Thrombotic Complications During Induction Chemotherapy of Acute Childhood Lymphoblastic Leukemia

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Abstract

The incidence of thrombosis during induction chemotherapy of acute childhood lymphoblastic leukemia (ALL) patients was 6 found to be in 105 (5.7%). There were 4 cerebral infarctions, 1 superior vena cava (SVC) obstruction and 1 deep vein thrombosis. Among these, 2 of them died. A prospective study was further conducted of the change in coagulation and anticoagulation factors during 6 weeks of induction chemotherapy. It was found that the activated partial thromboplastin time (aPTT) was within normal range in all cases throughout 6 weeks, while prothrombin time (PT) and thrombin time (TT) were slightly prolonged, especially during the first 3 weeks of this phase. The natural anticoagulant panels which included protein C (PC), protein S (PS) and antithrombin III (AT III) and also fibrinogen level, were lower during the first 3 weeks and reached its nadir during the second and third week. The lower level of natural anticoagulants might be an important predisposing factor for the occurrence of thrombosis in these patients.

Key word : Thrombosis, Induction Chemotherapy, Acute Childhood Lymphoblastic Leukemia

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Many conditions complicate the treatment outcome of acute lymphoblastic leukemia (ALL) patients, which usually occur in the induction phase of chemotherapy. This phase comprised of combination a chemotherapeutic agents, including vincristine, prednisolone, adriamycin and L-asparaginase. Most complications were infection, organ dysfunction (either kidney, liver, pancreas) and also throm-

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bosis (both intracranial and extracranial site). Many factors contributed to the occurrence of complicating are either the disease condition itself, chemotherapeutic effects or underlying hereditary defects(1).

The causal role of cancer and thrombosis is widely accepted, but the pathogenic mechanisms are poorly understood and are difficult to investigate because of the multiple confounding factors that are involved. Alterations in coagulation factors, anticoagulant proteins and endothelial damage have all been shown to occur following cytotoxic agents(2). The best-studied drugs with definite hypercoagulable effects are L-asparaginase and tamoxifen. L-asparaginase can cause deficiencies of plasma hemostatic proteins, especially antithrombin, plasminogen and fibrinogen(3), resulting in associated risk for thrombosis and hemorrhage(4). The majority of hemostatic complications (90%) occurred during the induction phase, in particular during the period which included simultaneous administration of glucocorticoids and L-asparaginase(5).

Objectives of the study

To find the incidence of thrombosis during induction chemotherapy of ALL patients and also to study the change of coagulation and anticoagulation factors during this phase, and whether the imbalance of both factors is related to the occurrence of thrombosis.

MATERIAL AND METHOD

To study the incidence of thrombosis, retrospective review of all ALL patients who attended the Hematology-Oncology clinic, Department of Pediatrics from 1996 to 1999 was done. Data sources were hematological files and in-patient record charts.

To study the change of coagulation and anticoagulation factors during induction chemotherapy, a prospective study was conducted on 105 ALL patients and 11 newly diagnosed ALL patients were enrolled in the study. Their blood was collected pretreatment and then serially every week thereafter during the 6 weeks course of induction chemotherapy.

Their blood was tested for complete blood count, coagulogram, natural inhibitors (protein C, free protein S antigen, antithrombin III level), and fibrinogen level.

Induction chemotherapy was a combination of 4 drugs, prednisolone 40 mg/m^2/day orally for 4 weeks and subsequently 50 per cent decrease for another 2 weeks, Vincristine 1.5 mg/m^2 intravenously every week, adriamycin 25 mg/m^2 intravenously every week, L-asparaginase 500-700 u/kg/day in NSS 500 ml intravenously for 10 days (starting on day 10), and methotrexate 15 mg/m^2 intrathecally 3 times (day 14, 21, 28).

