Annals of Hematology (2019) 98:745–752
https://doi.org/10.1007/s00277-019-03604-2

ORIGINAL ARTICLE

The incidence and risk factors of hepatic veno-occlusive disease after hematopoietic stem cell transplantation in Taiwan

Chien-Chang Lee[1] · Hsiu-Hao Chang[2] · Meng-Yao Lu[2] · Yung-Li Yang[2,3] · Shu-Wei Chou[2] · Dong-Tsamn Lin[2,3] · Shiann-Tarng Jou[2] · Ming Yao[4] · Chi-Cheng Li[5,6] · Su-Peng Yeh[7] · Mei-Hui Chen[8] · Jyh-Pyng Gau[9] · Sin-Syue Li[10] · Po-Nan Wang[11] · Yi-Chang Liu[12] · Tso-Fu Wang[6] · Tran-Der Tan[13] · Ming-Yang Lee[14] · Ming-Sun Yu[15] · Chuan-Cheng Wang[16] · Shih-Chiang Lin[17] · Yeu-Chin Chen[18] · Yung-Cheng Su[19] · Ko-Ying Su[1] · Kai-Hsin Lin[2]

Received: 5 September 2018 / Accepted: 3 January 2019 / Published online: 21 January 2019

Abstract

Hepatic veno-occlusive disease (VOD) is a potentially fatal complication of hematopoietic stem cell transplantation (HSCT). We conducted this study to investigate the incidence and risk factors of hepatic VOD for patients receiving HSCT in Taiwan. We retrospectively analyzed the data from a nationwide registry for patients receiving HSCT, which was collected by the Taiwan Society of Blood and Marrow Transplantation. The data collection period was from 2009 to 2014. A total 2345 patients were reviewed and 39 patients among them were diagnosed as having hepatic VOD. The cumulative incidence of hepatic VOD in the whole cohort of 2345 patients was 1.66%. In multivariate analysis, disease diagnosis of myelodysplastic syndrome, chronic HCV infection, condition regimens of bulsulfan intravenously administered, and antithymocyte immunoglobulin were independent factors to predict higher risk of hepatic VOD. The overall mortality rate for patients with hepatic VOD was 79%. Patients with hepatic VOD had significant worse survival outcomes when compared with those without hepatic VOD ($P = 0.00063$). In conclusion, although the incidence is low, hepatic VOD remains a serious complication after HSCT in Taiwan. The findings of this study could be the basis for developing prophylactic or early treatment strategies for hepatic VOD.

Keywords Hematopoietic stem cell transplantation · Incidence · Risk factors · Veno-occlusive disease

Introduction

Veno-occlusive disease (VOD), or sinusoidal obstruction syndrome, of the liver is a potentially fatal complication of hematopoietic stem cell transplantation (HSCT) [1]. The pathogenesis of it is complex and it begins with injury and activation to sinusoidal endothelial cells [2] due to toxic metabolites generated by high-dose chemotherapy in transplantation conditioning regimens [2, 3], leading to cytokine release, activation of the fibrinolytic pathway, fibrotic obliteration of the terminal hepatic venules and sublobular veins, sinusoidal fibrosis, dilatation, and necrosis of the hepatocytes in zone 3 of the liver acinus [4, 5]. Ionizing radiation may also induce the same type of damage [3].

✉ Hsiu-Hao Chang
changhh2001@ntu.edu.tw

Extended author information available on the last page of the article

Hepatic VOD is clinically characterized by fluid retention and ascites, jaundice, body weight gain (≧ 5%), and painful hepatomegaly, in the absence of other identifiable causes of liver disease [6, 7]. It often occurs during the first 21 days of transplantation, but cases with late onset have also been described [8, 9]. The diagnosis of hepatic VOD is usually established by fulfillment of the certain clinical criteria. Although liver biopsy is a gold standard for the diagnosis of hepatic VOD, it is rarely performed because of clinical conditions of patients unsuitable for invasive procedure, such as thrombocytopenia or bleeding tendency. There are two definitions for clinical diagnosis of hepatic VOD: the Baltimore [6] and modified Seattle criteria [7, 10]. These two criteria have been widely used in clinical practice, research studies, and trials in the past three decades [3, 4]. In addition, hepatic VOD is usually classified as mild, moderate, or severe retrospectively based on the severity of the disease and the need for treatment [7]. However, the severities of hepatic VOD are mostly loosely defined and cannot be used to guide treatment or predict risk [3]. For more accurate identification of patients

with hepatic VOD, the European Society for Blood and Marrow Transplantation revised diagnosis and severity criteria recently [9, 11].

