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Management of adverse effects associated with pegylated *Escherichia coli* asparaginase on coagulation in the treatment of patients with NK/T-cell lymphoma

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Abstract

Natural killer/T-cell lymphoma (NK/TL) is a chemotherapy-sensitive disease, and asparaginase-based chemotherapy has become the standard primary treatment for patients with this malignancy recently. The objective of this study was to evaluate the adverse reactions on blood coagulation of the administered pegylated *Escherichia coli* (*E coli*) asparaginase (PEG-ASP) to the NK/TL patients. Clinical data of 71 NK/TL patients (range 13–73 years), who received 239 cycles of chemotherapy treatment containing PEG-ASP in the Hematology Department of Shanxi Province Cancer Hospital of China from January 2016 to December 2019 were analyzed retrospectively. Data of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FBG), and antithrombinIII (ATIII) were obtained at the time points routinely and statistically analyzed. There were statistical differences between the monitored parameters of baseline day0 (the day before use of PEG-ASP, named day0) and those of day3 (the 3rd day after treatment) to day6, and data showed all of the indicators could recover within 21 days. The events included PT prolonged in 33 patients (46.5%), APPT prolonged in 41 patients (57.7%, 20 patients with APTT >60 seconds), FBG decreased in 49 patients (69.0%, 12 patients with FBG <1 g/L), and ATIII decreased in 52 patients (73.2%). The patients' average number of cycles received was 2.3 for PT (>14 seconds), 2.5 for APTT (>35 seconds), 2.7 for FBG (<2 g/L), and 2.6 for D-dimer (>550 ng/mL). Compared with those at day0, PT and APTT prolonged sharply at day3 ($P < .05$), reached the peak at day12, maintained the prolonged level from day3 to day15, and gradually recovered at day 21. FBG and ATIII significantly decreased at day6 and day3 respectively ($P < .05$), both of them fell to the minimum at day12, and then returned the normal. The D-dimer levels were no significantly change during the whole treatment course. The APTT >60 seconds or FBG <1 g/L side effects were improved by symptomatic treatment of supplementation of fresh frozen plasma or cryoprecipitate infusion, no concomitant bleeding or thrombotic events emerging. Our data suggested although chemotherapy including PEG-ASP impacted moderately on the coagulation function of NK/TL patients, clinically monitored regularly were necessary and most NK/TL patients can complete the chemotherapy cycles successfully.

Abbreviations: ALL = acute lymphoblastic leukemia, APTT = activated partial thromboplastin time, AspaMetDex = L-ASP, methotrexate, and dexamethasone, ATIII = antithrombinIII, *E. coli* = *Escherichia coli*, FBG = fibrinogen, L-ASP = L-asparaginase, NCCN = National Comprehensive Cancer Network, NK/TL = natural killer/T-cell lymphoma, OS = overall survival, PEG-ASP = pegylated *Escherichia coli* asparaginase, PT = prothrombin time, VTE = venous thromboembolism.

Keywords: coagulation function, natural killer/T-cell lymphoma, pegylated *Escherichia coli* asparaginase

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1. Introduction

Natural killer/T-cell lymphoma (NK/TL) is a distinct clinicopathologic subtype of non-Hodgkin lymphoma with an aggressive clinical course. Although rare in the world, NK/TL presents a remarkable geographical prevalence in Asia and South America.[1,2] Compared with B cell lymphoma, NK/TL has a poor prognosis rate, the reported 5-year overall survival (OS) and progression-free survival rate was 60% and 73% for stage I/II patients,[3] and the 1-year OS and progression-free survival rate for stage IV or relapsed/refractory patients was poor, which were 55% and 53% respectively.[4] Long-term use of multiagent chemotherapy is the mainstay treatment to the NK/TL patients, however, it is likely as there are high concentrations of P-glycoprotein within NK/TL cells, which results in the tumor cells have multidrug resistance, and >60% of patients with conventional cyclophosphamide and doxorubicin and vincristine and prednisone-based chemotherapy regimens relapsed.[5]