RESULTS

During the study period, there were 105 newly diagnosed ALL patients enrolled, 63 (66.2%) were males and 37 (38.8%) were females. Their ages were between 1 month to 12 years, with the mean of 5 years and 9 months. They were classified morphologically according to FAB classification as L1 69.4 per cent, L2 27.6 per cent and L3 3 per cent. After the 6-week-course of induction period, the remission rate was 91.8 per cent.

There were also 95 episodes of complications in this phase. 7 of them died (6.67%), and thrombosis was the leading cause of death among 2 of them.

Table 1. Initial hematologic study of 6 ALL patients with thrombotic complications.

Patient	Age	Sex	Cell-type	Immnunophenotype	Initial CBC			
					Hct %	WC (/mm^3)	Blast %	Plt. (/mm^3)
1	11 yr. 9 mo.	M	L2	T-cell	18.5	117,300	89	124,000
2	3 yr.	M	L1	Early pre B	17	32,800	78	41,000
3	8 yr. 3mo.	M	L2	Early pre B	12.9	11,400	56	96,000
4	4 yr.	F	L1	Early pre B	19.5	88,400	95	53,000
5	3 yr. 9 mo.	M	L1	Early pre B	36.6	7,500	81	208,000
6	4 yr.	F	L1	Early pre B	26	74,000	91	19,000
means	5 yr. ± 9 mo.	-	-	-	21.7	55,233	81	90,166

CBC = complete blood count, WC = white cell, PLT = platelet

Most of the complications (82.3%) were infectious complications (febrile neutropenia 65.6%, bacterial sepsis 10.4%, and fungal infection 6.3%), tumor lysis syndrome 4.2 per cent, organ dysfunction 6.2 per cent (acute pancreatitis 4.2%, liver impairment 1.1%, hyperglycemia 1.1%), and thrombosis 6.2 per cent (cerebral infarction 4.2%, SVC obstruction 1% and deep vein thrombosis 1%)

Emphasizing on 6 patients who had thrombotic complications, there were 4 males and 2 females, aged between 3 to 11 years and 9 months. They were 4 L1 and 2 L2 cell type by morphological classification. By immunophenotypic study, nearly all of them were early pre-B cell, only 1 was T-cell. Half of them had an initial white cell count above 50,000/mm^3 (Table 1).

Their complications included 4 cerebral infarction, 1 superior vena cava (SVC) obstruction and 1 deep vein thrombosis of the left leg. These events occurred during the third through the sixth week of induction phase. It occurred on initiation of chemotherapy or an average of 11 days post L-asparaginase infusion (5-19 Days). Among these, 2 of them died (death rate from thrombosis was 1.9% among all patients), 4 of them recovered with vigorous fresh frozen plasma infusion and anticoagulant therapy. Interestingly, 5 of them had concurrent infections, including 4 febrile neutropenia and 1 septicemia and all of them were found to have a lower level of natural anticoagulants, at least 2 of these 3 factors. The other predisposing factors identified were retained intravenous catheter and hypotensive state (Table 2), (Table 3).

The effect of chemotherapeutic agents, especially L-asparaginase, on was lowering hepatic production of natural anticoagulant (protein C, protein S and antithrombin III) was thought to be the significant predisposing factors. Therefore, 11 newly diagnosed ALL patients were enrolled into the prospective study. They were 9 males and 2 females. Their mean age was 5 years and 8 months (range 1 year 8 months - 12 years). There were 8 (72.7%) with L1 and 3 (27.3) with L2 cell type. The immunophenotypic study revealed 9 (81.8%) early pre-B cell and 2 (18.2%) having T-cell. Five of them had an initial white count higher than 50,000/mm^3, but none had hyperleukocytosis at the time of thrombotic complications (Table 4).

Serial coagulogram studies revealed no significant changes of all aPTT, PT and TT means.

Table 2. Hematologic and hemostatic study of 6 ALL patients with thrombotic complications at the time of occurrence.

