RESEARCH ARTICLE

Challenges of Hematopoietic Stem Cell Transplantation in the covid-19 pandemic situation, in low income settings BMT center, CMH Dhaka, Bangladesh

Md Mostafil Karim[1], Md Mizanur Rahman[2], Abul Kashem khan[3], and Shahina Akhter[4]

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a contagious disease caused by a virus, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It was first identified in Wuhan, China, in December 2019. The disease was quickly spreaded worldwide, resulting in the COVID-19 pandemic, was declared a pandemic by the World Health Organization on 11 March 2020. The world was witnessed a health crisis in the form of COVID-19 pandemic . As per World Health Organizations´ (WHO) data, in April 2020, one million of the population was infected and died more than 50000.

Some bone marrow transplantation societies across the globe had come together to unite against COVID-19. World experts and renowned scientists from various subspecialties had shared their individual and institutional experiences to strengthen the data collaboration so that the rest of the world could benefit from the same. With regard to HSCT, the European Hematology Association, European Society for Blood and Marrow Transplantation (EBMT), American Society of Hematology, American Society of Clinical Oncology who had collaborated at various levels to help transplant physicians across the world.

Widespread community transmission in the Bangladesh triggered a nationwide shutdown, raised major challenges to continue Hematopoietic Stem Cell Transplant (HSCT) activity in BMT Center, CMH Dhaka, Bangladesh. Though the procedure is life saving for the patient suffering from hematological malignancy and diseases. To maintain relentless transplant activity tremendous challenges faced by BMT Team and patient had faced economic stress as well as BMT Center faced expert staff crisis. Transplant activities at our center was continued, no patient has been infected with SARS-CoV-2. Social distancing, masking, education for patients and donors were major pillars of prevention for our BMT patients.

Repeated test for COVID-19 diagnosis by RT-PCR and for screening by Rapid Antigen Test (RAT) of our 30 transplant patient, BMT Team staff, caregiver and donor required extensive laboratory support. Which was very much cost effective and that required high alert services during this sophisticated transplant work. The COVID-19 pandemic was a major concern about the potential impact of the virus during patient treatment by salvage chemotherapy, stem cell collection, liquid nitrogen cryopreservation, conditioning chemotherapy, stem cell infusion and post-transplant period. Stem cell donor & care giver availability as per schedule, expert staff crisis, BMT medicine availability and economic crisis of the patient relatives were a big challenges for transplant team to provide effective services to the patient.

The main objectives of the study is to evaluate major challenges faced by BMT Team, how we have overcome it and effectively continued hematopoietic stem cell transplant activities smoothly during that adverse situation.

Methods: We retrospectively analyzed 30 consecutive patients who underwent allo-HSCT & auto-HSCT from December 15, 2019 to June 15, 2022 in our BMT Center. We reported baseline and pre-transplant procedural characteristics descriptively. We analyzed BMT procedural success rate, covid-19 infection, mortality, transplant related mortality, Relapse Mortality (RM), Non-Relapse Mortality (NRM), infection, Infection Related Mortality (IRM), duration of post-transplant hospital stay, duration of neutrophil engraftment, graft failure of our patients. We had to take special care for allogeneic HSCT patients due to donor issue. We changed our arrangement in donor selection, screening as well as cryopreservation patterns of donor products.

We concerned a lot that COVID-19 could have a significant challenge during bone marrow transplantation or on post-transplantation outcomes although data was limited on the epidemiology, clinical manifestations and optimal management of Coronavirus Disease 2019 in HSCT candidates, donors, recipients. So, as per given experience with other respiratory viruses, we anticipated that patients might develop severe clinical disease. For this reason, we followed the practical emergency precautions to conduct successful HSCT of our patients.

PCR test was mandatory for virus detection before any transplant process among BMT Team members, nurses, cleaners, care givers, donors as well as recipients for allogeneic and autologous stem cell transplant. Rapid Antigen Test (RAT) test also done several times in every steps.

During the transplant period, whenever we saw any symptom like fever, cough or chest imaging abnormalities, we advised to do PCR test for detecting virus. We followed WHO recommendations diligently to prevent COVID-19. Our healthcare staff, patients and donors followed the WHO recommended prevention procedure also. It was vital to be very careful with hygiene routines, including hand washing, use of protective mask, alcohol-containing hand sanitizers and restriction of visitors in our center.