The incidences of hepatic VOD are varied in different reports which can be ranged from 0 to 60% [12, 13]. In fact, the incidence and prevalence of hepatic VOD are dependent on the proportion of patients who are at high risk to develop this complication and their exposure to predisposing agents. Patients with severe hepatic VOD have more than 80% of multiple organ failure and mortality rate [12]. The current clinical approach for the management of hepatic VOD includes reversal of risk factors, pharmacological prevention, and pharmacological treatment. Thus, it is important to identify patients at high risk of hepatic VOD and then prophylactic or therapeutic intervention can early apply to such patients to improve their outcomes. However, the data of hepatic VOD in patients receiving HSCT in Taiwan is limited. Therefore, we conducted this study to investigate the incidence and risk factors of hepatic VOD after HSCT by national wide registry data from the Taiwan Society of Blood and Marrow Transplantation.

Materials and methods

Study design

The data collected by the Taiwan Society of Blood and Marrow Transplantation was a national wide data registry for patients receiving HSCT in Taiwan and there were 15 hospitals in Taiwan participated in this data registration. The data collection period for analysis in this study was from January 2009 to December 2014. This study was approved by the Institutional Review Board of the National Taiwan University Hospital. Informed consent was obtained from all individual participants included in the study.

Hepatic VOD

The diagnosis of hepatic VOD was established when two of the following clinical findings presented according to the modified Seattle criteria [7, 10]: (1) hyperbilirubinemia more than 2 mg/dL; (2) ascites (radiographic or physical examination) and/or unexplained weight gain (2% above baseline weight); and (3) hepatomegaly over baseline or pain in right upper quadrant. The onset of hepatic VOD after day 21 post HSCT was defined as late onset hepatic VOD. There were no patients receiving prophylactic treatment for hepatic VOD in this study. The diagnosis of patients with hepatic VOD was determined by different hospitals participated in this study and then registry to the database.

Statistical analysis

We compared demographic and clinical characteristics between patients with and without VOD. Categorical variables were presented as frequency and percentage and compared using Chi-squared test. Continuous variables were presented by mean or median and compared by *t* test. We used single-predictor logistic regressions to identify significant associations between putative risk factors and VOD. Variables with significant between-group difference ($P < 0.2$) are included in the final multivariate Cox proportional hazard model. The proportional hazard assumption was examined by adding interaction terms of exposure with follow-up time in the model. We checked variables for multicollinearity using tolerance and the variance inflation factor. For the variables used in the final model, both the tolerance and the variation inflation factor were very close to unity. To build a parsimonious Cox model, we used Akaike's information criterion to select variables. Lastly, we tested the survival impact of VOD by plotting the Kaplan-Meier survival curve stratified by VOD and tested the difference with Log-rank test. All statistical analyses were performed by SAS 9.4 (SAS Inc. Cary NC) and a P value of < 0.05 was deemed as significant.

Results

Incidence of hepatic VODs

A total of 2345 patients were in the extracted data from the registry database and 39 patients among them were diagnosed as having hepatic VOD. The cumulative incidence of hepatic VOD in the whole cohort of 2345 patients was 1.66%. In different age groups, the incidence of hepatic VOD was 1.55% in adult patients and 2.79% in pediatric patients, respectively. The incidence of hepatic VOD was not significantly different between adult and pediatric patients. In contrast, patients receiving allogeneic HSCT had significantly higher incidence of hepatic VOD when compared with those in patients receiving autologous HSCT (2.87% vs. 0.1%, $P < 0.0001$). Patients with HLA-matched unrelated donor also had significantly higher incidence of hepatic VOD (4.5%) when compared with those in other types of HSCT donors ($P < 0.0001$). However, the incidence of hepatic VOD between patients with different HSCT grafts, such as bone marrow (BM), peripheral blood stem cell (PBSC), or umbilical cord blood, was not significantly different (Table 1). There were no hepatic VOD for patients with haplotype HSCT donor or BM graft in our study.

