Effectiveness of antiplatelet thromboprophylaxis in myeloma patients using immunomodulators in Kurdistan region-Iraq

Rezhin N. Rajab*, Firiad Hiwaizi*, Ahmed K. Yassin, Kanar J. Karim***, Abid M. Hassan****, Hisham A. Getta*****, Najmaddin Salih Husen Khoshnaw***, Sana D. Jalal*****, Akram M. Mohammed***, Kawa M. Hasan**, Dana A. Abdulla*****, Ameer I.A. Badi******, Nassir A. S. Al-Allawi******, Banaz M. Safar***, Basil K. Abdulla***, Rawand P. Shamoon*******, Truska A. Amin***, Zeki A. Mohamed****, Ali I. Mohammed*****, Diveen J. Hussein*, Nawsherwan S. Mohammed**.**

Department of Hematology, Nanakali Hospital, Erbil, Kurdistan region, Iraq,**Department of of Medicine, College of Medicine, Hawler Medical University, Kurdistan region, Iraq,Department of Hematology, Hewa Cancer Hospital, Sulaymaniyah, Ministory of Health, Kurdistan region, Iraq,****Department of Hematology, Azadi Teaching Hospital, Duhok. Kurdistan region, Iraq,*****Department of Pathology, College of Medicine, University of Sulaymaniyah, Kurdistan region, Iraq,******Department of Hematology, College of Medicine, University of Duhok, Duhok, Kurdistan region, Iraq,*******Ministry of Higher Education, Kurdistan region, Iraq**

Correspondence:rezhenbotany@gmail.com

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ABSTRACT

Objective: To evaluate the effect of antiplatelet in preventing thrombosis in multiple myeloma patients treated by immunomodulatory drugs.

Methods: The study was conducted on one hundred seventy-six patients treated in the hematology unit in three centers in the Kurdistan region of Iraq from February 2014 to July 2019, of them, one hundred two males and seventy-four females. Demographic data were obtained from the patient's file, including the type of immunomodulatory drugs, type of antiplatelet, thrombotic events and their site, presence of other comorbidities, and the time onset between diagnosis and beginning of the thrombotic events.

Results: Regardless of the type of therapy in the study sample, 11.1% who were taking antiplatelet therapy developed a thrombotic attack compared with 46.9% who were not receiving the anti-platelets treatment. The incidence of the thrombotic attack among those myeloma patients who used immunomodulatory drugs was 9.6% who were on antiplatelet drugs, which is significantly lower than the rate (52%) among patients not taking the antiplatelet drugs.

Conclusions: As multiple myeloma is a malignant disease and treatment with immunomodulatory drugs associated with increased risk of thrombosis, the antiplatelet medicine is a useful measure when used as a prophylaxis for preventing thrombosis.

Keywords: Multiple myeloma, Thrombosis, Antiplatelet .

فعالية العقاقير المضادة للأقراص الدمويه للوقاية من الجلطة الوعائية لمرضى الورم النقياني المتعدد مستخدمي العقاقير المغيره للمناعة في اقليم كوردستان العراق

ريزين نوزاد رجب*،فرياد حويزي*،احمد خضير ياسين،كنار جلال كريم***، عابد محي الدين حسن****، هشام عارف كطه*****، نجم الدين صالح حسين خوشناو***، سانا دلاور جلال*****،أكرم محمود محمد***، كاوه محمد أمين حسن**، دانا احمد عبدالله*****، امير ابراهيم احمد******، نصيرالعلاوي******، بناز مبارك صفر***، باسل كاظم عبدالله***، روند بولس شمعون*******، تروسكه ئاوات أمين***، زكي علي محمد****، علي ابراهيم محمد*****،ديفين جلال حسين*، نوشيروان صادق محمد****