During the past decade, several novel chemotherapy regimens based around L-asparaginase (L-ASP) have emerged, such as gemcitabine, L-ASP, and oxaliplatin,[6,7] dexamethasone, methotrexate, ifosfamide, L-ASP, and etoposide,[4,8] and L-ASP, methotrexate, and dexamethasone.[9] L-ASP is an important agent in the therapy of acute lymphoblastic leukemia (ALL) for approximately 50 years.[10] Asparaginase can enzymatically cleave asparagine into aspartic acid and ammonia. Depletion of asparagine in blood results in inhibition of protein-synthesis, DNA-synthesis, and RNA-synthesis, especially in some tumor cells, for example, leukemic and lymphomatous blasts, which are not able to synthesize asparagine, thus undergoing apoptosis. However, normal cells are capable of synthesizing asparagine and are less affected by its rapid depletion during treatment with the enzyme L-ASP.[11,12] Due to the special mechanism of L-ASP, its anticancer effect cannot be affected by multidrug resistance. Several clinical data showed chemotherapy regimens cornerstoned by L-ASP for NK/TL have obtained 55.6% complete response (CR), and 66.9% 5-year OS rates.[13–16] In 2010, L-ASP was recommended as the first-line therapy for NK/TL by National Comprehensive Cancer Network (NCCN). Although this *Escherichia coli* (*E. coli*) derived enzyme has been used as front-line therapy for so many years, it is associated with notable side-effects. The toxicities of L-ASP include 2 main categories, one related to immune sensitization to an exogenous protein which resulted in a poorer outcome due to the inactivation of asparaginase by antibodies; another related to the inhibition of protein synthesis.[11,12,17–22] Once the patients treated with L-ASP, less protein is synthesized in the liver cell, for example, the blood coagulant and anticoagulant proteins associated with coagulation and fibrinolytic system, thus the balance between coagulation and the fibrinolytic system is broken. The body responds by a series of blood coagulation and fibrinolytic changes to regain balance. This suggests that there may be a global inhibition of the production of both coagulant and anticoagulant proteins in the liver.[23,24]

In China today, there are 2 preparations of asparaginase commonly for treating NK/TL: native *E coli* L-ASP and pegylated *E coli* asparaginase (PEG-ASP). PEG-ASP is a form of *E coli* L-ASP covalently linked to polyethylene glycol, to decrease the immunogenicity of the enzyme and could prolong its half-life about 5 times.[21,25] Thus that allows one injection of PEG-ASP to replace multiple injections of native *E coli* L-ASP. In 2013, PEG-ASP has been granted approval by the National Comprehensive Cancer Network (NCCN)[26] as a first-line drug for the treatment of NK/TL. Mounting evidence showed PEG-ASP has a good therapeutic effect against NK/TL in recent clinical trials.[27–29]

Similar to L-ASP, early after PEG-ASP has been a standard component of ALL and lymphoma regimens, this drug was noted mainly to have a very common adverse effect on laboratory coagulation parameters. According to papers, the incidence of grades 3 and 4 coagulopathy ranged 2% to 18% during the treatment of ALL with PEG-ASP.[30,31] The risk of grades >3 thrombosis reportedly was 4% to 9%[11,31] and central nervous system thrombosis was 3% for the first-line treatment of childhood acute lymphoblastic leukemia.[11] Although PEG-ASP associated coagulation system complications are well described in ALL patients treated with PEG-ASP, there are few reports to discuss the adverse effect of the PEG-ASP on the coagulation function during the treatment in NK/TL. In 2016, Zhang et al[27] showed the newly diagnosed advanced-stage NK/TL patients treated with PEG-ASP regimen had activated partial thromboplastin time (APTT) elongation in 50% of patients and hypofibrinogenemia in 58.3% of patients. In 2018, the report[32] had observed 45.5% fibrinogen (FBG) reduction, 57.6% APTT prolonged, and 27.3% prothrombin time (PT) prolonged in the chemotherapy for lymphoma, there were 3% thrombosis and no hemorrhage within the study. This retrospective study aimed to summarize the adverse effects of PEG-ASP on coagulation and the management experience.

