

Hematopoietic Stem Cell Transplantation in Vietnam: Current Status and Future Directions

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Abstract: In recent years, there have been an increasing number of hematologic patients in Vietnam. Hematopoietic stem cell transplantation (HSCT) is fast becoming an effective method to cure many benign and malignant blood disorders. Nine transplant centers are operating throughout Vietnam. HCMC Blood Transfusion Hematology Hospital (BTH) is one of these centers where bone marrow, peripheral blood and cord blood stem cell transplantation were first conducted in our country. At BTH, half of the patients received allogeneic HSCT, mainly from matched sibling donors due to lack of a national bone marrow donor registry. While acute myeloid leukemia was a common indication of allogeneic HSCT, most of the patients undergoing autologous HSCT had multiple myeloma. One major issue we encountered concerned bacterial and fungal infections during neutropenia period. Because of an endemic area, CMV reactivation frequently occurred. Five-year overall survival (OS) and event-free survival (EFS) were 47% and 46%, respectively. To create more opportunities for patients, our future directions will focus on some new transplant procedures, such as haploidentical, unrelated and cord blood transplantation.

Key words: HSCT, Vietnam, BTH, allogeneic, autologous.

1. Introduction

Vietnam is a developing country in Southeast Asian with a population of over 90 million. Lack of economic and human resources have resulted in many healthcare issues: tuberculosis, HIV, HBV infection and cancer. Data from World Health Organization have identified that number of new cancer cases in Vietnam was 125,000 [1]. Hematologic malignancies are one of top cancers which are having promising outcomes attributed to enhanced chemotherapy protocols and supportive care. In addition, hematopoietic stem cell transplantation (HSCT) plays an important role in improving survival in numerous patients.

There are nine hospitals in Vietnam which have ability to conduct HSCT. Recently, the number of newly established transplant centers is increasing

gradually. However, only several centers can implement allogeneic HSCT (Table 1). According to data of 2016, a total of 579 patients received HSCT and more than half of them were autologous cases. Majority of transplants occurred in two large hospitals: Blood Transfusion Hematology Hospital (Hochiminh city) and National Institute of Hematology and Blood Transfusion (Ha Noi).

Based on the requirements for the improving the quality of therapy for Hochiminh city and the Southern Vietnam, the first stem cell transplant unit has been established at BTH since 1995 (Table 1). At that time, we performed successfully the first case of allogeneic stem cell transplantation for a patient with chronic myelogenous leukemia. Then, our stem cell transplant unit conducted the first case of autologous HSCT in Vietnam in 1996, and the first case of cord blood stem cell transplantation in 2002. Ten years later, the first case of haploidentical stem cell transplant in Vietnam also took place at BTH. Along with

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Table 1 Distribution of patients by hospitals^a.

Transplant units	Starting year	Number of patients		Total
		Autologous	Allogeneic	
HCMC Blood Transfusion Hematology Hospital (BTH)	1995	113	109	222
Hue Central Hospital	2003	07	00	07
108 Military Hospital	2004	21	02	23
National Institute of Hematology and Blood Transfusion (NIHBT)	2006	123	102	225
National Hospital of Pediatrics	2006	04	23	27
Bach Mai Hospital	2012	30	9	39
Nghe An Oncology Hospital	2016	01	0	01
Cho Ray Hospital	2013	30	0	30
Nghe An Oncology Hospital	2013	05	00	05
Total		334	245	579

^a Data from 2016.

the progression of clinical management, since 2001, we have also contributed a stem cell bank for supplying stem cell resources to patients who have indications of HSCT. We officially became a member of Asiaccord in 2014. By 2012, Ministry of Health allowed us to develop in both areas: public and private cord blood banking. The aim of the paper is to review some characteristics, challenges and outcomes of HSCT at BTH. Accordingly, we point out future directions to improve the application of HSCT in our conditions.

2. Characteristics of HSCT at BTH

In the first several years of our newly formed transplant unit, the number of patients receiving HSCT was rather limited, with under 10 cases per year. After building the capability of our staff as well as better facilities, since 2012, there has been a gradual rise in the number of transplanted cases (Fig. 1).