Patient	Post-Chemotherapy (day)	Post L-asp (day)	CBC			Coagulogram			Natural inhibitor		
			Hct %	WC (/mm^3)	Plt (/mm^3)	aPTT (sec)	PT (sec)	TT (sec)	Protein C %	Protein S %	AT-III %
1	34	19	33	1,600	111,000	39	14.7	-	66	<10	43
2	23	8	25.5	3,500	202,000	29.6	11.4	-	90	78	85
3	40	5	22	900	80,000	43	14.6	12.2	49	85	47
4	19	13	24.8	400	15,000	-	-	-	47	58	51
5	9	9	22.4	6,400	125,000	45.8	15.1	16.1	25	22.23	456
6	18	12	18.7	1,340	35,000	43	11.8	-	31.5	75	42

Note : normal range aPTT 33.5-48.5 sec Protein C 60–125%
PT 12.5-15.9 sec Protein S 60–125%
TT 11.2-15.5 sec Antithrombin-III 80–130%

Table 3. Risk factor, treatment and outcome of 6 ALL patients with thrombotic complications.

Patient	Event	Symptoms			Predisposing factors	Diagnostic studies	Therapy	Outcome
		First symptom	Other symptoms	Other complications				
1	Cerebral Infarction	Generalized Tonic clonic Seizure	Confusion, Rt.hemiparesis Aphasia	Dilated cardiomyopathy Nephrotic nephritis	• Febrile neutropenia Low PS, • AT-III	CT: Hypodensity lesion at Lt. Frontal and Rt. Occipital area	Dexamethasone FFP, Dilantin	Complete clinical recovery
2	Deep vein Thrombosis Lt. Leg	Edema of Lt. Leg	Tender at Lt. leg		Retained catheter	Doppler U/S: Lt. Femoral v. thrombosis	Heparin then Coumadin	• Complete clinical recovery • Doppler U/S: no thrombosis (49 day)
3	Cerebral Infarction	Focal seizure		Thrombocytopenia	• Febrile neutropenia Low PC, • AT-III	CT: mild brain edema	Dexamethazone FFP, Dilantin	Complete clinical recovery
4	Cerebral Infarction with hemorrhage	Generalized Tonic-clonic Seizure		Thrombocytopenia	• Febrile neutropenia • Low PC, PS, AT-III	CT:hemorrage at Lt. Basal genglia & occipital area	Dexamethazone Pltl, FFP Dilantin	Expired (34 hrs)
5	SVC obstruction	Edema of Face	Lethargy, Agitation		• Hypovolemic shock • Bacterial septicemia • Retained catheter • Low PC, PS	Echocardiogram: Thrombus at SVC-RA junction	Heparin then Coumadin	Repeat Echo. (70 days) : smaller thrombus
6	Cerebral infarction	Lethargy	Generalized Tonic-clonic seizure	Hyponatremia	• Febrile neutropenia • Low PC, AT-III	CT : normal	FFp, Dilantin 3% NaCl	Expired (54 hrs)

Table 4. Initial hematologic data of 11 prospective studied ALL patients.

Patient	Age	Sex	Cell-type	Immnunophenotype	Initial CBC			
					Hct %	WC (/mm^3)	Blast %	Plt. (/mm^3)
1	6 yr.	M	L1	Early pre B	19	729,000	89	237,000
2	12 yr.	F	L1	T- cell	32.4	637,000	93	85,000
3	3 yr. 9 mo.	F	L1	Early pre B	24	6,900	35	57,000
4	3 yr	M	L1	Early pre B	16.1	18,670	65	34,000
5	5 yr. 7 mo.	M	L1	Early pre B	11.8	130,000	63	28,000
6	3 yr. 11 mo.	M	L2	Early pre B	30.3	22,300	50	469,000
7	8 yr.	M	L2	Early pre B	12.9	11,400	56	96,000
8	2 yr. 8 mo.	M	L1	Early pre B	23.8	13,800	76	54,000
9	1 yr. 1 mo.	M	L2	Early pre B	15.2	74,000	28	80,000
10	10 yr.	M	L1	Early pre B	28.7	3,200	29	13,000
11	9 yr	M	L1	T-cell	29.7	360,000	96	55,000
means	5 yr. 8 mo.	-	-	-	22.2	182,388	61.8	109,818

