A retrospective review of infections and outcomes within 100 days of hematopoietic stem cell transplantation: insights from a new transplant program in the Philippines

Jia An G. Bello a,1, Angela Beatriz Cruz b, Ma. Patricia Virata b, Alma Calavera c, Cybele L. Abad a,1,*

a Department of Medicine – Section of Infectious Diseases, The Medical City, Ortigas Avenue, Pasig City, Philippines
b Department of Medicine, The Medical City, Ortigas Avenue, Pasig City, Philippines
c Department of Medicine – Section of Hematology, The Medical City, Ortigas Avenue, Pasig City, Philippines

ABSTRACT

Background: Few hematopoietic stem cell transplantations (HSCT) are performed in lower-middle income countries. Only four institutions in the Philippines are able to perform transplants. This study describes the experience of a newly established program.

Methods: The charts of all adult patients who underwent HSCT at The Medical City from May 1, 2016 to December 31, 2019 were reviewed retrospectively.

Results: A total of 33 patients were included in the cohort, of whom 31 (93.9%) underwent autologous HSCT and only two (6.1%) underwent allogeneic HSCT. Most were female (21/33, 63%), and median age was 51 years (range 21–67 years). The primary indication for transplantation was multiple myeloma (n = 21), followed by diffuse B-cell lymphoma (n = 6). Fifteen of the 33 patients had a history of treated tuberculosis (TB) disease (n = 4) or latent TB infection (n = 11). The median time for neutrophil recovery was 7.4 days (range 4–13 days). Transplant complications included neutropenic fever (n = 33, 100%) and mucositis (n = 14, 42.4%). Bacterial infection was documented in 12 (36.4%) patients, with nine (24.2%) developing a bacterial blood stream infection of which seven were related to a central line. The overall mortality rate was at 6.1% (2/33) in the first 30 days post-transplant, with no additional mortality in the succeeding days until day 100.

Conclusions: This cohort with mostly autologous HSCT had favorable outcomes in the first 100 days. Rates of bacterial infection were high in the early post-transplant period. Latent TB infection was common, but no reactivation was observed. Longer-term follow-up of patients is needed to determine late post-transplant complications and outcomes.

1. Introduction

The number of hematopoietic stem cell transplantation (HSCT) procedures has continued to rise since the initial success of this treatment in 1957, but there is a huge geographic disparity in transplantation rates, ranging from as low as 0.1/10 million population in South East Asia and Africa to as high as 100/10 million in North America and Europe (Niederwieser et al., 2016). Limitations in terms of expertise, financial restrictions, lack of a national health insurance system and governmental support, and the inability to develop local transplant centers have contributed to the overall low numbers of procedures performed (Baylon et al., 2008).

In the Philippines, the first successful HSCT was performed in 1990 in a government hospital (Baylon et al., 2008). Three decades later, only three institutions are capable of performing HSCT, with only two actively performing transplants. In 2016, The Medical City (TMC) inaugurated its own HSCT program, the fourth in the country overall. Published data on the local experience remain scarce, and gaining a perspective on the potential infectious complications that are endemic in settings outside of the USA and Europe is also important. This study was performed to provide insights into the authors’ transplant experience, focusing on early complications and outcomes of patients undergoing HSCT.

2. Materials and methods

2.1. Study design and setting

All adult patients ≥18 years old admitted to TMC for either an autologous or allogeneic HSCT from May 1, 2016 to December 31, 2019 were included in this study. There were no non-myeloablative allogeneic stem cell transplants during this period. A retrospective chart review was performed and the following information was collected and recorded: baseline demographics (including age and sex), relevant medical history (co-morbidities), history of the underlying disease (including the stage at time of transplant, remission vs relapse, prior chemotherapy, etc.), and details of the transplant (including type of donor, transplant type (autologous/allogeneic), number of CD34 cells transplanted, condi-

* Corresponding author: Cybele L. Abad, Department of Medicine – Section of Infectious Diseases, MATI 1706, The Medical City, Ortigas Avenue, Pasig City, Philippines. Tel: (+632) 8988-1000 ext 5236.

E-mail addresses: cybelemd@yahoo.com, crabad@up.edu.ph (C.L. Abad).

Jia An G. Bello and Cybele L. Abad contributed equally to this work.

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tioning regimen, prophylaxis and medications, and in-hospital complications (including infections). Outcomes (death or survival) at 30 days and 100 days are described. The study was conducted in accordance with ethical guidelines and with the regulatory approval of the Institutional Review Board of TMC (TMC IRB # GCS MED 2018-105).

