Original Article

Chemotherapy-induced thrombocytopenia and platelet transfusion in patients with diffuse large B-cell lymphoma

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Background: Currently, the risk factors associated with chemotherapy-induced thrombocytopenia (CIT) in patients with diffuse large B-cell lymphoma (DLBCL) are still undefined. Our study aimed to analyze the effects of risk factors on thrombocytopenia and to identify the threshold for infusion platelets of CIT patients who have received platelet transfusions.

Methods: We conducted a retrospective analysis of 523 patients with DLBCL from 2011 to 2013. The clinical and demographic parameters were extracted, and the risk factors associated with CIT were analyzed. The threshold for platelet transfusions in DLBCL patients with a central venous catheter (CVC) was evaluated.

Results: A total of 227 (43.4%) DLBCL patients had thrombocytopenia, and 63 (12.0%) had thrombocytopenia without concomitant cytopenia. We found that the choice of chemotherapy regimen was positively correlated with thrombocytopenia (P<0.001). The chemotherapy regimens most likely to result in thrombocytopenia were dexamethasone, cytarabine, cisplatin (DHAP) (92.3%), isophosphamide, carboplatin, etoposide (ICE) (89.7%), gemcitabine, dexamethasone, cisplatin (GDP) (89.7%), gemcitabine, and oxaliplatin (Gemox) (69.0%). In addition to these, high lactate dehydrogenase (LDH) (P=0.004) and Ann Arbor stage III/IV (P=0.024) were determined to be risk factors leading to thrombocytopenia. Forty patients (17.6%) had transfused platelets, and all of them were placed in the CVC. The high-threshold group (platelet count $\leq 20\times10^9$/L had a significantly lower amount of platelet transfusions than the low-threshold group $\leq 10\times10^9$/L. The platelet transfusion amount was 1.44±0.77 *vs.* 2.05±1.13 (P=0.047), respectively.

Conclusions: The chemotherapy regimens of DHAP, ICE, GDP, and Gemox can easily lead to thrombocytopenia. A high level of LDH in the peripheral blood and Ann Arbor stage III/IV are also associated with risk factors for thrombocytopenia. A 20×10^9/L prophylactic platelet transfusion threshold value is safer, more effective, and thus a better choice for DLBCL patients with CVC.

Keywords: Diffuse large B-Cell lymphoma; platelet transfusion; chemotherapy regimen; chemotherapy-induced thrombocytopenia; central venous catheterization

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is a highly aggressive form of B-cell lymphoma, and DLBCL encompasses many different disease entities with distinct clinical, pathological and biological features (1,2). As the most common subtype of lymphoma, it accounts for approximately 30–35% of the non-Hodgkin lymphoma (NHL) cases worldwide (3,4).

Chemotherapy-induced thrombocytopenia (CIT), which is a dose-limiting toxicological response to chemotherapeutic drugs, is considered one of the most common complications that occur during tumor treatment. CIT can be particularly harmful as it can delay chemotherapy, decrease the dose of chemotherapy drugs, increase medical expenses, cause induced bleeding, and intensify the mental burden of patients (5-7). In short, CIT seriously reduces the efficacy of chemotherapy and the life quality of patients.

Thus far, only a few studies have investigated the relationship between the incidence of CIT and different chemotherapy drug types, while research on the severity and risk factors of myelotoxicity associated with clinical features is similarly scant. The existing studies primarily focus on solid tumors, with the incidence of CIT in hematological tumors reported to be as high as 75% (8,9). In light of this, it is particularly important to investigate the incidence of thrombocytopenia caused by different chemotherapy regimens in the field of hematological tumor studies, which can provide valuable information in facilitating the prevention and treatment of CIT. Additionally, to improve patients' quality of life, clarifying the relationship between CIT and different clinical features is of utmost importance.

Platelet transfusions are used in modern clinical practice to prevent and treat bleeding in thrombocytopenic patients with bone marrow failure secondary to chemotherapy, and a platelet-count threshold for prophylactic platelet transfusion in DLBCL recipients has yet to be determined. Giving prophylactic platelet transfusions at a lower prespecified threshold platelet count may increase the risk that bleeding will occur, which may cause morbidity and even mortality, whereas giving platelet transfusions at a higher prespecified threshold platelet count may mean that people receive unnecessary platelet transfusions (10,11).