Nearly half of the patients received allogeneic HSCT. Acute myeloid leukemia was the most common indication of allogeneic HSCT at BTH. Otherwise, most of the autologous HSCTs were performed for multiple myeloma (Table 2).

Despite the high frequency of thalassemia and aplastic anemia in Vietnam, allogeneic HSCT has not been used extensively for these types of disease. If no sibling donor is available, it will be difficult to find

unrelated donors due to lack of a national bone marrow donor registry.

Peripheral blood stem cells have been the main stem cell source for transplantation in Vietnam. Bone marrow harvesting requires an equipped operation room which is hardly set up in a specialist hospital. In addition, reluctance to donate affected the amount of patients receiving bone marrow stem cells. Although we tried to develop a cord blood bank from the beginning, cord blood stem cell transplantation remains a challenging procedure which requests a lot of experience. This is the reason why only 7.2% of cord blood stem cell transplantations were conducted at BTH. Majority of patients received stem cells taken from HLA-identical sibling donors. Therefore, incidence of aGvHD and cGvHD were 31.4% and 23.5%, respectively [2]. Currently, our efforts have concentrated on developing haploidentical stem cell transplantation which will be a promising opportunity for hematologic malignancy patients without full match donors.

Our conditioning regimen for AML or ALL is usually myeloablative, such as busulfan and cyclophosphamide (BuCy) or busulfan and fludarabine (BuFlu). Reduced intensity conditioning (RIC) is associated with lower morbidity and mortality but higher rate of relapse [3]. However, it is merely used in several patients who are elderly or have

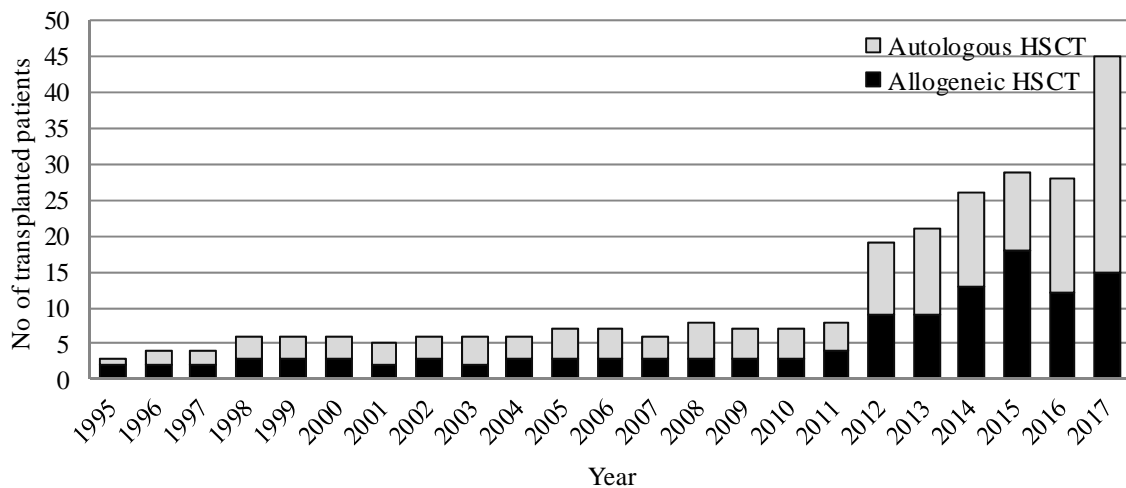


Fig. 1 Number of transplanted patients by year at BTH.

Table 2 Number of transplanted patients by diagnosis at BTH^b.

Diagnosis	Number of patients	
	Allogeneic HSCT	Autologous HSCT
Acute myeloid leukemia (AML)	72	43
Acute lymphoblastic leukemia (ALL)	11	5
Chronic myeloid leukemia (CML)	17	5
Chronic myelomonocytic leukemia (CMML)	2	0
Multiple myeloma	0	70
Non-Hodgkin lymphoma	2	26
Myelodysplastic syndrome	4	0
Neuroblastoma	0	5
Aplastic anemia	16	0
Total	129	149

^b Data from 2017.

multiple comorbidities because modalities preventing post-transplant relapse are insufficient in Vietnam. Conditioning regimens vary significantly according to the types of disease. Total body irradiation (TBI) has not been developed at BTH, that may be a disadvantage for effective integration in conditioning regimens for malignant lymphoid disorders and haploidentical or unrelated donor transplantation.