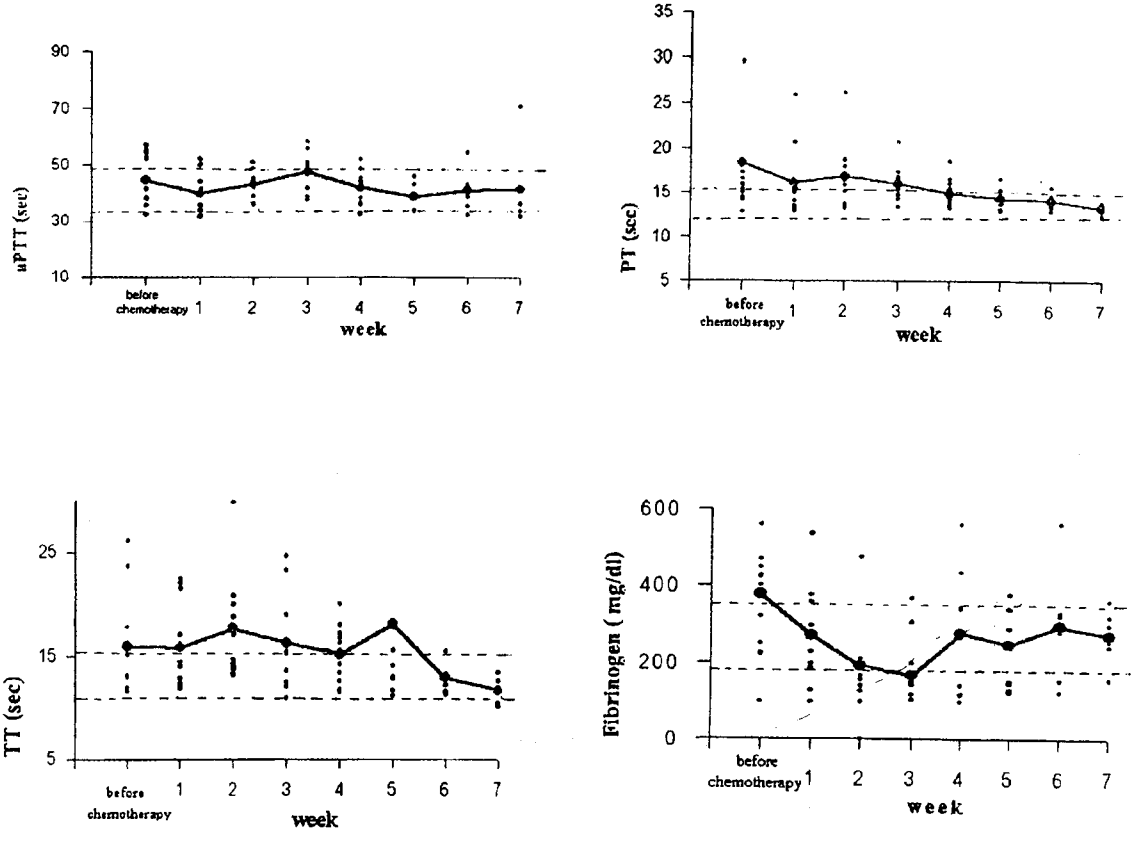

Fig. 1. Screening coagulagram (PT, aPTT, TT) and fibrinogen level weekly, before and after chemotherapy.