Prompted by this dilemma, we conducted a study that retrospectively analyzed the rate of CIT in patients with diffuse large B-cell lymphoma and completed a matched case-control study between CIT and without CIT cases. Clinicopathological features were compared to shed light on the unique features of this disease. We surveyed those patients who received platelet transfusions and performed a retrospective study focusing on 10×10^9/L versus 20×10^9/L prophylactic transfusion thresholds in DLBCL patients to compare transfusion requirements and the incidence of bleeding and treatment outcomes.

Methods

Patients

The data collected from patients diagnosed with DLBCL at the Fujian Cancer Hospital from July 1, 2011, to December 31, 2013, were retrospectively analyzed. The research recruitment criteria were as follows: (I) cases were in accordance with the 2008 World Health Organization (WHO) classification criteria of hematopoietic and lymphoid tumors, and were confirmed by pathological biopsy and immunohistochemistry; (II) patients were aged ≥18 years; (III) sampling patients had received clinical adjuvant chemotherapy during the observation period; (IV) platelets, hemoglobin (Hb), and white blood cells were counted before and after each chemotherapy session, and sampling patients received at least 2 blood tests per week during the course of chemotherapy; (V) before chemotherapy, platelet count was $\geq100\times10^9$/L; (VI) platelet count was confirmed by a manual slide review when values fell below 50×10^9/L. In total, 523 DLBCL patients were included.

Chemotherapy regimen

Patients who received 1 or more courses of a specific chemotherapy regimen in the observation period were incorporated into 1 research group, and the regimen consisted of a series of sequential chemotherapies. If a patient in the observation period received 2 or more chemotherapy regimens, the first chemotherapy regimen was selected as the primary regimen, and the patient was followed up until the end of it, thus avoiding the misclassification caused by chemotherapy exposure. Among the groups of chemotherapy regimens studied in this research, the chemotherapy regimen for the CHOP group was CHOP21 (cyclophosphamide + adriamycin + vinblastine + prednisone), RCHOP21 (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone), CEOP

(cyclophosphamide + etoposide + vincristine + prednisone), and CDOP (cyclophosphamide + liposomal doxorubicin + vincristine + prednisone). The chemotherapy regimen for the ACVBP group was (cyclophosphamide + doxorubicin + vincristine + bleomycin + prednisone). The chemotherapy regimen for the EPOCH group was (cyclophosphamide + etoposide + adriamycin + vinblastine + prednisone) ± rituximab. The chemotherapy regimen for the ICE group was (isophosphamide + carboplatin + etoposide) ± rituximab. The chemotherapy regimen for the GDP group was (gemcitabine + dexamethasone + cisplatin) ± rituximab. The chemotherapy regimen for the Gemox group was (gemcitabine + oxaliplatin) ± rituximab. The main chemotherapy regimen for the DHAP group was (dexamethasone + cisplatin + cytarabine) ± rituximab.

Thrombocytopenia

The judgment of thrombocytopenia is based on the number of the measured platelet counts during chemotherapy. According to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE 4.03) established by the National Institute of Health (NIH), the platelet count in peripheral blood <100×10^9/L in the course of chemotherapy can be defined as thrombocytopenia. Thrombocytopenia can be divided into 4 grades (CTCAE 4.03): Grade I, 75×10^9–99×10^9/L; Grade II, 50×10^9–74×10^9/L; Grade III, 25×10^9–49×10^9/L; Grade IV, <25×10^9/L.

Thrombocytopenia during chemotherapy is often accompanied by a reduction of other blood cell counts. The definition of isolated thrombocytopenia is platelet count <100×10^9/L and without anemia Hb <120 g/L for males and <110 g/L for female) and leucopenia (white blood cell count <4×10^9/L). The lowest level of platelet count during the same chemotherapy regimen was recorded to determine whether the patient has CIT and whether there is simple thrombocytopenia.

