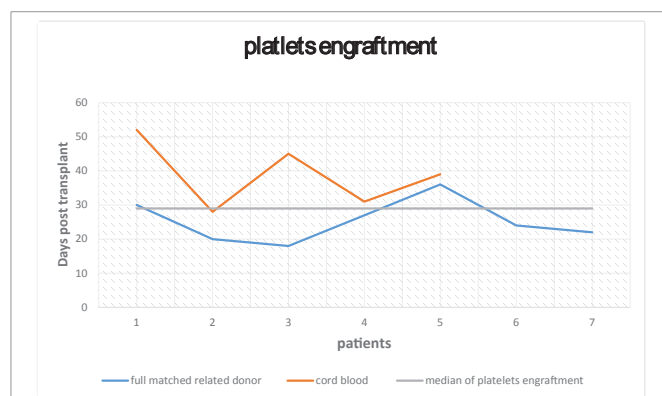

Figure 1: Platelets engraftment; comparing Cord Blood Stem cell transplant with Full matched related donor stem cells.

- **Total number of patients posttransplant is 20, FMRD is 14 with no deaths, CBT is 6 with 2 deaths.**
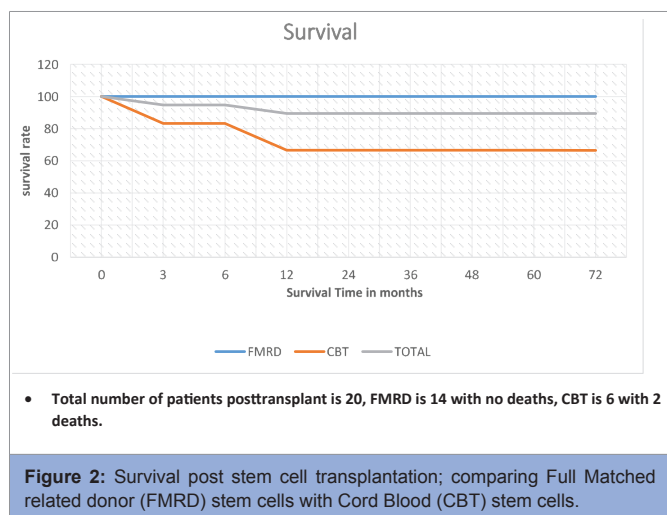
Figure 2: Survival post stem cell transplantation; comparing Full Matched related donor (FMRD) stem cells with Cord Blood (CBT) stem cells.

The main complications post HSCT was hemorrhage, seizures secondary to intracranial hemorrhage (2 patients), mucositis, skin GVHD grade I-II (4 patients), bacterial infection, Molluscum contagiosum infection (1 patient), CMV infection (3 patients), short stature (1 patient), thyroid adenoma (one patient) and autoimmune manifestations (2 patients one developed AIHA while the other had severe colitis). None of our patients had malignancy.

All surviving patients are free from any WAS manifestations, with stable and normal platelets count (except the previously mentioned patient), and normal immune functions with absence of any infectious complications (Table 1).

In the non- transplanted group, the overall survival rate was 56%. Four out of nine patients died. The main two causes of death were hemorrhage and infections. Two patients had no recent follow up, the other 3 patients still alive but with poor quality of live as most of them have recurrent and severe infections especially due to pneumococcal microorganism. In addition, they require frequent platelets transfusion and hospital admissions (Table 2).

Discussion

The experience of our center confirms the benefit of HSCT as the curative therapy of WAS patients when performed early in life and from HLA identical donor.

The overall survival rate of our transplanted patients was 89.5 % with superior survival in the HLA-matched related stem cell recipients (100%) than the matched unrelated Cord blood stem cell recipients (66.6%) with a mean follow up time of 13.5 years. Our results are comparable to the results from other centers worldwide.

S-Y PaiD DeMartiis et al. in Italy [1,2] reported 100% survival in WAS patients who received stem cells from a matched sibling donor but the overall survival rate was 78.2%. This survival rate is related to the different types of donor stem cell included in the study like RID, MUD, MMRD [26].

The international bone marrow transplant registry study which was overlapping with the European cohort confirmed (as our study) that matched sibling donor (MSD) recipient had superior 5 years survival (87% of 55 patients) compared with other donor types [27].

In The largest report by Kobayashi R, et al. [28] from japan which

described 57 WAS patients, The overall survival rate was (73.72%) and at the same time it showed nearly equal 5 year survival rate for both CBT & MSD transplant recipient 80% and 82% respectively. They used different sources of donor stem cells including MRD, MMRD, MUD & MUCB stem cells.