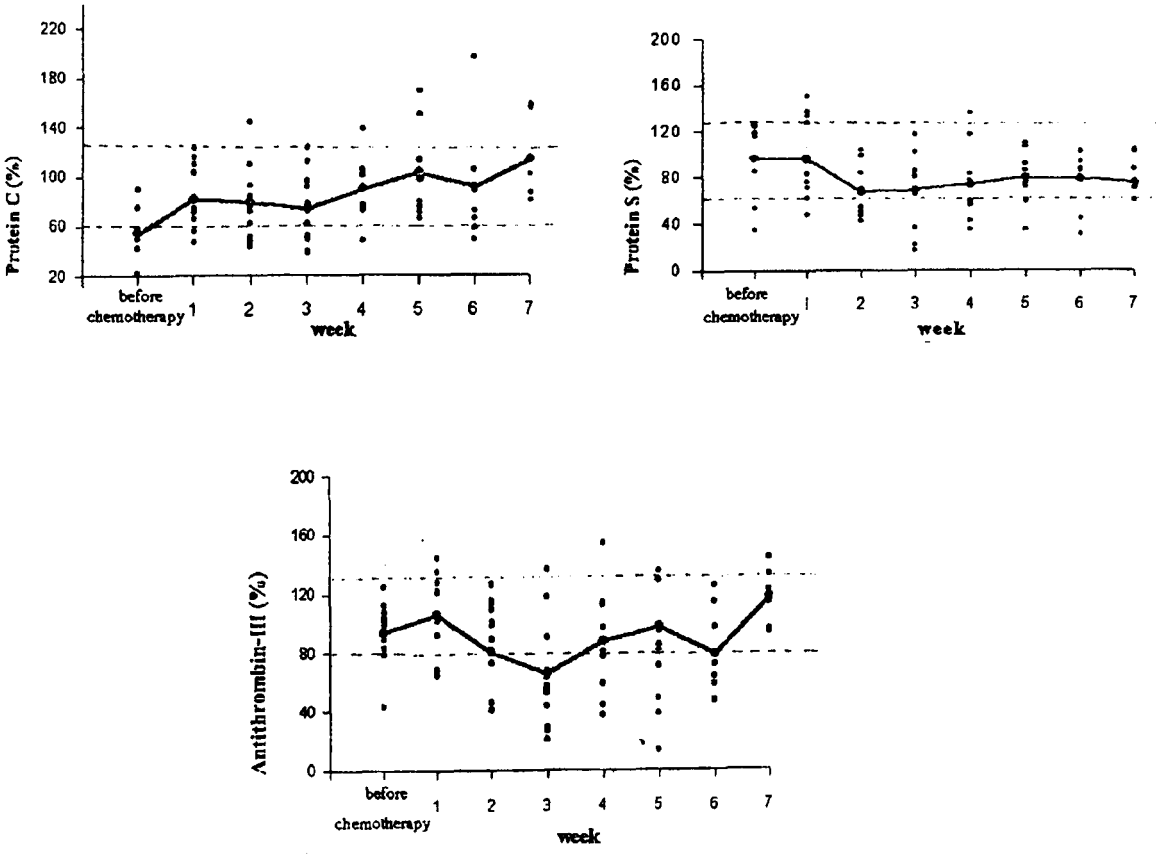

Fig. 2. Level of natural anticoagulant (Protein C, Protein S, and antithrombin III) weekly, before and after chemotherapy.

Although PT and TT seemed to be longer than control levels during the first three weeks of the induction phase (Fig. 1). The serial study of natural anticoagulants and fibrinogen levels showed that protein C was lower than normal at the baseline and slowly increased to its normal range within six weeks. Protein S was in the normal range in all weeks, but tended to decrease at the beginning and reach its nadir at the third week. Antithrombin III also ran the same pattern with protein S, but was markedly low at the third week and sixth week (Fig. 2). Fibrinogen level was higher than normal at the beginning, but markedly decreased to less than normal during the first three weeks and then gradually increased to its normal level thereafter (Table 5) (Fig. 1).

DISCUSSION

Thrombosis is not an uncommon complication in ALL patients during the induction phase. The reported incidence of thrombotic events is around 2.8 per cent[6] which is quite close to the present study (5.7%). This complication is quite serious, 28 per cent (2 deaths among 7) of deaths during the induction period due to cerebral infarction. The death rate from thrombosis was 1.9 per cent in the present study.