The selection and comparison of DLBCL platelet transfusion thresholds

For the enrollment of platelet transfusion, patients were divided into 2 groups for receiving platelet transfusions depending on if their platelet counts were ≤20×10^9/L (lower transfusion threshold) or ≤10×10^9/L (lower transfusion threshold). The control procedure employed strict matching criteria: gender (male or female), age, cell origin, pretransfusion platelet count chemotherapy-induced anemia (CIA), chemotherapy-induced leucopenia (CIL), standard international prognosis index (IPI) score, lactate dehydrogenase level, and Ann Arbor stage, B symptoms were recorded before transfusion, and data types, including the occurrence of hemorrhage and infection, the morning body temperature, the number of platelets transfused, the increase platelet count posttransfusion, days in the hospital, the use of thrombopoietin, chemotherapy and some biochemical indexes after transfusion, were compared. All patients received ABO-compatible single-donor apheresis platelet products, when available, and all platelet products were leukocyte-depleted and irradiated. One therapeutic dose of the apheresis platelets contained about 2.5×10^{11} platelets.

Statistical analysis

All data were analyzed by IBM SPSS version 19.0. The clinical data of patients and the percentages of CIT for different chemotherapy regimens are presented by exact percentages or median values. Chi-square or t-tests were used for univariate analysis. The logistic regression forward method was applied for multivariate analysis. A P value of <0.05 was considered to indicate a statistically significant difference. GraphPad Prism 7 was used for analyzing graphs.

Results

Incidents of CIT and CIT associated with different chemotherapy regimens

A total of 523 consecutive patients with de novo DLBCL were collected in this study. CIT occurred in 227 patients (43.4%), while isolated thrombocytopenia occurred in 63 patients (12.0%). *Table 1* displays the frequency of thrombocytopenia and isolated thrombocytopenia stratified by the grade of severity. The chemotherapy regimens used in DLBCL most commonly associated with thrombocytopenia included DHAP (92.3%), ICE (89.7%), GDP (89.7%), and Gemox (69%). The highest frequencies of isolated thrombocytopenia occurred in patients receiving the ACVBP (22.2%), ICE (20.7%), Gemox (20.7%), and GDP (19.4%) chemotherapy regimens (*Table 2*). The platelet count nadir in patients caused by different chemotherapy regimens was 24.54±44.13 for DHAP, 55.53±35.72 for ICE, 78.28±38.22 for Gemox, and 78.72±45.83 for GDP (*Figure 1*).

Table 1 Frequency of overall and isolated thrombocytopenia classified by the grade of severity based on the platelet count nadir

Grade	Frequency, n (%)	
	Overall thrombocytopenia	Isolated thrombocytopenia
Overall	227 (43.4)	63 (12.0)
I	89 (17.0)	34 (6.5)
II	53 (10.1)	20 (3.8)
III	42 (8.0)	9 (1.7)
IV	43 (8.2)	0 (0.0)

I, platelets 75×10^9–99×10^9/L; the lower limit of normal was defined as 100×10^9/L; II, (50×10^9–74×10^9/L; III, 25×10^9–49×10^9/L; IV, <25×10^9/L.

Table 2 Frequency of clinically significant thrombocytopenia based on the chemotherapy regimen

Type of cytotoxic drug	No. of patients	Frequency of overall thrombocytopenia, n (%)	Frequency of isolated thrombocytopenia, n (%)
ACVBP	18	8 (44.4)	4 (22.2)
CHOP	246	62 (25.2)	22 (8.9)
DHAP	13	12 (92.3)	0 (0.0)
EPOCH	123	48 (39.0)	12 (9.8)
GDP	36	25 (69.4)	7 (19.4)
Gemox	29	20 (69.0)	6 (20.7)
ICE	58	52 (89.7)	12 (20.7)

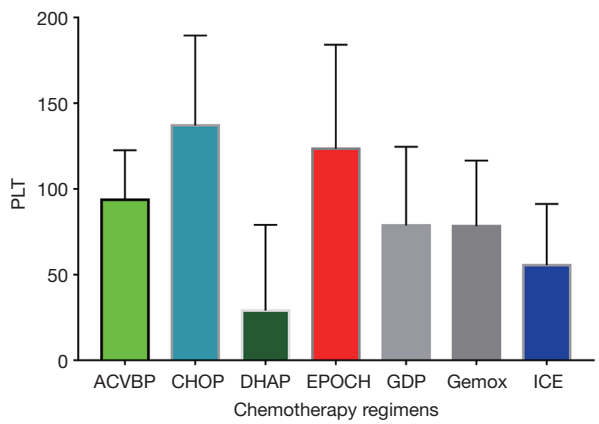

Figure 1 The platelet count of different chemotherapy regimens in diffuse large B-cell lymphoma (DLBCL).

