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Bone marrow transplantation/non-bone marrow transplantation gap: to what extent does it exist in the Egyptian children with acquired aplastic anemia? Retrospective descriptive study

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Abstract

Background Bone marrow transplantation (BMT) is not always feasible in resources-limited countries for treatment of acquired aplastic anemia (AA); accordingly, an alternative and acceptable non-BMT is required to avoid missing many cases who are liable to die while waiting for BMT. The aim of this study was to determine the extent of the gap between BMT and non-BMT in Egypt. The resolution and survival outcomes of BMT versus non-BMT therapy (isolated IST, combined IST & Eltrombopag (EPAG) (double therapy) and combined IST and EPAG and anti-thymocyte globulin (ATG) (triple therapy)) were evaluated.

Methods Medical records were reviewed for epidemiological and clinical data, as well as response to BMT and non-BMT used. Sixty patients with acquired AA were involved. BMT was performed in 18 patients, while non-BMT was performed in 42 patients.

Results Resolution occurred in 13/18 (72.2%) patients treated with BMT, 5/14 (35.7%) isolated IST, 10/12 (83.3%) combined IST-EPAG, and 12/16 (75%) triple ATG-IST-EPAG with an overall resolution occurring in 27/42 (64.2%). The percentage of survivors in those treated with BMT was 72.2%, isolated IST 5/14 (35.7%), double therapy 10/12 (83.3%), and triple therapy 10/16 (62.5%) with an overall survivor occurring in 25/42 (59.5%). Despite the lack of a statistically significant correlation, it was found that patients who received BMT had 1.769 times higher survival rates than those who received non-BMT.

Conclusion In Egypt, BMT is the ideal therapy for acquired AA with acceptable results for non-BMT regarding resolution and survival. Double therapy is the best modality of non-BMT regarding resolution and survival. Accordingly, it is recommended to be initiated in case of unavailable matched donor.

Keywords Aplastic anemia, Bone marrow transplantation, Immunosuppressive therapy

Background

Aplastic anemia (AA) is a serious form of bone marrow failure characterized by hypocellular bone marrow and peripheral pancytopenia with resulting serious anemia, infection, and hemorrhage [1]. The incidence is 2–3 cases per million, with regional variability across the world that may be due to genetic susceptibility and/or

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environmental triggers [2]. Even though there have been reports of AA in North Africa, the incidence and prevalence have not been addressed [3].

The exact etiology of AA is unknown, so different genetic and environmental predisposing factors have been suggested [4]. Genetic factors play an important role in the pathogenesis of AA. The specificity of human leucocytic antigen (HLA) alleles make the human body susceptible to AA [5]. AA may be considered as an immune-mediated disorder following exposure to environmental factors as drugs, toxins, radiations, chemicals, or viral hepatitis [6].

Patients with AA are typically diagnosed either due to symptomatic anemia, bleeding secondary to thrombocytopenia, infectious complications related to neutropenia, or asymptomatic cytopenia found on peripheral blood sampling [7]. The diagnosis of AA requires at least two of the following criteria: hemoglobin < 100 g/L, platelets < 50 10^3/μL, and neutrophils < 1.5 10^3/μL, together with a hypocellular BM and in the absence of abnormal infiltrates or fibrosis [8]. Once the diagnosis of AA is confirmed, and based on peripheral blood absolute neutrophil count (ANC), disease classification should be done into non-severe aplastic anemia (NSAA), *ANC* > 500 PMNs/μL; severe aplastic anemia (SAA), 200–500 PMNs/μL; and very severe aplastic anemia (VSAA), 0–200 PMNs/μL [9]. Disease classification may affect treatment decision, as patients with NSAA may be observed for a short period of time without treatment, while patients with SAA have a worse prognosis with delay in therapy [10].

AA is a more complex disease than expected with considerable morbidity and mortality [6]. Survival in AA has markedly improved over the past four decades because of advances in hematopoietic stem cell transplantation (HSCT), immunosuppressive therapy (IST) and biologic drugs, and supportive care [4].

Based on the reviewed literature, BMT from an HLA-matched family donor (MFD) is the treatment of choice for acquired AA [11]. However, when MFD is not available, non-BMT (IST combined with anti-thymocyte globulin and cyclosporine) is used as an alternative therapy [12]. Recently, in the era of advanced pharmacology, new combinations of IST are being used, with only few studies examining the outcome of these combinations. In Egypt, no comparative studies present between the newly used combinations versus BMT. Implementation of different new combinations with IST on wide scale could minimize losing many patients who died while waiting for HLA-matched BMT. So, this retrospective study was conducted to evaluate the response (resolution & survival) of various lines used in treatment of acquired AA in Egypt. These lines are BMT, isolated IST, combined IST and eltrombopag (EPAG) (double therapy), and combined IST and EPAG and anti-thymocyte globulin (ATG) (triple therapy)). It was hypothesized that BMT is the ideal line of therapy with acceptable outcomes for non-BMT. Based on this hypothesis, non-BMT could be used as rescue therapy for many patients.