*قسم امراض الدم-مستشفى نانكلي للامراض الدم-اربيل-اقليم كردستان-العراق،**قسم الباطنية-كلية طب-جامعة هولير الطبية-اقليم كردستان-العراق،***قسم امراض الدم-مستشفى هيوا للامراض الدم و السرطان-سليمانية-اقليم كردستان-العراق،****قسم امراض الدم-مستشفى ازادي التعليمي-دهوك-اقليم كردستان-العراق،*****قسم علم الامراض-كلية طب-جامعة سليمانية-اقليم كردستان-العراق،******قسم امراض الدم-كلية طب-جامعة دهوك-دهوك-اقليم كردستان-العراق،*******وزارة التعليم العالي-اقليم كردستان-العراق**

الخلاصة

الهدف : تقييم تأثير مضاد الاقراص في منع تجلط الدم في العديد من مرضى الورم النقياني المتعدد الذين عولجوا بأدوية مناعية.

الطريقة : أجريت الدراسة على مائة وستة وسبعين مريضاً عولجوا في وحدة أمراض الدم في ثلاثة مراكز في إقليم كردستان العراق منفبراير 2014 إلى يوليو 2019 ، منهم مائة واثنان وأربعة وسبعون أنثى .تم الحصول على البيانات الديموغرافية من ملف المريض ، بما فيذلك نوع الأدوية المعدلة للمناعة ، ونوع مضاد الاقراص ، والأحداث التخثرية وموقعها ، ووجود أمراض مصاحبة أخرى ، ووقت البدء بين التشخيص وبداية الأحداث الخثارية.

النتائج : بغض النظر عن نوع العلاج في عينة الدراسة ، فإن11.1 ٪ ممن تناولوا العلاج المضاد الاقراص طوروا نوبة تخثرية مقارنة بـ46.9 ٪ممن لم يتلقوا العلاج المضاد الاقراص .كانت نسبة حدوث الجلطة الخثارية بين مرضى الورم النقياني المتعدد الذين استخدموا الأدوية المناعية 9.6 ٪ ممن كانوا يتناولون الأدوية المضادة للاقراص ، وهو أقل بكثير من المعدل 52) ٪ (بين المرضى الذين لا يتناولون الأدوية المضادة للاقراص.

الاستنتاجات : بما أن الورم النقوي المتعدد هو مرض خبيث وعلاج بالأدوية المناعية المرتبطة بزيادة خطر تجلط الدم ، فإن الدواء المضاد للاقراص هو مقياس مفيد عند استخدامه كوقاية للوقاية من تجلط الدم.

الكلمات المفتاحية : الورم النقوي المتعدد ، تخثر ، مضاد الاقراص.

INTRODUCTION

Cancer patients are at high risk for thrombosis and pulmonary embolism, especially when known risk factors present, such as the history of venous thromboembolism(VTE), immobilization, dehydration, obesity, old age, and other factors [1, 2]. Genetic inheritance and mutations that predispose to thrombosis[3].

As multiple myeloma is a malignant disease that affects both genders, there is increased incidence of VTE that is highest during the first 3 to 4 months following diagnosis and occurs in approximately 3 to 4 percent of patients receiving either dexamethasone alone or Melphalan Prednisolone, but it is much higher when newer agents are combined with dexamethasone and melphalan such as thalidomide and lenalidomide[4, 5].

Thalidomide is effective in treating patients with multiple myeloma[6]. High-dose dexamethasone, when combined with Lenalidomide, is one of the active and highly accepted strategies for treating patients with relapsed and refractory multiple myeloma[7], and is similarly effective in patients with newly-diagnosed multiple myeloma[8]. Though, high-dose dexamethasone plus lenalidomide is associated with venous thromboembolism rates of 25%-67% in patients with newly-diagnosed MM [8].

Prevention of thrombosis has become a significant concern during the treatment of multiple myeloma because of increased use of combined immunomodulatory agent-based therapy [9-12]. Prevention of VTE is based on the assessment for known risk factors for VTE such as myeloma-related (hyper viscosity), therapy-related, individual factors (age, history of VTE, inherited thrombophilia, obesity, immobilization, central venous line, infections, surgery and administration of erythropoietin) and comorbidities (acute infection, diabetes mellitus, cardiac or renal disease)[13].

