Original article

Long term outcomes of hematopoietic stem cell transplantation in Thailand- a 20-year, single center, retrospective cohort study

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Abstract:

Background: *Data regarding Hematopoietic Stem Cell Transplantation (HSCT) in a developing country are limited. This study aimed to analyze the long term HSCT outcomes at the 20th anniversary of our program.* ***Methods:*** *Data were gathered retrospectively among patients who received transplants between January 2000 and December 2020. The statistical method used for analyzing the categorical data involved the Chi square method, and the independent T-test was used for continuous data. OS and RFS were analyzed using the Kaplan-Meier method and the test of differences between types of HSCT and between disease indications for HSCT were assessed using the log rank test.* ***Results:*** *A total of 201 transplantations were performed, and 186 patients were eligible for the survival analysis. The five-year overall survival (OS) and relapse-free survival (RFS) for the whole cohort were 62.3 and 55%, respectively. The ten-year OS and RFS were 50.5 and 53.2% respectively. For auto-, allo-, and haplo-HSCT, five-year OS were 63.9, 60.3 and 50%; while ten-year OS were 52.8, 47.7 and 50%, respectively (p = 0.411). Five-year RFS were 38, 71.3 and 50.5%; and ten-year RFS were 30.4, 71.3 and 50.5%, respectively (p = 0.002). Transplant-related mortality rates were 4.6, 12.9 and 21.4%, respectively. Nonrelapse mortality occurred among 36 patients (20.3%). For allo- and haplo-SCT, the incidence of acute graft-versus-host disease (GVHD) were 30.7 and 12.5% respectively, and chronic GVHD incidences were 32 and 37.5%, respectively.* ***Conclusion:*** *This study provided long term transplant outcome and showed impressive outcome both for autologous and allogeneic SCT despite a limited setting. This encouraged performing the procedure in developing countries.*

Keywords : ● *Hematopoietic stem cell transplantation* ● *Transplant outcomes* ● *Transplant-related mortality* ● *Graft-versus-host disease*

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นิพนธ์ต้นฉบับ

ผลการรักษาระยะยาวด้วยการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดในประเทศไทย: ผลการศึกษาแบบ retrospective cohort แบบสถาบันเดี่ยว 20 ปี

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บทคัดย่อ

ภูมิหลังการศึกษา *ข้อมูลการศึกษาด้วยการปลูกถ่ายเซลล์ต้นกำเนิดในประเทศกำลังพัฒนามีจำกัด การศึกษานี้เป็นการวิเคราะห์ผลการรักษาระยะยาวของการปลูกถ่ายเซลล์ต้นกำเนิดในโอกาสครบรอบ 20 ปีของโปรแกรมนี้ในวิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า* ***วิธีการศึกษา*** *เป็นการเก็บข้อมูลแบบย้อนหลังของผู้ป่วยที่ได้รับการปลูกถ่ายเซลล์ต้นกำเนิดระหว่าง มกราคม 2543 ถึง ธันวาคม 2563 สถิติที่ใช้สำหรับข้อมูลแบบหมวดหมู่จะใช้หลักการของ Chi square สำหรับข้อมูลแบบต่อเนื่องจะใช้ independent T-test การวิเคราะห์อัตราการรอดชีวิตโดยรวม (overall survival; OS) และอัตราการรอดชีวิตโดยปราศจากการกลับเป็นซ้ำ (relapse-free survival; RFS) จะใช้ Kaplan-Meier method และการทดสอบความแตกต่างระหว่างกลุ่มใช้ log rank test* ***ผลการศึกษา*** *ได้ทำการการปลูกถ่ายเซลล์ต้นกำเนิด 201 ราย โดยผู้ป่วย 186 รายมีข้อมูลเพียงพอสำหรับการวิเคราะห์อัตราการรอดชีวิต OS และ RFS ที่ 5 ปีของทั้งหมดคือ ร้อยละ 62.3 และ 55 ตามลำดับ OS และ RFS ที่ 10 ปีคือร้อยละ 50.5 และ 53.2 ตามลำดับ สำหรับ auto-, allo- และ haploidentical OS 5 ปีคิดเป็นร้อยละ 63.9, 60.3 และ 50 ตามลำดับ และ OS ที่ 10 ปีคิดเป็นร้อยละ 52.8, 47.7 และ 50 ตามลำดับ (p = 0.411) RFS ที่ 5 ปีคิดเป็นร้อยละ 38, 71.3 และ 50.5 ตามลำดับ RFS ที่ 10 ปีคิดเป็นร้อยละ 30.4, 71.3 และ 50.5 ตามลำดับ (p = 0.002) อัตราการเสียชีวิตจากการปลูกถ่ายคิดเป็นร้อยละ 4.6, 12.9 และ 21.4 ตามลำดับ อัตราการเสียชีวิตจากสาเหตุอื่นที่ไม่ใช่การปลูกถ่ายเป็นร้อยละ 20.3 สำหรับ allo-SCT และ haplo-SCT อุบัติการณ์ของการเกิด acute graft versus host disease (GVHD) คิดเป็น ร้อยละ 30.7 และ 12.5 ตามลำดับ อุบัติการณ์ของการเกิด chronic GVHD คิดเป็นร้อยละ 32 และ 37.5 ตามลำดับ* ***สรุป*** *การศึกษานี้แสดงถึงผลการรักษาระยะยาวและแสดงให้เห็นผลการรักษาที่น่าประทับใจทั้ง autologous และ allogeneic SCT ในความจำกัดทางทรัพยากร และเป็นข้อมูลที่จะเสริมความมั่นใจในการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดในประเทศกำลังพัฒนา*

คำสำคัญ : ● *Hematopoietic stem cell transplantation* ● *Transplant outcomes* ● *Transplant-related mortality* ● *Graft-versus-host disease*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2567;34:45-56.

Introduction

Hematopoietic stem cell transplantation (HSCT) has been used as a curative tool to treat several hematologic diseases including malignant and nonmalignant conditions, since the 1970s. Moreover, HSCT has been increasingly indicated in several nonhematologic diseases such as several solid cancers and autoimmune diseases. According to the Worldwide Network for Blood and Marrow Transplantation Group (WBMT) registry, currently 60,000 to 70,000 patients undergo HSCT annually[1,2]. In Thailand, this transplantation procedure was first initiated in 1986. Presently, ten academic hospitals and six private hospitals are able to perform HSCT but only six centers can perform allogeneic HSCT. From 2007 to 2008, approximately 120 to 150 patients underwent transplantation annually,[4] but with the increase in the number of transplantation centers, a marked increase occurred reaching approximately 250 to 300 cases/year. However, major obstacles remain in Thailand, a developing country; including both limited human resources and budget. In the earlier years of providing HSCT services in Thailand, the majority of patients undergoing HSCT were confined to government officers with state-sponsored health coverage and patients who were financially capable to afford the procedure. As a result, the decision of transplantation was solely based on physicians' opinions. Later, thanks to the efforts of the administrators in the Thai Society of Hematology together with patients and their relatives, coverage was extended to other patient groups. Committees were formed to consider and approve the eligibility of each patient so that the transplant center could reimburse from the patients' coverage. The decisions of the committee were based on evidence-based principles.

Our institution started autologous HSCT (auto-HSCT) in 1999, swiftly followed by allogeneic (allo-HSCT) in 2000 and haploidentical HSCT (haplo-HSCT) in 2002. As a result, our institute is one of only four major HSCT centers in Thailand that can perform both auto- and allo-HSCT. In 2020, it successfully reached its twentieth anniversary so that this study aimed to analyze long term outcomes of transplantation procedures in a limited resources environment. Hopefully, the results will constitute informative reference for a long term follow up for HSCT in a developing country with limited resources.

Patients and Methods

1. Study design and data collection

This retrospective study collected data from patients undergoing HSCT at our institute from January 2000 to December 2020. Inclusion criteria included (1) patient age > 15 years, (2) patients undergoing auto-, allo- and haplo-HSCT with either bone marrow or peripheral blood as the source of stem cells and (3) inclusion of both myelo-ablative and reduced intensity conditioning regimen. The exclusion criteria comprised (1) incomplete important data on outcome evaluation and (2) patients lost to follow-up early after HSCT.

2. Treatment

The three major types of transplantation performed in our institute comprise auto-HSCT, allo-HSCT - most involved sibling donors and only a small number were matched unrelated donors and haplo-HSCT. Regarding myeloablative conditioning regimen, Bu-Cy (cyclophosphamide 120 mg/kg + busulfan 16 mg/kg orally or 12.8 mg/kg intravenously) was used for leukemia; BEAM (carmustine or BCNU 300 mg/m^2 + etoposide 800 mg/m^2 + cytarabine 800 mg/m^2 + melphalan 140 mg/m^2) or BEAC (BCNU 300 mg/m^2 + etoposide 800 mg/m^2 + cytarabine 800 mg/m^2 + cyclophosphamide 140 mg/kg) were used for lymphoma. Moreover, Mel-200 (melphalan 200 mg/m^2) was used for multiple myeloma, except patients with impaired renal function the dose attenuation with Mel-140 (melphalan 140 mg/m^2) was used instead. For reduced intensity conditioning, Cy-ATG (cyclophosphamide 200 mg/kg + anti-thymocyte globulin 125 mg/kg) was used for severe and very severe aplastic anemia; Flu-Bu +/- ATG (fludarabine 150 mg/m^2 + busulfan 8 mg/kg orally or 6.4 mg/kg intravenously +/- anti-thymocyte globulin 4.5 to 10 mg/kg) were used for

malignant diseases. Regarding graft-versus-host disease prophylaxis in allogeneic stem cell transplantation, calcineurin inhibitors (either cyclosporine A or tacrolimus) combined with either methotrexate or mycophenolate mofetil were used. For matched sibling and matched unrelated donor, cyclosporine A and methotrexate were used while for haplo-HSCT, tacrolimus and mycophenolate mofetil were used.