Methods

Study setting

After reviewing the medical records of 97 Egyptian children suffering from AA and admitted to the Pediatric Hematology Unit of Cairo University's hospital from January 1, 2015, to December 31, 2019, 29 (29.8%) and 68 (70.1%) patients were found to have inherited and acquired AA, respectively. The study was conducted on 60 patients with acquired AA only after excluding the eight patients who died shortly after being diagnosed and before receiving any treatment.

After establishing the diagnosis, different forms of therapy were initiated in an attempt to control the progression of the disease. According to the received therapy, two groups were studied: BMT ($n=18$) and non-BMT ($n=42$). BMT was performed in 18 patients (30%). Isolated IST, combined therapy, and triple therapy were administered in 14 (20.6%), 12 (17.6%), and 16 (23.5%) patients of the non-BMT group respectively.

Study population

The patient inclusion criteria involved age ranging between 1 month and 18 years of both sex. Patients were excluded if they had malignancy, systemic lupus erythematosus, and conditions associated with pancytopenia other than AA such as myelodysplastic syndrome and paroxysmal nocturnal hemoglobinuria.

Procedure

Data were collected by reviewing the medical records of the enrolled patients that included patient history, clinical examination, investigations, and received treatment. Patient history involved age at presentation, gender, drug history, detailed infection history, detailed bleeding history, and causes of hospital admission. The clinical examination involved anthropometric measurements (height and weight) and BMI and Z-score and detailed general and local examination. The investigations involved CBC with differential, bone marrow aspirate and biopsy, liver function tests, and virology profile. The received treatment involved BMT, IST, ATG, and EPAG. Non-BMT patients with moderate or severe AAA were given immunosuppressive therapy (IST), which included cyclosporine or IST and EPAG in cases of resistance, in accordance with our center's treatment protocols. Due to

cost considerations, anti-thymocyte globulin (ATG) was only applied in certain circumstances.

According to the response to treatment, patients were classified into 3 groups: complete response, partial response, and no response. A complete response was defined as neutrophils > 1.5×10^9/L, platelets > 100×10^9/L, and hemoglobin value normal for age and sex. A partial response was defined when the counts were not sufficient for a complete response and the absolute neutrophil count (ANC) was > 0.5×10^9/L, platelets > 20×10^9/L, and hemoglobin > 80 g/L in patients with severe AA and ANC > 1.0×10^9/L and platelets > 30×10^9/L and hemoglobin > 80 g/L in patients with moderate AA [13]. According to the outcome, the patients of both groups were classified into survivors and non-survivors. Survival was defined as that period from diagnosis until the last date known to be alive.

Data management and statistical analysis

Data were collected, coded, and analyzed by the Statistical Package for Social Science (IBM SPSS version 23). The quantitative parametric data were presented as means, standard deviations, and ranges. Qualitative variables were also presented as frequencies and percentages. Chi-square test was used for comparing among the tested groups for the resolution and outcome.

Results

From January 1, 2015, to December 31, 2019, 97 Egyptian children with AA were admitted to the Pediatric Hematology Unit at Cairo University's hospital. After evaluating their medical records, it was found that 29 (29.8%) and 68 (70.1%) of the patients had hereditary and acquired AA, respectively. After excluding the eight patients who passed away soon after being diagnosed and prior to receiving any therapy, the study was just conducted on the remaining 60 patients with acquired AA.

Different types of therapy were started when the diagnosis was made in an effort to slow the disease's progression. Two groups were examined based on the type of therapy they had received: BMT ($n=18$) and non-BMT ($n=42$). The BMT group in the current study consisted of 7 (38.8%) females and 11 (61.1%) males, with a mean age of 83.89 ± 43.89 months. In the non-BMT group, there were 16 (38.1%) females and 26 (61.9%) males, with a mean age of 76.45 ± 45.94 months. The study's overall male-to-female ratio was 1.8:1. The two groups did not significantly differ in terms of age or sex ($p=0.56$ and 0.58, respectively).