Clinical features of CIT

Patients who developed clinically significant CIT were examined for predictive factors that impacted the development of clinical complications. These factors are listed in *Table 3*. Overall, Ann Arbor stage was a significant predictor of the risk of CIT (P<0.001), while the level of LDH appeared to increase the risk of CIT (P<0.001), with IPI scores (P=0.015) and gender (P=0.029) also being prominent factors for CIT. Five variables were chosen to contribute to the model in the multivariate logistic regression analysis (*Table 4*). Results of this analysis (*Table 4*) revealed that chemotherapy regimens (P<0.001), LDH (P=0.004), and Ann Arbor Stage (P=0.024) were independent risk factors for thrombocytopenia.

Platelet transfusion

Of the 227 patients with thrombocytopenia, 40 (17.6%) were administered platelet transfusions. *Figure 2* shows the comparison of platelet counts before and after transfusion. The median (range) pre-transfusion platelet count was 11×10^9/L (3×10^9–23×10^9/L) and increased significantly post-transfusion to 29×10^9/L (6×10^9–53×10^9/L) (P<0.001). The pre-transfusion preclinical characteristics of the patients are shown in *Table 5*. The 2 groups were similar, with only the pretransfusion platelet count being different (7.53±2.03 *vs.* 14.00±3.00) (P<0.001). The difference in the numbers

Table 3 Comparison of the demographic, histopathological, clinical, and laboratory characteristics of patients with CIT and without CIT

Variables	Patients with CIT (n=227)	Patients without CIT (n=296)	c(t)	P*
Gender, n (%)			4.75	0.029*
Male	142 (62.6)	157 (53.0)		
Female	85 (37.4)	139 (47.0)		
Age, mean ± SD, years	51.36±14.22	51.40±14.09	0.03	0.976
Cell origin, n (%)			1.238	0.539
GCB	61 (26.9)	75 (25.3)		
Non-GCB	120 (52.9)	170 (57.4)		
No test	46 (20.3)	51 (17.2)		
HBsAg, n (%)			0.024	0.876
Positive	72 (31.7)	92 (31.1)		
Negative	155 (68.3)	204 (68.9)		
B symptoms, n (%)			0.712	0.399
A	192 (84.6)	258 (87.2)		
B	35 (15.4)	38 (12.8)		
LDH, n (%)			20.744	<0.001*
<190	111 (48.9)	203 (68.6)		
≥190	116 (51.1)	93 (31.4)		
Ki67, n (%)			0.109	0.947
<80%	93 (41.0)	123 (41.6)		
≥80%	105 (46.3)	138 (46.6)		
No test	29 (12.8)	35 (11.8)		
IPI scores, n (%)			5.928	0.015*
0/1/2	178 (78.4)	256 (86.5)		
3/4/5	49 (21.6)	40 (13.5)		
Ann Arbor stage, n (%)			20.166	<0.001*
I/II	27 (11.9)	83 (28.0)		
III/IV	200 (88.1)	213 (72.0)		

Data were analyzed using Pearson's χ^2 test for categorical variables and t-tests for continuous variables. *P<0.05 indicates a statistically significant difference when comparing values at the same measuring points. LDH, lactic dehydrogenase.

of patients with platelet transfusions per patient in the 2 groups was statistically significant (P=0.047), while the other clinical characteristic and endpoints after transfusion showed no significant difference between the two groups.

Discussion

DLBCL, the most common subtype of NHL, is an invasive clinical process and a highly heterogeneous malignant tumor in morphology, immunology, molecular genetic abnormality, and clinical biology (2,12). Approximately 60% of DLBCL patients can reach clinical recovery, but the other 40% may suffer recurrence or treatment failures at an early stage (13). These treatment-related complications have gained increasing clinical attention, and CIT has long been regarded as a major complication of cancer treatment.