2. Patients and methods

2.1. Patients

Seventy one patients received and 239 treatments of PEG-ASP used at the Department of Hematology, Shanxi Province Cancer Hospital of China from January 2016 to December 2019 included in this retrospective study, which under the approval of Human Research Ethics Committee of the hospital. The clinical characteristics of these cases are presented in Table 1. Inclusion criteria were as follows: histological diagnosed as NK/TL, based on WHO classification of tumors of hematopoietic and lymphoid tissues; not treated with chemotherapy or radiotherapy previously; no contraindication for use of chemotherapy drugs: hemoglobin ≥90 g/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet $\geq 100 \times 10^9$/L, alanine and aspartate aminotransferase ≤120 μ/L, serum bilirubin ≤20 mg/L, serum creatinine ≤133 μ mol/L, serum albumin ≥30 g/L; no other severe illness, the cardiopulmonary function is normal; no other relative treatments including the Chinese herbal medicine, immunization therapy, and biotherapy; all of the patients were enrolled in this study with informed consent. Pregnant and lactating women, psychopaths were excluded.

2.2. Methods

Eligible patients were assigned by the study from the Department of Hematology, Shanxi Province Cancer Hospital of China to treatment with the 6 chemotherapy regimens containing PEG-ASP (Table 1). Two thousand five hundred International Units of PEG-ASP per square meter on the first day (day1) of each cycle, which was administered intramuscularly by 3 injection sites. Cycles were repeated on medical advice. Blood specimens for coagulation testing were obtained day0, day3, day6, day9, day12, day15, day21 after PEG-ASP injected intramuscularly

Table 1

Clinical characteristics of total 71 patients.

Patient characteristic	No.
Median age (range), yrs	44 (13–73)
Sex, n (%)	
Male	52 (73.2)
Female	19 (26.8)
Subtype of NK/TL, n (%)	
UAT-NTCL	65 (91.5)
NUAT-NTCL	6 (8.5)
Ann Arbor stage, n (%)	
I	13 (18.3)
II	31 (43.7)
III	11 (15.5)
IV	16 (22.5)
Cycles, n (%)	
1	13 (18.3)
2	18 (25.4)
3	7 (9.9)
4	14 (19.7)
5	11 (15.5)
6	4 (5.6)
7	1 (1.4)
8	0 (0)
9	3 (4.2)
Chemotherapy regimen, case (%)	
P-GEMOX	111 (46.5)
SMILE	66 (27.6)
L-GDP	22 (9.2)
AspaMetDex	21 (8.8)
L-CTOP	13 (5.4)
DDGP	6 (2.5)

AspaMetDex = PEG-ASP, methotrexate and dexamethasone; DDGP = cisplatin, dexamethasone, gemcitabine, and PEG-ASP; L-CTOP = PEG-ASP, cyclophosphamide, pirarubicin, vincristine and prednisone; L-GDP = PEG-ASP, gemcitabine, cisplatin, prednisone; NUAT-NTCL = extra-upper aerodigestive tract NK/T-cell lymphoma; P-GEMOX = gemcitabine, oxaliplatin and PEG-ASP; SMILE = dexamethasone methotrexate, ifosfamide, PEG-ASP, and etoposide; UAT-NTCL = upper aerodigestive tract NK/T-cell lymphoma.

respectively. Patients were routinely monitored for blood tests at each cycle. A low-fat diet was consumed during the period of chemotherapy. The results are depicted as median and range. Lab parameters to assess coagulation function included the PT (10–14 seconds), APTT (23–35 seconds), FBG (2–4 g/L), Antithrombin III (ATIII, 80–135%), and D-dimer (0–550 ng/mL). When APTT was >60 seconds or FBG was <1.0 g/L, fresh frozen plasma or cryoprecipitate was administered until the indexes recovered. Twenty one (29.5%) patients received fresh frozen plasma only which can be recovered the parameters, and five (7.0%) required fresh frozen plasma and cryoprecipitate infusion. Data on these cases did not enroll in the study.