3. Indications for transplantation

Auto-HSCT was indicated for multiple myeloma (MM) as both upfront postinduction consolidation and as a consolidative tool after salvage treatment for patients with chemo-sensitive relapse/refractory MM. In addition, auto-HSCT was performed among patients with malignant lymphoma as upfront consolidation for patients with a high international prognostic index or as a consolidation for patients with chemo-sensitive relapse/refractory lymphoma (both Hodgkin- and non-Hodgkin lymphoma). Also, a few patients with solid cancer underwent this type of transplant.

Allo-HSCT was indicated for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), in first complete remission (CR) for patients with karyotypes other than favorable ones, or in second CR for patients with relapse/refractory disease. Additionally, allo-HSCT was performed among patients with chronic myeloid leukemia (CML) before the tyrosine kinase inhibitors (TKI) era. Furthermore, in the first decade of our service, allo-HSCT was the standard of care in severe aplastic anemia (SAA) with available donor. Subsequently, with more evidence and approval of the use of immunosuppressives, i.e., antithymocyte globulin and cyclosporine A, particularly among patients older than 40 years, allo-HSCT became less frequent. Other indications were primary myelofibosis and myelodysplastic syndromes (MDS). Reduced intensity conditioning regimen were used for patients aged more than 60 years, patients with relapsed/refractory lymphoma in whom auto-HSCT failed to cure the disease and young patients with multiple myeloma who were transplanted before the era of novel agents.

4. Source of stem cell

The decision to choose either bone marrow or peripheral blood stem cell was basically based on the patient's underlying disease. For underlying malignant disorders, peripheral blood stem cell was preferred to bone marrow for more graft-versus-tumor effects whereas for benign disorders, i.e., SAA and thalassemia, bone marrow was preferred. We started our service when peripheral blood stem cell source had become more popularity as bone marrow harvest required more experienced staffs, e.g., medical technologists to prepare bone marrow graft and an anesthesiologist team to sedate patients and donors, etc. However, in the second decade of service the team was more prepared. As a member of the World Marrow Donor Association (WMDA), we constituted a center for unrelated donor bone marrow harvest and the procedure was performed regularly, but when antithymocyte globulin and cyclosporine A were approved as a frontline therapy for SAA in Thailand, the number of patients with SAA requiring HSCT decreased to only a few cases in the second decade of our service. As a result, bone marrow source has not been used in our institution.

5. Engraftment, response evaluation and GVHD

Engraftment was defined as time that absolute neutrophil count > 0.5 $x10^9$/L and time for the platelet count > 50 $x10^9$/L for three consecutive days (using the first day) for neutrophil and platelet engraftment, respectively. Bone marrow was evaluated approximately 100 days after performing HSCT. Acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD) were graded according to Glucksberg[5] and NIH[6] grading systems, respectively.

6. Statistical methods

The primary end points for this cohort were overall survival (OS), relapse-free survival (RFS), and cumulative incidence of relapse (CIR). Secondary end points were incidences of aGVHD and cGVHD, and transplant-related mortality (TRM). The statistical method used to analyze the categorical data was the Chi square (χ^2) test, while the independent T-test was used for continuous data.

OS and RFS were analyzed using the Kaplan-Meier method. The subgroups analysis for survival rates in four major indications for HSCT according to diseases, i.e., MM, lymphoma, AML, and CML; were also performed using the Kaplan-Meier method. The test of differences between types of HSCT and indications for HSCT were determined using the log rank test, whereas the differences in CIR of each type of transplantation were analyzed using the log rank test. Nonrelapsed mortality (NRM) was collected using the Kaplan-Meier method. Microsoft Excel® (Redmond, WA, USA) 15 for Microsoft Windows® (Redmond, WA, USA) was used to collect data. STATA/MP, Version 12 (College Station, TX, USA) for Microsoft Windows® was used for statistical analysis.

Results

Patient characteristics

Two hundred and one transplantations were performed. The median age at transplantation was 43 years (range; 17 to 67), 121 (60%) were male and 80 (40%) were female patients. Auto-, allo- and haplo-HSCT were carried out in 89 (44.3%), 96 (47.8%) and 16 patients (7.9%), respectively. One hundred and forty-seven patients (73.1%) received myeloablative conditioning and 54 patients (26.9%) received reduced intensity conditioning. The median follow-up totaled ten years. Detailed patient characteristics are shown in Table 1. The leading disease for the indication of HSCT was CML in the first decade of service and MM in the second decade of service.