Results: We evaluated the challenges of BMT procedures and clinical outcomes for 30 HSCT patients with hodgkin`s lymphoma, non-hodgkin`s lymphoma, multiple myeloma, AML, ganglioneuroblastoma, mantle cell lymphoma, angio-immunoblastic t-cell lymphoma, aplastic anemia at BMT Center, CMH Dhaka, in the COVID-19 pandemic. Among 30 patients, there were 22 autologous HSCT (73%) and 8 allogeneic HSCT patients (27%) in our center.

We focused on early transplant outcomes, such as covid-19 infection, infection rates, neutrophil engraftment and mortality at day 100. We analyzed BMT procedural success rate, covid-19 infection, mortality, transplant related mortality, Relapse Mortality (RM), Non-Relapse Mortality (NRM), infection, Infection Related Mortality (IRM), duration of post-transplant hospital stay, duration of neutrophil engraftment, graft failure of our patients , Our HSCT patients were not contacted COVID-19 patients between days 0 and 100. We reported baseline and pre-transplant procedural characteristics descriptively. Our data shown that BMT procedure was 100% successful throughout the ongoing COVID-19 pandemic with appropriate safeguards. But, 4 patients died after successful bone marrow transplantation due to infections & disease relapse. Among them, 3 patients died due to infection. One patient died of CMV reactivation at day 60 and 2 patient died due to severe infection of *klebsiella spp* and *Pseudomonas aeruginosa* after successful BMT. Post-transplant follow-up in most cases were uneventful but one patient relapsed after BMT due to disease aggressiveness and patient expired as failed to receive advanced

[1]Department of Clinical Hematology & BMT Center, CMH Dhaka, Bangladesh; [2]Chief Instructor and Deputy Commandant, AFIP,Dhaka, Bangladesh; [3]District Sales Manager, Oncology, Renata Limited, Dhaka Bangladesh; and [4]Department of Gynaecology, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh.

Correspondence: Md Mostafil Karim, Department of Clinical Hematology & BMT Center, CMH Dhaka, Bangladesh E-mail: mostafil100911@yahoo.com

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treatment as advanced treatments were not available in Bangladesh. We have shown that BMT procedural success rate was 100%, mortality was 4 (13%), Relapse mortality (RM) and non-relapse mortality (NRM) were 1 (3%) & 0 (0%) respectively.

Conclusions: During Covid-19 pandemic, the situation was so critical all over the world. We needed to follow WHO recommendations carefully. So, we have taken emergency measures to minimize the impact of COVID-19 on transplant activity. The common and essential preventive measures were social distancing, mask wearing, hand washing & hygiene for our BMT patients, donors, BMT staffs. We have not allowed any visitors and used minimum BMT staff with minimum direct contact with patient. We proposed some strategies to manage transplant-related activities and high alert system during the Covid-19 pandemic. We found that BMT procedural success rate was 100% but there were so many challenges we had to overcome with maximum workload during transplant activities in Covid-19 pandemic. As a result Transplant cost was c omparatively high than pre-pandemic period.

Key Words: *Hematopoietic Stem Cell Transplantation (HSCT); Bone Marrow Transplantation (BMT); Relapse Mortality (RM); Non-Relapse Mortality (NRM); Transplant Related Mortality (TRM).*

INTRODUCTION

Though Hematopoietic Stem Cell Transplantation (HSCT) is a world well-established procedure for many acquired or inherited disorders of the hematopoietic system, benign or neoplastic, including those of the immune system, and as enzyme replacement in metabolic disorders, to maintain relentless transplant activity tremendous challenges faced by BMT Team and patient in economic stress as well as expert staff crisis in COVID-19 pandemic [1-6].

For the virulence of COVID-19, we also faced many obstacles and difficulties for the transplant course such as a lack of blood donors, available medicines, and lack of stem cell donors for allogeneic stem cell transplant because of a shutdown.

Repeated tests for COVID-19 diagnosis by RT PCR and for screening by Rapid Antigen Test (RAT) of our 30 transplant patients, BMT Team staff, caregivers, and donors required extensive laboratory support. Which was very cost-effective and required high-alert services during this sophisticated transplant work. The COVID-19 pandemic was a major concern about the potential impact of the virus during patient treatment by salvage chemotherapy, stem cell collection, and liquid nitrogen cryopreservation, conditioning chemotherapy, stem cell infusion, and post-transplant period. Stem cell donor & caregiver availability as per schedule, expert staff crisis, BMT medicine availability, and economic crisis of the patient relatives were big challenges for the transplant team to provide effective services to the patient [7-10].