Table 1 Incidence of hepatic VOD

Patient characteristics	No. with hepatic VDO/ No. evaluated (incidence %)	*P* value
Whole cohort	39/2345 (1.66%)	
Adult patients (age ≧ 18 years old)	33/2130 (1.55%)	0.1749
Pediatric patients (age < 18 years 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%)	

Risk factors of hepatic VOD

The patient characteristics and univariate analysis of risk factors associated with hepatic VOD were listed in Table 2. In univariate analysis, disease diagnosis of multiple myeloma, non-Hodgkin's lymphoma, and autologous transplantation were associated with significant lower risk of hepatic VOD. On the other hand, disease diagnosis of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), thalassemia major, patients having chronic hepatitis, especially hepatitis C virus (HCV) infection, higher serum total bilirubin levels, higher serum ferritin levels, condition regimens of bulsulfan intravenously administered, antithymocyte immunoglobulin, and cyclophosphamide were associated with significant higher risk of hepatic VOD.

In multivariate analysis, disease diagnosis of MDS, chronic HCV infection, condition regimens of bulsulfan intravenously administered, and antithymocyte immunoglobulin were independent factors to predict higher risk of hepatic VOD (Table 3).

Outcomes of patients with hepatic VOD

For the onset of hepatic VOD in our patients, 28 (71.8%) patients were before and 11 (28.2%) patients were after day 21 post HSCT. Among 39 patients with hepatic VOD, 10 patients received treatment including defibrotide and 29 patients received supportive care without defibrotide. There were 31 patients who died. The overall mortality rate for our patients with hepatic VOD was 79.5%. In these 31 patients, 8 patients died of hepatic VOD, 9 patients died of disease relapse or progression, 9 patients died of infection, 4 patients died of GVHD, and one patient died of poor HSCT graft function. For patients who received defibrotide treatment, there were no patients who died of hepatic VOD. The overall survival probability of day 200 post HSCT were 74 ± 7.1% in patients with hepatic VOD and 88 ± 7.3% in patients without hepatic VOD, respectively. (Fig. 1) Patients with hepatic VOD had significantly worse survival outcomes when compared with those in patients without hepatic VOD ($P = 0.00063$, log-rank test).

Discussion

The different incidences of hepatic VOD between reports may be related to different types of transplantation, patient populations, conditioning regimens, and the use of different diagnostic criteria in different studies [3]. The incidence of hepatic VOD after HSCT rarely exceeds 5% in patient receiving autologous HSCT, but can be up to 60% in patients receiving allogeneic HSCT [13]. A prospective study from the European Group for Blood and Marrow Transplantation showed that the present of several risk factors have an additive effect on the incidence of hepatic VOD after HSCT [14]. Our study results were compatible with these observations. The incidence rates of hepatic VOD were 1.66% in our whole cohort, 0.1% in our patients receiving autologous HSCT, and 2.87% in patients receiving allogeneic HSCT. The current study is the first report to define the incidence and risk factors of hepatic VOD after HSCT in Taiwan. The cohort in our study included all kinds of patients receiving HSCT and therefore draws a whole picture of hepatic VOD in HSCT.

Understanding risk factors associated with the development of hepatic VOD is critical for early initiation of treatment or prophylaxis to prevent the occurrence of hepatic VOD. The risk factors of hepatic VOD can be categorized into pre-transplantation patient characters and transplantation related factors. The common pre-transplantation patient-related factors associated with risk of hepatic VOD are including young

Table 2 Univariate analysis of characteristics between patients with and without hepatic VOD