Outcomes

One hundred and eighty-six patients were available for survival analysis. The five- and ten-year OS was 62.3% (95% confidence interval; CI: 53.9 to 69.6) and 50.5% (95%CI: 40.6 to 59.6), respectively (Figure 1A). Similarly, the five- and ten-year RFS was 55% (95%CI: 46.0 to 63.2) and 53.2% (95%CI: 43.7 to 61.8), respectively (Figure 1B). For auto-HSCT, the five- and ten- year OS were 63.9% (95%CI: 49.4 tov75.3) and 52.8% (95%CI: 36.1

Table 1 Patient Characteristics

Parameter	Overall (n = 201) (%)	Type of transplantation			Haplo-HSCT (n = 16) (%)
		Auto-HSCT (n = 89) (%)	MAC-HSCT (n = 74) (%)	RIC-HSCT (n=22) (%)	
Median age (range)	43 (17-66)	52 (17-66)	39 (17-63)	48 (21-63)	28 (19-61)
Sex					
Male	121 (60)	47 (53)	61 (64)	17 (77)	13 (81)
Female	80 (40)	42 (47)	35 (46)	5 (23)	3 (19)
Diagnosis:					
AML	36 (18)	2 (2)	25 (34)	7 (32)	2 (13)
ALL	2 (1)	0	1 (1)	0	1 (6)
NHL	33 (16)	23 (26)	3 (4)	4 (18)	3 (19)
HL	10 (5)	9 (10)	0	0	1 (6)
MDS	3 (2)	0	2 (2)	1 (5)	0
CML	29 (15)	0	17 (23)	8 (36)	4 (25)
AA	11 (5)	0	10 (14)	0	1 (6)
MM	61 (30)	54 (61)	6 (8)	0	0
Others	16 (8)	1 (1)	10 (14)	2 (9)	4 (25)
Disease status before SCT					
1st remission	131 (65)	43 (48)	59 (10)	17 (77)	11 (69)
CMT-sensitive relapsed/refractory	70 (35)	46 (52)	15 (20)	5 (23)	5 (31)

Note: *p-value compared autologous HSCT with allogeneic+haploidentical HSCT

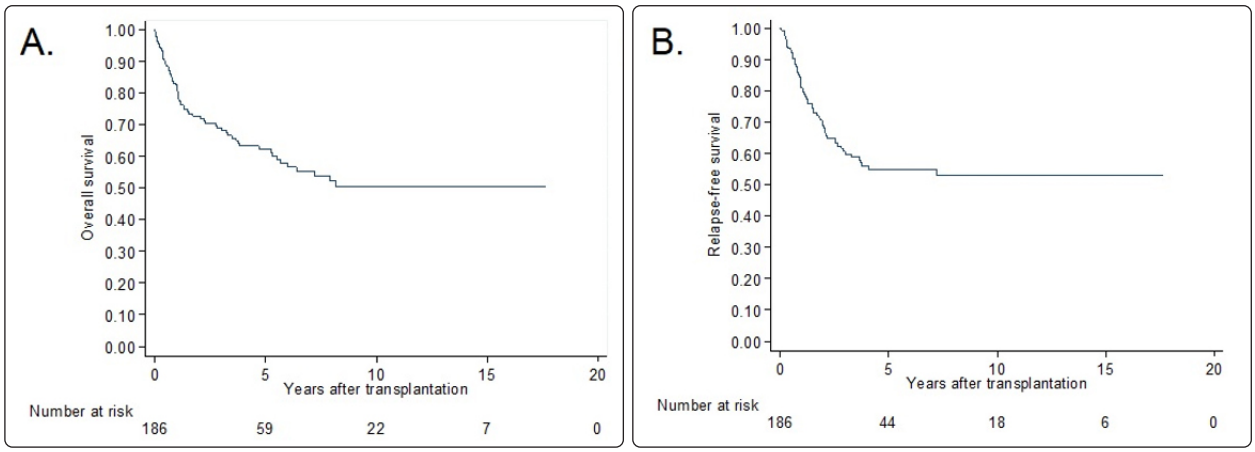

Figure 1 Kaplan-Meier curves for the entire cohort study A. overall survival, B. relapse-free survival

to 67.0), respectively; the five- and ten-year RFS were 38.0% (95%CI: 24.9 to 51.0) and 30.4% (95%CI: 14.8 to v47.5), respectively (Table 2, Figures 2A and 2B). For allo-HSCT, the five-year OS for MAC-HSCT, RIC-HSCT and haplo-HSCT were 66% (95%CI: 51.7 to 77), 42.9% (95%CI: 20.9 to 63.2) and 50% (95%CI: 22.9 to 72.2), respectively. The ten-year OS were 52.5% (95%CI: 35.9 to 66.6), 32.1% (95%CI: 13.2 to 52.9) and 50% (95%CI: 22.9 to 72.2), respectively; p = 0.174 (Table 2, Figure 2C). The five- and ten-year RFS were similar for each subgroup of allo-HSCT reflecting the plateau of survival curves which comprised 76.7% (95%CI: 61.6 to 86.5), 53.1% (95%CI: 25.3 to 74.7) and 50.5% (95%CI: 18.7 to 75.7), respectively; p = 0.073 (Table 2, Figure 2D). The subgroup survival analyzes for the four main indications of HSCT, i.e., AML, CML, MM and lymphoma, are shown in Table 3 and Figures 3A and 3B. For auto-HSCT, CIR was 69.6% (Figure 4A). The CIR for MAC-HSCT, RIC-HSCT and haplo-HSCT were 23.3, 46.9 and 49.5%, respectively; p = 0.073 (Figure 4B). Allo-HSCT was also performed among 12 patients with SAA, all were successfully engrafted. However, one patient later lost the graft and subsequently died after several episodes of septicemia. As of the last follow-up, nine patients with SAA remained alive.