2.3. Statistical analysis

All data were evaluated using Social Sciences (SPSS) version 22.0 (SPSS Inc, IL, USA). $P < .05$ was considered statistically significant. The results of the change of PT, APTT, FBG, ATIII, D-dimer were depicted as median and range. The sequential coagulation measurements between day0 and day3, day3 and day6, day6 and day9, day9 and day12, day12 and day15, day15 and day21 were compared respectively by use of the Mann–Whitney *U* test.

3. Results

3.1. Patient characteristics

From January 2016 to December 2019, a total of 71 Chinese patients treated with 6 chemotherapy regimens containing PEG-ASP were registered to our cohorts. Histologic diagnoses of all patients were confirmed as NK/TL by the pathologists of Shanxi Province Cancer Hospital. The baseline characteristics of the patients are listed in Table 1. The patients included 52 men and 19 women aged 13 to 74 years (median, 44 years). At diagnosis 65 patients (91.5%) had upper aerodigestive tract NK/T-cell lymphoma and 6 (8.5%) had extra-upper aerodigestive tract NK/T-cell lymphoma. Forty four patients (62%) were diagnosed with stage I or stage II disease, 11 patients (15.5%) were diagnosed with stage III disease, and 16 patients (22.5%) were diagnosed with stage IV disease. No patients had central nervous system involvement or bone marrow invasion. The average Karnofsky performance status score was 79.4 ± 4.1. The total cycles of the regimen received by all patients were 239, with a median of 3 cycles (range, 1–9 cycles). The coagulation function was estimated in all the 71 patients who received the scheduled treatment (in Table 2). Eight patients (11.2%) completed ≥6 cycles of chemotherapy. Eleven patients (15.5%) received 5 cycles of the regimen. Fourteen (19.7%) patients received 4 cycles. There were 31 (43.7%) patients followed by radiotherapy as sequential therapy after 1 or 2 cycles of chemotherapy. No serious adverse events on coagulation function in the whole chemotherapy course. Table 2 presents the coagulation parameters of the total 239 cases observed during the PEG-ASP-containing phases of chemotherapy. Overall, the adverse events of PEG-ASP were tolerable in the group. Of the 71 patients with

Table 2

The change of PT, APTT, FBG, ATIII, and D-dimer of the patients (median, range).

Time	PT, s	*P*	APTT, s	*P*	FBG, g/L	*P*	ATIII (%)	*P*	D-dimer, ng/mL	*P*
day0	11.7 (9.2, 16.7)	–	30.8 (22.1, 48.8)	–	2.8 (1.6, 5.7)	–	88.0 (54.0, 114.0)	–	295 (0, 1690)	–
day3	12.8 (9.5, 16.9)	.000	33.1 (21.7, 57.7)	.000	2.7 (0.8, 6.6)	.074	76.2 (37.4, 130.0)	.000	290 (0, 1990)	.527
day6	12.3 (9.5, 20.3)	.971	34.5 (21.7, 74.9)	.003	2.6 (0.6, 5.4)	.011	73.0 (30.2, 118.0)	.006	310 (20, 1990)	.412
day9	12.5 (9.5, 22.4)	.323	35.9 (21.7, 74.9)	.453	2.5 (0.5, 5.4)	.307	71.4 (30.8, 118.0)	.150	310 (20, 1990)	.535
day12	12.6 (9.5, 20.3)	.908	36.4 (21.7, 89.2)	.719	2.5 (0.5, 5.4)	.380	70.0 (25.2, 117.5)	.837	310 (20, 1970)	.478
day15	12.5 (9.5, 20.3)	.588	35.5 (21.8, 65.4)	.155	2.5 (0.6, 5.2)	.283	75.0 (33.8, 117.5)	.147	310 (119, 1970)	.665
day21	11.6 (9.2, 17.9)	.000	29.4 (23.0, 50.3)	.000	2.5 (1.2, 7.6)	.005	83.6 (38.6, 119.4)	.000	360 (92, 2030)	.940

