

# Study of Hypercoagulability in Patients with Acute Leukaemia in the Hematology Department of Teaching Hospital of Yopougon (Abidjan)

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## Abstract

### Introduction

Acute leukaemia are the clonal and malignant proliferation of immature hematopoietic cells (blast), blocked in their differentiation process. There is an interaction between cancer cells and the clotting process. This could be the expression of Tissue Factor (TF) on the surface of tumor cells; or a lesion of the vascular endothelium and platelet activation. The result is an activation of clotting that can lead to disseminated Intravascular Coagulation (DIC). The objective of this study was to assess the risk of DIC occurring in patients with acute leukaemia.

### Methods

This was a cross-sectional study for analytical purposes that took place on 40 frozen samples from the biobank of the haematology laboratory of Teaching Hospital Yopougon for which the diagnosis of acute leukaemia had been taken from myelogram. The myelogram results were accompanied by hemogram data. PTTa, QT, fibrinogen and D-Dimers were performed on these samples. The risk assessment of DIC occurred was determined on the recommendations of the International Society of Thrombosis and Hemostasis (ISTH).

### Results

We noted a female predominance with a Sex Ratio (M / F) of 0.90. The average age of the patients was 38 years ( $\pm$  23 years) with extremes ranging from 2 to 84 years. ALL represented 20 % of cases against 80 % for AMLs. Hemogram parameters were characterized by severe anaemia (Tx Hb < 6 g / dL) in 52.5 % of cases; hyperleukocytosis >  $100.10^3 / \text{mm}^3$  in 35 % of cases; thrombocytopenia <  $25.10^3 / \text{mm}^3$  in 40 % of case; and significant blood and spinal cord blastosis (> 80 %). The lengthening of the PTTa was observed in 50 % of cases, compared to 40% for the QT. Similarly, hyperfibrinemia was present in 65% of cases. D-Dimers were high in almost all subject (95 % of cases). According to the ISTH criteria, 17.5 % of subjects were at risk of developing a DIC.

### Conclusion

The risk of occurrence of DIC is indeed present during acute leukaemia. The parameters of haemostasis are thus found to be crucial data in the follow-up assessment during the diagnosis of acute leukaemia.

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## Introduction

Acute leukaemia (AL) is the clonal and malignant proliferation strains of immature hematopoietic cells, which are blocked in their differentiation process, which invade the bone marrow then the peripheral blood and finally other organs. They are characterized by at least 20 % infiltration of blast [1]. World Health Organization (WHO) reports in 2018 estimate 5.2 million new cases of leukaemia worldwide; with 3.5 million deaths [2].

During AL, hyperleukocytosis ( $> 50.10^3 / \text{mm}^3$ ) represents an emergency situation and the latter may be associated with leukostasis syndrome [3]. In addition, blasts express procoagulant factors, such as tissue factor (TF), procoagulant cancer and inflammatory cytokines (interleukin 1 [IL-1]), and induce an increased generation of thrombin, leading to hypercoagulability state [4]. Indeed, the adhesion of blasts at the level of endothelial cells lead to the loss of the antithrombotic properties of cells, which moreover become procoagulant [5]. This activation of coagulation can cause disseminated intravascular coagulation (DIC) [6].

DIC is a systemic pathophysiologic process and not a single disease entity, resulting from an overwhelming activation of coagulation that consumes platelets and coagulation factors and causes microvascular fibrin and thrombin, which can result in multiorgan dysfunction syndrome [7]. During normal haemostasis, the clot formation at the site of vessel injury is followed clot resolution orchestrated by the fibrinolytic mechanism. This process is regulated by multiple checkpoints which prevent non-site specific activation of coagulation or clot production in the absence of endothelial damage. In DIC, these processes are dysregulated leading to massive thrombin

generation which is disseminated to sites away from endothelial injury leading to organ damage [8].

Many studies have already established the relationship between DIC and acute promyelocyte leukaemia 9-12. But what could be the risk of DIC occurring during other types of acute leukaemia? We have therefore set ourselves the general goal of studying hypercoagulability in acute leukaemia in Abidjan.

## Material and Methods

This was a descriptive cross-sectional study with an analytical focus; which took place from September to October 2019 in the Hematology Unit of the Central Laboratory of the Teaching Hospital of Yopougon and the National Institute of Public Health; due to the accessibility of technical equipment. The study population was represented by frozen samples from the biobank of the haematology Unit of the Central Laboratory of Yopougon. Samples for which the diagnosis of acute leukaemia was made at myelogram were selected for the study. For each of these samples, the myelogram results were accompanied by the hemogram data. A total of forty samples were selected for the study. The analyses were carried out on the Sysmex CA 600 series coagulation automaton.