NRM occurred among 36 patients (20.3%) (95%CI: 14.5 to 28.1%) (Figure 5). TRM rates were 4.6, 12.9 and 21.4%, respectively. For allo- and haplo-HSCT, the incidences of aGVHD were 30.7 and 12.5%, respectively; and the incidences cGVHD were 32 and 37.5%, respectively.

Discussion

In this article, we report the long term outcomes of HSCT at our institute. Our study encountered limitations mainly due to the retrospective nature of the collected data, as some may have been in-homogeneously gathered and lack completeness. Furthermore, as a single-center cohort, this article might not fully reflect the situation in developing countries; however, it can hopefully serve as a reference to represent the situation of this country group. In the first decade of service, the leading indication for HSCT was CML but it changed to MM in the second decade. This could have been due to the alterations in the trend of CML treatment from upfront allogeneic HSCT to TKI and the evidence supporting the role of auto-HSCT in MM. These issues will be discussed later for each disease.

The median age at transplantation was significantly higher in auto-HSCT because the main indication of transplantation in the auto-HSCT group was MM, which is found among elderly patients and in lymphoma, whereas the main indications for allogeneic HSCT were AML and CML, occurring mostly among younger patients. The Thai myeloma working group reported that the median age at diagnosis of Thai patients with MM was 62 years[14], and the Thai lymphoma study group reported the median age at diagnosis to be 56 years[15]. On the other hand, the Thai acute leukemia working group reported the median age of diagnosis to be 52 years[16], and the Thai CML registry reported that the median age of diagnosis was 38 years[17]. Disease status

Table 2 Survival outcomes of each type of transplantation

	OS (95%CI)	*p*-value		RFS (95% CI)	*p*-value	
5-year results						
Auto-HSCT	63.9% (49.4-75.3)			38.0% (24.9-51.0)		
RIC-HSCT	42.9% (20.9-63.2)	0.067	0.174	53.1% (25.3-74.7)	0.059	0.073
MAC-HSCT	66% (51.7-77)	0.332		76.7% (61.6-86.5)	0.06	
Haplo-HSCT	50% (22.9-72.2)			50.5% (18.7-75.7)		
10-year results						
Auto-HSCT	52.8% (36.1-67.0)			30.4% (14.8-47.5)		
RIC-HSCT	32.1% (13.2-52.9)	0.067	0.174	53.1% (25.3-74.7)	0.059	0.073
MAC-HSCT	52.5% (35.9-66.6)	0.332		76.7% (61.6-86.5)	0.06	
Haplo-HSCT	50% (22.9-72.2)			50.5% (18.7-75.7)		

