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RESEARCH ARTICLE

COVID 19 Infection in Autologous Stem Cell Transplant Recipients: A Single Institution Observational Cohort

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ABSTRACT

COVID 19 infection had significant impact, including high mortality rate, in immunosuppressed patients including patients with hematological malignancies undergoing hematopoietic stem cell transplantation. This retrospective study describes the characteristics and outcomes of COVID 19 infection in autologous stem cell transplantation (ASCT) recipients. The time period for the study was Feb 2020 to Feb 2022. During that time 29 patients (28%) out of 102 ASCT recipients became infected with COVID 19 diagnosed by PCR test. 22 and 7 were multiple myeloma (MM) and lymphoma (Ly) patients, respectively. Infection rate was 30.5% among MM patients and 23% among Ly patients. Median age was 59 years, 16 were females, 45% were Caucasians. Eight patients had infection prior to first ASCT, and one prior to second ASCT. Nine developed the infection within 12 months post ASCT. 6 patients had 2nd episode of infection within 8-20 months from 1st episode, only one patient required hospitalization. One MM patient contracted the infection from his relatives while in the hospital undergoing ASCT. He was one of total of 3 deaths from COVID infection. All 3 patients had significant comorbidities including 2 on dialysis and the 3rd had chronic kidney failure stage 3B, all were MM patients within < 1 year from ASCT. Two of them were vaccinated with the primary shots but no boosters. Overall, 8 patients were hospitalized due to COVID infection, 7 had multiple comorbidities and 6 had low absolute lymphocyte counts (ALC). Sixteen patients were noted to have low ALC around the time of infection, 5 were Ly patients. Seven patients had no symptoms, only 3 of them were vaccinated. Overall, 12 were vaccinated at the time of infection. 10 patients received monoclonal antibodies after they became positive for COVID. Evusheld was given to 2 patients. Other treatments used mainly in hospitalized patients include dexamethasone, remdesivir, and fresh frozen plasma. In conclusion, our patient population seems to have done better than published reports with about 10% mortality from COVID infection. Comorbidities, especially advanced renal failure, and low ALC may have contributed to worse morbidity and mortality outcomes.

Introduction

Published studies on outcomes of COVID infection in recipients of hematopoietic stem cell transplantation (HSCT) reported worse outcomes and high mortality in immunosuppressed patients including patients with hematological malignancies undergoing HSCT.

A CIBMTR study reported the diagnosis of COVID infection in 318 patients, 184 were post allogeneic HSCT (Allo-HSCT) while 134 were post ASCT.[1] Overall, 14% required mechanical ventilation. At 30 days after the diagnosis of COVID-19, overall survival was 68% for recipients of allo-HSCT and 67% for recipients of ASCT. Age 50 years or older, male sex, and development of COVID-19 within 12 months of transplantation were associated with a higher risk of mortality among allo-HSCT recipients, and a disease indication of lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma in ASCT recipients.

Similar study from the EBMT and GETH groups on 382 patients, 236 allogeneic HSCT and 146 ASCT patients, showed overall survival at 6 wks to be 77.9% and 72.1%, respectively.[2] Children had better survival of 93.4%. Older age, need for ICU and moderate/high immunodeficiency index increased the risk of mortality, while better performance status decreased the risk.

A systematic review and meta-analysis of published reports on COVID infection in HSCT recipients showed the cumulative COVID-19-related death rate of 21%, while mechanical ventilation and ICU admission rates were 14% and 18%, respectively.[3] Subgroup analysis showed higher death rates in patients who developed COVID-19 within 12 months of HSCT, within 6 months of receiving immunosuppressant drugs or in the context of active graft-versus-host disease. At least one study reported favorable outcomes in patients post Allo HSCT, ASCT and CAR T cell therapy.[4]

In this retrospective study, we sought to study the frequency and outcomes of COVID infection in our autologous stem cell transplant patient population. Our impression before we initiated the study was that our patients fared better than what was described in the literature.