The parameters studied were the partial thromboplastin time with activator (normal values: Patient / control ratio  $< 1.2$ ), the Quick time (normal values: 9.1 -12.3 seconds), fibrinogen (normal values: 2 - 4 g / L) and D-Dimers (normal values  $< 500 \text{ ng} / \text{mL}$ ). The risk of DIC occurring has been determined according to the recommendations of the International Society of Thrombosis and Haemostasis (Table 1) [13].

Statistical analyzes were performed with XLSTAT 2014 and EPI INFO version 7.2 software for Windows®.

Table 1. Diagnostic Criteria for Disseminated Intravascular Coagulation (according to ISTH)

Parameters	Values	Score
Quick Time	≥ 3 sec	1
	≥ 6 sec	2
Fibrinogen	≤ 1 g/L	1
D-Dimers	>500 ng/mL	2
Platelets	≤ 100.10 <sup>3</sup> /mm <sup>3</sup>	1
	≤ 50 .10 <sup>3</sup> /mm <sup>3</sup>	2

If Score ≥ 5: Risk of disseminated Intravascular Coagulation

If Score <5: No risk of disseminated Intravascular Coagulation

The test results of the parameters studied were reported as an average (± standard deviation). The comparison of quantitative variables was carried out with the exact Fischer-Snedecor test. The comparison of the means was carried out using Student's t tests.

## Results

The Sex Ratio M / F was 0.9; while the most represented age group was 20 to 40 years old with 30% of cases. Clinically, tumor syndrome was present in 45% of cases. Table 2 shows the parameters of the hemogram.

We reported hyperleukocytosis greater than 100.10<sup>3</sup>/mm<sup>3</sup> in 35% of cases, while 87.5 % of subjects had thrombopenia. From a cytologic point of view, we observed 80 % of AMLs versus 20 % of ALLs. Within the myeloid lineage, AML 1 came first with 37.5 %, while ALL 2 came first in the lymphoid lineage with 15 % of cases.

At haemostasis, a prolongation of the PTTa was observed in 50 % of cases and a prolongation of the QT in 40 % of the cases. D-dimers were high in 95 % of subjects, while only 65 % of subjects had fibrinogen elevation. Table 3 presents haemostasis data.

According to the ISTH criteria, only 17.5 % of subjects were at risk of developing a DIC. Table 4 shows the distribution of DIC according to the leukemic type.

Table 5 presents the results of the comparison between the parameters of the study population and the risk of DIC.

## Discussion

The global burden of cancer has now reached

18.1 million new cases and 9.6 million deaths in 2018. In Africa, particularly in Ivory Coast, the incidence of AL is increasing and according to Globocan [2], the number of new cases is 162. Tumor syndrome and bone marrow failure were the components of the patient's clinic and are the result of malignant and clonal proliferation. During the study, tumor syndrome was 45 % present. This result can be superimposed on that obtained by Lachachi: 43.5 % [14]. However, it differs from that observed by Packo [15], which found 51.8 % of cases. Tumor syndrome is almost present during LA. It is the result of infiltration of the haematopoietic organs by leukaemia cells (blasts).

The AL hemogram showed hyperleukocytosis with an average white blood cell count of 103,000 / mm<sup>3</sup>. Important hyperleukocytosis (> 100,000 / mm<sup>3</sup>) was observed in 35 % of patients. This result is different from those obtained by Lachachi and Jmili & al. [14,16] who observed frequencies of 12 % and 14.5 % respectively. A late diagnosis, and therefore at an advanced stage of pathology could explain this difference. Indeed, in our socio-demographic context, patients come to see months after the first signs appear. And therefore, because of cell proliferation, hyperleukocytosis would occur.

Observation of different peripheral blood smears had reported peripheral blastosis in 100 % of cases. This result is in perfect agreement with those obtained by Lachachi (93.9 %) as well as Jmili & al. (92 %) [14,16]. At the medullary level, blastosis was just as present with an average blast rate of 57 %. However, this result is different from that obtained by Lachachi, [14] who

Table 2. Hemogram and Myelogram Data

	Average	SD	Min	Max
<b>CBC</b>				
hemoglobin level (g/dL)	7	2.7	3.4	14.4
WBC ( $10^3/\text{mm}^3$ )	103.7	151.1	0.9	634
Platelets ( $10^3/\text{mm}^3$ )	73.2	114.2	5.8	690
Peripheral Balsts (%)	64.5	20.6	22.0	92
<b>Myelogram</b>				
Spinal Blasts (%)	57	22.9	23.0	97

Table 3. Haemostasis data.