During the COVID-19 pandemic, the management of transplanted patients was very difficult. For overcoming the threat and challenges, we had taken emergency measures. We declared that any low-risk non-urgent transplant would have been postponed and for freezing stem cells if mobilization was already scheduled. During the transplant period, whenever we have seen any symptoms like fever, cough, or chest imaging abnormalities, we were advised to do PCR test for diagnosis of COVID-19. We followed WHO recommendations diligently to prevent COVID-19. Our healthcare staff, patients, and donors followed the WHO-recommended prevention procedure also. It was vital to be very careful with hygiene routines, including hand washing, use of protective masks, alcohol-containing hand sanitizers, and limited visits in our center.

We adopted actions based on the WHO recommendations to ensure the safety of our transplanted patients. We are concerned a lot that COVID-19 could have a significant challenge during bone marrow transplantation or post-transplantation outcomes although data was limited on the epidemiology, clinical manifestations, and optimal management of Coronavirus Disease 2019 in HSCT candidates, donors, and recipients. So, as per the given experience with other respiratory viruses, we anticipated that patients might develop severe clinical diseases. For this reason, we followed the practical emergency precautions to conduct successful HSCT of our patients as below:

Prioritizing stem cell transplantation

We prioritized urgent patients with a high risk of disease progression and high-grade malignancy and deferred transplant for patients with low-risk progression, poor outcome, or high risk of immunosuppression. We took decisions and discussed the risks and benefits as part of the multidisciplinary team.

Hygiene procedures

We have followed strict hygiene procedures for patients, donors, BMT staff, and visitors. We have isolated suspected patients and infected persons & limit access to the transplant unit.

Recommendations for patients

We have done Covid-19 testing by PCR in all candidates before any steps of transplantation & deferred transplant in any suspect contact or contagion of Covid-19.

Recommendations for donors

We have done test all donors before harvesting stem cells & mobilized stem cell with growth factors without chemotherapy. We collected stem cells and underwent cryopreservation.

Considerations for evaluation before HSCT

We screened the patient by using PCR to detect Covid-19 prior to pre-transplant or infusion procedures. Whenever we got the negative result for the patient, we proceeded with transplant or infusion and continued adherence to good practice measures such as wearing masks, hand hygiene, and social distancing. In our center, we did not get any positive cases of Covid-19 of our BMT patients.

METHODS

We retrospectively analyzed 30 consecutive patients who underwent HSCT with Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, AML, ganglioneuroblastoma, mantle cell lymphoma, angioimmunoblastic T-cell lymphoma, aplastic anemia from December 15, 2019, to June 15, 2022, in our BMT Center where there were 22 autologous HSCT and 8 allogeneic HSCT patients.

We reported baseline and pre-transplant procedural characteristics descriptively. We analyzed BMT procedural success rate, covid-19 infection, mortality, Transplant Related Mortality, Relapse Mortality (RM), Non-Relapse Mortality (NRM), infection, Infection Related Mortality (IRM), duration of post-transplant hospital stay, duration of neutrophil engraftment, graft failure of our patients. We had to take special care of allogeneic HSCT patients due to donor issues. We changed our arrangement in donor selection, screening as well as cryopreservation patterns of donor products. We are concerned a lot that COVID-19 could have a significant challenge during bone marrow transplantation or post-transplantation outcomes although data was limited on the epidemiology, clinical manifestations, and optimal management of Coronavirus Disease 2019 in HSCT candidates, donors, and recipients. So, as per the given experience with other respiratory viruses, we anticipated that patients might develop severe clinical diseases. For this reason, we followed the practical emergency precautions to conduct a successful HSCT of our patients.

PCR test was mandatory for virus detection before any transplant process among BMT Team members, nurses, cleaners, caregivers, donors as well as recipients for allogeneic and autologous stem cell transplants. The Rapid Antigen Test (RAT) test was also done several times in every step.

During the transplant period, whenever we saw any symptoms like fever, cough or chest imaging abnormalities, we advised to do PCR test for detecting the virus. We followed WHO recommendations diligently to prevent COVID-19. Our healthcare staff, patients, and donors followed the WHO-recommended prevention procedure also. It was vital to be very careful with hygiene routines, including hand washing, use of protective masks, alcohol-containing hand sanitizers, and restriction of visitors in our center.

Patient data were collected from a local database that was used for keeping all the patient-related documents in the BMT unit of CMH, Dhaka.