2.2. The transplant unit

All patients are admitted to a dedicated transplant unit with eight single rooms, of which five are positive-pressure and three are negative-pressure. All patients are admitted to positive-pressure rooms unless there is an active airborne infection (e.g., tuberculosis (TB)). Fronting the unit is an ante-room for donning and doffing personal protective equipment (PPE). All providers and visitors wear disposable hair caps, gowns, and shoe covers. Each room is equipped with high-efficiency particulate air (HEPA) filters. Patients are eligible for discharge from the unit once they are clinically improved, afebrile >48 hours, engrafted (absolute neutrophil count (ANC) >500 cells/mm³ for more than 2 days), and once they are no longer transfusion-requiring.

2.3. Pre-transplant screening, prophylaxis, and other protocols

Pre-transplant serological screening included testing for blood-borne pathogens (including HIV, hepatitis B virus, hepatitis C virus), cytomegalovirus (CMV), and herpes simplex virus 1 and 2 (HSV-1 and 2). Screening for latent TB infection (LTBI) was performed via interferon gamma release assay (IGRA), and the decision to treat was left to the discretion of the healthcare team. None of the patients were treated during the period of highest risk. All HSCT recipients were started on the following medications at the start of the conditioning regimen: ciprofloxacin 400 mg intravenous (IV)/oral (PO) every 12 hours as antibacterial prophylaxis, acyclovir at 400 mg IV/PO twice daily as antiviral prophylaxis, and fluconazole 400 mg by IV/PO once daily as antifungal prophylaxis. For allogeneic transplant recipients, an echinocandin was preferred until neutrophil engraftment, after which a shift to an oral azole was recommended and left to the discretion of the transplant team. Granulocyte-colony stimulating factor (G-CSF) was given on day 5 at 300 μg/day, until the ANC was >800 cells/mm³.

All transplant recipients received peripheral blood stem cells. The conditioning regimen was melphalan for all myeloma patients, BeEAM (i.e., bendamustine or carmustine, etoposide, cytarabine, and melphalan) for all lymphoma patients, and busulfan, fludarabine, and cyclophosphamide for patients with acute myelogenous leukemia (AML).

2.4. Definition of terms

Febrile neutropenia was defined as a single oral temperature measurement of >38.3°C (101°F) or a temperature of >38°C (100.4°F) sustained over a 1-hour period, with an ANC of <500 cells/mm³ or an ANC that is expected to decrease to <500 cells/mm³ during the next 48 hours. Severe neutropenia was defined as an ANC <100 cells/mm³ (Freifeld et al., 2011). Catheter-related bloodstream infection (CRBSI) was defined using the principle of differential time to positivity (DTP) (Raad et al., 2004). LTBI was defined as a state of persistent immune response as documented by a positive TB-specific IGRA and the absence of symptoms of active disease. Standard definitions were used for common infections such as urinary tract infection (UTI), cellulitis, and hospital-acquired pneumonia (HAP) (Gupta et al., 2011; Kalil et al., 2016).

2.5. Data analysis

Descriptive statistics were used, and the frequency distributions of demographic and clinical characteristics were determined for quantitative variables. The median was used as the measure of central tendency in this small patient population with small and large values.

3. Results

3.1. Baseline characteristics

Of the 33 patients included in the study, 21 (63.6%) were female and 12 (36.4%) were male. Median age was 51 years (range 21–67 years). An underlying lymphoid disorder was the primary reason for transplantation in an overwhelming majority (32/33, 97%). Thirty-one patients (93.9%) underwent autologous HSCT and only two (6.1%) underwent allogeneic HSCT. The median number of CD34 cells infused was 6 x 10⁶ cells/kg body weight (range 4–23.3 x 10⁶ cells/kg body weight).