Methods

In this retrospective study, we identified patients who contracted COVID infection in our group of transplant patients between Feb 2020 and Feb 2022, either before or after ASCT. During that time, 102 transplants were performed in patients with plasma cell dyscrasias and lymphomas. Of those, 29 patients (28%) were diagnosed with COVID 19 infection which was diagnosed based on clinical symptoms and positive PCR test. This study was approved by our institutional Review Board.

In our practice, patients are hospitalized for the high dose chemotherapy and ASCT until recovery. They are placed in heap filtered negative pressure rooms and receive supportive care treatments including prophylactic antibiotics and growth factor support starting on day +5. Use of masks is required to enter the rooms. Once the COVID pandemic started, more strict policy was implemented for visitors. All patients were tested for COVID by PCR test prior to admission.

We collected the following data: age, sex, disease type, disease status, disease treatment, immunotherapy use, Covid vaccination status at the time of disease, hospitalization frequency, treatment types in hospitalized patients, and mortality rate. We collected data on absolute lymphocyte counts (ALC) as possible risk factor for worse infectious seriousness and outcomes.

We did mainly descriptive analysis in order to determine the seriousness of the symptoms in this patient population, potential predictive factors and risks of mortality. We also describe our infection control policies during the peak of the pandemic in outpatient clinic and inpatient unit where the care of patients took place.

RESULTS

Patient characteristics

The 29 patients who developed COVID were representative of our typical transplant patient population with majority of patients transplanted during the study period having myeloma (71%). The average age was 59 y, while 55% were females (Table 1). According to the literature, one of the risk factors for bad COVID infection outcome is contracting the infection within 12 months from ASCT. Nine of our patients contracted COVID within 12 months from ASCT. All 3 patients who died from COVID infection (Table 2) contracted the infection within < 12 months post ASCT. Twenty of the 29 patients developed the infection post ASCT while 9 had the infection in the few weeks before the transplant resulting in delaying the transplant in some of them. The guidelines in our institution specified that patient with COVID infection should stay away from the clinic or hospital for 21 days from diagnosis and should have symptoms resolved. Curbside checkup tents were established for those patients.

Interestingly, 6 patients had 2 or more COVID infection and they all survived it, even without vaccination in some of them, and while on active

treatment that had to be halted while having active infection symptoms.

At the time, there were many reports about increased risks for contracting the infection with certain blood type. The distribution of blood types in our population, as shown in Table 1, reflects the frequency of blood types in the general population with type O and A being the most frequent blood types.

Table 1: Patient Characteristics

Variable	**Patients with COVID (n=29)**
Age, median (range)	59 (27-74)
Sex, F/M	16/13
Race, AA/C/Others	13/13/3
Disease type	
MM	21
Amyloidosis	1
NHL	6
HL	1
Within 12 mo post ASCT, n	9
Before ASCT*, n	9
Patient with ≥ 2 episodes**	6
Blood type O/A/B	15/11/3

*One patient was before 2nd ASCT, and had one more episode after 2nd ASCT, was never vaccinated.
**Within 8-20 months from 1st episode

Table 2: Patients who died from COVID 19 infection

Variables	**Patient 1**	**Patient 2**	**Patient 3**
Age, year	60	65	71
Sex, F/M	M	M	F
Disease type	MM	MM	MM
Disease Status	PR (Pre-ASCT)	CR	sCR
Active Treatment	MEL140	Bort.	Len.
Time from ASCT, Days	26	330	255
ALC X $10^3/mm^3$*	0.2	0.6	0.5
Prior vaccination	No	Yes	Yes
Co-morbidities	DM, dialysis	CKD, dialysis	HTN, obesity, CKD stage 3B, Hyperlipidemia
COVID treatment	Remdesivir, FFP, IVIg, Dexamethasone	Remdesivir, Dexamethasone	Remdesivir, FFP

*ALC, absolute lymphocyte count, with normal range 1.0-4.5X$10^3/\mu L$.