Anthropometric assessments of the enrolled patients revealed that the mean weight of BMT patients was 22.91 ± 11.19 kg, and that of non-BMT patients was 22.38 ± 9.52 kg. The difference in weight between the two groups was not statistically significant ($p=0.85$). Groups BMT and non-BMT had respective mean heights of 113.44±19.80 cm and 113.97±21.18 cm. Between the two groups, there was not a significant difference in height ($p=0.92$).

The frequency of hospital admission in the current study was 3.83 ± 1.75 and 5.21 ± 3.36 times, respectively, for the BMT and non-BMT groups. Hospital admissions were mainly caused by fever and neutropenia in 48 (80%) patients, bleeding in 38 (63.3%), and severe pallor in 16 (26.6%). Pallor 56/60 (93%) and petechiae 51/60 (85%) were the most noticeable physical findings, according to a general and comprehensive examination. The ANC revealed that the condition was mild in 9 (15%) cases, severe in 34 (56.6%), and very severe in 17 (28.3%) cases ($p=0.04$) (Table 1).

Reduction in the frequency of PRBS and platelet transfusions in our study served as an indirect measure of the clinical response to the used treatment strategy (Table 2). In 13/18 (72.2%) and 27/42 (64.2%) of the BMT and non-BMT groups, respectively, the disease was totally or partially resolved in response to the utilized lines of treatment (Table 3). In the non-BMT group, isolated IST, double therapy, and triple therapy each assisted 5/14 (35.7%), 10/12 (83.3%), and 12/16 (75%) patients achieve resolution (partial or total).

BMT and non-BMT treatment types significantly correlated with response ($\chi^2=8.982$, $p=0.011$). According to Table 3, there was a strong correlation between the type of treatment (BMT, isolated IST, combination IST & eltrombopag (EPAG) (double therapy), and combined IST and EPAG and anti-thymocyte globulin (ATG) (triple therapy) and response ($\chi^2=27.626$, $p=0.000$).

Patients in the BMT and non-BMT groups achieved full resolution in 12/18 (66.6%) and 13/42 (30.9%), respectively. However, only one patient who had BMT obtained partial resolution and, in contrast, 2, 10, and 5 patients who got IST, double therapy, or triple therapy, respectively (Fig. 1).

Table 1 Comparison of the main clinical manifestations between BMT and non-BMT

		BMT	Non-BMT	*T*-value	*p* = value
Petechiae	No	2	7	0.36	0.45
	Yes	16	35		
Pallor	No	3	1	4.13	0.07
	Yes	15	41		
Severity of AA	Moderate	3	6		1
	Severe	10	24	0.05	
	Very severe	5	12		

Table 2 Comparison of the frequency of blood and blood product transfusions between BMT and non-BMT

	BMT X ± SD	Non-BMT X ± SD	*T*-value	*p* = value
Time between diagnosis and treatment (days)	7.27 ± 8.62	4.04 ± 4.73	1.49	0.14
Frequency of blood transfusion before treatment (time)	3.16 ± 1.88	3.73 ± 1.76	− 1.12	0.26
Frequency of blood transfusion after treatment (time)	0.83 ± 1.24	1.45 ± 1.29	− 1.71	0.09
Frequency of platelet transfusion before treatment (time)	4.50 ± 2.06	5.07 ± 2.02	− 0.99	0.32
Frequency of platelet transfusion before treatment (time)	1.11 ± 1.56	2.09 ± 1.88	− 1.94	0.05

Table 3 Comparison of the response between BMT and non-BMT

	Total number	Response			χ^2	*p* = value
		Full	Partial	No		
BMT	18	12	1	5		
Non-BMT	42	13	17	12	8.98	0.011
IST	14	5	2	7	27.82	0.001*
Double therapy	12	0	10	2		
Triple therapy	16	8	5	3		

* Significant at $p < 0.05$

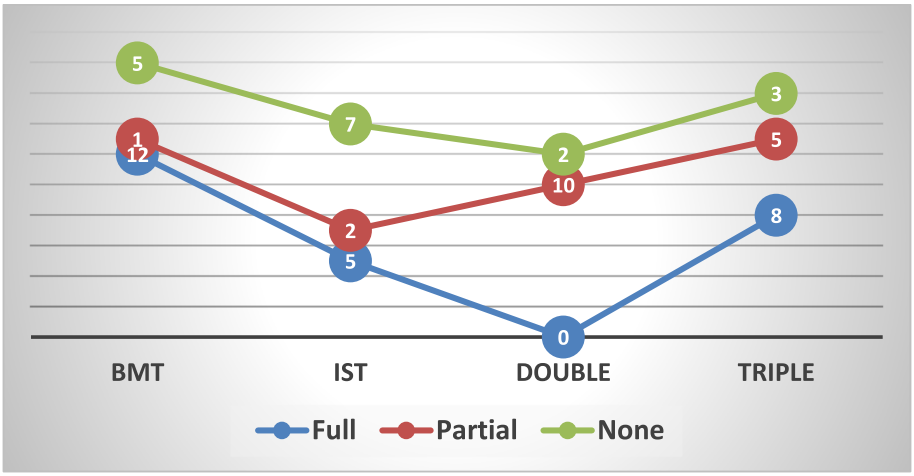

Fig. 1 Frequency distribution of full, partial, and no response in different types of treatment groups