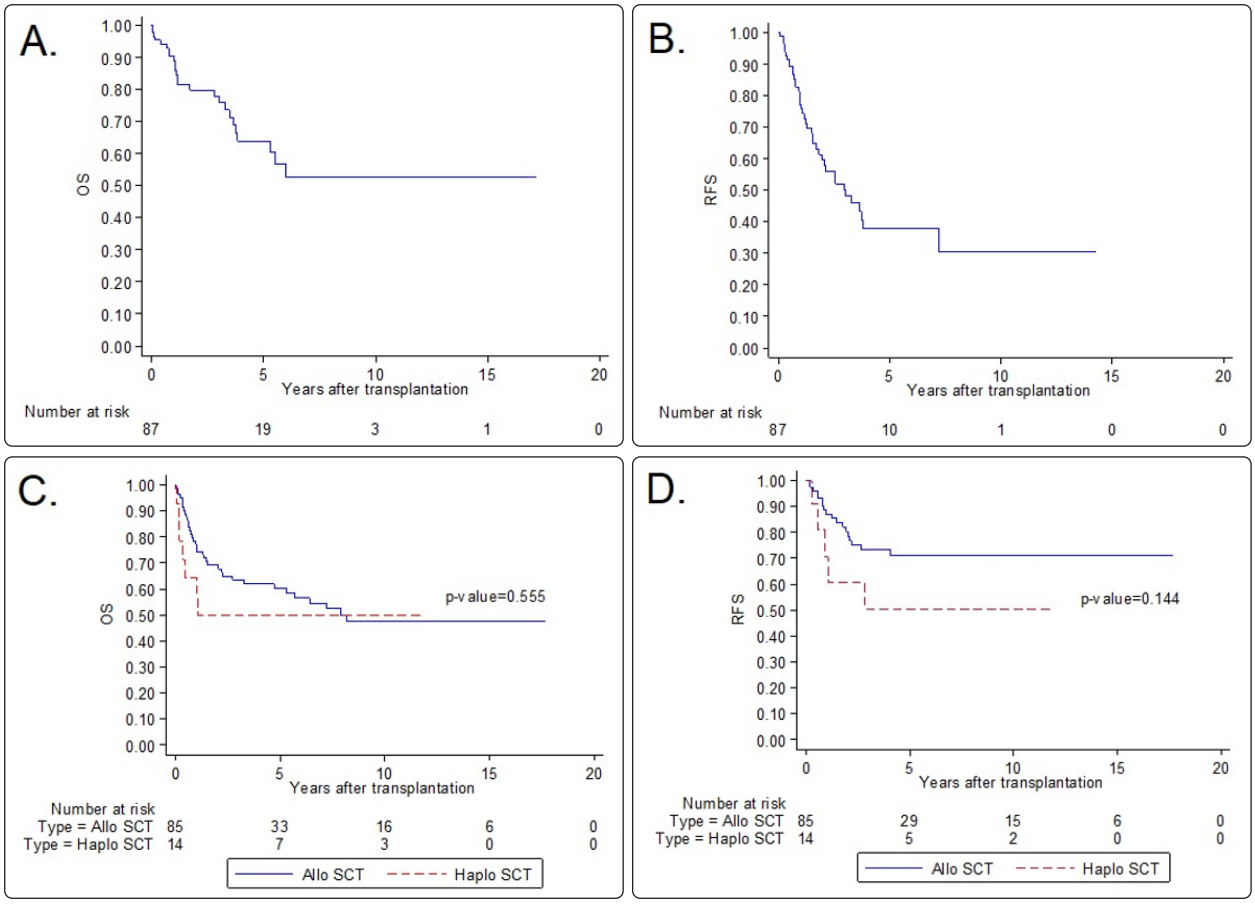

Figure 2 Probability of survival according to type of transplantation A. overall survival for auto-HSCT, B. relapse-free survival for auto-HSCT, C. overall survival for allo-HSCT, D. relapse-free survival for allo-HSCT

Table 3 Survival outcomes for each disease indication for HSCT

Diagnosis	Overall survival		Relapse-free survival	
	5 yr (95%CI)	10 yr (95%CI)	5 yr (95%CI)	10 yr (95%CI)
Acute myeloid leukemia	60% (41.1-74.7)	60% (41.1-74.7)	76.1% (53.9-88.6)	76.1% (53.9-88.6)
Lymphoma	67.2% (48.7-80.2)	55.4% (33.9-72.5)	61.8% (42.2-76.4)	61.8% (42.2-76.4)
Chronic myeloid leukemia	59.7% (39-75.5)	40.7% (21.1-59.5)	61.5% (38.7-78)	61.5% (38.7-78)
Multiple myeloma	60% (42-74.1)	50% (30.3-66.6)	23.1% (11-37.8)	0 (0-0)

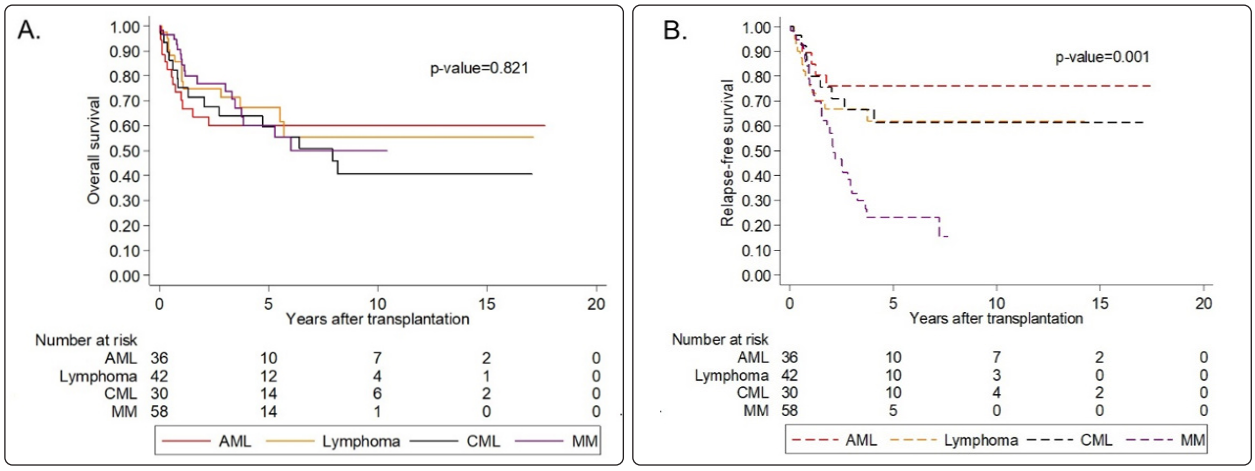

Figure 3 Probability of survival according to indication for transplantation including 4 main indications A. overall survival, B. relapse-free survival