All 3 patients who died from COVID were MM patients, age ≥60 y, 2 males, and all had renal failure and other co-morbidities (Table 2). All of them were within the first 12 months post ASCT and on active treatment and immunosuppressed as reflected by very low ALC. Two had prior anti COVID vaccination. Patient 1 was in end stage renal failure and on dialysis undergoing high dose melphalan 140 mg/m^2 (MEL140) and ASCT. He was 26 days post ASCT in the hospital with delayed engraftment when he was diagnosed with COVID infection due to respiratory symptoms. He contracted the infection from one of his children. This was before anti COVID vaccination was introduced. He died on day +47 post ASCT from multiple organ failure and cardiac arrest despite receiving multiple anti COVID treatments (see Table 2). After this case of in hospital COVID infection, our guidelines changed and patients coming to transplant were asked to have only one caregiver that will commit either to stay in the hospital all the time with the patient or be allowed to leave the hospital but avoid contact with other people or any crowds. This policy was in practice for about 2 years.

Risk Factors and Treatment Outcomes

There were known published risk factors for contracting COVID and predictive of bad outcomes,[1-8] which we studied in our patient population. The potential risk factors are listed in Table 3. There were 5 patients on active treatment, 6 patients were exposed to immunotherapy such as anti CD20 (Rituximab) and 2 to anti CD38 (mainly Daratumumab), and total of 12 patients with ≥ 2 comorbidities while 7 had ≥ 3 comorbidities. In addition to these known risk factors, we examined the immune status by looking at the absolute lymphocyte count (ALC) on or around the day the COVID infection was diagnosed and discovered that many patients (n=16) indeed had low ALC.

COVID vaccination in the USA started on Dec 14th 2020. Ten of our 29 patients received COVID vaccine before they developed the COVID infection. Overall, 17 patients received the vaccines. There were patients who knowingly refused the vaccine, and one of them had the infection on 2 occasions and survived it, while her husband died from COVID in the early days of the pandemic.

Table 3: Risk Factors

Variable	**patients with COVID infection**
On active treatment, n	5
Disease Status,	
CR	13
< CR	10
Relapse	6
Exposure to immunotherapy, n	
Anti CD20	5
Anti CD38	2
ALC below normal*, n	16
Anti COVID vaccination**, n	10
Comorbidities, n	
≥2	12
≥3	7

*Normal Absolute lymphocyte count (ALC) is 1-4.5 X 10^3/µl
**Received vaccination before COVID infection; but overall, 17 received vaccination.

Several treatments were available to COVID patients, especially hospitalized patients, in the USA. The type of treatments used is reflected in our data (Table 4). Some of these treatments were experimental early on and later data showed lack of effectiveness, such as fresh frozen plasma transfusions, while others became more established treatments with proven benefit, anti-COVID monoclonal antibodies, remdesivir, and dexamethasone.

The severity of the COVID infection in our patient population was relatively mild in most of the patients as reflected by the facts that only 9 had proven lung infiltrates and 5 required hospitalization (Table 4). Only 3 patients required admission to ICU and those are the patients who died (Table 2). Furthermore, with 3 patients dying out of 21 patients who underwent ASCT, the mortality rate in our transplant population was 14.3%. One of these 21 patients, opponent of vaccination, had two transplants for multiple myeloma and developed infection basically after each transplant and survived both of them.

Table 4: Severity of COVID Infection and Treatments

Variable	Patients with COVID infection
Pulmonary infiltrates, n	9
Anti COVID treatments	
Monoclonal Abs	10
Remdesivir	3
Dexamethasone	5
Outcomes	
Hospitalization	5
ICU admission	3
Death	3

Discussion

AS of May 11 2023, there have been 1,127,928 deaths from COVID since the pandemic started in the USA according to the CDC website (https://covid.cdc.gov/covid-data-tracker/#datatracker-home). That date is also the date declared as the end of the pandemic and the end of the US federal COVID-19 public health emergency. Indeed, we in the transplant community have seen less COVID infections in general but also less severe infections. Looking back, there were some fears and uncertainties in the treatment of COVID infections in patients needing autologous or allogeneic stem cell transplants. COVID infection is not over, but we have learned to deal with it and we are better equipped at the present time. In this retrospective study, we wanted to review and share our experience in dealing with COVID infection in patients undergoing ASCT.

