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Review Article

Recent advancements in hematopoietic stem cell transplantation in Taiwan

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Abstract

Hematopoietic stem cell transplantation (HSCT) can cure malignant and nonmalignant hematological disorders. From 1983 to 2022, Taiwan performed more than 10,000 HSCT transplants. The Taiwan Blood and Marrow Transplantation Registry collects clinical information to gather everyone's experience and promote the advances of HSCT in Taiwan to gather everyone's experience and promote advances of HSCT in Taiwan. Compared with matched sibling donors, transplants from matched unrelated donors exhibited a trend of superior survival. In Taiwan, transplant donors showed remarkable growth from unrelated (24.8%) and haploidentical (10.5%) donors. The number of older patients (17.4%; aged ≥61 years) who underwent transplantation has increased markedly. This review summarizes several significant developments in HSCT treatment in Taiwan. First, the use of Anti-thymocyte globulin (ATG) and intravenous busulfan regimens were important risk factors for predicting hepatic sinusoidal obstruction syndrome. Second, a new, machine learning-based risk prediction scoring system for posttransplantation lymphoproliferative disorder has identified five risk factors: aplastic anemia, partially mismatched related donors, fludarabine use, ATG use, and acute skin graft-versus-host disease. Third, although the incidence of idiopathic pneumonia syndrome was low (1.1%), its mortality rate was high (58.1%). Fourth, difficult-to-treat mantle cell and T-cell lymphomas treated with autologous HSCT during earlier remission had higher survival rates. Fifth, treatment of incurable multiple myeloma with autologous HSCT showed a median progression-free survival and overall survival of 46.5 and 70.4 months, respectively. Sixth, different haploidentical transplantation strategies were compared. Seventh, caution should be taken in administering allogeneic HSCT treatment in older patients with myeloid leukemia with a Charlson Comorbidity Index ≥3 because of a higher risk of nonrelapse mortality.

Keywords: *Allogeneic, Autologous, Hematopoietic stem cell transplantation, Taiwan*

Introduction

Hematopoietic stem cell transplantation (HSCT) is an important treatment option for patients with benign or malignant hematological disorders [1]. To date, more than one million HSCTs have been performed worldwide, including autologous (auto-) and allogeneic (allo-) types [2]. The Taiwan Society of Blood and Marrow Transplantation (TBMT) was initiated in 1992 as a nationwide gathering to foster communication and learning on HSCT. The founding purpose of TBMT is to provide a robust platform for academic discussion, clinical research, and ongoing education for physicians specializing in transplantation and medical personnel working in related fields. Currently, TBMT comprises 932 members, including physicians, nurses, other comedical professionals, and clinical coordinators. The core TBMT activities include organizing an annual congress and quarterly workshop/meeting, publishing bimonthly TBMT E-communication, collecting clinical data of transplant patients, publishing the Annual Report of the Nationwide Survey for transplant recipients, promoting more than 12 working groups, and publishing several guidelines for HSCT.

The Taiwan Blood and Marrow Transplantation Registry (TBMTR), which is operated and maintained by the TBMT, collects HSCT data to gather everyone's experience and promote advances of HSCT in Taiwan. From 1983 to 2022, a cumulative total of 10,236 HSCTs were performed in Taiwan, as illustrated in Figure 1, which signifies a substantial

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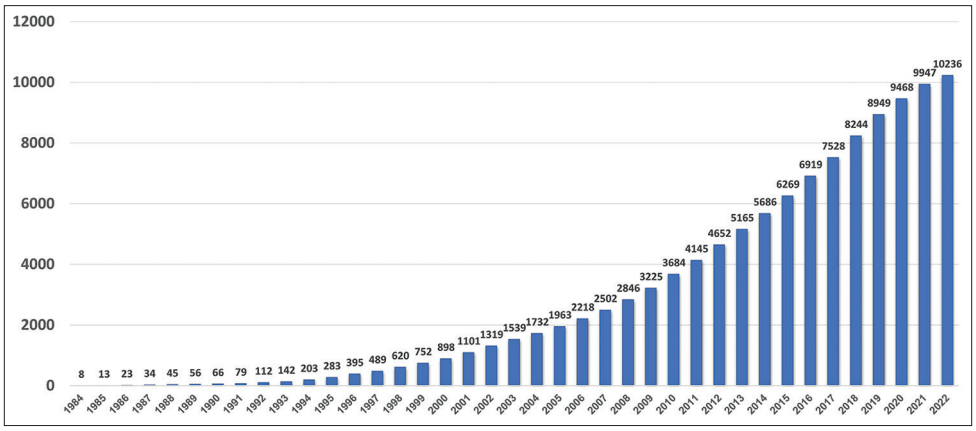

Figure 1: Cumulative numbers of patients receiving hematopoietic stem cell transplantation in Taiwan

milestone. In the past 10 years, the number of HSCT Transplant centers has burgeoned from 14 to 23, making the maturation and widespread adoption of HSCT as a therapeutic procedure for patients with hematologic diseases in Taiwan. This review discusses the outcomes of transplantation in Taiwan and highlights the advancements in HSCT based on data from the TBMTR database.