RESULT

We evaluated the challenges of BMT procedures and clinical outcomes for

30 HSCT patients with Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, AML, ganglioneuroblastoma, mantle cell lymphoma, angioimmunoblastic t-cell lymphoma, aplastic anemia at BMT Center, CMH, Dhaka Cantonment in the COVID-19 pandemic. Among 30 patients, there were 22 autologous HSCT (73%) and 8 allogeneic HSCT patients (27%) in our center (Table 1). We had to take special care of allogeneic HSCT patients due to donor issues. We changed our arrangement in donor selection, screening as well as cryopreservation patterns of donor products.

We focused on early transplant outcomes, such as covid-19 infection, infection rates, neutrophil engraftment, and mortality rate at day 100. We analyzed BMT procedural success rate, mortality, transplant-related mortality, Relapse Mortality (RM), Non-Relapse Mortality (NRM), infection, Infection-Related Mortality (IRM), covid-19 infection, duration of post-transplant hospital stay, duration of neutrophil engraftment, graft failure in our patients (Table 2), Our HSCT patients were not contacted

TABLE 1

Types of hematopoietic stem cell transplantation

No. of Patients	Auto-HSCT	%	Allo-HSCT	%
30	22	73%	8	27%

TABLE 2

Characteristics of patients (N=30)

Characteristics	HL (6)	NHL (5)	MM (6)	Ganglio-neuroblastoma (2)	AITCL (1)	Mantle Cell Lymphoma (2)	AML (4)	Aplastic Anemia (4)
Age, Year	24-48	22-46	38-63	05-10	44	42-47	23-57	32-42
Auto-HSCT	6 (100%)	5 (100%)	6 (100%)	2 (100%)	1 (100%)	2 (100%)		
Allo-HSCT							4 (100%)	4 (100%)
BMT Procedural Success Rate	6 (100%)	5 (100%)	6 (100%)	2(100%)	1 (100%)	2 (100%)	4 (100%)	4 (100%)
Mortality	2 (7%)	1 (3%)					1(3%)	
Infection related mortality	1(3%)	1(3%)					1(3%)	
Covid-19 infection	0	0	0	0	0	0	0	0
Relapse mortality	1(3%)							
Non-relapse mortality	0	0	0	0	0	0	0	0
Neutrophil Engraftment (Days)	10-13	10-13	09-10	10	10	09-10	12-15	10-17
Graft failure	0	0	0	0	0	0	0	0
Post-transplant hospital stay (Days)	22-30	16-17	19-56	28-40	26	22	22-55	22-120

TABLE 3

Causes of death

No. of Cases	Causes of Death	No. of Death	%
30	Infections	3	7%
	Relapse; Patient expired because patient could not take advanced treatment due to economic burden.	1	3%

TABLE 4

BMT procedural success rate, Mortality, Infection Related mortality (IRM) and Relapse Mortality (RM) & Non-Relapse Mortality (NRM)

No. of cases	BMT procedural success rate (%)	Mortality	%	Infection related mortality (IRM)	%	Relapse mortality (RM)	%	Non-relapse mortality (NRM)	%
30	30 (100%)	4	13%	3	7%	1	3%	0	0%

TABLE 5

Status of Covid-19 infection of BMT specialist, BMT team staffs, caregivers, donors & patients

BMT Specialist, Staff, Donor & Patient	Total	Covid-19 Positive	%	Covid-19 Negative	%
BMT Specialist	5	1		4	
BMT team staff	15	4		11	
Caregiver	30	2		28	
Donor	8	0		8	
Patient	30	0	0%	30	100%

COVID-19 patients between days 0 and 100. We reported baseline and pre-transplant procedural characteristics descriptively. Our data shows that the BMT procedure was 100% successful throughout the ongoing COVID-19 pandemic with appropriate safeguards. But, 4 patients died after successful bone marrow transplantation due to infections & disease relapse. Among them, 3 patients died due to infection. One patient died of CMV reactivation at day 60 and 2 patients died due to severe infection of *Klebsiella spp* and *Pseudomonas aeruginosa* after successful BMT. Post-transplant follow-up in most cases was uneventful but one patient relapsed after BMT due to disease aggressiveness and the patient expired as failed to receive advanced treatment as advanced treatments were not available in Bangladesh (Table 3). We have shown that BMT procedural success rate was 100%, mortality was 4 (13%), Relapse Mortality (RM) and Non-Relapse Mortality (NRM) were 1 (3%) and 0 (0%) respectively (Table 4).