	Average	SD	Min	Max
PTTa (seconds)	32.6	16.0	19.8	103
QT (seconds)	13.07	2.26	10	21.7
FIBRINOGEN (g/L)	5.3	1.8	2.1	8.8
D-DIMERS (ng/mL)	3769	2947	404	8945

Table 4. Distribution of DIC by leukaemia type.

Type of leukaemia	DIC workforce / Total workforce
ALL 1	0/2
ALL 2	1/6
<b>Subtotal AML</b>	<b>1/8</b>
AML 0	1/4
AML 1	2/15
AML 2	2/11
AML 3	1/1
AML 5	0/1
<b>Subtotal AML</b>	<b>6/32</b>
<b>TOTAL</b>	<b>7/40</b>

Table 5. Parameters of the study population according to the risk of DIC

Parameters	DIC risk present	DIC risk absent	p Value ( $\alpha = 5\%$ )
Age (average)	40	38	0,8
Sex: M/F (workforce)	2/5	17/16	0,4
hemoglobin level g/dL (average)	7,3	7	0,8
WBC $10^3/\text{mm}^3$ (average)	180,6	87,4	0,3
Spinal Blasts (%) (average)	63,1	64,8	0,9
Peripheral Balsts % (average)	56	57,2	0,9
PTTa seconds (average)	33,1	32,4	0,5

observed an average rate of spinal blasts of 65.74 %.

Cytology has shown a predominance of acute myeloid leukaemia (80 %) and 20% of acute lymphoid leukaemia. These results are in agreement with those obtained by Lachachi [14] who observed 74.8 % of LAM and 25.2 % of LAL. Harioly et al. [17] and Nafil & al. [18] also observed a predominance of the myeloid lineage in their respective series. However, Packo [15] had observed a predominance of the lymphoid line with 51.8 % of cases.

At haemostasis, a prolongation of the PTTa was observed in 50 % of cases and an extension of the QT in 40 % of cases. These results are different from those of Dixit & al. [19] which recorded extended PTTA and QT values in 6% and 49.3% of cases respectively [19]. The study showed that 65 % of subjects had fibrinogen elevation and 95 % had D-Dimers's elevation. These results are different from those observed by Dixit & al. [19] who obtained a normal value of fibrinogen in the entire study population; and an increase in D-Dimers in 29.9 %.

Cancer cells can interact with clotting processes both directly and indirectly. The direct route could be the expression of TF on the surface of the tumor cell. The result would be the formation of a procoagulant cancer cell, which would cause the direct activation of the X-factor. Many authors have shown that a high proportion of patients with acute leukaemia have a clotting abnormality at the time of diagnosis. This would contribute to both the thrombotic tendency and the bleeding.

The risk of occurrence of Disseminated Intravascular Coagulation was present in 17.5 % of cases. This result is different from that obtained by Dixit & al. and Yanada & al who observed values of 14.9 % and 29 % respectively [20]. Within the lymphoid lineage, one subject in eight (12.5 %) presented a risk of DIC occurring. In contrast, 6 out of 32 subjects (18.75 %) in the myeloid lineage were at risk of DIC occurring. These results are different from those of Yanada & al. [20] who observed values of 28 % within the lymphoid lineage and 29 % in the myeloid lineage.

By increasing some characteristics of the study population (such as age, sex, hemoglobin level, white blood cells, blastosis and PPTa) with the presence or not of the risk of DIC occurring, no statistically significant

variation was been observed. The same constant was realized by Yanada & al. [20] for hemoglobin, white blood cells and platelets. However Dixit & al. [19] have shown a significant variation for the PPTa within the lymphoid lineage.

## Conclusion

The study of hypercoagulability on 40 samples of acute leukaemia demonstrated that there was a risk of disseminated intravascular coagulation in 17.5% of cases according to the criteria of ISTH. Thus, the risk of DIC occurring is indeed present during acute leukaemia. The parameters of haemostasis thus appear to be essential data in the additional assessment during the diagnosis of acute leukaemia.

Nevertheless, understanding the set of pathophysiological mechanisms that support thrombosis formation during acute leukemias would require further exploration by the dosage of FT, factor VII, and some physiological clotting inhibitors such as antithrombin III, C protein and S protein.

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