Because many myeloma patients are taking aspirin for other reasons(such as a cardiac cause or as prophylaxis)and it needs no monitoring while it is easily accessible and cheap, and the recommended dose of aspirin is between 81-325 mg/day is an option for those myeloma patients with at least one or no risk factor[14].

Data suggests that aspirin is as effective as warfarin, compared with LMWH except in elder age group were LMWH showed more efficacy than warfarin [14]. Furthermore, when comparing aspirin with other anticoagulant aspirin carries a significantly lower risk of complication than its counterpart anticoagulants. There are some concerns regarding aspirin use, such as there is a chance of aspirin resistance and no specific information regarding effective dose. Nevertheless, aspirin remains a reasonable prophylaxis option in low-risk multiple myeloma patients[15].

The aim of the study is to evaluate the effectiveness of antiplatelet in preventing thrombosis in a patient with multiple myeloma receiving immunomodulatory drugs.

PATIENTS AND METHODS

It's a retrospective study that was conducted on one hundred seventy-six symptomatic multiple myeloma patients treated in hematology unit in three centers in Kurdistan region of Iraq(Nanakali hospital at Erbil, Hiwa hospital at Suleimani, and Azadi hospital at Duhok) from February 2014 to July 2019, of them, one hundred two males and

seventy-four females. Demographic data were obtained from the patient's file, including the stage of myeloma according to the revised criteria by an international working group in myeloma (reference) type of immunomodulatory drugs, type of antiplatelet (aspirin 81mg- 325mg or clopidogrel 75mg for those who had a gastric problem, thrombotic events and their site, presence of other comorbidity and the time onset between diagnosis and beginning of the thrombotic events.

We recruited all newly diagnosed as well as symptomatic multiple myeloma in cancer-treating centers in the Kurdistan region of Iraq. Those cases with a history of thrombosis prior to the diagnosis of multiple myeloma and those who were on anticoagulation due to other reasons had been excluded.

The only available immunomodulatory medications at the time of the study were (thalidomide and lenalidomide)

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 22). Numerical variables were summarized by calculating the means and the standard deviations. Categorical variables were presented in the form of frequencies and proportions. The Chi-square test of association was used to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells of the table was less than 5. A p-value of ≤ 0.05 was considered statistically significant.

The ethical approval of the present study was obtained from the Kurdistan Board for Medical Specialties (KBMS) in Erbil in 2016.

RESULTS

The total number of the studied sample was 176 patients who had symptomatic multiple myeloma. Their mean age ± SD was 60.49 ± 11.56 years, the median was 61 years, and the age range was 35-89 years. Table 1 shows that the highest proportion of the patients (31.8%) were in the age group 60-69 years, and 29% were in the age group 50-59 years. The ECOG performance stage was 3, 4, 5 among 59.1% of the patients, and ECOG stage 0, 1, 2 in 40.9% of them. About (54.5%) of the patients were of stage II, (29%) were of stage III, and the rest (16.5%) were of stage I (Table 1).

Antiplatelet was used in 144 (82%) of cases, of which 16 (11.1%) developed thrombosis while only 32(18%) were not on antiplatelet agents, of which around 15 (46.9%) developed thrombotic attack. ($p < 0.001$)as shown in table 2.

