Clinically Useful and Cost-Effective of Recombinant Human Thrombopoietin in Treatment of Chemotherapy Induced Thrombocytopenia

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Research

Keywords: recombinant human thrombopoietin, rhTPO, chemotherapy-induced thrombocytopenia, economic analysis, days of platelet increasing

Posted Date: November 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-104357/v1

Abstract

Background

The bone marrow suppression during chemotherapy will cause severe platelet decline in the human body, resulting in critical organ hemorrhage and intracranial hemorrhage. Therefore, the efficacy and economics of recombinant human thrombopoietin (rhTPO) in treating different degrees of thrombocytopenia caused by chemotherapy were analyzed.

Methods

From January 2018 to July 2019, 233 with diagnosed lung cancer treated with the course of chemotherapy or chemoradiotherapy were enrolled. After treatment with chemotherapy or chemoradiotherapy, they all happened thrombocytopenia and received rhTPO. We divided patients into three groups according to the level of platelet decline. Changes in blood platelet count, treatment plan and cost performance between them were analyzed.

Results

Of all the included patients, 39.5% was undergoing concurrent radiotherapy or chemotherapy; 42.9% had thrombocytopenia of grade II; 40.3% had thrombocytopenia of grade III; 16.7% had thrombocytopenia of grade IV; 52.8% postponed the next cycle of chemotherapy or radiotherapy due to platelet decline; 12.0% changed the treatment plan for malignant tumors due to severe platelet decline; 15.5% reduced the dose of chemotherapy drugs due to thrombocytopenia; 23.6% had platelet transfusions during this period. During the extended hospitalization period caused by thrombocytopenia, the medical expenses of patients would increase significantly, which was dominated by the cost of rhTPO.

Conclusions

For different degrees of thrombocytopenia, the treatment of rhTPO could increase platelet counts effectively. During the treatment, patients might have varying degrees of economic and the difference between the treatment duration of different patients.

Background

As human society develops, medical conditions and disease treatments are becoming increasingly advanced. Consequently, human lifespan and life behaviors have undergone tremendous changes. At present, malignant tumors are a critical factor affecting human health and lifespan [1-3]. With the increase in the morbidity of malignant tumors, the treatments of malignant tumors are also being explored intensely. Currently, the standard treatments of malignant tumors include surgery, radiotherapy, chemotherapy, and targeted therapy. Due to its comprehensive advantages in side effects and curative effects, chemotherapy has become the primary treatment for malignant tumors at present [4, 5]. However, during the courses of chemotherapy, negative impacts on normal human cells are inevitable. Of all the

side effects, the most serious is bone marrow suppression. This toxic response will make the host suffer severe platelet decline, leading to critical organ hemorrhage and even intracranial hemorrhage, which is very likely to threaten the lives of patients [6].

Thrombocytopenia has always been an essential issue in tumor treatment. However, consensus on the best way to prevent and/or treat this vital complication is not reached [7, 8]. Currently, recombinant human thrombopoietin (rhTPO) injection therapy is one of the primary treatment options for thrombocytopenia. Before chemotherapy and within five days after chemotherapy, Winer et al. (2017) administered 100 mg eltrombopag or placebo to tumor patients randomly at a ratio of 2:1. They found that the platelet count of patients administered with eltrombopag before chemotherapy was higher than that of placebo [9]. After a clinical study on thrombocytopenia caused by chemotherapy, Weycker et al. (2019) suggested that thrombocytopenia caused by chemotherapy could lead to delayed, reduced, or discontinued chemotherapy doses, as well as an increased risk of severe hemorrhage events [10].

Despite the numerous researches on platelet-boosting drugs, explorations about grading comparisons based on rhTPO are rarely reported. Therefore, the method of retrospective analysis was utilized to analyze the occurrence of thrombocytopenia at all grades, the utilization of drugs, and the costs of treatment, hoping to provide theoretical support for treating patients with thrombocytopenia.

Methods

Selection of subjects

From January 2018 to July 2019, 311 tumor patients treated in the hospital were chosen. Finally, 233 patients were included for retrospective analysis, including 179 male patients and 54 female patients. The average age of all patients was 61.94 ± 7.87 years old. The inclusion and exclusion criteria were shown below.