Update on transplantation outcomes in Taiwan until 2022

Clinical information on HSCTs in Taiwan has been recorded in the TBMTR since 2009 and is reported annually. As of 2022, 7,390 transplants had been analyzed [3]. Of these, 4078 (55.2%) and 3312 (44.8%) cases were allogeneic and autologous, respectively. The four leading indications for transplantation are acute myeloid leukemia (AML, 25.6%), non-Hodgkin lymphoma (22.7%), multiple myeloma (MM, 18.8%), and acute lymphoblastic leukemia (11.4%). In total, 1283 older patients (aged ≥61 years; 17.4%) underwent various types of HSCT. Compared to 2009–2017, patients with age ≥61 increased from 14.0% to 21.8% in 2018–2022. The different age groups of all patients who underwent HSCT are shown in Figure 2. Of the transplant donors, 44.8% were autologous, 19.9% were human leukocyte antigen (HLA)-matched siblings, 24.8% were unrelated donors (including cord blood), and 10.5% were HLA-mismatched, mainly haploidentical related donors [Figure 3]. Notably, because of the low birthrate and fewer children per family in Taiwanese society, the proportion of unrelated donors exceeds that of matched siblings. In 1993, the Buddhist Tzu Chi Stem Cells Center, which is affiliated with the Buddhist Tzu Chi Foundation, established an independent, compassion-based bone marrow stem cell registry in Taiwan. It has provided >6,000 unrelated hematopoietic stem cell donors worldwide and maintains a donor pool of approximately 450,000 per year [4]. As the improvement of prophylaxis and treatment of graft-versus-host disease (GvHD), and posttransplant care, transplantations using mismatched donors increased from 8% in 2009–2017 to 17.5% in 2018–2022. The rise in elderly patients and mismatched transplants collectively represent the evolving landscape and progression of HSCT in Taiwan.

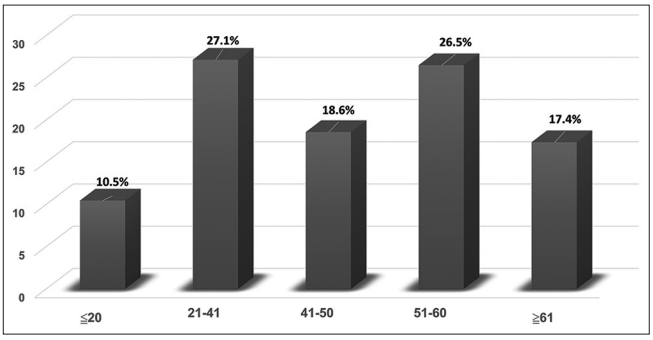

Figure 2: Ages at hematopoietic stem cell transplantation in Taiwan

Auto-HSCT and allo-HSCT are associated with a median overall survival (OS) of 11.15 years (95% confidence interval [CI]: 10.25–not estimable [NE]) and 3.68 years (95% CI: 2.85–4.63), respectively [Figure 4]. The cumulative 30- and 100-day mortality rates for auto-HSCT were 1.0% and 3.4%, respectively, whereas those for allo-HSCT were 3.2% and 12.2%, respectively [Figure 5]. Notably, the median OS of HSCTs performed using HLA-matched unrelated donors tended to be higher than that of HSCTs performed using matched sibling donors (7.68 years [95% CI: 6.02–NE] vs. 4.28 years [95% CI: 3.11-5.76]; $P = 0.05$). This is attributable to the introduction of antithymocyte globulin (ATG) in Taiwan, which has been covered by the National Health Insurance since 2001. The subsequent widespread use of ATG as prophylaxis for GvHD in unrelated donor transplants has significantly reduced the incidence of severe acute and chronic GvHD. Moreover, the universal use of high-resolution HLA typing to identify suitable unrelated donors has been crucial. Among benign hematological disorders, severe aplastic anemia is most indicated for allo-HSCT. The TBMTR records 249 cases of severe aplastic anemia, and the median OS across age groups has not yet been reached. The distribution of 95% CI shows NE–NE in age ≤20 years; NE–NE in 20 <age ≤40; NE–NE in 40 < age ≤50, 0.69–NE in 50 < age ≤60, and 0.86–NE in age >60. Of 7390 patients who underwent transplantation, 214 (2.9%) developed secondary malignancies, the most common of which are posttransplant lymphoproliferative disorders (PTLD) and solid tumors. Of those who underwent allo- and auto-HSCT, 1,441 (35.3%)