Table 4 Clinical characteristic and endpoints at a lower transfusion threshold *vs.* a higher transfusion threshold

Variables	Lower transfusion threshold (n=15)	Higher transfusion threshold (n=25)	c(t)	P*
Pretransfusion				
Gender			0.541	0.462
Male	9 (60.0)	12 (48.0)		
Female	6 (40.0)	13 (52.0)		
Age, years	47.33±12.37	45.08±14.73	0.496	0.623
Cell origin			0.711	0.701
GCB	2 (13.3)	6 (24.0)		
Non-GCB	10 (66.7)	14 (56.0)		
No test	3 (20.0)	5 (20.0)		
Pretransfusion platelet count ($\times10^9$/L)	7.53±2.03	14.00±3.00	7.377	<0.001*
CIA			1.946	0.163
Yes	15 (100.0)	22 (88.0)		
No	0 (0)	3 (12.0)		
CIL			0.889	0.346
Yes	10 (66.7)	20 (80.0)		
No	5 (33.3)	5 (20.0)		
B symptoms			1.615	0.204
A	10 (66.7)	21 (84.0)		
B	5 (33.3)	4 (16.0)		
LDH			2.416	0.12
<190	2 (13.3)	9 (36.0)		
≥190	13 (86.7)	16 (64.0)		
IPI scores			0.239	0.625
2000/1/2	11 (73.3)	20 (80.0)		
2003/4/5	4 (26.7)	5 (20.0)		
Ann Arbor stage			0.667	0.414
I/II	2 (13.3)	6 (24.0)		
III/IV	13 (86.7)	19 (76.0)		
Posttransfusion				
Bleeding			0.615	0.433
Yes	6 (40.0)	7 (28.0)		
No	9 (60.0)	18 (72.0)		
Infection			0.171	0.68
Yes	7 (46.7)	10 (40.0)		
No	8 (53.3)	15 (60.0)		

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Lower transfusion threshold(n=15)	Higher transfusion threshold (n=25)	c(t)	P*
Fever			0.96	0.327
Yes	9 (60.0)	11 (44.0)		
No	6 (40.0)	14 (56.0)		
Thrombopoietin			1.742	0.187
Yes	13 (86.7)	17 (68)		
No	2 (13.3)	8 (32)		
Chemotherapy			0.296	0.586
CR/PR	13 (86.7)	23 (92.0)		
SD/PD	2 (13.3)	2 (8.0)		
Platelet transfusions per patient	2.05±1.13	1.44±0.77	2.05	0.047*
Days in hospital	34.13±19.71	37.04±27.48	0.357	0.723
The increase platelet count of posttransfusion ($\times 10^9$/L)	17.93±12.31	20.68±11.68	0.696	0.492
Bilirubin (0–22 μmol/L)	18.99±24.79	8.62±4.18	1.606	0.13
Albumin (35–54 g/L)	31.55±3.94	33.40±6.44	1.128	0.267
ALP (34–104 IU/L)	138.93±119.81	107.08±40.38	1.227	0.227
LDH (80–190 IU/L)	342.80±465.96	207.52±144.02	1.094	0.291
CR (60–130 μmol/L)	77.53±31.65	64.28±15.84	1.512	0.148
BUN (3.1–7.4 mmol/L)	4.43±3.44	4.01±1.46	0.543	0.59

Data are reported as number (%) or mean ± SD. Data were analyzed using Pearson's χ^2 test for categorical variables and the *t*-tests for continuous variables. *P<0.05 indicates a statistically significant difference when comparing values at the same measuring points. ALP, alkaline phosphatase; LDH, lactic dehydrogenase; GCB, germinal center b; cell-like; CR, creatinine; BUN, blood urea nitrogen.

Table 5 Risk factors related to CIT in 523 patients: multivariate logistic regression analysis

Variables	SE	OR	95% CI	P
Gender	0.200	1.359	0.535-1.172	0.244
LDH	0.202	8.265	0.376-0.831	0.004*
Ann Arbor stage	0.265	5.064	0.328-0.926	0.024*
Chemotherapy regimens	0.059	59.549	0.563-0.711	<0.001*

Univariate comparisons were performed according to the Log-Rank Test. *P<0.05.