Inclusion criteria: (1) patients diagnosed as malignant tumors after examination; (2) the estimated survival time obtained at the initial diagnosis was more significant than three months; (3) before chemotherapy, the platelet count was more than $100*10^9$/L, the white blood cell count was more than $4.0*10^9$/L, and the hemoglobin was more than 100g/L; (4) no organ dysfunctions and no hematological diseases except for malignant tumors; (5) chemotherapy plans designed after diagnosis were standard plans of drug combination containing platinum; (6) serum creatinine, urea nitrogen, and transaminase were all below 1.5 times the upper limit of normal levels; (7) 18 years old and above; (8) patients had no contraindications to the usage of rhTPO and were willing to receive the treatment of rhTPO; (9) the platelet count was less than $75*10^9$/L after chemotherapy; (10) patients and their families were informed about this experiment and signed informed consent forms.

Exclusion criteria: (1) active hemorrhage was found; (2) with more than one primary malignant tumor; (3) women who were breastfeeding or pregnant.

Grading of platelet decline

According to the classification of thrombocytopenia stipulated by the World Health Organization, thrombocytopenia after chemotherapy was divided into I-IV grades [11, 12]. Grade I: the platelet count was more than $75*10^9$/L; grade II: the platelet count was $50*10^9$/L and $<75*10^9$/L; grade III: the platelet count was $\geq 25*10^9$/L and $<50*10^9$/L; grade IV: the platelet count was less than $25*10^9$/L.

Therapeutic plans

Patients were diagnosed to have some kinds of primary malignant tumors. After the medication of chemotherapy drugs, in the peripheral blood of patients, the platelet count declined to below $75*10^9$/L. After excluding other possible non-chemotherapy causes of platelet decline, the patients were diagnosed as thrombocytopenia. Once the diagnosis was made, the confirmed patients would be treated with rhTPO. rhTPO was given though daily subcutaneous injection at a dosage of 15000U. During the rhTPO treatment, patients received blood routine examinations every day. The days of rhTPO treatment, the day when platelet count started to increase, and the length of extended hospital stays due to platelet decline were recorded [13]. The entire observation process was not terminated until the patient was discharged.

Economic analysis methods

Economics analysis included the expenses of drugs used, the expenses of non-drugs, and the expenses of platelet transfusion. All expenses during the hospitalization of each patient were recorded before the patient was discharged. During rhTPO treatment, all rhTPO usage costs, all drug usage costs, the platelet usage costs, and non-drug costs were recorded. During the hospitalization, some analysis was performed because of the increase or decrease in the platelet count of patients.

Statistical methods

SPSS 22.0 statistical software was used for data processing and analysis [14]. If the measurement data followed the normal distribution, they would be expressed in the form of mean ± standard deviation, and the difference between the three groups was analyzed by variance analysis. Otherwise, they were expressed by median and upper-lower quartiles; meanwhile, the difference between the two groups was tested by the Mann-Whitney U test, and the difference between the three groups was tested by Kruskal-Wallis H test [15]. The count data were expressed by the number of cases and the composition ratio, and the comparison of the composition ratio of two or more groups used the χ^2 test. $P<0.05$ indicated the statistical significance of the difference.

Results

Descriptive analysis of included patients

The general information of the included patients was shown in Figure 1. Generally, the included patients were older; the average age of all patients reached 61.94 years. The youngest patient was 26 years old,

and the oldest patient was 79 years old. As shown in Figure 1 above, Of the selected 179 male patients and 54 female patients, Also, 100 patients had thrombocytopenia of grade II, accounting for 42.9%; 94 patients had thrombocytopenia of grade III, accounting for 40.3%; 39 patients had thrombocytopenia of grade IV, accounting for 16.7%. Ninety-two patients were undergoing concurrent radiotherapy or chemotherapy during the rhTPO treatment of thrombocytopenia, which accounted for 39.5%. Besides, 123 patients postponed the next cycle of chemotherapy or radiotherapy due to platelet decline, accounting for 52.8%; 28 patients changed the treatment plan for malignant tumors due to severe platelet decline, accounting for 12.0%; 36 patients reduced the dose of chemotherapy drugs due to thrombocytopenia, accounting for 15.5%; 55 patients had platelet transfusions during this period, accounting for 23.6%.