The *P* values was obtained by analyzing the result at day0 and day3, day3 and day6, day6 and day9, day9 and day12, day12 and day15, day15 and day21 with the Mann–Whitney *U* test. APTT = activated partial thromboplastin time, ATIII = antithrombinIII, day0 = before the treatment of PEG-ASP, day12 = the 12 day after the treatment of PEG-ASP, day15 = the 15th day after the treatment of PEG-ASP, day21 = the 21th day after the treatment of PEG-ASP, day3 = the 3th day after the treatment of PEG-ASP, day6 = the 6th day after the treatment of PEG-ASP, day9 = the 9 day after the treatment of PEG-ASP, FBG = fibrinoge, PT = prothrombin time.

239 times of PEG-ASP used enrolled in the study, 6 chemotherapy regimens was administrated, including 111 cases (46.5%) with gemcitabine, oxaliplatin and PEG-ASP (P-GEMOX), 66 cases (27.6%) with dexamethasone, methotrexate, ifosfamide, L-ASP, and etoposide, 22 cases (9.2%) with L-GDP, 21 cases (8.8%) with L-ASP, methotrexate, and dexamethasone, 13 cases (5.4%) with L-CTOP, and the 6 cases (2.5%) with cisplatin, dexamethasone, gemcitabine, and PEG-ASP.

3.2. Coagulation dysfunction

The major coagulation dysfunctions of our patients were the elongation of PT (12.6 [9.5, 20.3]) in 33 patients (46.5%) and APTT (36.4 [21.7, 89.2]) in 41 patients (57.7%), within which 20 patients APTT >60 seconds, the decreased FBG (2.5 [0.6, 5.2]) in 49 patients (69.0%), within which 12 patients FBG <1 g/L, and ATIII (70.0 [25.2, 117.5]) in 52 patients (73.2%) (Tables 2 and 3). In this study, the mean number of cycles administered was 2.3 for PT (>14 seconds), 2.5 for APTT (>35 seconds), 2.7 for FBG (<2 g/L), and 2.6 for D-dimer (>550 ng/mL). Compared with those at day0, PT and APTT prolonged sharply at day3 ($P < .05$), reached the peak at day12, maintained the prolonged level from day3 to day15, and gradually recovered at day 21. FBG and ATIII significantly decreased at day6 and day3 respectively ($P < .05$), both of them fell to the minimum at day12, and then returned to normal. The D-dimer levels were no significantly change during the whole treatment course. It is clear that the median of PT, APTT, and FBG fluctuated in the normal range, and the duration of the adverse reactions was about 15 days. It is worth noting that these parameters roughly began to recover at day12 (Fig. 1), which may be related to the bioactivity and half-life period of PEG-ASP in patients. And in the present study, no bleeding event was observed. It was interesting that the ATIII of the day0 of our patients was on the ground of the normal range, and it was considerably lower at day3–15 (Fig. 1D). However, among the ATIII decreased population there were 76.9% (40/52) patients that the corresponding D-dimer were normal (0–550 ng/mL). The above adverse reactions were improved by symptomatic treatment of supplementation of fresh frozen plasma and/or cryoprecipitate infusion, with no concomitant thrombotic events emerging.

Table 3

Incidence of coagulation abnormalities and number of cycles received in 71 patients.

Coagulation testing, n (%)	Incidence (%)	Number of cycles received (mean, SD)
PT (>14 s)	46.5% (33/71)	2.3 (1.4)
APTT (>35 s)	57.7% (41/71)	2.5 (1.7)
APTT (>60 s)	9.9% (7/71)	2.7 (1.8)
FBG (<2 g/L)	69.0% (49/71)	2.7 (1.8)
FBG (<1 g/L)	16.9% (12/71)	2.8 (1.6)
ATIII (<80%)	73.2% (52/71)	2.5 (1.6)
D-dimer (>550 ng/mL)	18.3% (13/71)	2.6 (1.8)

APTT = activated partial thromboplastin time, ATIII = antithrombinIII, FBG = fibrinogen, PT = prothrombin time.