CIT can lead to a dose reduction of chemotherapeutic drugs, cause delays in chemotherapy and bleeding cases, and even endanger the patient's life.

According to the relevant literature, the incidence of CIT among DLBCL patients is 43.4%, and the incidence of isolated thrombocytopenia is 12%. Clinical studies on the incidence of CIT are limited in number, and there are even fewer reports about CIT in specific diseases. As reported in a study on different solid tumors conducted by Ten Berg *et al.*, the CIT incidence of the solid tumor was 21.8%, and the incidence of isolated thrombocytopenia was 6.2% (14). The incidence of CIT and isolated thrombocytopenia among DLBCL patients was about 2 times that of solid tumors. In the case of hematological diseases, 1 report

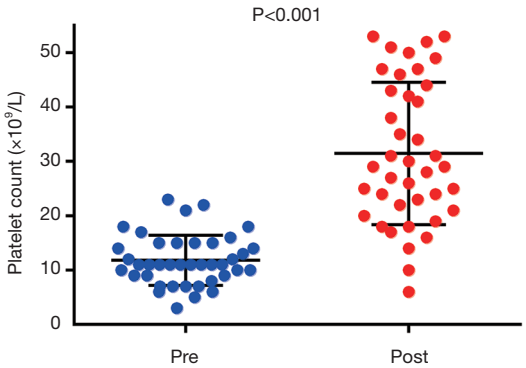

Figure 2 Platelet count before and after platelet transfusion. Horizontal solid bars represent the mean and standard deviation.

on the incidence of thrombocytopenia in myelodysplastic syndromes found an incidence rate of about 40–65%, which is similar to the incidence of CIT in DLBCL patients. It can be seen in *Table 1* that, among CIT patients, the incidence of thrombocytopenia from Grade III to Grade IV was 37.4%. This might be a significant factor in increasing the risk of clinical bleeding (7,15,16).

The incidence and severity of CIT vary according to the type of chemotherapy regimen applied. Our research showed that the thrombocytopenia incidences of the DHAP and the ICE were 92.3% and 89.7%, respectively, and the average platelet count after chemotherapy decreased to $(24.54\pm44.13)\times10^9$/L and $(55.53\pm35.72)\times10^9$/L. Furthermore, the CIT incidences of the GDP regimen and the Gemox regimen were 69.4% and 69.0%, respectively. Clinically, there are few reports on the thrombocytopenia caused by different lymphoma chemotherapy regimens, and the existing studies have largely focused on solid tumors. In 2011, 1 study involving a total of 614 solid tumor patients found that the CIT incidences of therapeutic alliance with carboplatin or gemcitabine were 58.2% and 64.4%, respectively; meanwhile, the therapeutic alliance of gemcitabine + carboplatin and that of gemcitabine + cisplatin had higher CIT incidences of 85.7% and 54.8%, respectively (14). In their research on solid tumor chemotherapy regimens, Wu *et al*. revealed that the incidences of Grade III and Grade IV thrombocytopenia of platinum-based chemotherapy regimens were 6.5% and 4.1%, respectively, while the incidences of thrombocytopenia in gemcitabine-based chemotherapy regimens were 7.8% for the Grade III and 3.4% for Grade IV types. Accordingly, it can be inferred that platinum-based and gemcitabine-based drugs are the ones most likely to cause thrombocytopenia (17). Weycker *et al*. retrospectively examined a cohort comprising adults who received selected myelosuppressive chemotherapy regimens for solid tumors or non-Hodgkin's lymphoma. They found the CIT incidence ranged from 6.1% (5.9–6.3%) for regimens containing cyclophosphamide to 13.5% (12.7–14.3%) for regimens containing gemcitabine (18). In our study, the DHAP, ICE, GDP, and Gemox regimens all contained platinum-based drugs, and the GDP and Gemox regimens contained gemcitabine-based drugs. The BC Cancer Agency pointed out that thrombocytopenia induced by the application of cytarabine chemotherapy was frequent (19) and that the incidence of thrombocytopenia induced by etoposide reached 22–41% (20). The mechanism of thrombocytopenia varies according to therapeutic regimens; for example, alkylating chemotherapeutic drugs mainly affect multipotent stem cells (21,22); cyclophosphamide mainly affects megakaryocyte progenitor cells (23); bortezomib causes thrombocytopenia by inhibiting nuclear transcription factor κB (24), etoposide stimulates platelet apoptosis by reducing the activity of Bcl-x (L) (25), and gemcitabine and mitomycin C induce thrombocytopenia by mediating endothelial cell injuries (26). Ultimately, the fundamental cause of thrombocytopenia induced by chemotherapeutic drugs in normal doses is the underdevelopment of bone marrow megakaryocyte (27). In addition to bone marrow suppression, thrombocytopenia is also partially attributable to immune-mediated factors (14,28). In regards to isolated thrombocytopenia, we acknowledge that it may be caused by the effect of drugs being inhibited by megakaryocytopoiesis, but it may also be a specific clinical manifestation of immune-mediated thrombocytopenia (29,30). In the present study, it was observed that isolated thrombocytopenia was commonly caused by the ACVBP (22.2%), ICE (20.7%), Gemox (20.7%), and GDP (19.4%) chemotherapy regimens. Considering the limited number of specimens in the current research, we recommend a larger-scale study that includes more participants and medical centers are conducted in order to confirm the incidence of isolated thrombocytopenia caused by different chemotherapy regimens and to further establish the existence of immune-mediated thrombocytopenia by measuring drug-related antibodies.