The ages of patients and the days of rhTPO treatment were counted. After rhTPO treatment, the day when platelet count started to increase was counted. Meanwhile, the postponed days of chemotherapy, the length of extended hospital stay, and the increased costs of hospitalization due to platelet decline were counted. The initial therapy of patients was shown in Table 1.

Patients included were generally older, with an average age of 61.94 years old; the youngest patient was 26 years old, and the oldest patient was 79 years old. The standard deviation of the rhTPO treatment days of patients was huge. Personal differences might cause this. The median of rhTPO treatment days was 5; the average value was 5.99, indicating that the treatment duration of some patients was longer. The most prolonged treatment duration reached 40 days. Due to personal differences of patients, the day when platelet count started to increase was different. Some patients began to have increased platelet levels on the 1st day of rhTPO treatment, while some patients showed improved platelet levels after 21 days of rhTPO treatment. The postponed days of the next chemotherapy cycle reached 91, consistent with the length of extended hospital stay due to platelet decline. As indicated in the increased hospitalization costs due to platelet decline, the increases in hospitalization costs due to the platelet decline were tremendous; the possible reason was that patients suffering from malignant tumors require not only the treatment of thrombocytopenia but also the monitoring of other physical conditions.

Comparison of rhTPO usage between patients with different degree of thrombocytopenia

The comparison of rhTPO usage between patients with different degree of thrombocytopenia and the information of radiotherapy/chemotherapy were shown in Table 2.

The differences in “days of rhTPO treatment,” “the day when platelet count started to increase,” “postponed days of the next cycle of chemotherapy,” “length of extended hospital stay due to platelet decline,” “increased hospitalization costs due to platelet decline,” and “with or without platelet transfusion” of patients with different thrombocytopenia grades were statistically significant. Also, the difference in “with or without concurrent radiotherapy/chemotherapy” of the three thrombocytopenia degrees was statistically significant ($P < 0.05$). In patients with grade II thrombocytopenia, those who received concurrent radiotherapy/chemotherapy accounted for 32%. In patients with grade III thrombocytopenia, those who received concurrent radiotherapy/chemotherapy accounted for 48.9%. In

patients with grade IV thrombocytopenia, those who received concurrent radiotherapy/chemotherapy accounted for 35.9%. Therefore, the difference in “with or without concurrent radiotherapy/chemotherapy” of patients with grade II and grade III thrombocytopenia was huge. Then, the pairwise analyses of χ^2 values and P values were performed.

The difference in concurrent radiotherapy/chemotherapy of patients with grade II and grade III thrombocytopenia was statistically significant ($P < 0.05$), that of patients with grade II and IV thrombocytopenia was not statistically significant ($P > 0.05$), and that of patients with grade IV and III thrombocytopenia was also not statistically significant ($P > 0.05$). These results were with the results presented in Table 3.

Pairwise analyses obtained the statistical data between the two groups, as shown in Table 3 and Table 4.

In Tables 3 and 4, the difference in each variable between patients with grade II and IV thrombocytopenia was statistically significant ($P < 0.05$). Between patients with grade III and grade IV thrombocytopenia, only the variable “with or without platelet transfusion” had a statistically significant difference ($P < 0.05$). Besides, the difference in each variable between patients with grade II and III thrombocytopenia was statistically significant ($P < 0.05$).

Economic analysis results

After statistics, the expenses of all patients were obtained. The results were shown in Figure 2. The medical expenses of patients during the extended hospital stay due to platelet decline increased dramatically, in which the expenses on rhTPO occupied the majority. Besides, during the same period, the expenses on other drugs were the same as those on rhTPO, indicating that the medication of patients during this period was dominated by rhTPO. However, in severe cases, some patients required platelet transfusion. Therefore, extra expenses on platelet transfusion were generated. The above figure also suggested that patients with IV thrombocytopenia had the most platelet transfusion, resulting in increased costs during treatment; as the degree of thrombocytopenia increased, the cost of treatment also increased.

The length of extended hospital stays and the increased cost of hospitalization due to platelet decline were described. As the platelet decreased, the length of hospital stays and the costs of hospitalization would increase. Therefore, thrombocytopenia would bring more significant economic burdens on patients.