Hereditary prothrombotic risk factors (such as factor VG1691A mutation, the prothrombin G20210A variant, the TT677 methylene tetrahydrofolate reductase genotype, hereditary deficiency of protein C, protein S, antithrombin III, elevated lipoprotein a) have been shown to increase the risk of

Table 5. Coagulogram testing and natural anticoagulants study of 11 prospective studied ALL patients.

Test	Before chemotherapy		After chemotherapy (weeks)											
			1		2		3		4		5		6	
	mean	range	mean	range	mean	range	mean	range	mean	range	mean	range	mean	range
APTT (sec)	44.1	31.4-57	38.3	23.4-52	43.3	35.7-50.5	47.5	37.5-58.3	41.8	32.6-52	54.4	33.6-180	41.8	31.2-54.4
PT (sec)	18.1	12.8-35	15.9	12.9-25.9	16.8	13.2-26.2	15.9	13.3-20.6	14.9	13.2-18.5	14.4	13.1-16.5	14.3	12.9-15.6
TT (sec)	15.5	10-26.1	15.5	11.8-22.4	17.2	12.2-29.8	17.2	11-24.6	14.9	11.6-20	18.2	11.2-60	12.6	11.3-15.3
Protein C (%)	57.8	22-97	81.8	47-123	77.5	44-144	71.1	39-123	90.7	48-138	103.3	66-169	90.6	49-196
Protein S (%)	95.8	34-126	95.4	48-150	66.6	42-103	67.9	17-116	72.8	34-135	78.6	34-109	77.6	31-102
AT-III (%)	93.5	43-125	105.7	64-144	80.5	41-126	65.5	21-136	87.5	38-154	96.7	48-135	78.6	47-125
Fibrinogen (ng/dl)	376.4	100-560	270.9	100-534	191.2	100-474	168	100-368	276.7	100-560	246.6	123-432	294.6	125-560

Normal range : aPTT 33.5-48.5 sec Protein C 60–125% Fibrinogen 180–350 mg/dl
PT 12.5-15.9 sec Protein S 60–125%
TT 11.2-15.5 sec

venous thrombosis in children treated with the combination of L-asparaginase and steroids. But these hereditary defects are rare condition, its prevalence among ALL patients is quite similar to healthy controls[6]. Acquired disturbance of coagulation related with treatment should play a more important role in the development of thrombosis among these patients. Many previous studies have demonstrated disturbances in the coagulation system in cancer. The outstanding features included a marked tendency to elevation of coagulation factor levels (especially factor I, V, VIII, IX and XI) with an associated acceleration of thromboplastin generation[7]. Other certain conditions also increase the risk of thrombosis such as immobilization, hypotensive state, concurrent infection and chemotherapy effects. The pathophysiology of thrombosis in cancer is likely to be multifactorial.

Although a direct causal relation between specific chemotherapeutic agents and thromboembolism is difficult to establish because of the many concurrent risk factors that are potentially involved, some such associations are becoming increasingly evident and certain clinical patterns are emerging. Many chemotherapeutic agents have effects on either endothelial cell injury or disturbance of hemostatic system[8]. L-asparaginase have been known to be attributed to both thrombotic and hemorrhagic complications. A syndrome of thrombosis and hemorrhage complicated L-asparaginase therapy for childhood acute lymphoblastic leukemia was well-described in 1982[9]. Many others have reported thrombotic complications either cerebral or extensive extremities involvement[10]. As a protein synthesis inhibitor, L-asparaginase causes deficiencies of several plasma hemostatic proteins, including antithrombin III, plasminogen, fibrinogen and von Willebrand factor[11] and these complex coagulation abnormalities are probably involved in the pathophysiology of L-asparaginase induced thrombosis and bleeding. For example, there are reports of cerebral thrombophlebitis causing homonymous lateral hemianopsia[12] and sagittal sinus thrombosis[13] which are associated with transient free protein S deficiency after L-asparaginase infusion. As shown in this and a previous study[3,9] complications during the first three weeks of induction chemotherapy of ALL patients are critical. Most thrombotic complications usually occur during this phase, correlated with the changes of all natural anticoagulants