Factors	Non-VOD ($N = 2306$)	VOD ($N = 39$)	Odds ratio (95% CI)	P value
Age (year)	41.27 ± 16.51	39.95 ± 16.62	NA	0.796
Adult (age ≧ 18 years old)	2097(90.94%)	33(84.62%)	0.55 (0.23–1.32)	0.1749
Male	1299 (56.3%)	20 (51.3%)	0.82 (0.43–1.54)	0.528
Disease				
AML	608 (26.4%)	18 (46.2%)	2.39 (1.27–4.52)	0.006*
ALL	300 (13.0%)	7 (17.9%)	1.46 (0.64–3.34)	0.365
CML	50 (2.2%)	0 (0%)	NA	0.353
NHL	505 (21.9%)	2 (5.1%)	0.19 (0.05–0.80)	0.012*
Hodgkin's disease	116 (5.0%)	0 (0%)	NA	0.151
MM	391 (17.0%)	1 (2.6%)	0.13 (0.02–0.94)	0.017*
MDS	87 (3.8%)	6 (15.4%)	4.64 (1.89–11.36)	< 0.001*
Thalassemia major	4(0.17%)	1(2.56%)	15.14 (1.65–138.7)	0.0013*
Pre-BMT liver condition				
Chronic Hepatitis	275 (11.9%)	11 (28.2%)	2.90 (1.43–5.89)	0.002*
Liver cirrhosis	17 (0.7%)	1 (2.6%)	3.54 (0.46–27.31)	0.195
Pre-BMT laboratory test				
Chronic HBV infection	262/2089 (12.5%)	8/36 (22.2%)	2.00 (0.90–4.44)	0.081
Chronic HCV infection	49/2023 (2.4%)	3/35 (8.6%)	3.78 (1.12–12.75)	0.022*
Total bilirubin (mg/dL)	0.63 ± 0.02	1.02 ± 0.38	NA	0.0055
ALT level (U/L)	33.22 ± 0.88	86.97 ± 50.10	NA	0.188
Serum Ferritin (ng/mL)	1571.63 ± 65.81	3016.86 ± 1036.34	NA	0.002*
Pre-BMT disease status				
Complete remission	1131 (53.6%)	14 (40.0%)	0.58 (0.29–1.14)	0.109
Relapse	254 (12.0%)	8(22.9%)	2.16 (0.97–4.81)	0.053
Type of HSCT				
Autologous	1017(44.1%)	1(2.6%)	0.03 (0.00–0.24)	< 0.0001*
Allogeneic	1288 (55.9%)	38(97.4%)	30 (4.11–218.91)	< 0.0001*
Type of conditioning				
No conditioning	27(1.17%)	0(0%)	NA	0.496
Myeloablative	1420(61.8%)	21(53.9%)	0.72 (0.38–1.36)	0.3115
Non-myeloablative	167(7.3%)	2(5.1%)	0.69 (0.16–2.89)	0.6091
TBI	500 (21.7%)	9 (23.1%)	1.08 (0.51–2.30)	0.834
Oral bulsulfan	96(4.2%)	3(7.7%)	1.91 (0.58–6.31)	0.2802
IV bulsulfan	317(13.8%)	15(38.5%)	3.90 (2.03–7.52)	< 0.0001*
ATG (rabbit)	797 (34.6%)	30 (76.9%)	6.31 (2.98–13.36)	< 0.0001*
Cyclophosphamide	1179 (51.1%)	29 (74.4%)	2.77 (1.34–5.71)	0.004*
Fludarabin	47(2.0%)	1(2.6%)	1.26 (0.17–9.41)	0.818

*$P < 0.05$

age, pre-existing liver disease, advanced underlying malignant disease, deteriorated health or performance status, previous liver transplantation or HSCT, prior abdomen radiation, and impaired pulmonary functions [3]. The transplantation-related factors associated with risk of hepatic VOD are usually including types of transplantation, such as allogeneic or autologous and myeloablative or reduced-intensity therapy, the use of total body irradiation, drugs used for GVHD prophylaxis, and post-HSCT liver GVHD [3]. Previous studies showed that thalassemia major was a high risk factor of hepatic VOD for patients receiving HSCT which may be attributed to pre-existing liver damage cause by iron overload [15, 16]. The association of hepatic VOD with iron overload was also reported by another study which showed that elevated pre-transplant levels of serum ferritin were the most important risk marker for hepatic VOD [17]. In our study, disease diagnosis of thalassemia major and higher pre-transplant serum ferritins levels were both associated with higher risk of hepatic VOD.

Table 3 Multivariate analysis of risk factors for hepatic VOD

Factors	Hazard ratio (95% CI)	*P* value
MDS	3.10 (1.18–8.14)	0.0217*
Chronic HCV infection	6.38 (1.89–21.47)	0.0028*
IV Bulsulfan	2.62 (1.23–5.56)	0.0123*
ATG (rabbit)	4.69 (2.02–10.86)	0.0003*

*$P < 0.05$

Thus, our study results confirmed the impact of thalassemia major and iron overload on the risk of hepatic VOD. In addition, although several factors were associated with higher risk of hepatic VOD in our univariate analysis, only disease diagnosis of MDS, chronic HCV infection, condition regimens of bulsulfan intravenously administered, and antithymocyte immunoglobulin were independent factors to predict higher risk of hepatic VOD. This observations may be due to most of the allogeneic HSCT were using intravenously administered bulsulfan as conditioning regimens and antithymocyte immunoglobulin as drug of GVHD prophylaxis in our study.