Discussion

Lung cancer has the highest morbidity and mortality in worldwide and chemotherapy is one of the important treatments for advanced lung cancer. There are many adverse reactions to chemotherapy drugs and patients often give up because they cannot tolerate the adverse reactions of chemotherapy. Thrombocytopenia is a common adverse blood system reaction during chemotherapy, which can cause

bleeding, and even death in severe cases. Different degrees of thrombocytopenia caused by chemotherapy refers to the bone marrow suppression caused by chemical drugs [18, 19]. Currently, rhTPO is a common clinical drug applicable for thrombocytopenia caused by chemotherapy; it has been confirmed to have superior clinical efficacy in increasing the platelet count [20]. rhTPO is currently the most vital hematopoietic growth factor found in the myeloid system, which is the most potent acting factor of megakaryocytes. This study found that rhTPO can reduce the degree of PLT reduction caused by chemotherapy or chemoradiotherapy in patients with lung cancer. rhTPO can be used when the PLT decreases in the II degree, which can accelerate the return of PLT to normal levels and decrease relevant treatment cost.

Study has shown that the decrease in PLT after chemotherapy usually for 1 week after the start of chemotherapy, which can be reduced to a minimum around 10 days, and then gradually recovered after 2 to 3 weeks [21]. Treatment of PLT reduction is also particularly important in the treatment of cancer patients. Treatment options include IL-11, the use of rhTPO, and infusion of PLT [22]. PLT infusion can reduce bleeding complications, but PLT infusion also has potential disadvantages, such as repeated infusions can increase blood transfusion response and transfusion infection. The risk and the probability of producing anti-PLT antibodies related to transfusion that sources are relatively limited, what's more, increase medical cost. At present, clinical trials in China and abroad have proven that rhTPO can effectively reduce the degree of PLT reduction after chemotherapy in solid tumor patients, shorten its duration, promote the recovery of PLT counts, and is well tolerated [23]. We focused on the effects of rhTPO clinical application, as well as the economic advantages of rhTPO. The purpose of this study is to retrospectively analyze the importance of exploring the clinical application of rhTPO in the treatment of PLT decline time, because it has a certain impact on the minimum value of PLT and recovery after intensive treatment to reduce the severity of early PLT decline and the loss of PLT demand rate. As shown in the results, rhTPO could increase the platelet count in patients with thrombocytopenia effectively. Our study showed that, after rhTPO treatment, patients with PLT reductions of □, □, and □ degrees showed that the time of PLT recovery after rhTPO treatment gradually extended, and the treatment time of rhTPO was the same, the proportion of PLT infusion gradually increased. For patients with the reducing PLT of grade III and IV, the proportion of patients who needed PLT infusion was significantly higher than that of patients with reducing PLT of grade II. Prolonged hospital stays due to thrombocytopenia also gradually increased. In addition, our research results show that the median time to use rhTPO after □, □, and □ degrees thrombocytopenia was 5 days, 6 days and 6 days, respectively which was statistically different. Although the value was not very different, we thought this might be caused by more patients using platelet transfusion at □, and □ degrees thrombocytopenia which due to the shortened rhTPO use.

It can be seen from our data that the cost of hospitalization in II, III, and IV levels is rising. Treatment costs include direct costs, indirect costs, and hidden costs. The direct cost reflects the medical resources used in the course of the disease, including the cost of hospitalization, medicine, and consultation. Due to the different stages of lung cancer patients, different treatment options, physical conditions, age, and economic conditions. Among treatment costs, direct dial-up treatment costs are the most obvious explicit costs, while indirect costs and hidden costs are more predictable. From the perspective of the hospital,

this study only considers direct costs. The analysis showed that the total drug costs, inspection costs, hospitalization costs, and average total costs (the average direct costs incurred during the hospitalization of each person) suggest that the □ degrees cost is the lowest, followed by the □ degrees, and the highest is the □ degrees.

Despite the achieved research results, limitations were found in the exploration process. Since the above analyses were retrospective, accurate data on the efficacy of rhTPO could not be obtained. Therefore, in the future, clinical trials would be performed to consolidate the above results. Besides, while exploring the usage of TPIAO, no control groups were set; thus, the results were not sufficiently robust.

Conclusion

Pay close attention to the status of PLTs after chemotherapy, and use TPO in time, especially in the case of II degree PLT decline. It can shorten the duration of thrombocytopenia, avoided or reduced the transfusion of "platelet PLT suspension". It may reduce the cost of treatment for patients. Therefore, it is worthy of clinical promotion and application.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Institutional review board approval was obtained at Zhejiang Cancer Hospital and was in accordance with the guidelines of the Helsinki Declaration (as revised in 2013) and individual consent for this retrospective analysis was waived.