Table 4 is the information of representative patients with APTT >60 seconds and/or FBG <1 g/L received a blood transfusion or cryoprecipitate therapy administrated. The median administration time was 8 days (range, 2–17 days), the average blood transfusion volume was 1400 ± 1000 mL, the average cryoprecipitate infusion volume was 2.8 ± 1.1 International Units, and the median recovery time was 12 days (range, 3–19 days).

4. Discussion

As the pegylated form of L-ASP, PEG-ASP has similar enzymatic properties of L-ASP and is associated with a lower incidence of induction of anti-asparaginase antibodies and exhibits more prolonged asparaginase activity than native asparaginase. In recent years some reports showed that L-ASP, a commonly used agent for ALL, is effective against NK/TL. Now, PEG-ASP has

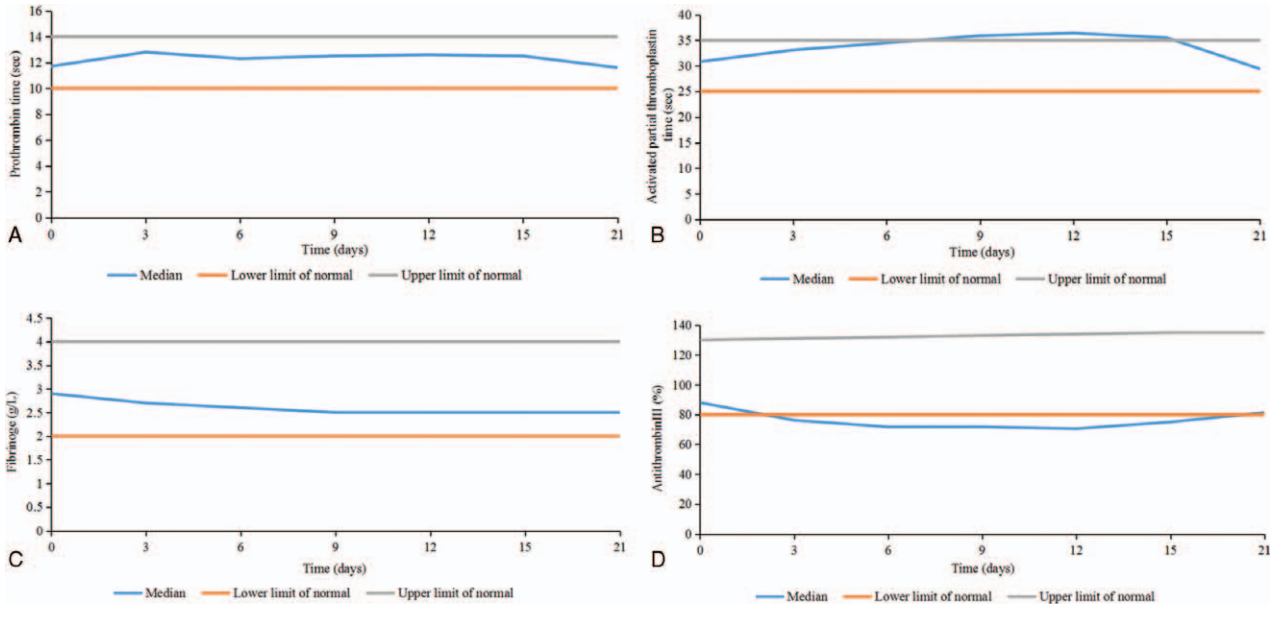

Figure 1. The major coagulation dysfunctions of our patients. The median of prothrombin time, PT (A); activated partial thromboplastin time, APTT (B); fibrinoge, FBG (C), and antithrombinIII (D) fluctuated in the range.

Table 4

The characteristics of the representative patients with APTT >60 seconds or FBG <1 g/L side effects.

