ASSESSING THROMBOTIC RISK IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: AN ALGORITHM AND AN ADAPTED RISK SCORE

ROMEO-GABRIEL MIHĂILĂ¹, GABRIELA COCIȘIU²
¹”Lucian Blaga” University of Sibiu, Romania
²Emergency County Clinical Hospital Sibiu, Romania

SUMMARY

Introduction: It is generally accepted that neoplasms favor thrombosis occurrence. There is also a score that estimates this risk, but it is not designed specifically for patients with chronic lymphocytic leukemia. We aimed to study the peculiarities and factors that could be responsible for the occurrence of thrombotic events in patients with this type of cancer.

Materials and Methods: We analyzed retrospectively the clinico-biological parameters with possible thrombotic potential of all patients existing in electronic database of the Hematology Department of Sibiu Hospital in 2011 and we compared them with the risk score from the perspective model for chemotherapy-associated venous thromboembolism. We elaborate an adapted risk score based on better representation of overweight or obesity status, platelet count and mean platelet volume, and an algorithm for better assessing their thrombotic risk.

Results: 17.19% had a high risk score and the others – an intermediate one. The main thrombotic factor in early stages of our patients was the increased platelets count, to which the presence of metabolic syndrome components, a history of thrombotic stroke and hypercholesterolemia add. In advanced stages, to increased mean platelet volume, which is the main thrombotic risk factor, it can be added chemotherapy, including lenalidomide, erythropoietin, and the decreased activity of CD39.

Conclusions: In early stages of chronic lymphocytic leukemia, increased platelet count is the main thrombotic risk factor, and in advanced stages - increased mean platelet volume. The best correlation was established between the number of thrombotic events in the history and adapted risk score.

Abbreviations: ARS = adapted thrombosis risk score; CLL = chronic lymphocytic leukemia; MPV = mean platelet volume; RS = thrombosis risk score; RSo = thrombosis risk score modified for overweight status; VTE = venous thromboembolism

Key words: chronic lymphocytic leukemia, mean platelet volume, thrombotic risk

RÉSUMÉ

L’évaluation du risque thrombotique chez les patients avec leucémie lymphoïde chronique: un algorithme et un score de risque adapté

Introduction: Il est généralement admis que les néoplasmes favorisent la survenue de thromboses. Il y a aussi un score qui estime ce risque, mais il n’est pas conçu spécifiquement pour les patients atteints de leucémie lymphoïde chronique. Nous nous sommes efforcés d’étudier les particularités et les facteurs qui pourraient être responsables de l’occurrence des événements thrombotiques chez les patients atteints de ce type de cancer.

Méthods: Nous avons analysé rétrospectivement les paramètres clinico-biologiques à possible risque thrombotique de tous les patients existant dans la base de données électronique du service d’Hématologie de l’Hôpital Départemental de Sibiu en 2011 et nous les avons comparé avec le score de risque du modèle perspective de la thrombo-embolie veineuse associée à la chimiothérapie.

Résultats: 17.19 % avaient un score de risque élevé et les autres – un intermédiaire. Le principal facteur thrombotique dans les premiers stades de nos patients a été le taux plaquettaire accru, auquel on ajoute la présence de composantes du syndrome métabolique, les antécédents d’accident vasculaire cérébral thrombotique et l’hypercholestérolémie. Dans les stades avancés, à une augmentation du volume moyen plaquettaire, qui est le principal facteur de risque thrombotique, il peut être ajouté la chimiothérapie, y compris le lenalidomide, l’érithropoïétine et la diminution de l’activité du CD39.

Conclusions: Dans les premiers stades de la leucémie lymphoïde chronique le taux plaquettaire accru est le principal facteur de risque thrombotique et dans les stades avancés – l’augmentation du volume moyen plaquettaire. La meilleure corrélation a été établie entre le nombre d’accidents thrombotiques dans l’histoire et le score de risque adapté.