Thirteen/eighteen (72.2%) patients of the BMT group, and 25/42 (59.5%) patients of the non-BMT group, survived (Table 4). The survival distribution in the non-BMT group involved 5/14 (35.7%), 10/12 (83.3%), and 1/16 (62.5%) patients who received isolated IST, double therapy, and triple therapy, respectively (Fig. 2).

There was no significant association between type of treatment (BMT and non-BMT) and survival ($\chi^2 = 0.875$, $p = 0.263$). Although there was no statistical significant association, it was found that if patients were treated with BMT, the odds of being survived were 1.769 times higher than if treated with non-BMT. There was no significant association between type of treatment (BMT, isolated IST, combined IST & eltrombopag (EPAG) (double therapy) and combined IST and EPAG and antithymocyte globulin (ATG) (triple therapy)) and survival ($\chi^2 = 7.283$, $p = 0.066$) (Table 4). Sepsis was the primary cause of death in the current study, accounting for 18/29 (62%), and it was more common in the non-BMT group than in the BMT group (10:2).

Table 4 Comparison between BMT and non-BMT regarding to the survival outcome

	Total number	Non-survivors	Survivors	χ^2	p = value
BMT	18	5	13		
Non-BMT	42	17	25	0.875	0.263
IST	14	9	5	7.283	0.066
Double therapy	12	2	10		
Triple therapy	16	6	10		

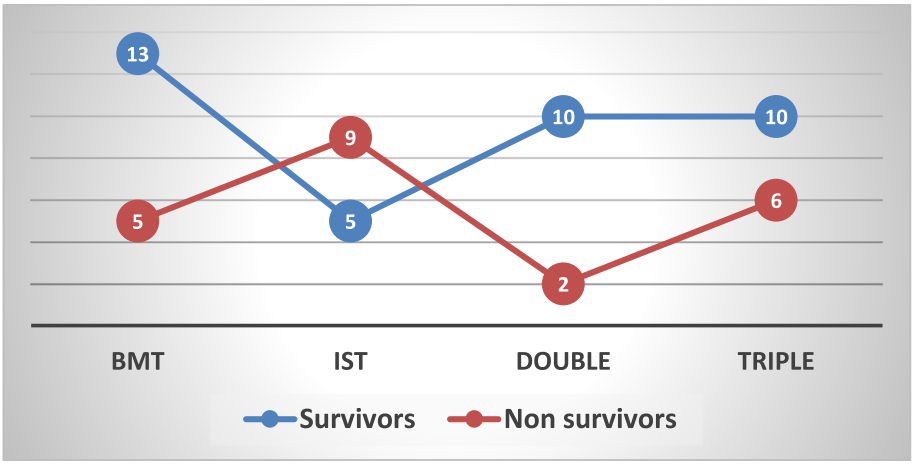

Fig. 2 Frequency distribution of survivors and non-survivors in different types of treatment groups

Discussion

In the current study, the male constituted higher percentage than females with a ratio of 1.8:1. This is in accordance with what was reported by Abdel-Salam et al. [14] and Afridi et al. [15] that male-to-female ratio was 1.6:1 and 1.2:1, respectively.

The major presenting feature was fever and neutropenia (80%). These was in concordance with Wali et al. [16] where the major presenting feature was fever in 71.4% of cases in their study. Our study was disagreeing with the study done by Abdel-Salam et al. [14] in which pallor was the main presenting feature, being present in 80%. The difference could be attributed to different patient types, the latter included cases of pure red cell aplasia (sever pallor is the main feature) in their study.

In our study, the overall resolution (partial/complete) was achieved in 42/60 (70%) patients. This finding is supported by a similar finding (64.8%) reported by Zhu et al. (2019) [17]. The latter found that full resolution, partial response, and no response occurred in 41.6%, 18 (30%), and 17 (28.3%), respectively.

In our 60 acquired AA patients, 18 (30%) were treated by BMT which was successful in 13 (72.2%). This response is lower than that reported by Erdem et al. [18]. The latter found that complete response was achieved in all patients (100%) who underwent HSCT. The difference could be due to the precursor of HSCT itself as type, quality, time of transplantation, and post transplantation care.