We did not get any COVID-19-positive patients among our 30 BMT candidates during the covid-19 pandemic. But, we have found that some of our BMT team staff, caregivers, donors were affected by COVID-19 (Table 5). We have isolated them quickly and deferred their BMT activities until RT-PCR for COVID-19 negative. So with a minimum BMT staff, done maximum workload with maintaining 12 hourly roaster duties of our staff, we conducted HSCT of our 30 patients successfully. In this way, we have seen that there was no Covid-19 positive patient among 30 BMT patients.

DISCUSSION

We started bone marrow transplantation work in 2016 at BMT Center, CMH Dhaka to deliver modern sophisticated healthcare to the defense and civil patients who required this treatment. We had been successfully conducting allogeneic bone marrow transplantation and autologous bone marrow transplantation in this center from the beginning. But, In December 2019, with widespread community transmission of COVID-19 in Bangladesh, we faced the greatest threat and major challenges for the administration of Hematopoietic Stem Cell Transplant (HSCT) in our center.

In this study, we retrospectively analyzed 30 consecutive patients who underwent HSCT during the COVID-19 pandemic to evaluate the challenges of Hematopoietic Stem Cell Transplantation in our BMT unit as a single center.

We had to take special care of allogeneic HSCT patients due to donor issues. We changed our arrangement in donor selection, screening as well as cryopreservation patterns of donor products.

We are concerned a lot that COVID-19 could have a significant challenge during bone marrow transplantation or post-transplantation outcomes although data was limited on the epidemiology, clinical manifestations, and optimal management of Coronavirus Disease 2019 in HSCT candidates, and donors. So, as per the given experience with other respiratory viruses, we anticipated that patients might develop severe clinical diseases. For this reason, we followed the practical emergency precautions to conduct a successful HSCT of our patients.

PCR test was mandatory for virus detection before any transplant process among BMT Team members, nurses, cleaners, caregivers, donors as well as recipients for allogeneic and autologous stem cell transplants. Rapid Antigen Test (RAT) test is also used several times in every step. We have isolated infected specialists, staff, and caregivers at once and worked with minimum staff, taken maximum workload.

During the transplant period, whenever we saw any symptoms like fever, cough, or chest imaging abnormalities, we were advised to do a PCR test for detecting the virus also we have done RAT test every day of our patient, caregiver, and staff. Before giving every day round inside BMT Center, all staff did RAT test, if the result is negative, then they were permitted to enter the BMT Center. We followed WHO recommendations diligently to prevent COVID-19. Our healthcare staff, patients, and donors followed the WHO-recommended prevention procedure also. It was vital to be very careful with hygiene routines, including hand washing, use of protective masks, alcohol-containing hand sanitizers, and restriction of visitors in our center.

We have found that BMT procedure was 100% successful throughout the ongoing COVID-19 pandemic with appropriate safeguards. But, 4 patients died after successful bone marrow transplantation due to infections & disease relapse. Among them, 3 patients died due to infection. One patient died of CMV reactivation at day 60 and 2 patients died due to severe infection of *Klebsiella spp* and *Pseudomonas aeruginosa* after successful BMT. Post-transplant follow-ups in most cases were uneventful but one patient relapsed after BMT due to disease aggressiveness and the patient expired as failed to receive advanced treatment as advanced treatments were not available in Bangladesh. We have shown that BMT procedural success rate was 100%, mortality was 4 (13%), and Relapse Mortality (RM) and Non-Relapse Mortality (NRM) were 1 (3%) and 0 (0%) respectively. Among our staff, caregivers and donors, 7 were infected with the COVID-19 Virus without any mortality. We have isolated them rapidly before they contact BMT patients and start their daily activity related to bone marrow transplantation.

CONCLUSION

During the Covid-19 pandemic, the situation was so critical all over the world. We needed to follow WHO recommendations carefully. So, we have taken emergency measures to minimize the impact of COVID-19 on transplant activity. The common and essential preventive measures were social distancing, mask-wearing, hand washing and hygiene for our BMT patients, donors, BMT staff. We have not allowed any visitors and used minimum BMT staff with minimum direct contact with a patient. We proposed some strategies to manage transplant-related activities and a high alert system during the Covid-19 pandemic. We found that BMT procedural success rate was 100% but there were so many challenges we had to overcome with the maximum workload during transplant activities in the Covid-19 pandemic. As a result Transplant cost was comparatively high than the pre-pandemic period.

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