CIT, as predicted in this research, can also be attributable to other risk factors. Therefore, our study also collected patients with clinical characteristics and baseline data before they received chemotherapy in order to determine other risk factors that may affect the incidence of thrombocytopenia. *Table 3* shows that gender (P=0.029),

LDH (P<0.001), IPI score (P=0.015), and Ann Arbor stage (P<0.001) may be factors that can potentially influence the patient's thrombocytopenia after chemotherapy. CIT may be more directly affected by choice of chemotherapy regimen; thus, the validity of the clinical data collected in this research might have been significantly influenced by the chemotherapy regimen type. Therefore, we conducted a multivariate analysis in order to identify other risk factors that may affect CIT by reducing the effects of the chemotherapy regimen. *Table 4* shows that in addition to chemotherapy regimens, LDH (P=0.004) and Ann Arbor stage (P=0.024) were possible risk factors influencing CIT. LDH is a glycolytic enzyme that exists in the cytoplasm of all body tissues. The kidney, in particular, has a higher level of LDH. The level of LDH contained in serum increases in hematological tumors, such as in Hodgkin's lymphoma tumors, NHL, and multiple myeloma, etc. (31). LDH has been identified as a significant risk factor in the IPI (32). An elevated level of LDH in serum suggests a poor prognostic condition, as it is indicative of NHL tumor proliferation activity and tumor burden. Although no correlation between CIT and LDH or Ann Arbor staging has been identified in this research, statistically speaking, increases in serum LDH and Ann Arbor stage III/IV were associated with a higher incidence of thrombocytopenia among DLBCL patients. Kim *et al*. (33) revealed that an increase of serum LDH and a decrease of platelets could increase the risk of bleeding for acute promyelocytic leukemia patients; based on these findings, we conclude that an elevated level of LDH and a reduced level of platelets are closely associated, and these 2 factors are responsible for an increased risk of bleeding. We appeal for the completion of more prospective studies that can provide additional empirical data to analyze further the impact of LDH and Ann Arbor staging on platelets.