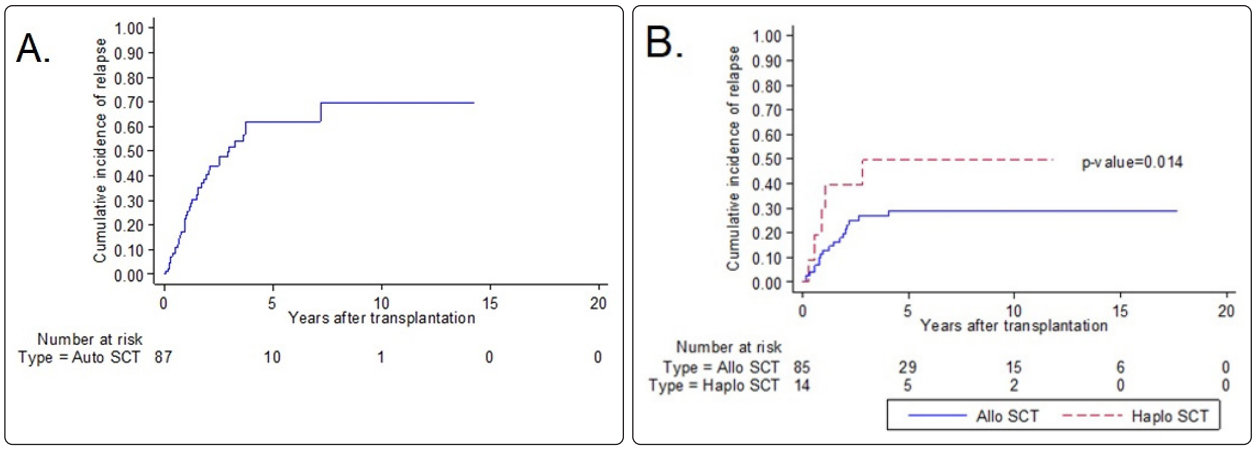

Figure 4 Cumulative incidences of relapse A. autologous HSCT, B. allogeneic HSCT

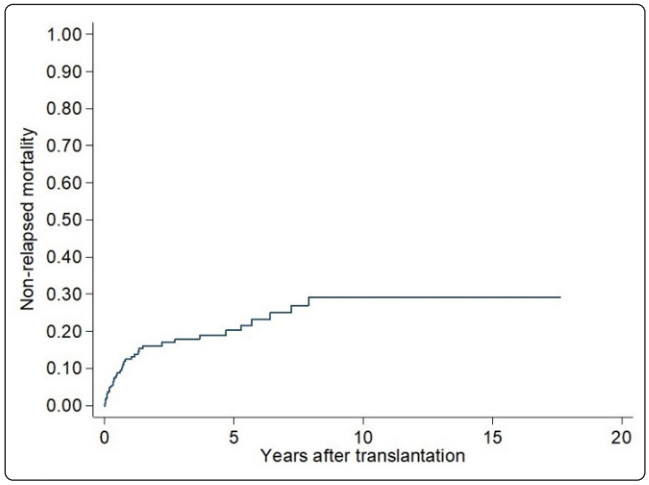

Figure 5 Nonrelapse mortality

before HSCT also differed between auto- and allo-HSCT; auto-HSCT exhibited a higher proportion of patients with chemosensitive relapsed/refractory disease due to disease indications, i.e., lymphoma and MM. Moreover, the patient group undergoing allo-HSCT was mainly in the first CR as the majority in this group presented AML and CML.

For allo-HSCT, five-year OS and RFS were 60.3 and 71.3%, respectively, and ten-year OS and RFS were 47.7 and 71.3%, respectively. These transplant outcomes indicated a plateau in the RFS curve but not in the OS curve. This suggested that patients, surviving more than five years after transplantation died from NRM that continued to occur thereafter (Figure 2). Data regarding transplant outcomes in other developing countries remains limited; most reports focused mainly on the accessibility to the procedure. The OS of the procedure was reported from India, Mexico and Egypt and was stated to be 40 to 59% which was similar to our outcomes. However, those studies possessed a shorter median follow-up period (one to five years)[29-31].

CML used to be the leading indication for HSCT in the first decade of our service until availability of TKI. Much evidence supported the trend change; after a long term follow-up, the report from the Center for International Blood & Marrow Transplant Research (CIBMTR) noted patients with CML chronic phase (CML-CP) undergoing allo-HSCT experienced a similar result[9]. However, these patients had more transplant-related toxicities. A recent comparative, retrospective cohort study involving patients with CML showed that patients with CML-CP receiving imatinib reported a better five-year OS and EFS compared with those undergoing HSCT[10]. In this study the subgroup analysis for CML showed that five-year OS and RFS were comparable with the outcomes reported by CIMBTR[16]. The ten-year OS and RFS of our study were 40.7 and 61.5%, respectively, indicating that patients who died five years following HSCT did not die from disease flare up but mainly from long term complications of HSCT. In the second decade of our service, TKI became the main treatment for CML in 2010. Consequently, HSCT was strictly reserved only for patients with CML who had failed two lines of TKI- accelerated or blast phase, and patients with T315I mutation, according to the European Leukemia Net's recommendations[18].

AML became a major indication for allo-HSCT in our institute during the second decade. Recently, CIBMTR reported transplantation outcomes among patients with AML undergoing allo-HSCT with an MSD or MUD. The survival for patients receiving transplants early experience better outcomes compared with those of delayed and relapsed/refractory disease. The OS of MUD was slightly less than that of MSD[7]. The five- and ten-year survival outcomes for our cohort study indicated a plateau on both OS and RFS, i.e., 60 and 76.1%, respectively, and were comparable with the study mentioned above[16]. The plateau in both survival outcomes in AML differed from those of CML, in which the OS reached a plateau before RFS indicating the differences in the natural course after transplantation. These may be from the fact that patients with AML undergoing HSCT were all treated with intensive chemotherapy, which suppresses the immune system resulting in less TRM.