Patients who were using immunomodulatory drugs seen in Table 3 describes the association of thrombosis and anti-platelet use in each of the treatment groups. Considering patients not taking the immunomodulatory drugs, a significant association was found between anti-platelets intake and the incidence of thrombosis after MM ($p >0.546$). Regarding patients who were on Lenalidomide only, the rate of thrombotic attack was 5.4% among patients taking the anti-platelets therapy compared with 50% among patients not taking them ($p = 0.014$). If we consider patients who were using thalidomide, the rate of thrombotic attack among patients taking the antiplatelet drugs was 9.5% compared with 30.8% among patients not taking the mentioned drugs ($p = 0.056$). Finally, significant ($p = 0.002$) association was detected between the use of anti-platelets and the incidence of thrombosis after MM among patients who were exposed to lenalidomide and thalidomide sequentially due to toxicity or side effects. The incidence was 21.4% among patients taking the anti-platelets, compared with 100% among patients not taking these drugs. A total number of deaths were 33 out of 176 cases, of which 12 of them were due to thrombosis or thrombosis related complications.

Table 1. Basic characteristics of the studied patients.

Age (years)	**No.**	**(%)**
< 50	30	(17.0)
50-59	51	(29.0)
60-69	56	(31.8)
≥ 70	39	(22.2)
Gender		
Male	102	(58.0)
Female	74	(42.0)
Performance status according to the Eastern Cooperative Oncology Group (ECOG)		
Stage 0,1,2	72	(40.9)
Stage 3,4,5	104	(59.1)
Stage of disease (international staging system)		
Stage I	29	(16.5)
Stage II	96	(54.5)
Stage III	51	(29.0)
Total	176	(100.0)

Table 2. Incidence of thrombotic attack after Multiple Myeloma by antiplatelet intake.

	Thrombotic attack after MM						
Use of anti-platelets	No		Yes		Total		
	No.	(%)	No.	(%)	No.	(%)	P*
No	17	(53.1)	15	(46.9)	32	(100.0)	
Yes	128	(88.9)	16	(11.1)	144	(100.0)	< 0.001
Total	147	(83.5)	29	(16.5)	176	(100.0)	

*By Chi-square test.

Table 3. Incidence of thrombotic attack after Multiple Myeloma by antiplatelet intake in each of the chemotherapy groups.

	Thrombotic attack after MM						
	Absent		Present		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Neither lenalidomide nor thalidomide							
Use of anti-platelets							
No	5	(71.4)	2	(28.6)	7	(100.0)	
Yes	15	(78.9)	4	(21.1)	19	(100.0)	>0.999*
Total	20	(84.6)	6	(15.4)	26	(100.0)	
Lenalidomide only							
Use of anti-platelets							
No	3	(50.0)	3	(50.0)	6	(100.0)	
Yes	35	(94.6)	2	(5.4)	37	(100.0)	0.014*
Total	38	(88.4)	5	(11.6)	43	(100.0)	
Thalidomide only							
Use of anti-platelets							
No	9	(69.2)	4	(30.8)	13	(100.0)	
Yes	67	(90.5)	7	(9.5)	74	(100.0)	0.056*
Total	76	(87.4)	11	(12.6)	87	(100.0)	
Both lenalidomide and thalidomide							
Use of anti-platelets							
No	0	(0.0)	6	(100.0)	6	(100.0)	
Yes	11	(78.6)	3	(21.4)	14	(100.0)	0.002*
Total	11	(55.0)	9	(45.0)	20	(100.0)	

*By Fisher's exact test.

In Table 4, we see the incidence of the thrombotic attack among those patients who were on immunomodulatory drugs was 9.6% in those taking antiplatelet drugs, which is significantly lower than the rate (52%) among patients not taking the anti-platelet drugs ($p < 0.001$).

Table 4. Incidence of thrombotic attack after Multiple Myeloma by antiplatelet intake in patients taking immunomodulatory drugs.