Fourteen (33.3%) patients of the non-BMT group received isolated IST only with full resolution (35.7%), partial resolution (14.2%), and no response (50%). Our 50% overall response (complete/partial) to the used isolated IST is similar to the 68.1% that was reported by Jeong et al. [19].

Double therapy (IST & EPAG) was used in twelve (28.5%) patients of the non-BMT group. It failed to cause complete resolution in any patient. However, it caused partial resolution in 10 (83.3%) patients with a percentage similar to Youssef et al. [20], and both are higher than that (69.2%) reported by Desmond et al. [21]. The latter utilized EPAG in refractory severe AA with expected poor response; however, our patients were not restricted to refractory severe AA.

Triple therapy (IST, EPAG, and ATG) was used in 16 (38%) patients of our non-BMT group with an overall resolution in 13/16 (81.25%). To the best of our knowledge, no previous study examined the response to the combined effect of IST, EPAG, and ATG (triple

therapy). Accordingly, no previous study results were available with which our results could be compared.

In our study, the overall mortality was 22/60 (36.6%) which is higher than that reported by Wali et al. [16] who found that the overall mortality in their study was 24.4%. The difference between both studies could be explained by the different studied sample. We studied acquired AA only, while Wali et al. studied both acquired and inherited AA. Inherited AA has lower mortality than acquired AA; thus, they had lower percentage than us. In addition, the percentage of severe and very severe AA in our study was 85% versus 61% in the study conducted by Wali et al. Both severe and very severe grades are associated with high mortality. Regarding the cause of death, sepsis was the main predominant cause in 18/22 (81.8%) of deaths. This agrees with Wali et al. [16] who reported that infection was the predominant cause of death constituting 72.7% of their deaths.

In our study, the overall response and survival in non-BMT groups treated with double therapy were higher than those treated with IST. This was in concordance with Fang et al. [22] who reported that combined IST + EPAG was more effective than IST alone in children with AA [22]. The observed difference in the obtained results for EPAG when combined with IST could be that E-PAG is well-tolerated drug that cause recovery of blood cell counts, and restoration of trilineage hematopoiesis, even after drug discontinuation.

Based on our findings, our hypothesis is accepted as BMT was significantly superior to the non-BMT with acceptable resolution and survival outcomes for the later.

In children, the choice of an appropriate treatment is particularly influenced by the long-term sequelae of the disease and its therapy. Thus, failure-free survival is much more important than survival alone when analyzing the long-term outcomes of children with aplastic anemia. With the variable risks, benefits, and outcomes of available treatments, it is recommended to form consortia for better diagnosis and treatment of acquired AA. Being an existing disease, national registries of acquired AA are advisable to improve prospective study of the disease.

Our study had a point of strength; it is one of the few studies conducted on acquired aplastic anemia in children in developing countries to evaluate the gap between BMT and non-BMT especially in the presence of new generations of pharmacological agents. However, it had several limitations. The limitations involve small sample size, the absence of comparable research in pediatric populations, and being conducted in single center. It is recommended to repeat this study in the future on larger sample size within the pediatric population in multiple centers especially in resource-limited countries to gain its benefit.

Conclusion

In Egypt, BMT is the ideal therapy for acquired AA with acceptable results for non-BMT regarding resolution and survival. Double therapy is the best modality of non-BMT regarding resolution and survival. Accordingly, it is recommended to be initiated in case of unavailable matched donor.

Abbreviations

AA	Aplastic anemia
ANC	Absolute neutrophil count
ATG	Anti-thymocyte globulin
BMI	Body mass index
BMT	Bone marrow transplantation
CBC	Complete blood count
EPAG	Eltrombopag
HLA	Human leucocytic antigen
HSCT	Hematopoietic stem cell transplantation
IST	Immunosuppressive therapy
MFD	Matched family donor
NSAA	Non-severe aplastic anemia
SAA	Severe aplastic anemia
SPSS	Statistical Package for Social Science
VSAA	Very severe aplastic anemia

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Authors' contributions

MAA drafted the work and revised it, being the major contributor in writing the manuscript. RAA made substantial contribution to the concept and design of the work and interpretation of data. HAA contributed to data acquisition. All authors read and approved the final manuscript. Each agreed both to be personally accountable for the author's own contributions and ensured that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

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Availability of data and materials

All data are available upon request.

Declarations

Ethics approval and consent to participate.

This study was approved by the Institutional Ethical Review Board, Faculty of Medicine, Cairo University.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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