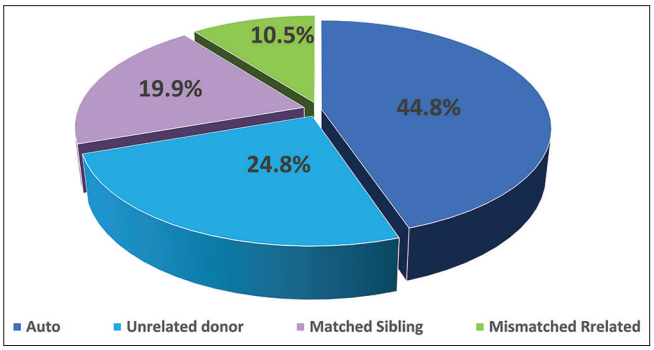

Figure 3: Types of hematopoietic stem cell transplantation in Taiwan

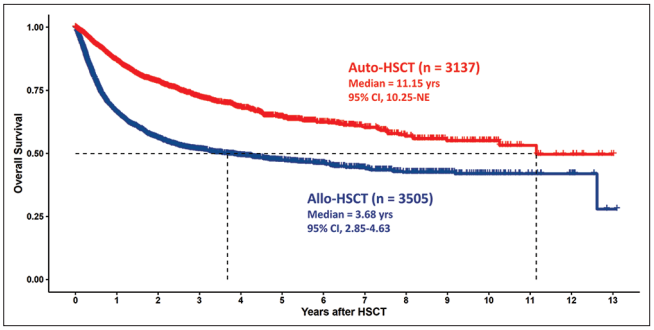

Figure 4: Overall survival of patients receiving either auto-hematopoietic stem cell transplantation (HSCT) or allo-HSCT. HSCT: Hematopoietic stem cell transplantation. HSCT: Hematopoietic stem cell transplantation

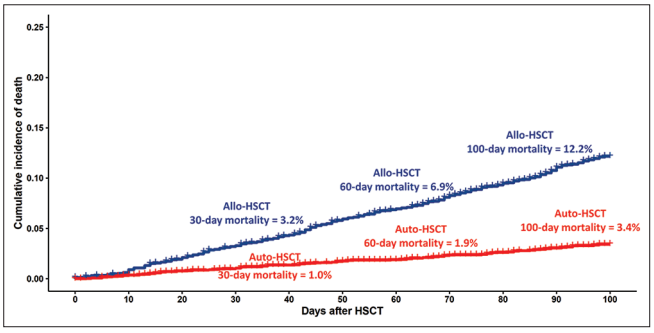

Figure 5: The cumulative 30-, 60-, and 100-day mortalities of patients receiving either auto-hematopoietic stem cell transplantation (HSCT) or allo-hematopoietic stem cell transplantation

and 656 (19.8%) died, respectively, with disease relapse as the main cause of death (49.5% and 57.9%, respectively).

Special hematopoietic stem cell transplantation advancements in Taiwan

Liver sinusoidal obstruction syndrome/veno-occlusive disease

Hepatic sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is an unpredictable and potentially life-threatening complication of HSCT [5,6]. Clinically, hepatic SOS/VOD is characterized by fluid retention, weight gain, ascites, hyperbilirubinemia, and painful hepatomegaly in the absence of other identifiable causes of liver disease. It most commonly occurs in the first 20 days after transplantation [7,8]. The pathophysiology of SOS/VOD involves primary toxic injury of sinusoidal endothelial cells caused by high-dose chemotherapy or radiation, which leads to central venous occlusion and sinusoidal obstruction [9,10]. The incidence of hepatic SOS/VOD varies widely, ranging from 0% to 60%, and mortality and multiple organ failure rates can be as high as 80% [11,12].

Lee *et al.* [13] analyzed the 2009–2014 TBMTR records and found that of the 2,345 patients who underwent transplantation, 39 (1.66%) developed hepatic SOS/VOD, with auto-HSCT and allo-HSCT accounting for 0.1% and 2.87% of these cases, respectively [Table 1] [13]. Multivariate analysis identified chronic hepatitis C virus infection (hazard ratio [HR]: 6.38, 95% CI: 1.89–21.47), ATG (rabbit) use (HR: 4.69, 95% CI: 2.02–10.86), diagnosis of myelodysplastic syndrome (MDS; HR: 3.10, 95% CI: 1.18–8.14), and intravenous busulfan administration (HR: 2.62, 95% CI: 1.23–5.56) as independent predictors of a higher risk for hepatic SOS/VOD. The overall mortality rate was 79.5%. Thus, this cohort study provides important data on the incidence of hepatic SOS/VOD and its risk factors.

Establishing new risk prediction scores for posttransplant lymphoproliferative disorders using machine learning

PTLD is a potentially lethal allo-HSCT complication that is typically associated with Epstein–Barr virus reactivation and infection resulting from HSCT-induced immunosuppression [14-16]. Although the mortality rate has historically been as high as 80%–90% [17,18], recent studies indicate that outcomes can improve significantly with frequent monitoring for circulating Epstein–Barr virus DNAemia and prompt treatment with rituximab, prompt immunosuppressant tapering, or adoptive immunotherapy [19,20]. Thus, identification of those at a high risk of developing PTLD and early intervention are crucial.

In 2019, using data from the Japanese national transplant registry, Fujimoto *et al.* [21] proposed a scoring system for PTLD prediction after allo-HSCT and identified three risk factors: ATG use (high dose = 2 points; low dose = 1 point), donor type (HLA-mismatched related donor = 1 point; unrelated donor = 1 point; cord blood = 2 points), and a diagnosis of aplastic anemia (1 point). The study classified risk into the following categories: low risk (0–1 points), intermediate risk (2 points), high risk (3 points), and very high risk (4–5 points).

A 2021 analysis of the TBMTR database by Lee *et al.* [22] revealed that of the 2,148 cases that underwent allo-HSCT between 2009 and 2018, 57 (2.65%) developed PTLD. In this group, based on the Fujimoto scoring system, the probability of developing PTLD after 5 years was 1.15%, 3.06%, 4.09%, and 8.97% for the low-, intermediate-, high-, and very high-risk groups, respectively. Furthermore, acceptable discrimination was determined as a C-statistic of 0.65. However, based on the same data, Lee *et al.* used machine learning to develop a superior risk prediction scoring system. Compared with the Fujimoto system, the machine-learning algorithm (least absolute shrinkage and selection operator [LASSO]) identified additional risk factors, including fludarabine use in the

conditioning regimen and the development of acute GvHD with skin involvement [Table 2]. Lee's LASSO prediction model stratified patients into low-risk (0–3 points; n = 771), intermediate-risk (4–6 points; n = 971), high-risk (7–8 points; n = 321), and very high-risk (9–12 points; n = 85) groups. Of the 57 patients reported with PTLD, the probability of developing low-, intermediate-, high-, or very high-risk PTLD was 0.52%, 2.47%, 5.92%, and 11.76%, respectively. Compared with patients in the low-risk group, the odds ratio revealed that patients in the intermediate-, high-, and very high-risk groups had 5, 12, and 26 times greater odds of developing PTLD, respectively, which was significantly superior to the findings of the Fujimoto system. Moreover, Lee's LASSO scoring system yielded an optimism-corrected area under the curve of 0.75 (95% CI: 0.69–0.81), which was higher than that obtained using the Fujimoto scoring system (0.65, 95% CI: 0.59–0.72), indicating better discrimination.

Altogether, these observations demonstrate that the TBMTR-based LASSO model is an effective system for predicting and scoring PTLD.

Incidence and predictors of idiopathic pneumonia syndrome after hematopoietic stem cell transplantation

Idiopathic pneumonia syndrome (IPS) is a rare but deadly complication of HSCT [23,24]. Its pathogenesis is multifactorial and includes direct pulmonary endothelial cell damage by conditioning toxicity and indirect damage through the activation of the host inflammatory response, which results in pulmonary surfactant disruption, capillary leakage, pulmonary edema, and alveolar epithelial injury [25,26]. IPS is diagnosed based on exclusion. It is characterized by progressive respiratory distress with signs and symptoms of diffuse pneumonitis in the absence of evidence of infection, cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as the underlying etiology [27]. The incidence of IPS after HSCT varies from 2% to 17% [26,28-32], and its mortality rate is >60% [33,34].

In 2022, Liu *et al.* [35] analyzed the 2009–2019 TBMTR data to determine the outlook of IPS in Taiwan. They found that of 3,924 patients who underwent HSCT, 43 (1.1%) were diagnosed with IPS. Compared with allo-HSCT, auto-HSCT was associated with a lower IPS incidence (0.68% vs. 1.44%, respectively; P = 0.022). Multivariate analysis revealed the use of total body irradiation or intravenous busulfan in the conditioning regimen as independent predictors of IPS. The overall mortality rate was 58.1% in our cohort. Thus, early IPS detection and prompt treatment can improve patient outcomes.

Stem cell transplantation for mantle cell and T-cell lymphoma

Mantle cell lymphoma (MCL) and T-cell lymphoma (except for anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma [ALCL]) are difficult to treat with conventional chemotherapy [36-38]. These lymphomas are generally aggressive and relapse frequently. Although SCT can improve survival, most studies on these lymphomas have been conducted in Western countries and Japan [39-42]. Nonetheless, two important Taiwanese studies based on the TBMTR database have been reported.

Table 1: Incidence of hepatic veno-occlusive disease

Patient characteristics	Number with hepatic VOD/number evaluated (incidence %)	*P*
Whole cohort	39/2345 (1.66)	
Adult patients (age ≥18 year old)	33/2130 (1.55)	0.1749
Pediatric patients (age <18 year old)	6/215 (2.79)	
Autologous HSCT	1/1018 (0.10)	<0.0001
Allogeneic HSCT	38/1326 (2.87)	
HLA-matched unrelated donor	13/289 (4.50)	<0.0001
HLA-mismatched unrelated donor	10/387 (2.58)	
HLA-matched sibling	13/552 (2.36)	
HLA partial mismatched related donor	2/66 (3.03)	
Haplotype donor	0/25 (0.00)	
BM graft	0/84 (0.00)	0.4917
PBSC graft	38/2223 (1.71)	
Umbilical cord blood	1/26 (3.85)	

PBSC: Hematopoietic stem cell transplantation, BM: Blood and marrow, HLA: Human leukocyte antigen, VOD: Veno-occlusive disease, HSCT: Hematopoietic stem cell transplantation

Table 2: Predictive model using least absolute shrinkage and selection operator regression

Predictors	OR (95% CI)	*P*	Lee's LASSO score
Aplastic anemia	2.14 (1.00–4.56)	0.050	2
Partially-mismatched related donor marrow	2.94 (1.49–5.80)	0.002	3
Use of fludarabine	1.71 (0.97–3.00)	0.062	1
Use of ATG	6.45 (2.3–18.08)	<0.001	4
Acute GVHD with skin involvement	1.76 (1.02–3.03)	0.044	2
Total score			12

LASSO: Least absolute shrinkage and selection operator, ATG: Anti-thymocyte globulin, GVHD: Graft-versus-host disease, CI: Confidence interval, OR: Odds ratio

International guidelines recommend early consolidative auto-HSCT for eligible patients with MCL, whereas allo-HSCT is reserved for the treatment of refractory cases. Wang *et al*. [43] analyzed the post-HSCT outcomes of 99 patients with MCL between 1999 and 2020 in Taiwan. Overall, 94 patients underwent auto-HSCT, 13 underwent allo-HSCT (including eight after auto-HSCT failure). Forty-nine (52.1%) patients who underwent auto-HSCT during their first complete remission (CR1) exhibited longer survival than those who were not in CR1 (progression-free survival [PFS]: 50.8 vs. 31.3 months, $P = 0.084$; OS: Not reached vs. 66.8 months, $P = 0.013$). Multivariate analysis identified blastoid variant MCL, transplantation not in CR1, and disease progression within 12 months after auto-HSCT as independent predictors of inferior OS.

Hsu *et al.* [44] surveyed 131 patients with T-cell lymphoma who underwent auto-HSCT ($n = 90$) or allo-HSCT ($n = 41$) in 2009–2014 in Taiwan. Their analysis revealed that patients with extranodal natural killer/T-cell lymphoma had the worst outcomes, with a 2-year OS rate of 23.5%. The OS rates for the other major subtypes of T-cell lymphoma, ALCL, angioimmunoblastic T-cell lymphoma, and peripheral T-cell lymphoma not otherwise specified, were 72.9%, 75.0%, and 51.4%, respectively. Most auto-HSCT patients had ALCL or were in CR, whereas most allo-HSCT recipients had advanced disease. Auto- and allo-HSCT had 2-year OS rates of 62.6% (95% CI: 51.0%–74.2%) and 47.2% (95% CI: 30.2%–64.2%), respectively. Patients who were in CR1 before transplantation obtained the best outcomes.

Autologous stem cell transplantation for the treatment of multiple myeloma

MM is a monoclonal plasma cell malignancy with traditionally low cure rates. Despite the development of numerous nonchemotherapeutic agents, induction therapy with novel agents, followed by upfront high-dose therapy and auto-HSCT, is still recommended for newly diagnosed, transplantation-eligible patients with MM [45,46]. Although the incidence of MM in Taiwan is lower than that in Western countries, it has increased from 0.75 to 1.83 persons per 100,000 people (mean age at diagnosis: 68.7 years) [47]. A higher prevalence of extramedullary myeloma in patients aged 55 years has also been reported [48].

Huang *et al.* [49] analyzed data on 396 patients with MM in the TBMTR database who underwent auto-HSCT from 2006 to 2015 to determine treatment efficacy and identify prognostic factors. In this transplant cohort, 61.9%, 23.7%, and 14.4% of the patients had Durie–Salmon disease stages III, II, and I, respectively. The median PFS and OS after auto-HSCT were 46.5 and 70.4 months, respectively. Compared with Durie–Salmon stages I and II, stage III was a poor prognostic factor, affecting both PFS and OS ($P = 0.006$ and 0.028, respectively) [Table 3]. In addition, patients with better treatment responses before transplantation had better PFS and OS than those who did not exhibit responses (both $P < 0.0001$). The overall incidence of transplantation-associated organ toxicity is low in Taiwan.

Haploidentical transplantation strategies in Taiwan

Because of the limited availability of HLA-matched related or unrelated donors, the use of haploidentical related donors for HSCT (haplo-HSCT) is rapidly increasing worldwide. Successful haplo-HSCT requires the adjustment of T-cell alloreactivity and induction of T-cell tolerance to allow engraftment and reduce GvHD. The main strategies for achieving this are the use of posttransplantation cyclophosphamide (PTCy) with or without ATG [50-56], administration of high-dose cyclophosphamide following graft infusion; and the use of granulocyte colony-stimulating factor (G-CSF)-primed bone marrow plus peripheral blood stem cells (GIAC: G-CSF mobilization, intensified posttransplantation immunosuppression, ATG to prevent GvHD and aid engraftment, and the combination of bone marrow and peripheral blood stem cell graft) [57-59]. However, a direct comparison of these two approaches is lacking. In Taiwan, the original GIAC has been modified into the simpler mGIAC, which retains the use of ATG and G-CSF-primed bone marrow plus peripheral blood stem cell graft but combines them with the more commonly available fludarabine-based conditioning regimens. Tsai *et al.* [60] analyzed the data recorded in the

Table 3: The univariate and multivariate cox regression analyses regarding overall survival for multiple myeloma patients after autologous stem cell transplantation

Factors	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Durie salmon stage						
Stage I			0.051			0.090
Stage II	3.723	1.077–12.875	0.038	3.489	1.003–12.140	0.049
Stage III	4.241	1.326–13.567	0.015	3.728	1.151–12.071	0.028
Response before ASCT						
sCR			<0.0001			<0.0001
CR	0.778	0.219–2.760	0.698	0.690	0.192–2.480	0.569
VGPR	0.744	0.220–2.515	0.635	0.680	0.200–2.309	0.536
PR	1.237	0.370–4.134	0.730	1.034	0.306–3.495	0.958
SD	1.503	0.371–6.088	0.568	1.312	0.321–5.359	0.705
PD	10.792	2.407–48.393	0.002	9.367	2.059–42.616	0.004
Infection	2.127	1.225–3.694	0.007	2.186	1.184–4.036	0.012

ASCT: Autologous stem cell transplantation, CR: Complete response, sCR: Stringent CR, PR: Partial response, VGPR: Very good PR, SD: Stable disease, PD: Progressive disease, CI: Confidence interval, HR: Hazard ratio

TBMTR database from 2011 to 2019 and compared the transplantation outcomes of mGIAC, PTCy with ATG, and PTCy without ATG. The clinical characteristics of the patients are shown in Table 4.