Mots-clés: leucémie lymphoïde chronique, volume moyen plaquettaire, risque thrombotique

Correspondence address: Romeo–Gabriel Mihaila, MD
Medical Clinic II, Emergency County Clinical Hospital, Corneliu Coposu Avenue, No. 2-4, 550245, Sibiu, Romania
Telephone: 0040 726 340655    Fax: 0040 269 218365    e-mail: romeomihaila@yahoo.com
INTRODUCTION

In hematologic malignancies there is a hypercoagulable state [1], dependent on tumor biology and their influence on angiogenesis [2]. Venous thrombo-embolism (VTE) appeared at 7.7% of 1178 patients with various types of cancer (17% had hematologic malignancies) during a median observation of 731 days. [3] The importance of subject is related to increased mortality due to VTE. In an analysis made in United States medical centers on 1,824,316 hospitalizations of cancer patients the mortality was 16.3% between patients who developed VTE, comparing with 6.3% in those without this complication. [2, 4] In a recent study, the incidence of VTE was 1.45% per patient with chronic lymphocytic leukemia (CLL) per year [5]. The cumulative incidence of VTE per year in patients with CLL in California was 2.7%. [6] But thrombotic risk varies greatly from one patient to another and is influenced by many factors. It is known that in CLL patients there are elevated serum levels of thrombin-antithrombin complexes, D-dimer, thrombomodulin and soluble vascular endothelial adhesion molecule 1 [1]. Elevated D-dimer levels favored increased mortality and decreased overall survival. [3]

If assessing the presence of antiphospholipid syndrome or thrombophilia markers (especially antithrombin III, protein C or protein S deficiency, factor V Leiden, hyperhomocysteinemia) is not a common determination, the risk of thrombotic events can be estimated by evaluating the history, clinical examination, blood count (including platelet count and mean platelet volume), blood lipids, presence of metabolic syndrome components and medication. Moreover, VTE clearly influences also short- and long-term prognosis of cancer patients. [4]

An elevated platelets count contributes to atherosclerosis development and arterial thrombosis appearance and their variation is heritable in over a half of subjects [7]. Platelet count is higher at females [8] and has an age-dependent decrease [9]. The mean platelet volume (MPV) is a measure of platelet reactivity, which varies from a subject to other. An increased MPV is involved in adverse cardiovascular events and its heritability is about 73% [7, 11, 12, 13, 14]. MPV was higher in females, in patients with a recurrent ischemic event [10, 15], in those with obesity and obstructive sleep apnea [16], and in smokers and decreases 3 months after smoking cessation. [17]

We aimed to study the role of platelet count and MPV in overall thrombotic risk factors in patients with CLL, allowing adaptation to this type of malignant hemopathy the thrombotic risk score from a predictive model for chemotherapy-associated VTE [18] of cancer patients, and helping to develop an algorithm for estimating the thrombotic risk in them.

METHODS

Study population

We studied retrospectively all 64 patients with CLL in 2011, which were in the electronic filing system of the Department of Hematology of Emergency County Clinical Hospital Sibiu. They were divided into 2 groups: A - who had chemotherapy during 2011 and B - without chemotherapy in 2011. We noted: gender, age, disease stage, and associated diseases, including the possible presence of the metabolic syndrome components (arterial hypertension, diabetes, hypertriglyceridemia, hypo-HDL-cholesterolemia, overweight or obesity), a possible history of thrombotic events, serum level of cholesterol, triglycerides, platelets count, and MPV. In group A patients, we have also studied the number of chemotherapy session and serum level of cholesterol, triglycerides, hemoglobin, and MPV before and after chemotherapy. The biological data from group B patients were taken from their first hospitalization in 2011. During all year 2011, between sampling and analysis in hospital lab there were no more than 2 hours. It was calculated for each patient the thrombosis risk score (RS) from the perspective model for chemotherapy-associated VTE, which was proposed by Khorana AA et al [18], and, in addition, two new risk scores. The first (RSo) kept the parameters of RS, but the presence of overweight status was noted with one point and with two points those of obesity; it is useful for better understanding the reason which conduced to the second score - an adapted thrombosis risk score (ARS) for patients with CLL. The parameters of RS were kept in this score, but for patients in early stages of CLL we added one point for platelet count ≥ 200000/mm³, and for patients in advanced stages of CLL we added one point for MPV ≥ 11 fl. We analyzed the correlations between data obtained from each group of patients and the risk of thrombosis, expressed by the three risk scores. Then, it was proposed an algorithm of thrombosis risk in CLL patients.

The study was previously approved by hospital ethical committee, and we kept the confidentiality of the identity of patients included in the study.

Statistical analyses

The results were statistically analysed with the arithmetic mean, the standard deviation and the t Student and Pearson tests.

RESULTS

In the whole group of patients, 11 (17.19%) had a high RS (3 points) and the others 53 (82.81%) – an intermediate one (1-2 points). There were more high risk patients in group B (9 – 20%) comparing with group A (2 – 10.53%). In the cohort where RS was validated, the frequency of symptomatic venous thromboembolism in high risk patients was 6.7% during 2.5 months of observation [19], but this study was made on patients with different types of neoplasms. In our group, 4 patients from group B (8.89%) (none in group A) had a thrombotic accident in their history. We studied the thrombotic risk factors in our CLL patients in order to adapt RS to them.

The group A

In group A mean age was 65.4+/−10.4 years; the
This thrombotic risk score for CLL thrombotic risk factor, is present in all patients with metabolic syndrome components could be an independent thrombotic risk factor in these patients. Because MPV is known to be a thrombotic risk factor, we propose to add one point for MPV ≥ 11 fl before chemotherapy to RSo (and not to RS, because overweight and obesity are better reflected in this score and obesity, known to be a thrombotic risk factor, is present in all patients with metabolic syndrome). This thrombotic risk score for CLL patients (ARS) had a mean value of 2.84+/−1.05 in patients from group A and correlated directly with MPV (r=0.606) and triglycerides (r=0.273) and indirectly with cholesterol (r=0.298), and didn’t correlate with age, disease stage and platelet count.

The group B

In patients of group B mean age was 66.9+/−10.7 years; the distribution by gender: 28 women (62.22%) and 17 men (37.78%). The clinical and biological mean data of these patients are presented in table 2. Disease stage of patients in group B was significantly lower than those in group A (p<0.00005) and correlated directly with age (r=0.315) and inversely with cholesterol (r=−0.255) and triglycerides (r=−0.280). Cholesterol was not significantly different in the 2 groups, but in group B was directly correlated with serum triglycerides (r=0.483), as in group A, but stronger. MPV of group B was higher than that of group A post-therapy (p=0.01) and correlated inversely with the cholesterol of group B (r=−0.470).

In this group, while RS correlates directly, slightly, with MPV (r=0.237), between RSo and MPV there was a discrete better direct correlation (r=0.281). The mean platelets count correlated directly better with RS (r=0.313) than with RSo (r=0.253). RS didn’t correlate with disease stage (r=−0.089), while RSo correlated inversely, slightly, with disease stage (r=−0.225). There was no correlation between platelet count and MPV, but it was a direct correlation between platelet number and number of thrombotic events in history (r=0.316).

Because 4 patients of this group had thrombotic accidents in their history, we studied the possible correlation of these events with other parameters. Thus, we find a significant direct correlation with platelets count (r=0.315), but not with MPV (r=0.019). RS and RSo correlated directly with the number of thrombotic accidents in the past (r=0.299, respectively r=0.273). We thought to elaborate a risk score (ARS) which could correlate better with thrombotic events in patients with CLL also in early stages. Thus, we added to the parameters of RSo one point for platelet count ≥ 200000/mm³. The mean value of ARS was 2.91+/−1.15 and correlated directly and better as RS or RSo (r=0.316) than with RSo (r=0.253). RS didn’t correlate with disease stage (r=−0.089), while RSo correlated inversely, slightly, with disease stage (r=−0.225). There was no correlation between platelet count and MPV, but it was a direct correlation between platelet number and number of thrombotic events in history (r=0.316).

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Table 1 - Clinical and biological mean data of patients from group A

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value</th>
</tr>
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<tbody>
<tr>
<td>Disease stage</td>
<td>2.16+/−1.12</td>
</tr>
<tr>
<td>Number of cures</td>
<td>3.95+/−2.07</td>
</tr>
<tr>
<td>Platelets count (/mm3)</td>
<td>149526.32+/−54810.15</td>
</tr>
<tr>
<td>Serum cholesterol (initial) (mg/dl)</td>
<td>177.44+/−49.61</td>
</tr>
<tr>
<td>Serum cholesterol (final) (mg/dl)</td>
<td>186.88+/−39.04</td>
</tr>
<tr>
<td>Serum cholesterol variation (mg/dl)</td>
<td>30.29+/−27.59</td>
</tr>
<tr>
<td>Serum triglycerides (initial) (mg/dl)</td>
<td>151.32+/−81.36</td>
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<tr>
<td>Serum triglycerides (final) (mg/dl)</td>
<td>181.11+/−112.24</td>
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<tr>
<td>Serum triglycerides variation (mg/dl)</td>
<td>35.63+/−80.51</td>
</tr>
<tr>
<td>Mean platelet volume (initial) (fl)</td>
<td>10.42+/−1.04</td>
</tr>
<tr>
<td>Mean platelet volume (final) (fl)</td>
<td>10.02+/−0.96</td>
</tr>
<tr>
<td>Components of metabolic syndrome</td>
<td>0.37+/−0.76</td>
</tr>
</tbody>
</table>

Table 2 - Clinical and biological mean data of patients from group B

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value</th>
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</thead>
<tbody>
<tr>
<td>Disease stage</td>
<td>1.02+/−0.82</td>
</tr>
<tr>
<td>Platelets count (/mm3)</td>
<td>192837.21+/−83277.20</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>195.65+/−49.72</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>148.77+/−67.07</td>
</tr>
<tr>
<td>Mean platelet volume (fl)</td>
<td>10.59+/−0.84</td>
</tr>
<tr>
<td>Components of metabolic syndrome</td>
<td>1.31+/−0.87</td>
</tr>
</tbody>
</table>
The whole group of patients

The mean age of the group was 66.93 +/- 10.70 years. Distribution by gender: women - 37 (57.81%), male - 27 (42.19%). The average number of platelets in peripheral blood was 192,837.21 +/- 83,277.20/mm^3. There was a moderate direct correlation between platelet count and thrombotic stroke in the history of patients (r=0.319). Those who had had thrombotic events have higher risk for new ones. There is a small but inverse correlation between the number of history of thrombotic events and the stage of CLL (r=-0.230). There was no correlation between thrombotic history and other analyzed data. It follows that the main thrombotic risk factor in our group is the increased number of platelets. Platelets are slightly, directly correlated with the number of components of metabolic syndrome (r=0.237). So, in early stages of disease, the presence of metabolic syndrome components could be an additional thrombotic risk factor. But, while the infiltration of bone marrow by leukemic cells grows, platelet count decreases, as reflected by moderate inverse correlation between platelet count and stage of disease (r=-0.343), and cholesterol decreases (average cholesterol 195.65 +/- 49.72mg/dl). There is a slight, direct correlation between platelet count and cholesterol (r=0.260). Disease stage correlates, also moderately and inversely, with cholesterol (r=-0.321), which in turn, correlates inversely, moderately, with the MPV, which was 10.59 +/- 0.84fl (r=-0.360). As a result, patients with advanced disease have a tendency to decrease in cholesterol (cholesterol is captured by leukemic cells and used for their proliferation), which correlates with increased MPV – a thrombotic risk factor. Between cholesterol and triglycerides there is a moderate direct correlation (r=0.407) and serum triglycerides correlate slightly and inversely with MPV (r=-0.140).

In the full group of patients there was no correlation between RS and MPV, but RSo correlated directly, slightly, with MPV (r=0.293). The mean platelets count correlates directly and slightly only with RS (r=0.233), and didn’t correlate with RSo (r=0.137). Both analyzed risk scores didn’t correlate with disease stages (r=-0.056, respectively r=-0.091). The number of thrombotic events correlated directly with RS (r=0.252), RSo (r=0.218) and ARS (r=0.336), but in our patients population there was no thrombotic event in advanced stage of disease. As it can be shown, the best correlation was established between the number of thrombotic events and ARS. In the whole group of patients the mean ARS was 2.90 +/- 1.11, and correlated directly with MPV (r=0.419), platelet count (r=0.359), and triglycerides (r=0.263), and didn’t correlate with age, disease stage, and cholesterol value.

The algorithm for assessing thrombotic risk in CLL patients

Such an algorithm, based on our results and literature data, starts from dividing patients according to disease stage. In early stages the main thrombotic risk factor is increased platelet count, to which it has to be added a history of thrombotic accidents, the possible presence of hypercholesterolemia, and one or more components of metabolic syndrome, including hypertriglyceridemia. As CLL progresses, bone marrow will be more infiltrated by leukemic cells, and especially because of this, megacaryocytes and platelets count decrease, cholesterol decreases (because cholesterol is used for leukemic cells proliferation), MPV increases (mainly as a result of platelet count decrease) and serum triglycerides value diminishes. In advanced stages of disease, the main thrombotic risk factor is increased MPV, to which can be added the decreased activity of CD39 [19] (with platelet inhibition decreasing), the effect of chemotherapy, including those of lenalidomide [5], and the anemia treatment with erythropoietin [21].

<table>
<thead>
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<th>Table 3 - The mean values of thrombotic risk scores</th>
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<tr>
<td>Group A</td>
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<tr>
<td>Group B</td>
</tr>
<tr>
<td>Whole group</td>
</tr>
</tbody>
</table>

RS = thrombosis risk score; RSo = thrombosis risk score modified for overweight status; ARS = adapted thrombosis risk score.

Figure 1 - Algorithm for assessing thrombotic risk in CLL patients

Legend: EPO = erythropoietin; MPV = mean platelet volume.

CHRONIC LYMPHOCYTIC LEUKEMIA

EARLY STAGES

- Increased platelet count;
- Thrombotic stroke in the history of patients;
- Metabolic syndrome components, including hypertriglyceridemia;
- Increased serum values of cholesterol.

PROGRESSION CHARACTERISTICS:

- Infiltration of bone marrow by leukemic cells grows;
- Platelet count decreases;
- Cholesteral knowledge decreases;
- MPV increases;
- Decrease of triglycerides.

ADVANCED STAGES

- Increased MPV;
- Chemotherapy, including lenalidomide [22];
- Decreased activity of CD39 [18];
- EPO.

Legend: EPO = erythropoietin; MPV = mean platelet volume.
In our study age, cholesterol and triglycerides correlate directly, slightly, with the number of components of metabolic syndrome. In patients with nonalcoholic fatty liver disease (the liver component of metabolic syndrome) the MPV is high and correlates inversely with the platelet number [22]. The value of MPV is higher in patients with type 2 diabetes mellitus compared with patients with normal glucose tolerance and with those with impaired glucose regulation. In addition, it can be influenced by increased age, serum creatinine value, LDL-cholesterol and fasting plasma glucose level [23]. In our study the number of metabolic syndrome components correlates directly and slightly with the number of thrombotic accidents in history and, especially, with platelet count. Platelet count correlated directly and slowly with metabolic syndrome components and moderately with the number of thrombotic events ($r=0.319$). Because in our study platelet count can be considered the main thrombotic risk factor in early stages of CLL, we proposed to include this parameter in the calculation of thrombotic risk score for this population of patients.

For patients with atrial fibrillation there are 2 risk scores for stroke (CHADS2 and CHA2DS2-VASC), where stroke, transient ischemic attack or thromboembolism present in the history of patients are assign with 2 points [24, 25, 26]. It was proved that MPV was a stroke risk factor predictor in patients with atrial fibrillation, which was not dependent of other CHADS2 parameters, age or gender. [27] But not only patients with atrial fibrillation with thrombotic events in the past can develop new ones. Previous studies advocate for a potential thrombosis risk estimation of MPV. [28, 29, 30, 31]

In our study, while RS correlated slowly only with MPV in early stages of disease, RSo correlated directly with MPV in early and late stages and in entire analyzed group of CLL patients. The best correlation between RSo and MPV was shown in group A patients (in advanced stages of CLL). This finding is consistent with our observation above, according to which MPV is a risk factor for thrombotic accidents in advanced stages of CLL. Instead, RSo correlated with mean platelet count only in early stages of CLL, while RS correlated with mean platelet count in early stages and in entire group of CLL patients. Only RSo correlated inversely and slightly with disease stage only in early stages of CLL. It follows that thrombotic risk is higher in early stage of CLL. According to this study, RSo is more appropriate for assessing thrombotic risk of patients with CLL compared to RS. The value of ARS correlates best with the number of thrombotic events in history, comparing with other 2 scores. A patient with a thrombotic event in the past, is predisposed to develop others. The VTE recurrence rate at 10 years is estimated to be 30% [32] or even almost 40% [33]. Between the risk factors for recurrence there are: increased body mass, immobilization, and an active cancer. [32] An active cancer increases the thromboembolism risk by 5-6 fold, independent if the patients is or not under chemotherapy. [34, 35]

In advanced disease stages, in addition to increased MPV, the chemotherapy, including lenalidomide [1], and erythropoietin [21] may contribute to increased thrombotic risk. Lenalidomide is an immunomodulatory drug active in many types of malignant hemopathies, including CLL: it decreases the level of proinflammatory cytokines, contributes to T-cells and natural killer cells activation, influences signal transduction and microenvironment, and has anti-angiogenesis and antitumor activity [36], but, sometimes, can produce thrombosis, as an adverse effect. In a study published by Ferrajoli A [37] one patient of 44 developed deep vein thrombosis after lenalidomide administration. This adverse effect increased markedly in myeloma patients when there were used thalidomide- or lenalidomide-containing regimens and not after a single agent administration. [4, 38, 39] The use of erythropoietin is justified to treat anemia from advanced stages of CLL, because in hematologic malignancies there is an inappropriately low response of erythropoietin. [40] In a study made on 269 patients with hematologic malignancies, after epoetin alfa administration (in dose of 40000 UI/week) there were 14.06% clinically relevant thrombotic events, especially in early treated patients. [21] After 6 months of erythropoietin treatment in patients with chronic renal failure it was shown a significant increase in MPV, not also in control groups, suggesting that erythropoietin can be involved in thrombopoiesis. [41] It seems that serum level of hemoglobin over 11 g/dl at the beginning of epoetin-$\beta$ treatment didn’t associate with an increased rate of thromboembolic events. [42] Because we had no thrombotic event in history of patients with advanced stages CLL, we consider that erythropoietin use didn’t require to adding supplementary points in thrombotic score risk formula calculation, but future clinical trials could evaluate better its risk.

Platelet inhibition is promoted by CD39. The activity of this ectonucleotidase is augmented on CLL B cells in stage I and II (RAI) and decreased in stage III and IV of disease compared to normal subjects. Therefore, in the late stages of CLL the patients are not protected against platelet activation by this ectonucleotidase [19].

In our opinion, RSo better predicts the thrombotic risk as RS in advanced stages of CLL patients, but we propose a new score for estimating the thrombotic risk in advanced stages of CLL: ARS, which includes the presence of increased MPV, which is the main risk factor for these patients. We didn’t include supplementary points in the thrombotic risk score formula for serum cholesterol or triglycerides level, although they are thrombotic risk factors, especially in early stages of CLL, because their mean value was normal in our group B (195.65+/-49.72 mg/dl for cholesterol and 148.77+/-67.07 mg/dl for triglycerides). In this group, a number of 8 patients had hypercholesterolemia and 21 – hypertriglyceridemia, but the value of these biochemical determinations are influenced by many factors, including the diet and the treatment. These values didn’t reflect the evolution in time of these parameters. In the same time, dyslipidemia diagnosis didn’t offer relations...
regarding the impact of these parameters on thrombosis development. Also metabolic syndrome components correlated only slowly with thrombotic events in the past of our patients. All the patients with thrombotic accidents in their history from group B had over 200000 platelets / mm³, so that we didn’t consider necessary to add points for these concomitant diseases. But there can be patients with multiple neoplasms. We consider that the situation of these patients must be analysed regarding the risk of thrombosis. Can they receive supplementary points? In our study there were only 2 patients with 2 neoplasms and they had no thromboses in the past. According to RS our patients received 1 point because they are in the high risk category corresponding to cancer site, but if they develop a very high risk cancer (pancreatic or gastric), they will receive 2 points. We think that only a clinical trial can establish if these patients will have a total of 2 or 3 points for their 2 neoplasms.

There may also be other causes of thrombosis. For example, sometimes, a thrombosis can appear by venous catheterization. A subclavian venous catheter produced 8 cases of thrombosis from 179 catheter introductions. [43]

The platelet count decreases and MPV increases in late stages of CLL. In our study MPV can be consider the main risk factor for these patients. This was the reason for adding 1 point to thrombotic risk score calculation for a MPV over 11 fl. The MPV continues to be studied in different clinical situations, but there is not doubt that its increase means more active platelets, which assume higher thrombotic risk. Regarding the studies which examines the value of MPV, in our opinion they must be carefully selected because this parameter didn’t have to be analyzed during a thrombotic event, when its value is influenced by many factors, including the thrombosis extension (where are consumed mainly active platelets, which are high MPV, and came from spleen reservoir) and age, the volume of spleen reservoir, a possible bone marrow dislocation (as in the 4th stage of CLL), a possible myelodysplasia, the treatment, etc. It is much better to study MPV before or after thrombotic event resolution. Thus, studying MPV during and 2 years after acute myocardial infarction it was showed more small platelets during thrombotic event, probably because large and medium platelets were consumed preferentially at the site of infarction, comparing with those of small size [44]. In a group of cancer patients MPV was significantly lower during thrombosis development comparing with its value at neoplasm diagnosis. [45]

In this study, there were thrombotic accidents only in the history of some patients with early stages CLL. This means that thrombotic risk may be higher in these patients, comparing with those in advanced stages of disease. A limitation of our study consists in the number of patients, but this is a single center study and we have included all our CLL patients. Despite this, we could obtain statistically significant results.

CONCLUSIONS

Cholesterol decreases as the disease stage increases and may be an indicator of mass growth of leukemia cells and of disease aggressiveness. Higher cholesterol and lower MPV after chemotherapy may be indicators to treatment response. [46] In early stages of CLL, the increased platelets count is an important prothrombotic factor, to which the presence of metabolic syndrome components adds. [47] In advanced stages, increased MPV, chemotherapy, and erythropoietin are the main thrombotic risk factors, to which one can add the decreased activity of CD39. [19]

We hope that our proposed algorithm and score will be tested in future clinical trials and contribute to the estimation and the prevention of thrombotic accidents in CLL patients.

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Authorship Contributions

R.G.M. and G. C. contributed equally to study design, data collection, statistical analysis, result interpretation, and writing of paper.

Disclosure of Conflicts of Interest

The author has no conflict of interest that are directly relevant to the content of this article.

Statement of prior presentation

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