It is a common practice that in the course of chemotherapy, patients with lymphoma or other tumors are infused with platelets in order to decrease the risk of bleeding (34,35). The American Association of Blood Banks (AABB) found that 70% of platelet transfusion cases are prophylactic in nature (36). Clinically, the threshold value of platelet transfusion may be different according to the types of the disease, bleeding conditions, and treatment prescriptions. This research retrospectively analyzed the platelet threshold value of DLBCL patients to identify the transfusion threshold value for DLBCL patients in the course of chemotherapy. Among the 227 CIT patients, 40 had been infused with platelets (17.6%). After platelet transfusion, the median level of their platelets reached 29×10^9/L (*Figure 2*), which proved that platelet transfusion had achieved significant results. Due to this ability, platelet transfusion has become an essential means to increase the level of platelets and prevent bleeding. Based on the pre-transfusion platelet threshold values, we divided the 40 patients into two groups: a low-threshold group and a high-threshold group. All 40 patients underwent CVC prior to their chemotherapy. Comparing the basic information of these 40 patients before platelet transfusion, we found that the 2 groups had no significant statistical differences, which indicates that these 2 groups were comparable. According to the analysis of the platelet transfusion data, the 2 groups only differed in the average amount of platelet infusion (the low-threshold group, 2.05±1.13 *vs.* the high-threshold group, 1.44±0.77). Generally, the low-threshold group's platelet infusion was higher than that of the high-threshold group, and the results showed no significant statistical differences in some other aspects. Given this, platelet counts $\leq20\times10^9$/L may be the better choice for DLBCL patients with CVC in the course of chemotherapy. Thrombocytopenia has long been considered a serious complication caused by cancer treatment, but there is currently a lack of consensus on the optimal threshold for platelet transfusion (37-39), Some physicians tend to use the platelet counts $\leq10\times10^9$/L in peripheral blood as a transfusion indicator (40-42), while others set the platelet transfusion threshold as $\leq20\times10^9$/L (43,44). Aside from these, there are also experts who prefer to adopt a higher cutoff value (43,45). Although there is an extensive number of studies aimed at solving the problem of the transfusion threshold, many platelet transfusion problems still have not been solved. Currently, there are 2 relatively large prospective studies on prophylactic platelet transfusions. One is the Investigators in the Trial of Prophylactic Platelets (TOPPS) research (41), and another is a study conducted in Germany (46). Both compared the advantages and disadvantages of prophylactic platelet transfusion (platelet counts $\leq10\times10^9$/L) and therapeutic platelet transfusion, reaching the conclusion that the prophylactic platelet transfusion group needed more platelets, which is consistent with our research findings. Similarly, Estcourt *et al*. compared a large number of empirical studies and also concluded that there were no obvious differences in platelet transfusion between the groups with platelet counts of $\leq10\times10^9$/L and $\leq20\times10^9$/L (34). The 40 platelet transfusion patients in this retrospective research had CVC prior to their chemotherapy. The clinical practice guideline on platelet transfusion released by the formerly known

AABB in 2015 also recommends that the optimal platelet transfusion threshold for patients with CVC be ≤20×10^9/L (47,48), which is consistent with our research results.

Conclusions

Among the DLBCL patients who have received chemotherapy, the incidence of thrombocytopenia reached 43.4%, and severe thrombocytopenia (Grade III and Grade IV) accounted for 37.4% of CIT cases. These results suggest that thrombocytopenia is a common side-effect of chemotherapy for DLBCL patients, which, therefore, warrants more in-depth studies. In the clinical literature, there are quite a few studies examining how lymphoma chemotherapy regimens influence the incidence of thrombocytopenia, and the limited existing empirical studies mainly focus on thrombocytopenia caused by monotherapy. Our study investigated the most frequently used DLBCL chemotherapy regimens, and concluded that the DHAP, ICE, GDP, and Gemox regimens could easily lead to thrombocytopenia. In addition to this, a higher level of LDH and Ann Arbor stage III/IV are also significant risk factors for thrombocytopenia. As such, clinicians should attach great importance to the possible side-effects induced by thrombocytopenia and its risk factors so as to actively prevent and treat relevant symptoms. In terms of DLBCL prophylactic platelet transfusion, we can conclude that PLT ≤20×10^9/L is the most reasonable transfusion pointer for patients with CVC. Finally, since our research is primarily retrospective in nature, the research results may be subject to the influence of clinician's medication experiences, the differences in the number of chemotherapy regimens, the choice of chemotherapy options, etc. Therefore, more prospective clinical research that includes a greater number of medical centers and larger sample sizes is warranted.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.01.64). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethical Committee of Fujian Cancer Hospital (YKT2019-024-01) and informed consent was taken from all individual participants.

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