3. Infections after HSCT in Vietnam

Bacterial and fungal infection are the major post-transplant complication that we always encounter. It has become a cumbersome issue in the transplant units of developing countries such as Vietnam, Indonesia, India... [4, 5]. Most of the infections

occurred before the time of engraftment. At BTH, the rate of infection remains very high even when patients are protected in the isolation rooms. A retrospective study analyzed 113 patients who received HSCT during Jan 2015-March 2018 at BTH. There were 108 patients (95.5%) presented febrile neutropenia and one-third of those had two or more infection episodes. Bloodstream infections were detected in 17 cases (15.0%). Gram-negative bloodstream infection was more frequent than Gram-positive (50.4% vs. 34.5%). Unfortunately, the emergence of multidrug-resistant bacteria has recently endangered our transplanted patients, especially in allogeneic HSCT.

Vietnam is an endemic area of hepatitis B virus (HBV), with 50-75% of the anti-HBc carrier in the

general population [6]. Overt hepatitis could thus be a dramatic consequence for patients who have to take prolonged immunosuppressive agents. Prophylaxis with antiviral drugs is compulsory for all these high-risk patients before, during and after transplantation. With very few patients suffering the flares of severe hepatitis, this strategy has offered an effective way to prevent HBV reactivation in our condition.

Most of stem cell donors and recipients had evidence of past CMV infection. According to serostatus, our patients were at high risk of CMV reactivation after transplantation [7]. Our previous study reported that the cumulative incidence of CMV infection at day 100 after allogeneic HSCT was 76.9% [8]. This complication may adversely impact the overall outcome of HSCT, such as increasing bacterial and fungal infections, graft failure and development of aGVHD [9]. At BTH, monitoring level of CMV-DNA in blood was performed weekly and preemptive ganciclovir therapy was administered if viral load is above 1,000 copies/mL. This way of management demonstrated efficiency to prevent CMV diseases in all patients. However, preemptive therapy frequently related to several side effects, such as acute renal failure ($n = 5$), neutropenia ($n = 5$), elevated liver transaminase ($n = 3$) [8].

4. Results of HSCT at BTH

According to data collected in 2016, of the total of 178 transplanted cases, 106 patients were alive without disease (60.7%) with median follow-up time of 21.5 months. Overall survival (OS) and event-free survival (EFS) after 5 years were 47% and 46%, respectively. Allogeneic HSCT had better 5-year OS and EFS (54.5% and 52.0%) than autologous HSCT (44.4% and 40.9%) (Fig. 2).

In the past, due to lack of facilities, many of AML patients received autologous HSCT as a consolidation therapy. By contrast, allogeneic HSCT has recently been a preferable option in order to take advantage of

graft-versus-leukemia effect, especially in high-risk or relapse/refractory AML patients. As shown in Fig. 3, allogeneic HSCT appears to have superior outcomes to autologous HSCT. Nevertheless, we found that they were not significantly different.

In the case of CML, despite rapid development of tyrosine kinase inhibitors, allogeneic HSCT remains to be an optimal therapy for patients who are resistant to imatinib or in accelerated phase/blast crisis (5-year OS and EFS were 59.4% and 57.1%, respectively).

Recently, autologous HSCT becomes a standard treatment for multiple myeloma at our hospital with 100% OS and 77% EFS after 2 years. Due to low number of patients, it is impractical to analyze the survival rates of other diseases after transplantation. However, we considered that stem cell transplantation has been still beneficial to most of patients with the hematologic disorders, such as thalassemia, aplastic anemia, myelodysplastic syndrome...

5. Cooperative Activities of BTH

As a large hospital of hematology, BTH played an important role in cooperating and sharing experiences about stem cell transplantation to other hospitals in Vietnam. We supported many hospitals in training the transplantation groups, such as Cho Ray Hospital, Nghe An Oncology Hospital, Da Nang Oncology Hospital... In addition, collaborating with some hospitals (Children's Hospital 2, Cho Ray Hospital, Oncology Hospital) was also our effort in order to provide HSCT therapy to as many patients as possible. Although HSCT has grown dramatically in recent years, lack of facilities, equipment as well as experiences is always our challenge. Thus, international cooperation with many advanced countries in the world has particularly had our attention. Some of our physicians, nurses and technicians had opportunities to be educated about transplantation in various countries such as Taiwan, Japan, France, Belgium, Singapore and the U.S. The goals of these training programs were developing transplant protocols

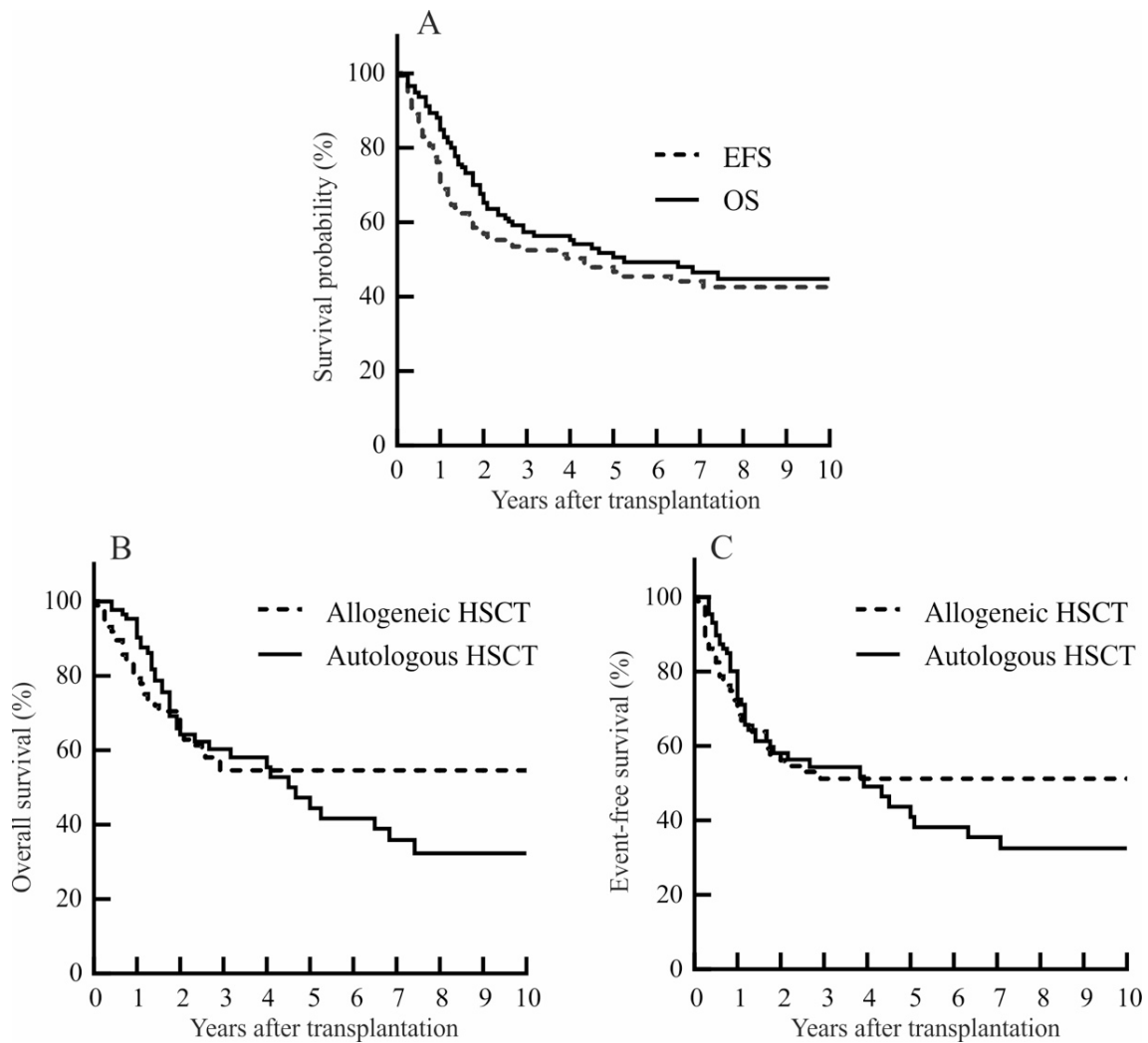


Fig. 2 (A) OS and EFS of total patients; (B) OS according to types of transplant; (C) EFS according to types of transplant.