Consent for publication

Not applicable.

Availability of data and materials

Authors confirm that all relevant data are included in the article.

Competing interests

The authors declare that they have no competing interests.

Funding

Funding for this study has been provided Zhejiang Traditional Chinese Medicine Science and Technology Plan (NO. 2021ZQ013).

Authors' contributions

WWX, SL, ZYP, and SZB contributed to the conception and design of the study. WWX, XYB and SL performed the data analysis. WWX, SL, and SZB drafted the manuscript. ZYP critically revised the manuscript for its intellectual content. All authors read and approved the final manuscript

Acknowledgements

Not applicable.

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Tables

Table 1 Descriptive analysis of initial therapy

Indicators	Mean value ()	Standard deviation (s)	Median (M)	Upper and lower quartile (P_{25}, P_{75})	Minimum (Min)	Maximum (Max)
Days of rhTPO treatment	5.99	4.30	5.00	3,00,7,50	1	40
The day when platelet count started to increase	5.27	3.88	4.00	3,00,7,00	0	21
Postponed days of the next cycle of chemotherapy	4.98	8.61	2.00	0,7.00	0	91
Length of extended hospital stay due to platelet decline	4.44	7.35	3.00	0,7.00	0	91
Increased hospitalization costs due to platelet decline	6932.45	4790.42	6048.00	4032,00,8566,00	1008.0	42120.0

Table 2 The usage and treatment process of rhTPO

Features	Thrombocytopenia degree of patients treated by rhTPO			χ2 values	P values
	Grade II (n=100)	Grade III (n=94)	Grade IV (n=39)		
Gender					
Male	80 (80.0%)	72 (76.6%)	27 (69.2%)	1.832	0.400
Female	20 (20.0%)	22 (23.4%)	12 (30.8%)		
Age (±s, years old)	60.66 ± 8.47	62.84 ± 7.33	63.03 ± 7.20	2.337	0.099
With or without concurrent radiotherapy/chemotherapy					
Without	68 (68.0%)	48 (51.1%)	25 (64.1%)	6.069	0.048
With	32 (32.0%)	46 (48.9%)	14 (35.9%)		
Whether to postpone the next cycle treatment					
Yes	56 (56.0%)	40 (42.6%)	14 (35.9%)	5.921	0.052
No	44 (44.0%)	54 (57.4%)	25 (64.1%)		
Whether to change the plan					
Yes	85 (85.0%)	88 (93.6%)	32 (82.1%)	4.962	0.084
No	15 (15.0%)	6 (6.4%)	7 (17.9%)		
Whether to reduce the chemotherapy drug dosage					
Yes	85 (85.0%)	81 (86.2%)	31 (79.5%)	0.970	0.616
No	15 (15.0%)	13 (13.8%)	8 (20.5%)		
Days of rhTPO treatment	5.00 (3.00, 6.00)	6.00 (4.00, 8.00)	6.00 (4.00, 11.00)	16.319	<0.01
The day when platelet count started to increase	3.00 (2.00, 5.00)	5.50 (3.00, 8.00)	3.00 (0.00, 8.00)	31.828	<0.01
Postponed days of the next cycle of chemotherapy	0.00 (0.00, 5.75)	3.00 (0.00, 9.25)	6.00 (3.00, 11.00)	8.460	0.015
Length of extended hospital stay due to platelet decline	1.00 (0.00, 6.00)	3.50 (0.00, 7.00)	5.00 (0.00, 8.00)	7.908	0.019

Increased hospitalization costs due to platelet decline	5040.00 (3024.00, 6979.00)	6503.00 (5040.00, 9474.00)	7440.00 (5874.00, 14410.00)	35.347	<0.01
With or without platelet transfusion	95 (95.0%)	67 (71.3%)	16 (41.0%)	47.616	<0.01
Without					
With	5 (5.0%)	27 (28.7%)	23 (59.0%)		

Table 3 Analysis results of χ2 values and P values between thrombocytopenia grades and other indicators

Variables	Days of rhTPO treatment			The day when platelet count started to increase			Postponed days of the next cycle of chemotherapy		
	Grade II	Grade III	Grade IV	Grade II	Grade III	Grade IV	Grade II	Grade III	Grade IV
Grade II	1	-3.610	-2.995						
Grade III	<0.01	1	-0.761						
Grade IV	0.003	0.447	1						
Grade II				1	-4.977	-4.235			
Grade III				<0.01	1	-1.023			
Grade IV				<0.01	0.306	1			
Grade II							1	-2.602	-2.235
Grade III							0.009	1	-0.094
Grade IV								0.925	1

Note: Above the diagonal was the z/χ2 value, below the diagonal was the P-value.