No.	Gender	Age	Ann Arbor Stage	Cycles	Post-treatment day	Total plasma (mL) injected	Total cryoprecipitate (International Unit) injected
1	M	67	II	4	9–15	3600	4
2	M	63	II	4	9–18	3600	4
3	M	67	IV	9	8–12	3200	2
4	M	42	II	4	12–14	3200	2
5	M	51	II	4	9–12	3200	2
6	M	44	IV	6	2–10	2800	-
7	M	17	III	5	5–13	2800	-
8	M	48	I	4	8–16	2400	-
9	M	17	II	6	7–16	2000	-
10	M	35	IV	5	12–14	1600	-
11	M	15	II	9	5–12	1600	-
12	M	48	II	2	8–16	1600	-
13	F	29	I	4	10–12	1200	-
14	M	54	I	4	11–16	1200	-
15	F	31	III	2	7–13	1000	-
16	F	56	IV	3	5–12	800	-
17	M	36	IV	5	5–8	800	-
18	M	21	III	5	17	400	-
19	M	63	IV	1	12	400	-

APTT = activated partial thromboplastin time, F = female, FBG = fibrinogen, M = male.

been granted approval by NCCN as a backbone chemotherapeutic agent in NK/TL. Similar to L-ASP, early after PEG-ASP has been a standard component of ALL and lymphoma regimens, this drug was commonly noted to have adverse effects on laboratory coagulation parameters. Several studies have demonstrated that low levels of coagulation factors and prothrombotic factors are common, the deficiencies of ATIII and FBG are also well described. The reported laboratory coagulation parameters have included alterations in the PT, APTT, FBG, and ATIII. As the first-line treatment of ALL, the incidence of grade 3 and 4 coagulopathy adverse reactions (prolonged PT or APTT; or hypofibrinogenemia) was 2%[30] and 18%,[31] and that of thrombosis grades >3 was 8%[11] and 9%[31] respectively in the treatment of children with newly diagnosed standard-risk ALL and high-risk, Philadelphia chromosome-negative ALL. Liang et al[18] presented the coagulation dysfunction during PEG-ASP containing chemotherapy with newly diagnosed ALL, of which the bleeding event was 4%, the beginning and the prolonged duration of coagulation dysfunction was 3.5 and 9.8 days respectively. With this study, the laboratory coagulation parameters of the PEG-ASP on the coagulation function of the NK/TL patients PT, APTT, FBG, and ATIII were monitored routinely. A statistically significant variation in the PT, APTT, and FBG was noted in our data, 46.5% (33/71) patients PT and 57.7% (41/71) patients APTT prolonged, 69.0% (49/71) patients FBG decreased. In our hematonosis therapeutic center, the patients received new frozen plasma and cryoprecipitate in the state of prolonged APTT (>60 seconds, 9.9% [7/71] patients) and/or hypofibrinogenemia (FBG was <1.0 g/L, 16.9% [12/71] patients). The main intervention was to supplement fresh frozen plasma. If the parameters did not recover, then cryoprecipitate was infused during the study period. 29.5% (21/71) patients received the prevention therapy during the study period. There was no thrombus or bleeding event in our observation. Results showed that the median levels of PT, APTT, and FBG noted are normal or nearly so, and do not reach values usually associated with clinical bleeding.

The most striking effect of PEG-ASP on hemostasis in our study was the significant reduction in levels of ATIII, which can be explained by a global reduction in hepatic protein synthesis induced by this drug. There were 73.2% (52/71) patients with ATIII deficiency occurred in our cohort. It was interesting that among the ATIII decreased population there were 76.9% patients that the corresponding D-dimer were normal. According to the Guidelines on prevention and treatment of tumor-associated venous thromboembolism (VTE),[34,35] that means these patients do not need thromboprophylaxis. As to the other 23.1% patients of this group whose D-dimer was increased, on the other side, the increase of D-dimer can be resulted from many clinical factors and clinical complications, for example, dizziness, sense of suppression in the chest, acroanesthesia, and wind-stroke syndrome, which need monitoring timely.