Table 1

| Characteristics of the patients included in the study |
|--------------------------------------------------------|
| Demographics                                           |
| Sex, n (%)                                             |
| Female                                                 | 21 (63.6) |
| Male                                                   | 12 (36.4) |
| Age (years), median (range)                            | 51 (21–67) |
| Co-morbidities, n (%)                                  | 6 (18.2)  |
| Diabetes mellitus                                      | 3 (9.1)   |
| Chronic kidney disease                                 | 11 (33.3) |
| Hypertension                                           | 19 (57.6) |
| None of the above                                      | 27 (81.8) |
| CMV recipient serostatus, n (%)                        | 4 (12.1)  |
| R+                                                     | 2 (6.1)   |
| R–                                                     | 1 (3)     |
| Primary reason for transplantation                     | 1 (3)     |
| Myeloid (AML/MDS/CML), n (%)                           | 1 (3)     |
| Lymphoid (ALL, CLL, HL, MM, NHL, and other lymphomas), n (%) | 1 (3)     |
| Characteristics of transplant                         | 32 (97)   |
| Type of graft, n (%)                                   | 33 (100)  |
| Conditioning regimen, n (%)                            | 2 (6.1)   |
| Otherᵡ                                                  | 10 (30.3) |
| Transplant prophylaxis                                 | 33 (100)  |
| Antifungal, n (%)                                      | 33 (100)  |
| Non-mold active azale (fluconazole)                    | 31 (93.9) |
| Echinocandin (micafungin)                              | 2 (6.1)   |
| Antibacterial, n (%)                                   | 32 (97)   |
| Fluoroquinolone (ciprofloxacin)                        | 31 (93.9) |
| Trimethoprim–sulfamethoxazole                          | 33 (100)  |
| Antiviral, n (%)                                        | 33 (100)  |
| Acyclovir                                               | 33 (100)  |
| Other transplant data                                  | 33 (100)  |
| Transfusions, number of units of pRBC until day 100, median (range) | 1 (0–15) |
| Duration of corticosteroids (days), median (range)     | 6 (4–23.3) |
| Laboratory data                                        | 6 (0–14)  |
| ANC <500 cells/mm³, n (%)                              | 33 (100)  |
| Duration of neutropenia (days), median (range)         | 7.4 (4–13) |
| ANC <100 cells/mm³, n (%)                              | 5.7 (2–11) |
| Complications                                          | 14 (42.4) |

(continued on next page)
ple myeloma was the main indication for HSCT (n = 21). Hypertension was the most common comorbidity (n = 11, 33.3%), followed by diabetes mellitus (n = 6, 18.2%) and chronic kidney disease (n = 3, 9.1%) (Table 1).

Of the cohort, 27 (81.8%) recipients were CMV-positive, four (12.1%) were CMV-negative, and two (6.1%) had an unknown CMV serostatus. Of the two allogeneic transplant recipients, one was CMV donor- and recipient-negative (D−/R−) and the other was CMV donor-negative and recipient-positive (D−/R+). Four (12.1%) had history of prior treatment for pulmonary TB, 11 (33.3%) had a reactive IGRA, 12 (36.4%) were non-reactive, and the rest were not tested (Table 1). All patients with a reactive IGRA were monitored closely and not given prophylaxis for LTBI.

### 3.2. Complications and outcomes

The median time for neutrophil recovery was 7 days (range 4–13 days) and the median length of hospital stay was 26 days (range 20–46 days). The duration of severe neutropenia was short, lasting a median of 5.7 days (range 2–11 days).

Transplant complications included neutropenic fever (n = 33, 100%) and mucositis (n = 14, 42.4%). Bacterial infection was documented in 12 (36.4%) patients, with nine (24.2%) developing a blood stream infection (BSI); eight bacterial and one (3%) fungal (Candida sp) BSI. Seven fulfilled the criteria for CRBSI using DTP, but four of seven had concomitant mucositis and could have had mucosal barrier injury (MBI) BSI. Of these infections, Klebsiella pneumoniae was the most common organism, followed by coagulase-negative staphylococci (Table 2). No patients developed CMV viremia or reactivation of TB within the first 100 days.

The overall mortality rate was at 6.1% (2/33) in the first 30 days post-transplant, with no additional mortality until day 100. The patient who underwent allogeneic HSCT for acute lymphocytic leukemia developed a cerebrovascular hemorrhage secondary to disseminated intravascular coagulation (DIC) on day 25. The other mortality was in a patient with natural killer (NK) T-cell lymphoma who developed septic shock secondary to severe Clostridium difficile enteritis on day 8.

### 4. Discussion

The Medical City is now only one of four tertiary hospitals in the Philippines to offer HSCT. This study describes the authors’ early experience with HSCT and highlights the following unique observations: autologous HSCT was associated with good outcomes; rates of early bacterial infection from CRBSI were high; and many recipients had evidence of LTBI.

Published data from the Philippines regarding transplants are scant, but an original article (Baylon et al., 2008) showed that of the first 21 transplants performed in two Philippine medical centers, 19 were allogeneic, reflecting the need for urgent transplantation in these patients. This is unusual, since it is usually recommended to start with autologous transplantations first, for several reasons: allogeneic HSCTs are very specialized, financially costly, and resource-intensive, often requiring human leukocyte antigen (HLA) laboratory equipment and expertise; allogeneic transplantations also have greater morbidity due to many factors, especially graft-versus-host disease (GVHD). In contrast, autologous transplants are less complex in nature, less financially draining, and associated with much better outcomes (Chaudhri et al., 2017). In the earlier series, there were three early transplant-related mortalities (3/21, 14.3%) from Candida sepsis, severe sinusoidal obstruction syndrome, and multiorgan failure, respectively (Baylon et al., 2008). In the present cohort, there were only two mortalities. The short-term outcomes in this study were excellent, likely because the majority of transplants were autologous HSCT. As more transplant programs are initiated in the country, it is highly recommended to begin with autologous transplants first in order to gain experience in a subspecialty that requires particular expertise and intense resources. Autologous transplantation is indicated and offered as a best chance of cure depending on the underlying disease (e.g. multiple myeloma, diffuse large B-cell lymphoma, Hodgkin lymphoma) and disease status (remission, relapse). As such, the decision to choose it over allogeneic transplantation may not always be in the hands of the provider. Regardless, the decision to transplant is difficult and best made after careful consideration of the alternatives, risks, and benefits of the procedure (Majhail et al., 2015). It is also difficult to directly compare the efficacy of autologous and allogeneic transplants because the populations are different, but in general the former is associated with higher survival rates and better outcomes.