There has been abundant literature on the impact of COVID infection on stem cell recipients, some of it summarized in our introduction. Most publications reported risk factors and outcomes of the infection, and fewer mentioned the incidence.[1-8] It is clear that the incidence and outcomes changed over time since the beginning of the pandemic, and one can divide the period of the pandemic according to the waves of infection, pre and post vaccination periods, and the contagiousness of the virus, Omicron Vs Delta.[9,10] Our results show 29 out of 102 ASCT patients (28%) contracted COVID 19 infection during the study period. Because some patients contracted COVID in the period preceding ASCT, the actual incidence of COVID infection in patients post ASCT was 20.5%. Eleven of them were diagnosed before vaccination introduced for the first time in the USA in Dec 2020. However, 10 patients (35%) had prior vaccination before they developed the COVID infection, and overall, during the span of the study, 17 of 29 patients (58.6%) received any vaccination doses. Earlier published large studies did not mention the rate of vaccination among their study populations, except for one[6] in which the rate of non-vaccination was 91%.

The outcome of COVID 19 infection in stem cell transplant recipients have been almost uniformly reported to be dismal. Several reports, from transplant data bases in the US and Europe, as well as, from specific countries, have all reported mortality rates of 20-38% in post ASCT COVID patients and 21% but as high as 62% in Allo-HSCT patients.[1,2,6,7,11] Two publications with meta-analysis showed similar outcomes.[3,8] In order to continue providing the transplant option for patients who need it without increased risk, guidelines were issued by special groups such as ASTCT and EBMT.[12-14] On the other hand, other studies reported better outcomes,[4,10,15,16] especially in pediatric population,[16] and one with much improved survival of Allo-HSCT patients that were fully vaccinated and only one death (0.5%) among 37 patients.[15] Our patient population seems to have done better than published reports with about 10% overall mortality from COVID infection, or 14.3% in patients post ASCT.

Furthermore, only 5 (17%) required hospitalization.

Three out of 21 (14.3%) post ASCT patients died of COVID infection, or 3 deaths in the whole group of 29 patient (10.3%). The 3 patients who died contracted COVID infection within 12 months from ASCT, one of them (Patient 1) developed hospital acquired COVID 19 while neutropenic and lymphopenic. Patient 1 contracted COVID from his daughter who fell sick at the same time, and all that happened in the early period of COVID infection before vaccines were introduced. The other two patients received vaccines, but were still within 12 months from ASCT. All 3 patients had MM, and all had significant comorbidities including renal failure. Furthermore, data on ALC was available on all 3 patients and was very low (≤ 600). Five cases of COVID infection in the pre-engraftment period were described in the literature[17-20], 2 post ASCT and 2 post Allo-HSCT. Two of them, one post Allo-HSCT and another post ASCT, while the other 3 recovered.

At least one publication looked at ALC as a marker for the depth of immunosuppression[6] and reported only 6% to have ALC ≤ 200/mm^3 at the time of active COVID infection in 199 Allo-HSCT patients who were on active immunosuppressive therapy in the 6 months prior to developing COVID infection. The EBMT and GETH report found that ALC ≥ 200 was significantly (P = 0.04) associated with resolution of COVID infection.[2] It is surprising that many of our patients did well despite large number of the patients not being vaccinated (41.4%), with low ALC (55%), and had ≥2 significant co-morbidities (41.4%). Comorbidities, especially advanced renal failure, and low ALC may have contributed to worse morbidity and mortality outcomes in our patients.

There have been several publications about the effects of ABO blood types on sensitivity to contracting COVID and infection outcomes.[21-26] Few studies suggested that patients with blood type A and AB have higher susceptibility to COVID infection, however later studies did not show relationship. These studies are reviewed by Kim et al.[27] Our study, although small, showed no association since patients were mostly divided between A and O blood types. The overall thought at this time is that blood type does not play any role as a risk or prognostic factor in COVID 19 infection.

Conclusions

Although our study limitations are obvious, being retrospective and small, however it shows that the outcomes of COVID infection in ASCT patient may not be as grim as it was reported earlier in the pandemic, however patients with advanced renal failure, low ALC, as well as other comorbidities could be at higher risk for worse outcome. On the other hand, since 35% of the patients were vaccinated, it is possible that anti COVID vaccination may have played an important role in reducing mortality in our study population.

Conflict of Interest

The authors have no conflicts of interest to declare.

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