Most of accurate methods to confirm the diagnosis of hepatic VOD, such as measurement of the hepatic venous gradient pressure through the jugular vein or liver biopsy, are invasive and difficult to perform in routine practice [18]. Therefore, the diagnostic of hepatic VOD is usually based on clinical symptoms/signs, which include jaundice, ascites, body weight gain, and painful hepatomegaly, in the real world. Two definitions for diagnosis of hepatic VOD, the modified Seattle criteria [7, 10] and the Baltimore criteria [6], have been widely used for the past three decades. The main difference between these two definitions is hyperbilirubinemia, which is necessary in the Baltimore, but not in the modified Seattle criteria. Hyperbilirubinemia is almost present in adults with classical hepatic VOD, but can be absent in hepatic VOD that develops later [19] and is often absent in children with hepatic VOD [4, 20]. Since our study included children and patients with late onset of hepatic VOD, we used Seattle criteria for the diagnosis of hepatic VOD in this study.

Patients with severe hepatic VOD have more than 80% of multiple organ failure and mortality rate [12]. In the past, the management of hepatic VOD was primarily supportive care, anticoagulants, and antifibrinolytics, but the efficacy of them was limited. Defibrotide is the only agent with approved indication for the treatment of hepatic VOD in European Union and USA [4]. In children, it was demonstrated that prophylactic or early use of defibrotide can reduce incidence of hepatic VOD or was associated with better clinical outcomes for patients with hepatic VOD [20, 21]. Although we did not classify our patients with hepatic VOD into different severity for analysis in this study, the overall mortality rate of our patients with hepatic VOD was as high as 79.5% (31/39) and 25.8% (8/31) of death was because of hepatic VOD. Due to the diagnosis of hepatic VOD was retrospectively determined and

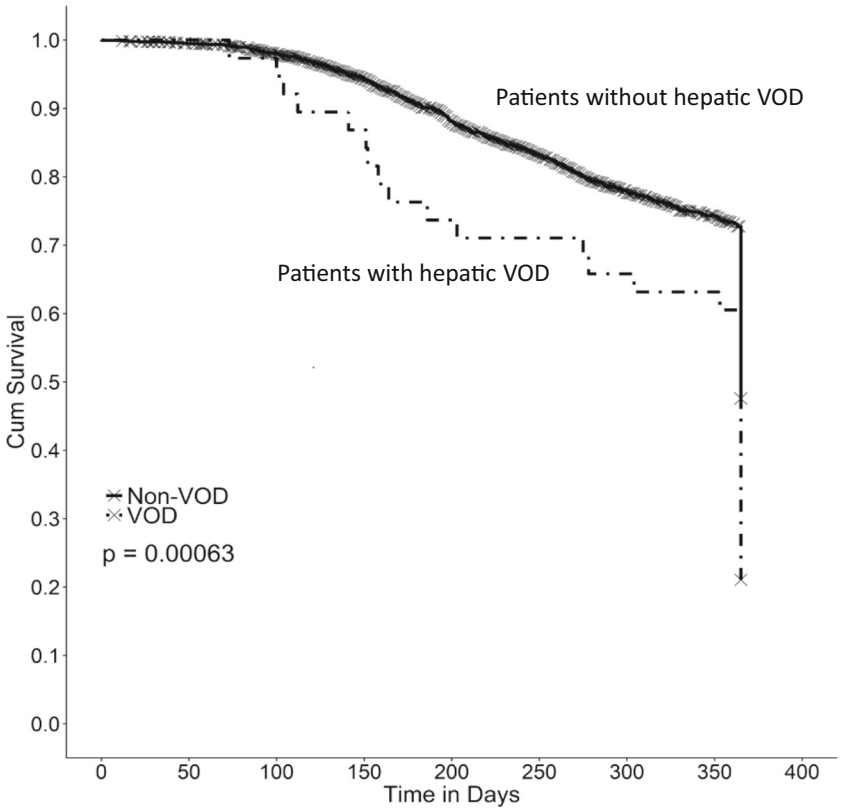

Fig. 1 The impact of hepatic VOD on overall survival for patients receiving HSCT. Kaplan-Meier's survival curves among all patients receiving HSCT, stratified by the presence of hepatic VOD ($P < 0.00063$ by log-rank test)

confirmed by the clinical team in this study, most of the recognized hepatic VOD may belong to severe form in our study.