Tsai *et al*. found that the three approaches had equivalent 60-day neutrophil engraftment rates (mGIAC: 99.3%; PTCy with ATG: 97.6%; and PTCy without ATG: 92.3%; $P = 0.113$). However, they differed significantly in neutrophil engraftment times (median: 12 days vs. 15 days vs. 17 days, respectively; $P < 0.001$). Moreover, the 100-day platelet engraftment rates (94.2% vs. 90.5% vs. 68.2%, respectively; $P = 0.001$) and platelet engraftment times (median: 18 days vs. 25 days vs. 32 days, respectively; $P < 0.001$) differed significantly. The cumulative incidences of grade III–IV GvHD at 100 days were similar among the three groups (16.4% vs. 14.3% vs. 11.5%, respectively; $P = 0.728$). However, mGIAC showed significantly higher, more extensive chronic GvHD 2-year cumulative incidences (38.8% vs. 8.7% vs 18.6%, respectively; $P = 0.020$). Furthermore, mGIAC attained the most favorable 2-year OS (48.9% vs. 38.1% vs. 22.0%, respectively; $P < 0.001$). Patients with low/intermediate risk at the time of

Table 4: Comparison of clinical characteristics among patients with different haplo-hematopoietic stem cell transplantation approaches

Variables	Total (*n*=178), *n* (%)	Modified GIAC (*n*=110, 61.8%), *n* (%)	PTCy without ATG (*n*=26, 14.6%), *n* (%)	PTCy with ATG (*n*=42, 23.6%), *n* (%)	*P*
Sex					
Male	88 (49.4)	52 (47.3)	12 (46.2)	24 (57.1)	0.518
Female	90 (50.6)	58 (52.7)	14 (53.8)	18 (42.9)	
Age (years)	45.2 (18.7–75.6)	42.3 (18.7–69.2)	50.1 (21.8–75.6)	49.4 (18.9–68.3)	0.098
Disease					
AML	106 (59.6)	65 (59.1)	13 (50.0)	28 (66.7)	0.391
MDS	11 (6.2)	9 (8.2)	0	2 (4.8)	0.270
MDS/MPN	5 (2.8)	1 (0.9)	3 (11.5)	1 (2.4)	0.013
ALL	32 (18.0)	24 (21.8)	3 (11.5)	5 (11.9)	0.237
MPAL	2 (1.1)	2 (1.8)	0	0	0.535
CML	6 (3.4)	3 (2.5)	1 (3.8)	2 (4.8)	0.816
NHL	12 (6.7)	3 (2.7)	6 (23.1)	3 (7.1)	0.001
HL	3 (1.7)	2 (1.8)	0	1 (2.4)	0.748
Myeloma	1 (0.6)	1 (0.9)	0	0	0.733
Conditioning					
Myeloablative	53 (29.8)	25 (22.7)	10 (38.5)	18 (42.9)	0.229
Reduced intensity	125 (70.2)	85 (77.3)	16 (61.5)	24 (57.1)	
ATG dose per kilogram	6.0 (2.0–7.5)	6.0 (5.0–7.5)	0	4.0 (2.0–7.5)	<0.001
Stem cell source					
BM + mobilized PB	110 (61.8)	110 (100)	0	0	<0.001
Mobilized PB	68 (38.2)	0	26 (100)	42 (100)	
Donor relationship					
Child	85 (47.8)	46 (41.8)	17 (65.4)	22 (52.4)	0.106
Parent	43 (24.2)	33 (30.0)	2 (7.7)	8 (19.0)	
Sibling	50 (28.1)	31 (28.2)	7 (26.9)	12 (28.6)	
Donor–recipient sex combination					
Female donor to male recipient	47 (26.4)	30 (27.3)	5 (19.2)	12 (28.6)	0.659
Other combinations	131 (73.6)	80 (72.7)	21 (80.8)	30 (71.4)	
Donor–recipient CMV serostatus					
Negative–negative	3 (1.7)	1 (0.9)	1 (3.8)	1 (2.4)	0.073[γ]
Negative–positive	40 (22.5)	23 (20.9)	11 (42.3)	6 (14.3)	
Positive–negative	11 (6.2)	9 (8.2)	1 (3.8)	1 (2.4)	
Positive–positive	121 (68.0)	77 (70.0)	12 (46.2)	32 (76.2)	
Missing	3 (1.7)	0	1 (3.8)	2 (4.8)	
CD34 (10^6/kg)	5.08 (1.3–21.2)	5.0 (2.2–8.5)	5.87 (3.0–20.7)	6.0 (1.3–21.2)	<0.001
Disease risk index					
Low	11 (6.2)	8 (7.3)	0	3 (7.1)	0.069
Intermediate	81 (45.5)	47 (42.7)	11 (42.3)	23 (54.8)	
High	71 (39.9)	46 (41.8)	15 (57.7)	10 (23.8)	
Very high	15 (8.4)	9 (8.2)	0	6 (14.3)	
Year of HSCT	2016 (2011–2019)	2016 (2012–2019)	2016 (2014–2019)	2016 (2011–2019)	0.980