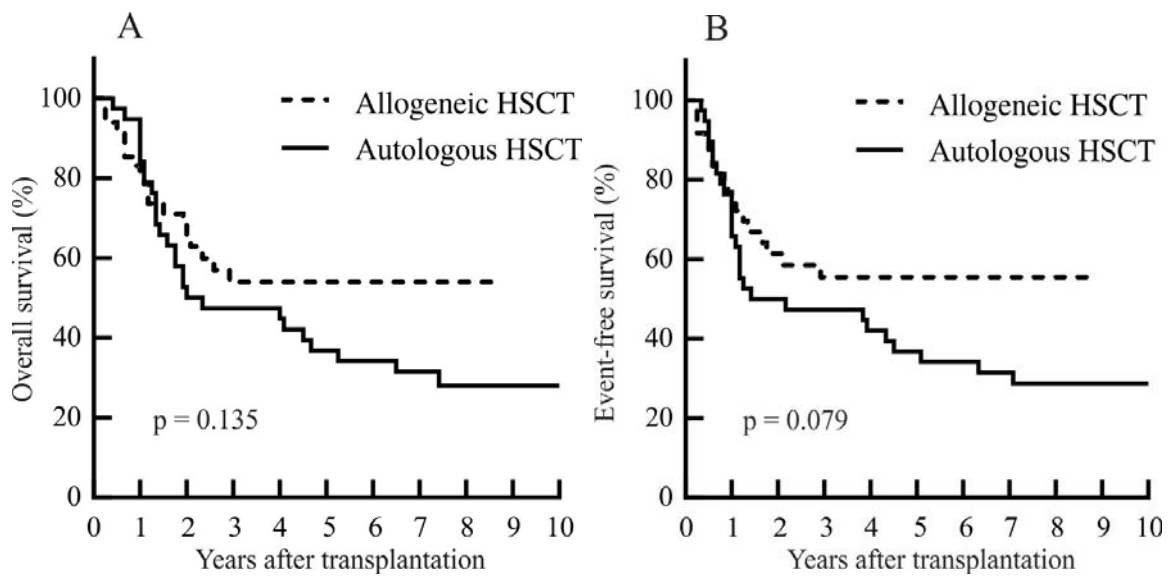


Fig. 3 Outcomes of transplantation in AML. (A) OS by types of transplant; (B) EFS by types of transplant.

and new procedures, improving nursing care, supplementing with laboratory tests relating to HSCT. Moreover, we have organized several international conferences: the annual Vietnamese-French transplantation conference, Asia-Pacific Blood and Marrow Transplantation Group (APBMT) conference... These expert meetings supported us with a lot of innovative updates and knowledge which are necessary to build effective transplant teams in Vietnam.

6. Future Directions

As a hematology hospital, coordination between other specialties has been an obstacle to us when patients had multiple comorbidities or complications during HSCT. Furthermore, insufficiency of modern equipment, medications impeded application of more advanced types of transplantation. In future, BTHs have plans to develop and expand HSCT, such as promoting mutual cooperation between hospitals, establishing a new standard for transplantation center. We are actively working with health care insurance to assist to have broad coverage of transplanted medications and procedures. Improving techniques of haploidentical and cord blood HSCT will be our major goals next few years, that will solve the problem of donor shortage. Additionally, we make the effort to link to stem cell bank of Taiwan to find unrelated donors. Finally, cooperation with international transplant groups will be further enhanced to provide more effective treatment to Vietnamese patients.

7. Conclusions

Taken together, this review has provided some important findings relating to current status of HSCT in Vietnam. Despite limitation of numerous resources, we achieved remarkable results with increasing number of transplanted patients in recent years. The more patients access to this treatment method, the more effort we make. In addition to developing new transplant technologies, promoting cooperation with

the worldwide transplantation groups will be our major purpose in order to offer therapeutic benefits to Vietnamese hematologic patients.

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