Friedrich W, et al. [29] from Germany reported the results of 39 transplanted WAS patients, in which Stem cell transplantation was performed from HLA identical sibling, HLA mismatched parents & HLA compatible unrelated donors. The overall survival rate was 90% in the matched donor recipient group.

The European registry for WAS reported 103 WAS patients with 62% overall survival rate, While in the matched sibling donor recipient group the 3 years survival was 71% [27].

It was observed that platelets engraftment was achieved earlier in FMRD recipients (median 24 days) than MUCBT recipients (median 39 days). The majority of the transplanted patients have attained normal platelets count except one patient with poor platelets engraftment & platelets count ranged between 31 to 50x106, The reason for suboptimal engraftment in this patient who received stem cells at age of 10 months from a full matched sibling is not clear.

The predominant causes of death post stem cell transplant were infection and hemorrhage in our study. Similar cases were reported by the study from Italy. In the Japanese study the predominant causes of death was infections followed by GVHD, followed by bleeding [26,28].

The most common complications post stem cell transplant in our patients were; hemorrhage, seizures disorders (2 patients), muocositis, GVHD of the skin which affected 21% of our WAS transplanted patients (4 patients), sepsis, viral infections in 21% of the transplanted patients (molluscum contagiosum in 1 patient and CMV infection in 3 patients), short stature (1 patient), thyroid adenoma (one patient) and autoimmune manifestations (2 patients one developed AIHA while the other had severe colitis).

Regarding GVHD, 21% of our transplanted patients (4 out of 19) developed acute GVHD. 7.6% of matched sibling donor and 50 % of CBT recipient had GVHD. All were grade I or II and resolved with corticosteroid treatment. There were no cases of acute GVHD of grade III or above. None of our patients developed chronic GVHD and no deaths were attributed to GVHD.

In the report from Italy similar results were observed, as there were no cases of acute GVHD or high grade GVHD (3 or more), no chronic GVHD, and no deaths due to GVHD [26].

The incidence of GVHD in our center was less than that recorded in Japan cohort in which Acute GVHD> grade 2 developed in 36.8 % of all patients, while in 27.3 % of HLA related SCT recipient and 33.3 % of cord blood stem cell recipient [28]. The lower rate of GVHD in the matched related donor group in our study in comparison to the japanese study may be attributed to that all our patients in the matched related group received stem cells from a sibling.

None of our patients developed chronic GVHD and no deaths were attributed to GVHD, while 7% of the patients in the European study had chronic GVHD [30], and in the Japanese study Chronic GVHD occurred in 40.4 % of all patients, 36.4 % and 33.3% in both HLA related SCT and unrelated CBT respectively. This difference

may also be related to the different sources of stem cell even among related donors which included siblings, parents and uncles, HLA Matched unrelated donor, mismatched related donor & unrelated cord blood donor [28].

None of our patients had secondary malignancy following HSCT. In the Japanese study they had 3 cases of EBV related lymphoproliferative disease post transplantation& in the international bone marrow transplant registry study which was overlapping with the European cohort none had malignancy post transplantation [27,28].

One of our patients had mixed chimerism, this patient had no auto immune manifestation. Only 10.5 % of our WAS transplanted patients (2 out of 19) had autoimmune manifestations in form of AIHA in one patient and colitis in the other patient despite full engrafnment. In the European study autoimmunity developed in 20% of the patients and it was mainly related to mixed chimerism [27,30].

WAS is a fatal PIDD if not treated early. The main cause of death is bleeding in the non-transplanted group. In our center the mortality rate for non-transplanted WAS patients was 44% all before age of 20 years. Bleeding was the leading cause of death in the majority of the patients followed by infection [12].

From the results of our WAS patients cohort we recommend early HSCT as a curative treatment for WAS patients from either a matched related donor if available. Cord blood hematopoietic stem cells transplantation offers another viable option with high rate of success, and long term disease free survival as proved by many studies including our own data.

Highlights

- Wiskott-Aldrich syndrome is a fatal Primary combined immune deficiency. The main cause of death is bleeding in the non-transplanted group followed by infection and Malignancy. Early Hematopoietic Stem Cell Transplantation represent the curative treatment for this disease

- From our WAS patients cohort the patients who were not transplanted carried a high mortality and morbidity. and those who survived to their second decade had very poor quality of life due to Thrombocytopenia and/or infections

- The HSCT from a full match related donor carried a 100% disease free survival rate for WAS patients, while CBT showed a 66.6% disease free survival rate regardless of the conditioning method.

Thus we highly recommend HSCT for WAS patients as it carries an excellent disease free survival rate with low mortality and morbidity regardless of patient age or stem cell source.

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