In the present study, the median time for neutrophil recovery was 7 days (range 4–13 days), which is shorter than in other studies, which have reported a range of 9–21 days for neutrophil engraftment in autologous recipients (Ergene et al., 2007; Gonçalves et al., 2009; Mushtaq et al., 2018; Pavlu et al., 2017), and between 16–23 days among allogeneic recipients (Gonçalves et al., 2009). Early engraftment plays a crucial role in the success of HSCT, especially since delayed recovery is associated with higher morbidity and mortality. It is hypothesized that the shorter time to engraftment was influenced by the type of disease (mostly multiple myeloma), by giving standard doses of G-CSF per protocol (on day 5 until ANC was >800 cells/mm³), and by the higher median number of CD34+ cells infused (6 × 10⁹ cells/kg body weight).

Not surprisingly, the most common complications encountered in this cohort were neutropenic fever (n = 33) and mucositis (n = 14). Neutropenic fever and mucositis are not unexpected, especially after transplant, and are commonly reported (Fanning et al., 2006; Wingard et al., 2010). In this cohort, it was possible to document the source of the febrile neutropenia infection in one third (36.4%) of transplanted patients, which is consistent with the existing literature (Freifeld et al., 2011). The majority of infections were bacterial in nature, which follows the timeline of infections post-transplant (Wingard et al., 2010).

The study findings also validate existing data that BSIs in the pre-engraftment period are frequent, ranging from 5% to 47.2% (Balletto and Mikulski, 2015; Gudiol et al., 2014; Lee et al., 2016). The ma-
Table 2
Summary of infections in the study cohort

| Age (years)/ sex | Types of infection | Pathogen | Timing, from day 0 | Outcome |
|------------------|--------------------|----------|-------------------|---------|
| 67/M             | CRBSI, HAP         | Staphylococcus epidermidis | 1 | Recovered |
| 33/M             | UTI, AGE           | Klebsiella pneumoniae | 3 |         |
| 25/F             | Secondary bacteremia | MDRO Klebsiella pneumoniae | 3 |         |
| 22/M             | CRBSI, AGE         | Staphylococcus haemolyticus | 3 |         |
| 56/F             | HAP, Cellulitis    | Acinetobacter baumannii, Klebsiella pneumoniae, Enterobacter cloacae | 7 |         |
| 42/M             | CRBSI              | Staphylococcus epidermidis | 4 |         |
| 25/F             | UTI, HAP           | Escherichia coli | 7 |         |
| 48/F             | UTI                | Klebsiella pneumoniae | 7 |         |
| 42/F             | Secondary bacteremia | Klebsiella pneumoniae ESBL-positive | 8 |         |
| 46/M             | HAP, CRBSI         | Pseudomonas aeruginosa, Staphylococcus hominis | 92 |         |
| 57/F             | GIT                | Clostridium difficile | 4 | Mortality |
| 63/F             | CRBSI              | Klebsiella pneumoniae ESBL-positive | 7 | Recovered |
| 61/M             | CRBSI              | Staphylococcus epidermidis | 6 |         |
| 28/F             | CRBSI              | Candida parapsilosis | 9 |         |

AGE, acute gastroenteritis; CRBSI, catheter-related blood stream infection; ESBL, extended-spectrum beta-lactamase; F, female; GIT, gastrointestinal tract; HAP, hospital-acquired pneumonia; M, male; MDR, multidrug-resistant; UTI, urinary tract infection.

In conclusion, this cohort with mostly autologous HSCT had favorable outcomes in the first 100 days. Bacterial infections remain a common cause of infectious complications. Despite a significant number of recipients with LTBI, reactivation was not observed. Longer-term follow-up of patients is needed to determine late post-transplant complications and outcomes, including the potential for reactivation of LTBI. Collaboration with other institutions and the development of a national Philippine transplant registry in the future would be ideal.

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Ethical approval

The work described was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was waived and the study was approved by the Institutional Review Board of The Medical City (TMC IRB # GCS MED 2018-105).

Conflict of interest

All authors have no conflict of interest to declare.

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