[γ]*P*-values <0.05 were considered to be statistically significant MDS: Myelodysplastic syndrome, MPN: Myeloproliferative neoplasm, MPAL: Mixed phenotypic acute leukemia, CML: Chronic myeloid leukemia, HL: Hodgkin lymphoma, NHL: Non-HL, BM: Bone marrow, PB: Peripheral blood, CMV: Cytomegalovirus, HSCT: Hematopoietic stem cell transplantation, AML: Acute myeloid leukemia, ALL: Acute lymphocytic leukemia, ATG: Antithymocyte immunoglobulin, PTCy: Posttransplantation cyclophosphamide, GIAC: Global information assurance certification

Table 5: Survival analysis for elderly patients after allo-hematopoietic stem cell transplantation

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >60 years	1.030 (0.714–1.485)	0.875	1.029 (0.711–1.489)	0.881
Sex (male)	0.986 (0.698–1.392)	0.936	1.030 (0.728–1.457)	0.867
HLA mismatch	1.284 (0.814–2.026)	0.282		
Unrelated donor source	1.043 (0.736–1.476)	0.814		
First remission as transplantation	0.717 (0.493–1.042)	0.081	0.690 (0.469–1.016)	0.06
Myeloablative conditioning	1.193 (0.816–1.745)	0.362		
TBI based conditioning	1.335 (0.751–2.371)	0.325		
Charlson Comorbidity Index ≥3	1.590 (1.124–2.250)	0.009	1.889 (1.316–2.713)	0.001
Donor's age >50 year old	1.188 (0.830–1.700)	0.346		

TBI: Total body irradiation, HLA: Human leukocyte antigen, CI: Confidence interval, HR: Hazard ratio

transplantation who received mGIAC also demonstrated the best 2-year OS (72.7% vs. 51.1% vs. 22.7%, respectively; $P < 0.001$).

Recent progress in PTCy-based protocols, which are becoming more popular and have passed a learning curve period in Taiwan, has improved transplantation outcomes (unpublished data).

Charlson Comorbidity Index predicts transplantation outcomes in older patients with acute myeloid leukemia and myelodysplastic syndrome

Although reports have shown that age is not a contraindication for allo-HSCT [61,62], the presence of comorbidities may increase overall mortality in patients with hematological malignancies [63]. AML and MDS are the most common hematological malignancies in older patients [64].

The Charlson Comorbidity Index (CCI) has been used since 1987 to estimate the risk of death from comorbid diseases [65]. Chien *et al*. [66] retrospectively analyzed the 2011–2018 TBMTR data on the use of allo-HSCT to treat AML or MDS in patients aged >50 years. They examined patient data in the context of other chronic underlying diseases relevant to the composition of CCI, including myocardial infarction, congestive cardiac insufficiency, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, diabetes, and liver disease.

Of 255 patients (median age: 57 years; range: 53–61 years), 38% had CCI scores ≥3. The 1- and 2-year OS rates were 58.8% and 47.6%, respectively. The predictors associated with OS are listed in Table 5. Multivariate analysis identified CCI scores ≥3 (HR: 1.88, 95% CI: 1.31–2.71; $P = 0.001$) and grade III–IV acute GvHD (HR: 3.18, 95% CI: 2.12–4.76; $P < 0.001$) as predictors of poor OS. The 1- and 2-year nonrelapse mortality (NRM) rates were 24.5% and 32%, respectively. Multivariate analysis revealed that CCI scores ≥3 (HR: 1.90, 96% CI: 1.20–3.01; $P = 0.006$) and grade III–IV acute GvHD (HR: 4.91, 95% CI: 3.05–7.92, $P < 0.001$) were significantly correlated with a higher NRM risk.

This cohort study indicates that the use of allo-HSCT should be cautiously considered in older patients with AML or MDS with pretransplantation CCI values ≥3 because of a higher NRM risk.

Conclusion

The nationwide activities of HSCT in Taiwan have developed up to international standards. This review demonstrates the significant advancements in HSCT based on data from the TBMTR database, including the incidence and risk of SOS/VOD, the development of a new PTLD scoring system, the incidence and predictors of IPS, stem cell transplantation for the treatment of mantle cell and T-cell lymphoma, autologous transplantation in MM, outcomes of haploidentical transplantation, and the application of the CCI to predict allo-HSCT outcomes in older patients with AML or MDS. Progress in cell therapies, such as chimeric antigen receptor T-cell therapy, should be among the research targets of the next era of advancements in HSCT.

Data availability statement

Data sharing was not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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