and fibrinogen. The co-decrement of these two factors might cause hemostatic balance among these patients during this phase. The decreased amount of fibrinogen may make hemostatic balance with the lower level of natural anticoagulants. If there are other factors that aggravate prothrombotic state, it may result in thrombosis. As in the 6 reported cases, all of them had other risk factors such as concurrent infections, indwelling catheter and shock. The fibrinogen level may rise instead of decrease in patients who have infection, because it is one of the acute phase reactant, and may aggravate the prothrombotic state that result in thrombosis.

In conclusion, the incidence of thrombotic complications during the induction phase of ALL is not low. Careful monitoring of complications and adequate supportive treatment is needed for good outcome. Especially during L-asparaginase therapy, the patients should be well-hydrated and unnecessary catheterization should be avoided. The caretaker should be aware of these complications especially in complicated patients. One study recommended prophylactic use of enoxaparin during L-asparaginase treatment in children with acute lymphoblastic leukemia(14).

Moreover, due to the lower level of all natural anticoagulants especially antithrombin III during this phase, heparin may not act well. The supplement of antithrombin III by concomitant transfusion of fresh frozen plasma should help in improving the heparin effect. However, all patients with thrombotic complications should be treated aggressively since full recovery is possible(15).

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ภาวะแทรกซ้อนจากเลือดแข็งตัวเป็นลิ่มอุดตันหลอดเลือดระหว่างการรักษาด้วยยาเคมีบำบัดเพื่อชักนำให้โรคสงบในเด็กโรคมะเร็งเม็ดเลือดขาวเฉียบพลัน ชนิดลิมโฟบลาสต์

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ในการศึกษานี้พบว่า อุบัติการณ์การเกิดภาวะแทรกซ้อนจากเลือดแข็งตัวเป็นลิ่มอุดตันหลอดเลือดในระหว่างการให้ยาเคมีบำบัดเพื่อชักนำให้โรคสงบในผู้ป่วยเด็กโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิด ALL เท่ากับ ร้อยละ 5.7 หรือเท่ากับ จำนวน 6 ราย ใน 105 ราย โดยแบ่งเป็น เนื้อสมองตายจากเส้นเลือดอุดตัน 4 ราย หลอดเลือดดำใหญ่ Superior vena cava อุดตัน 1 ราย และหลอดเลือดเลือดดำส่วนต้นที่ขาซ้ายอุดตัน 1 ราย มีผู้ป่วยเสียชีวิต 2 รายจากภาวะแทรกซ้อนนี้จึงได้ศึกษาต่อถึงการเปลี่ยนแปลงของการแข็งตัวของเลือดและปัจจัยต้านการแข็งตัวของเลือดในระหว่างเวลา 6 สัปดาห์ที่ให้ยาเคมีบำบัดระยะชักนำให้โรคสงบ พบว่า ค่า aPTT มีค่าอยู่ในเกณฑ์ปกติ แต่ค่า PT และ TT ยาวกว่าปกติเล็กน้อยโดยเฉพาะในช่วง 3 สัปดาห์แรก ระดับของปัจจัยต้านการแข็งตัวของเลือด คือ protein C, protein S, antithrombin III และระดับ fibrinogen มีค่าต่ำลงใน 3 สัปดาห์แรก โดยมีค่าต่ำสุดในสัปดาห์ที่ 2 และ 3 ซึ่งอาจเป็นปัจจัยเสี่ยงให้เกิดภาวะเลือดแข็งเป็นลิ่มอุดตันหลอดเลือดในผู้ป่วยกลุ่มนี้

คำสำคัญ : ลิ่มเลือดอุดตันหลอดเลือด, ยาเคมีบำบัดเพื่อชักนำให้โรคสงบ, มะเร็งเม็ดเลือดขาวเฉียบพลันในเด็ก

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