For auto-HSCT, regarding HSCT in MM, much evidence also indicated the benefit for consolidative auto-HSCT in MM before era of novel agents and in the era of novel agents. Before the era of novel agents, several landmark studies were conducted: the IFM90 trial and the MRC Myeloma VII. Both studies showed that PFS and OS in the transplantation arm were significantly better than for those receiving only conventional chemotherapy[11,12]. In the era of novel agents, this evidence made a significant change in treatment approach for patients with MM, as auto-HSCT became a standard treatment for younger patients with myeloma (age ≤ 65 to 70 years) without comorbidity. After availability of novel agents, particularly proteasome inhibitors and immunomodulatory agents, the role of auto-HSCT remained clearly stated. Adding novel agents without auto-HSCT was not comparable

with those undergoing auto-HSCT[20]. However, combining novel agents followed by auto-HSCT showed promising outcomes[21,22]. Auto-HSCT, followed by maintenance with lenalidomide, showed further benefits[22]. For the subgroup analysis in our study, MM had a five-year OS and RFS of 60 and 23.1%, respectively, and comparable with those stated in related studies with five-year OS of 37 to 52% and five-year EFS/PFS of 11 to 30%, before the era of novel agents[9,11,12,18,19]. The survival of patients receiving posttransplantation lenalidomide maintenance in our institution could not be analyzed because the use of lenalidomide for this setting is not routinely allowed by any medical coverage and patients need to pay for treatment by themselves, which mostly cannot afford. However, the OS curve for this cohort presented a plateau after five years (Figure 4A), indicating that the current salvage strategies after HSCT were effective.

Regarding HSCT for lymphoma, the indications for patients with HSCT in our institute are refractory/relapsed chemosensitive lymphoma and are used as upfront consolidative treatment for patients with high IPI-risk score, according to related milestone studies. Regarding relapsed chemo-sensitive lymphoma, the PARMA study, comparing auto-HSCT to conventional chemotherapy found that the survival of patient undergoing HSCT was better than that of patients receiving only chemotherapy alone. EFS and OS in transplantation were better than those of chemotherapy alone[23]. For patient with high IPI score as an upfront consolidation, Haioun and colleagues studied patients with poor risk aggressive lymphoma and compared HSCT with conventional chemotherapy. They found survival benefits among patients undergoing auto-HSCT over the conventional chemotherapy[24]. Subsequently, several studies also indicated the same trend[25,26]. For the role of HSCT during the rituximab era, the phase III SWOG-S9704 trial still indicated that among patients with high risk lymphoma, those undergoing consolidative auto-HSCT showed better survival outcomes. In the subset of high risk patients, the PFS and OS for patients undergoing HSCT were better than those for patients receiving chemotherapy. Regarding this study's outcomes for lymphoma, the five-year OS and RFS were 67.2 and 61.8%, respectively, and the ten-year OS and RFS were 55.4 and 61.8%, respectively, which were comparable with related studies[9,23,24]. Moreover, these also indicated the presence of a plateau in the RFS curve, but the OS curve did not exhibit any plateau, indicating that patients surviving more than five years died from other etiologies.

Conclusion

This cohort reported long term outcomes of HSCT performed in a developing country with limited resources; however, the outcomes were comparable with related studies. The outcome for AML, CML and lymphoma produced a plateau in RFS curve, indicating that HSCT could cure these malignancies. For MM, an incurable malignancy, this study showed an absence of a plateau in PFS curve and most diseases almost relapsed approximately five years after HSCT. However, the OS was 60 and 50% at five and ten years, respectively, indicating effective salvage therapy among relapsed posttransplant patients. The complication rates of HSCT were also similar to related studies.

Abbreviations

aGVHD: acute graft-versus-host disease; AML; acute myeloid leukemia; cGVHD: chronic graft-versus-host disease; CIR: cumulative incidence of relapse; CML: chronic myeloid leukemia; CI: confidence interval; HSCT: hematopoietic stem cell transplantation; MM: multiple myeloma; OS: overall survival; RFS: relapse-free survival; SAA: severe aplastic anemia; TKI: tyrosine kinase inhibitors; TRM: transplant-related mortality

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Ethics approval and consent to participate

This study was approved by the ethics committee and institution review board of the Royal Thai Army Medical Department according to the Declaration of Helsinki.

Consent of publication

Consent of publication was obtained from all enrolled patients.

Competing interests

The authors declare they have no conflict of interests.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors designed the study and participated in patient care. KP, and PK collected the data. PP prepared the proposal for ethics approval. PP and PK obtained the consent form. KP performed the statistical analyses, and KP drafted the manuscript and revised the final manuscript. All authors read and approved the final manuscript.

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