There were several limitations in this study which should be considered when interpreting the results. First, it was a retrospective analysis, not a prospective study, and it is possible to be associated with observation and selection biases. In addition, there were some data missing in the database and we were unable to accurately classify the hepatic VOD of patients into different clinical severity for analysis or to evaluate the treatment response.

In conclusion, our study defined the incidence and risk factors of hepatic VOD for a large cohort of patients receiving HSCT in Taiwan and the results showed that hepatic VOD remains a serious complication after HSCT. In addition, disease diagnosis of MDS, chronic HCV infection, condition regimens of bulsulfan intravenously administered, and antithymocyte immunoglobulin were independent factors to predict higher risk of hepatic VOD for our patients. Risks factors of hepatic VOD found in this study could be the basis to select patients who plan to receive HSCT to receive prophylactic or early treatment intervention with defibrotide for hepatic VOD.

Acknowledgments The authors thank all the patients and hospitals who participated in this study. The authors acknowledge the Taiwan Society of Blood and Marrow Transplantation for data collection and registry. The authors also wish to thank Mrs. Bor-Yu Tsai and Shin-Tsung Huang from the NAVI Biotherapeutics Inc. (Taiwan) for supports in data analysis and advice.

Funding This work was supported by grants from the National Taiwan University Hospital (NTUH 107-S3777, 108-S4194 to H.-H. C.) and Ministry of Science and Technology, Taiwan (MOST 103-2314-B-002-072 and 104–2314-B-002-168-MY3, to H.-H. C.).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Affiliations

Chien-Chang Lee[1] · Hsiu-Hao Chang[2] · Meng-Yao Lu[2] · Yung-Li Yang[2,3] · Shu-Wei Chou[2] · Dong-Tsamn Lin[2,3] · Shiann-Tarng Jou[2] · Ming Yao[4] · Chi-Cheng Li[5,6] · Su-Peng Yeh[7] · Mei-Hui Chen[8] · Jyh-Pyng Gau[9] · Sin-Syue Li[10] · Po-Nan Wang[11] · Yi-Chang Liu[12] · Tso-Fu Wang[6] · Tran-Der Tan[13] · Ming-Yang Lee[14] · Ming-Sun Yu[15] · Chuan-Cheng Wang[16] · Shih-Chiang Lin[17] · Yeu-Chin Chen[18] · Yung-Cheng Su[19] · Ko-Ying Su[1] · Kai-Hsin Lin[2]

1 Department of Emergency Medicine, National Taiwan University Hospital, National Taiwan University, College of Medicine, Taipei, Taiwan

2 Department of Pediatrics, National Taiwan University Hospital, National Taiwan University, College of Medicine, No. 8 Chung-Shan South Road, Taipei 10041, Taiwan

3 Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University, College of Medicine, Taipei, Taiwan

4 Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University, College of Medicine, Taipei, Taiwan

5 Tai-Cheng Stem Cell Therapy Center, National Taiwan University Hospital, Taipei, Taiwan

6 Department of Hematology and Oncology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan

7 Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan

8 Department of Nursing, Taichung Veterans General Hospital, Taichung, Taiwan

9 Division of Hematology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

10 Division of Hematology and Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan

11 Division of Hematology and Oncology, Department of Internal Medicine, Chang Gung Medical Foundation, Linkou Branch, Taoyuan, Taiwan

12 Division of Hematology and Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

13 Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan

14 Division of Hematology and Oncology, Department of Internal Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan

15 Division of Hematology and Oncology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

[16] Division of Medical Oncology in the Hematology-Oncology, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan

[17] Division of Medical Oncology and Hematology, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan

[18] Division of Hematology and Oncology, Department of Medicine, Tri-Service General Hospital, Taipei, Taiwan

[19] Division of Hematology and Oncology, Department of Medicine, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan