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Thrombocytopenic patients with hematological malignancy who underwent fiberoptic bronchoscopy are they really under a significant hemorrhagic risk?

Fatih Yıldırım[1*], Fahir Özkalemkaş[2] and Ahmet Ursavaş[3]

Abstract

Background: Fiberoptic bronchoscopy (FOB) is a very important procedure in hematology clinics. Clinicians often worry about thrombocytopenia before performing FOB because hemorrhagic complications may occur during and after FOB. We have planned a retrospective study about hemorrhagic complications in thrombocytopenic patients who underwent FOB and treated for hematological malignancy. In this study, we have analyzed hemorrhagic complications, which are related to thrombocytopenia, in 114 adult patients who have hematologic malignancy and underwent FOB between January 1, 2005 and October 20, 2015. The platelet counts of all the patients were below 100×10^9/L.

Results: The complications related to FOB were observed in 4 (3.5%) out of 114 patient. Three out of 4 the complications were related to hemorrhage. One out of these 3 patients who occured hemorrhage was in "no bleeding group" according to BTS classification. The other 1 out of these 3 patients was in "mild bleeding" group. No bleeding was observed during FOB in the third patient. Hemoptysis was observed after FOB in the third patient, it was not required replacement and hemoptysis regressed spontaneously.

In this study, we categorized all the patients into three groups. The first group was comprised of 32 patients whose platelet counts were between 0 and 30×10^9/L. The second group was comprised of 47 patients whose platelets counts were between 30 and 50×10^9/L and lastly, the third group was comprised of 35 patients whose platelets counts were between 50 and 100×10^9/L. When we compared the groups to each other, there was no significant difference between these three groups in regards to occurrence of hemorrhagic complications. We observed that there was no significant relationship between thrombocytopenia level and risk of hemorrhagic complications in thrombocytopenic patients who underwent FOB.

Conclusions: In conclusion, this study demonstrated that FOB is safe procedures in thrombocytopenic patients if it is performed in multidisciplinary centers by experienced pulmonologists.

Keywords: Thrombocytopenia, Bronchoscopy, Hematology, Malignancy

Background

Patients with hematologic malignancy often are exposed to infectious events during chemotherapeutic treatment periods. Clinicians frequently use fiberoptic bronchoscopy in the hematology clinical practice, especially for evaluation of pulmonary infiltrations which is

*Correspondence: f08fatih@gmail.com

[1] Department of Rheumatology, University of Health Sciences, Başaksehir Çam and Sakura City Hospital, Istanbul, Turkey
Full list of author information is available at the end of the article

detected by imaging methods. This methods have more importance especially during high-risk febrile neutropenia management. In addition, these patients generally have poor prognosis, they are often hypoxic and severely thrombocytopenic. Therefore, these conditions limit bronchoscopic techniques in these patients [1–5]. Thrombocytopenic patients who underwent FOB have risk of hemorrhagic complication and it is important for clinicians [6–8]. There is no international consensus on how to manage thrombocytopenic patients who the candidate FOB. Platelet counts which are safe for bronchoscopic techniques in thrombocytopenic patients are differential according to clinicians' own experiences or experts' opinions. This situation also occurs in different guidelines. To give an example, according to the British Thoracic Society (BTS), Platelet counts which are safe for bronchoscopy are 20×10^9/L. On the contrary, the safe platelet counts are 50×10^9/L according to the American Society of Clinical Oncology [9, 10]. In addition to that, the circulating platelet counts and platelet function abnormalities also are reason in the development of hemorrhagic complications. Drugs, uremia, paraproteinemia, and myeloproliferative diseases are the most common causes of secondary platelet dysfunctions. Primary thrombocyte dysfunctions are often related to hereditary origin [11]. Patients with hematological malignancy who candidate for FOB often have more comorbidities. These patients are exposed to a lot of drugs. For all these reasons, the management of these patients are very difficult. When we analyzed the current data as a whole, it seems that there are not enough studies on the management of thrombocytopenic patients who candidates for FOB. To get a consensus on this issues, prospective studies that include a large number of patients are needed. In this study, we investigated the hemorrhagic complications of thrombocytopenic patients who were treated for hematological malignancy and underwent FOB.

Methods

In the beginning, we determined 150 patients with hematological malignancy who underwent FOB, between 2005 and 2015 retrospectively. However, we excluded 36 of these patients because their platelet counts were above 100×10^9/L. Inclusion criteria were defined as being older than 18 years of age, having a hematological malignancy (may be of lymphoid or myeloid origin), having a platelet count below 100×10^9/L, and having history of bronchoscopic procedure in our center. Exclusion criteria were defined as having thrombocytopenia due to Disseminated İntravascular Coagulation (DIC) and having history of using anti-platelet drugs (acetylsalicylic acid, clopidogrel etc.) within 5 days before bronchoscopy. The patients were not investigated for the detection of diseases causing primary platelet dysfunction. The presence of diseases that may cause bleeding diathesis other than disseminated ıntravascular coagulation (liver disease, uremia etc.) were not included in the exclusion criteria. FOB had performed to all patients in the bronchoscopy unit by pulmonologists. The pulmonologists had used the 11001BN1 KARL STORZ Flexible Bronchoscope (Tuttlingen, Germany) and the PENTAX FB-15P Fiber Optic Bronchoscope (France) on the patients included in the study for bronchoscopic procedures. Bronchoscopy team was composed of a pulmonologist, a chest disease resercher and a bronchoscopy unit nurse. Patients' vital parameters had been recorded by the bronchoscopy team. We evaluated patients files retrospectively, and we recorded necessary data (prothrombin time, active partial thromboplastin time, INR value, blood count, blood urea level before bronchoscpy, type of bronchoscopic procedure, complications occurring during the procedure, need of blood product of patients with hemorrhagic complications). We classified the patients who developed hemorrhagic complications during FOB according to the BTS (British Thoracic Society) classification. IBM SPSS Statistics 22 package program was used for statistical analysis. Categorical variables were shown as "n" and percentage values. Fisher's exact test, chi-square test, and Fisher-Freeman-Halton test were used for comparisons. The conformity of the data to the normal distribution was determined by the Shapiro-Wilk test. Variables that did not fit the normal distribution were shown as median (minimum–maximum) values. The Mann-Whitney U test was used to compare these variables between the two groups. Finding "$p < 0.05$" was considered statistically significant. The research institute's committee approved study protocol on human research. There were not ethical conflicts to disclose between authors.

Results

In this study, platelet counts of all patients were below 100×10^9/L. 30 (26.3%) out of 114 patients were female and rest of the patients, which is 84 (73.7%), were male. The median age of the patients were 48 (18–67) years. The indications of FOB were isolated hemoptysis in 1 case, pulmonary infiltrates in 110 cases, and pulmonary infiltrates accompanying hemoptysis in 3 cases. One hundred one (89%) of the patients were febrile neutropenic. The median period of febrile neutropenia was 11 (3–36) days in febrile neutropenic patients. The mean platelet counts of the patients were 46.1 ($\pm$ 21.1) $\times 10^9$/L, and the median platelet counts were 46.6 (4–90) $\times 10^9$/L before performing the FOB. Since the vast majority of patients were febrile, septic, and receiving cytotoxic chemotherapy; thrombocyte transfusions had been performed to

the patients whose are platelet counts below 50×10^9/L one day before the procedure. 86 (75%) of the patients had been administered platelet transfusion before the procedure. We seperated into groups to the patients in terms of the input platelet counts, bronchoscopic techniques, complications, PT (prothrombin time), INR, and blood urea levels. The limit values of groups were 17 s for PT, 1.5 for INR, and 50 mg/dl for blood urea. Pulomonologists had performed only bronchoalveolar lavage to 106 patients; bronchoalveolar lavage and brush swab to 3 patients; bronchoalveolar lavage and mucosal biopsy to 4 patients; bronchoalveolar lavage, brush swab, and mucosal biopsy to 1 patient. Three (2.6%) of the complications were related to hemorrhage. Supraventricular tachycardia had developed in one (0.08%) of the patients. Hemorrhagic complications that developed during FOB were classified according to the BTS (British Thoracic Society) bronchoscopy guideline. According to BTS, hemorrhagic complications during FOB are classified into 4 groups: no bleeding (traces of blood with no need for continuous suctioning, bleeding stops spontaneously), mild bleeding (continued suctioning of blood from the airways, bleeding stops spontaneously), moderate bleeding (intubation of the biopsied segment with the bronchoscope into the wedge position, use of adrenaline or cold saline to stop bleeding), and severe bleeding (placement of bronchus blocker or catheter, applying fibrin sealant, resuscitation, blood transfusion, admission to critical care unit or death) [12]. One of the patients who had developed hemorrhagic complications was in the no bleeding group based on BTS classification, 1 patient was in the mild bleeding group based on BTS classification. After the procedure, spontaneously regressed hemoptysis had been occurred in 1 patient. Bleeding complication had developed in 3.33% ($n = 1$) of the women and in 2.8% ($n = 2$) of men. There was no significant difference in the incidence of bleeding complications between women and men ($p = 1000$). We seperated the patients into groups according to the input platelet counts. Platelet counts were 30×10^9/L in the first group, $30–50 \times 10^9$/L in the second group, and $50–100 \times 10^9$/L in the third group. There were bleeding complications in 1 (3.13%) out of the 32 patients in the first group and in 2 (4.26%) out of the 47 patients in the third group. There was no significant difference between patients groups according to input platelet counts ($p = 0.624$). There were bleeding complications in 1 (9.99%) out of the 11 patients whose PT value is above 17 s and in 2 (1.94%) out of the 103 patients whose PT value is below 17 s. There was no significant difference between patients whose PT value of > 17 s and < 17 s ($p = 0.265$). There was bleeding complication in 1 (9.09%) out of the 11 patients whose INR value of 1.5 and above, and 2 (1.94%) out of 103 patients whose an INR below 1.5. There was no significant difference between these two groups in terms of bleeding complications ($p = 0.265$). We detected bleeding complications in 1 (9.09%) out of 11 patients whose blood urea levels above 50 mg/dl and 2(1.94%) out of 103 patients whose blood urea below 50 mg/dl. There was no significant difference between patients whose blood urea level > 50 mg/dl and < 50 mg/dl ($p = 0.265$). No other disease that could cause bleeding diathesis was detected in any of the patients with hemorrhagic complications in the study. We evaluated the all patients according to the type of performed procedure. There were bleeding complications in 3 (2.83%) out of the 106 patients who had undergone only bronchoalveolar lavage. The pulmologists had performed bronchoalveolar lavage and brush swab to 3 patients; bronchoalveolar lavage and mucosal biopsy to 4 patients; bronchoalveolar lavage, brush swab and mucosal biopsy to 1 patient; there was no complication related to the procedure in these groups. There was no significant statistical difference between the patient groups according to the type of procedure ($P = 0.257$). In addition to, we compared the patients in terms of age, febrile neutropenia duration. There was no significant statistical difference in between these groups. The statistical findings were shown in Tables 1 and 2.

Discussion

The importance of FOB has been increased in hematology clinical practice day by day [13]. Clinicians must examine the respiratory system in the initial evaluation of febrile neutropenic patients and the clinicians frequently use diagnostic bronchoscopic techniques for patients who has febrile neutropenic and infiltrations in the their lungs [14]. FOB technics are composed of invasive and semi-invasive methods. Patients with hematological malignancy who is planned to perform FOB are often thrombocytopenic. This situation causes hesitation to clinicians in terms of hemorrhagic complications. Studies with large series had shown that the rate of hemorrhagic complication due to FOB in patients who had normal hemostasis was below 1% [15, 16]. In 1985, Papin et al. had reported 24 patients who had platelet count were below 60×10^9/L and undergone transbronchial biopsy. They detected endobronchial hemorrhage in 4 (6.2%) patients. The mean platelet counts of the patients who had developed hemorrhage were 20.6×10^9/L $\pm$ 10.8×10^9/L, and the mean platelet counts of the patients who had no hemorrhage were 32.4×10^9/L $\pm$ 17.1×10^9/L. There was no statistical significant difference [17]. In 1993, Weiss et al. had evaluated bone marrow transplant recipients who had undergone FOB during the peritransplant period. In this study, there were 66 patients who had been performed FOB and the researchers had

Table 1 Comparisons between various groups in terms of hemorrhagic complications

Variable	Hemorrhagic complication present	Hemorrhagic complication nonpresent	*p* value
Gender			
Female	1 (3.33)	29 (96.67)	1000
Male	2 (2.38)	82 (97.62)	
İmmunosuppressive therapy			
Receive	3 (2.86)	102 (97.14)	1000
Not receive	0 (0.00)	9 (100.00)	
Indication of bronchoscopy			
Pulmonary infiltrates	3 (2.73)	107 (97.27)	1000
İinfiltrates and hemoptysis	0 (0.00)	3 (100.00)	
Hemoptysis	0 (0.00)	1 (100.00)	
Platelet replacement			
Yes	3 (3.49)	83 (96.51)	1000
No	0 (0.00)	28 (100.00)	
Group according to platelet count			
Platelet count 0–30 K/mm^3	1 (3.13)	31 (96.88)	0.624
platelet count 30–50 K/mm^3	0 (0.00)	35 (100.00)	
platelet count 50–100 K/mm^3	2 (4.26)	45 (95.74)	
PT (second)			
PT > 17	1 (9.09)	10 (90.91)	0.265
PT < 17	2 (1.94)	101 (98.06)	
INR			
INR> 1.5	1 (9.09)	10 (90.91)	0.265
INR < 1.5	2 (1.94)	101 (98.06)	
Urea (mg/dl)			
Blood urea > 50	1 (9.09)	10 (90.91)	0.265
Blood urea < 50	2 (1.94)	101 (98.06)	
İntervention type			
Only Bronchoalveolar lavage	3 (2,83)	103 (97.17)	0.257
Bronchoalveolar lavage and brush swab	0 (0.00)	3 (100.00)	
Bronchoalveolar lavage and mucosal biopsy	0 (0.00)	4 (100.00)	
Bronchoalveolar lavage, brush swab and mucosal biopsy	0 (0.00)	1 (100.00)	
BTS classification group			
No evidence of bleeding	0 (0.00)	111 (100.00)	< 0.001
No bleeding	1 (100.00)	0 (0.00)	
Mild bleeding	1 (100.00)	0 (0.00)	

Table 2 Comparison of various groups in terms of hemorrhagic complications

Variable	Hemorrhagic complication present	Hemorrhagic complication non-present	*p* value
Age	55 (47–58)	48 (18–67)	0.295
Febrile neutropenia duration (days)	8.5 (7–10)	11 (3–36)	0.381
Processing input platelet count (k/mm^3)	51 (23–60)	46.60 (5–91.6)	0.920
PT value before intervention (second)	13 (13–31)	13 (9.7–24.7)	0.356
INR value before intervention	1.3 (1.3–2.6)	1.2 (0.8–2.08)	0.099
Blood urea value before intervention (mg/dl)	20 (18–59)	27 (5–110)	0.907

determined the thrombocytopenia threshold as 100 × 10^9/L for these patients. There were hemorrhagic complications in 6 out of 58 patients with platelet counts < 100 × 10^9/L. Out of these 6 patients who developed complications, 4 of them had epistaxis and 2 of them had hemoptysis. In this study, there was no evidence that Fob procedures had increased endobronchial haemorrhage in thrombocytopenic patients [18]. In 2015, Nandagopal et al. had published the results of a study. They had shared data of 150 thrombocytopenic patients who had undergone FOB. They had included 117 patients who had followed up for malignancy in the study. The platelet counts of the patients were below 100 × 10^9/L. There were FOB-related hemorrhagic complications in 10 patients (%6). Nine patients were in the no bleeding group and 1 patient was in the mild bleeding group according to the BTS classification. The statistical data had revealed that bleeding after FOB was not related to platelet counts in this study [19]. In our study, we detected FOB-related bleeding findings in 3 out of 114 patients (2.6%). One patient was in the mild bleeding group according to the BTS classification, and one patient was in the no bleeding group. In one patient, there was mild hemoptysis related to FOB and it regressed after the FOB spontaneously. Need of blood product replacement was not developed. We separated the patients into three groups in terms of input platelet counts before FOB and compared these groups in terms of hemorrhagic complication rates. In first group, there were 32 patients whose platelet counts were between 0 and 30 × 10^9/L. In the second group, there were 47 patients whose platelet counts were 30–50 × 10^9/L, and lastly there were 35 patients whose platelet counts were 50–100 × 10^9/L. There was no significant difference between these groups in terms of hemorrhagic complications. When we analyzed the patients who underwent FOB, there was no significant correlation between the degree of thrombocytopenia and the risk of hemorrhagic complications. Also, we compared the patients according to prothrombin time, INR value, blood urea level, and bronchoscopic procedures (bronchoalveolar lavage, brush swab, mucosal biopsy with forceps). There was no statistically significant difference between the groups in terms of hemorrhagic complications. The results of our study were similar to the previous studies. However, when we compared with old studies, our study was especially important in terms of the patients because the patients who included in this study were homogeneous.

Other important point related to this subject was the prophylactic thrombocyte replacement threshold before FOB. In our study, clinicians had performed prophylactic platelet transfusions to some patients whose platelet counts were below 50 × 10^9/L. The reasons of transfusions were that patients were febrile and aplasic. The most important limitation of this study is that prophylactic platelet transfusions were performed to some of the patients before the procedure. The obtained data in our study showed that there was no significant difference between thrombocytopenia degree and hemorrhagic complication rate. Up to date, there is no international threshold value which is agreed upon for prophylactic platelet replacement. In different centers, clinicians regard the recommendations of various guides and experts' opinions. To clarify this issue, there are needed prospective studies whose include large number patients. As a result, if FOB is performed in multidisciplinary centers by experts, it is safe procedure in terms of hemorrhagic complications in thrombocytopenic patients whose follow up due to hematological malignant disease.

Abbreviations
FOB: Fiberoptic bronchoscopy; BTS: British Thoracic Society; INR: International normalized ratio.

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Authors' contributions
FY has full access to the data, take responsibility for their integrity, and has the final responsibility for the decision to submit the paper for publication. All authors are responsible for the study concept and design, analysis or interpretation of data, drafting of the manuscript, and manuscript revision. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was planned in accordance with the Helsinki Declaration decisions, patient rights regulation and ethical rules. After the approval of Uludag University Faculty Of Medicine Clinical Research Ethics Committee with the decision dated 03 November 2015 and numbered 2015-19/20, the research was started.

Consent for publication
This article does not contain including individual details, images, or videos. All authors agree on the publication permission and declare it.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Rheumatology, University of Health Sciences, Başaksehir Çam and Sakura City Hospital, Istanbul, Turkey. [2]Department of Hematology, Uludag University, Uludag University Faculty of Medicine, Bursa, Turkey. [3]Department of Pulmonary Diseases and Tuberculosis, Uludag University, Uludag University Faculty of Medicine, Bursa, Turkey.

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