As we knew, L-ASP or PEG-ASP associated thrombotic complications are well documented in Western populations, especially in ALL patients treated with L-ASP or PEG-ASP, but there are few reports about the incidence of VTE in Asian populations during treatment of L-ASP or PEG-ASP in lymphoid malignancies. In general, Asians are known to have a markedly lower incidence of VTE than Western populations.[36] As lymphoma treated with the PEG-ASP regimen, the most adverse reactions were grade I–II. In the Zhang study,[26] the newly diagnosed advanced-stage NK/TL patients treated with cisplatin, dexamethasone, gemcitabine, and PEG-ASP regimen had APTT elongation in 50% and hypofibrinogenemia in 58.3%. Zheng et al[27] observed prolonged APTT in 57.6% of patients, prolonged PT in 27.3%, FBG reduction in 45.5%, and thrombosis in 3%. Cong et al[32] observed that within 129 patients with lymphoid malignancies received 443 times of PEG-ASP used, the coagulation dysfunction included prolonged APTT in 61 cases (47.3%), prolonged PT in 22 (17.1%), prolonged thrombin time in 15 (11.6%), and hypofibrinogen in 75 (58.1%). There was no patients who died of coagulation dysfunction, any associated clinical occurrence of mucocutaneous, or visceral hemorrhage to the best of our knowledge.

It is noteworthy that papers showed NK/TL patients were at lower risk of bleeding or thrombotic complications following PEG-ASP treatment than ALL and other lymphoma patients. We think there are several reasons for this.

It is known that PEG-ASP could kill lymphoblasts or leukemic cells selectively due to the depletion of plasma asparagine. During the PEG-ASP therapy course of ALL patients or lymphoblasts lymphoma patients, lymphoblasts or leukemic cells can be cleared quickly, which may affect the procoagulant activity and thus lead to bleeding and lymphatic system disarray.[31,33,37] The most common serious coagulopathy adverse events due to PEG-ASP treatment were thrombosis (4% in ALL of the Western population),[16] but data on L-ASP/PEG-ASP associated VTE in Asian lymphoma are scarce, there was no depicted report on thrombus in NK/TL in China to the best of our knowledge. Besides the differences from genome background of patients and the disease mechanisms, the administration dose and frequency decided the bioavailability and half-life of PEG-ASP, reports[38] said the bioavailability increased from 82% in single administration to 98% in repeated administration, and the half-life prolonged from 7.1 ± 4.7 days in single administration to 12.1 ± 6.8 days in repeated administration. The recommended dose of PEG-ASP for ALL patients ages $\leq$21 years and $>$21 years is 2500 and 2000 International Units/m^2 every 14 days, respectively, but that for NK/TL patients is 2500 International Units/m^2 every 21 days. So, the administration frequency is decreased obviously in NK/TL than that in ALL, leading to a decrease in the level of bioavailability and short the half-life of PEG-ASP in NK/TL, increasing the rate of PEG-ASP metabolism, decreasing the serum PEG-ASP concentration, thus the rate of the adverse reactions was reduced.

Several limitations of this study need to be discussed. Firstly, the number of NK/TL patients included in the present study was relatively small, so the conclusion remains to be confirmed in larger, multiple-center trials. Secondly, the Chinese independent generic drug of PEG-ASP was approved by China Food and Drug Administration for listing until 2009, which was a short time in the market and lack of large-scale therapeutic experiences, especially in NK/TL. Therefore, caution is needed when comparing our data to other studies.

In conclusion, this retrospective study demonstrated that PEG-ASP-containing chemotherapy is a well-tolerated treatment for patients with NK/TL. And careful patient monitoring is needed. It is suggested that our findings need to be further investigated with a larger patient group and a longer follow-up period. At present, our study is still recruiting to evaluate its efficiency and safety.

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Author contributions

Jing Yang and Xiangyun Guo conceived and designed the study and drafted the manuscript. Zhiying Hao and Liping Su edited the manuscript and were involved in the conception of the study. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work is appropriately investigated and resolved.

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