	Thrombotic attack after MM						
Use of anti-platelets	Absent		Present		Total		
	No.	(%)	No.	(%)	No.	(%)	p
No	12	(48.0)	13	(52.0)	25	(100.0)	
Yes	113	(90.4)	12	(9.6)	125	(100.0)	< 0.001*
Total	125	(83.3)	25	(16.7)	150	(100.0)	

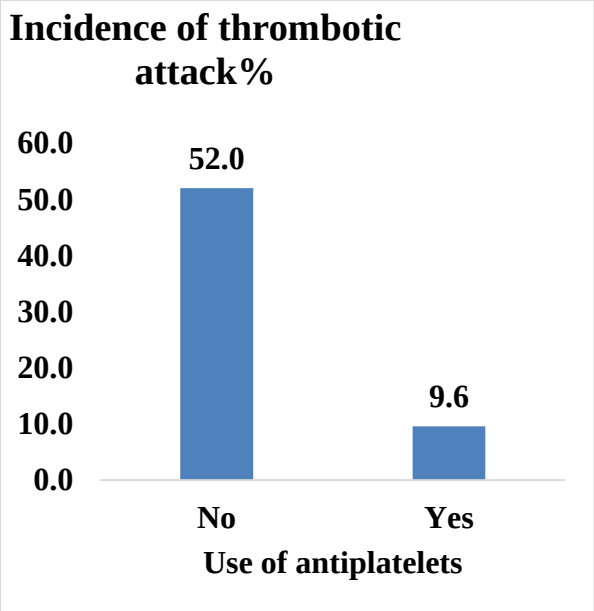

Figure 1. Incidence of thrombotic attack after Multiple Myeloma by antiplatelet intake in patients taking immune-modulatory drugs.

DISCUSSION

The development of thrombosis is regarded as a life-threatening complication of cancer patients, especially myeloma population because of increased use of new modalities of treatment like immunomodulators, which can lead to increase inpatient morbidity, treatment discontinuity and requirement of anticoagulation which is additional risk of morbidity, here comes the role of preventing thrombosis as an essential consideration while treating multiple myeloma patients [16-18].

In our study anti-platelet was given to most patients, the only a small group did not receive it either because of contraindications, patient's will or doctor decision. The thrombotic attacks after diagnosis and treatment of multiple myeloma include (DVT (deep venous thrombosis), PE (pulmonary embolism), stroke, MI (myocardial infarction)) most of them had been confirmed by clinical episode and imaging technique of (ECG, Doppler study, MRI brain, CT angiography). We considered comorbidities in all the patients that might increase the risk of thrombosis, but the results were non-significant.

A recent study has concluded that the rate of hospitalization for thrombosis related complication was double for cancer patients when compared with the general population(1.8 vs. 0.8 respectively), and this risk is about eight times higher than general population within the first year of cancer diagnosis but drop down to double then after[15,19].

The recent trials have found that thromboprophylaxis with aspirin seemed to be effective[20]. The combination of lenalidomide-bortezomib dexamethasone with aspirin prophylaxis found hopeful results, with a severe thromboembolism incidence of 5%[21].

In our study, we concluded that myeloma patients treated with multi-agent chemotherapy and immunomodulatory are at increased risk of thrombosis. Multivariate analysis, including all patients, revealed that subsequent use of lenalidomide, thalidomide was the most significant risk factor for thrombosis during treatment ($P < 0.002$).

Similar to our study another study also concluded that, in patients with newly diagnosed multiple myeloma who have no risk for thrombosis, no previous need for antiplatelet or anticoagulation treatment, the use of aspirin as prophylaxis for cases who treated with lenalidomide lead to a lower level of thrombosis when compared with those who didn't receive aspirin with the incidence of thrombosis around 2% in the aspirin group and there were neither reported case of CVA nor sudden death[22].

In the study by Antonio et al., The incidence of thrombosis in patients with myeloma without prophylaxis was around 15% for those who received thalidomide with melphalan and was approximately 20% for those treated with dexamethasone and thalidomide while the incidence of thrombosis dropped to 6% through 6 months for those who received prophylaxis aspirin

[23,24] while in our study patients on thalidomide plus dexamethasone and didn't use aspirin the incidence of thrombosis was 30% as compared to those who used aspirin 9% but statistically was non-significant.

CONCLUSION

Prophylactic antiplatelet is strongly recommended in patients receiving immunomodulatory alone or in combination with chemotherapy in symptomatic myeloma patients.

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