Table 4 Analysis results of χ2 values and P values between thrombocytopenia grades and other indicators

Variables	Length of extended hospital stay due to platelet decline			Increased hospitalization costs due to platelet decline			With or without platelet transfusion		
	Grade II	Grade III	Grade IV	Grade II	Grade III	Grade IV	Grade II	Grade III	Grade IV
Grade II	1	-1.821	-2.655						
Grade III	0.069	1	-0.094						
Grade IV	0.008	0.925	1						
Grade II				1	-4.900	-4.755			
Grade III				<0.01	1	-1.871			
Grade IV				<0.01	0.061	1			
Grade II							1	19.798	50.813
Grade III							<0.01	1	10.752
Grade IV							<0.01	0.001	1

Note: Above the diagonal was the z/χ2 value, below the diagonal was the P-value.

Figures

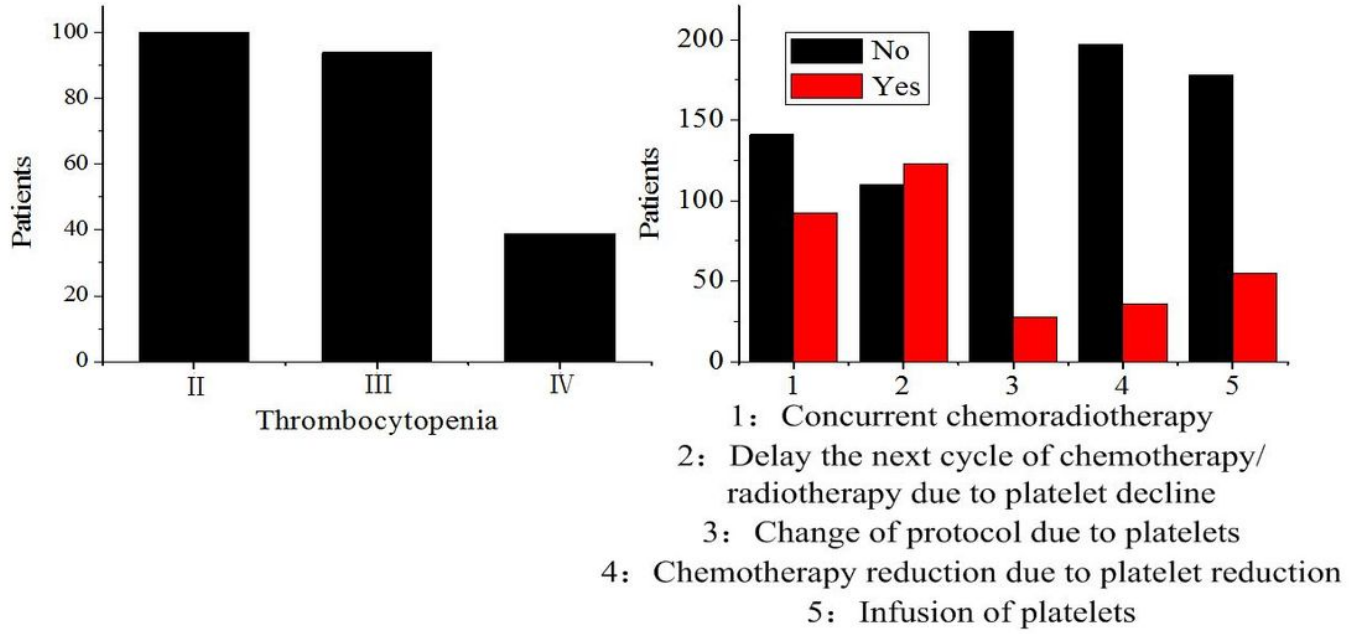

Figure 1

General information of included patients

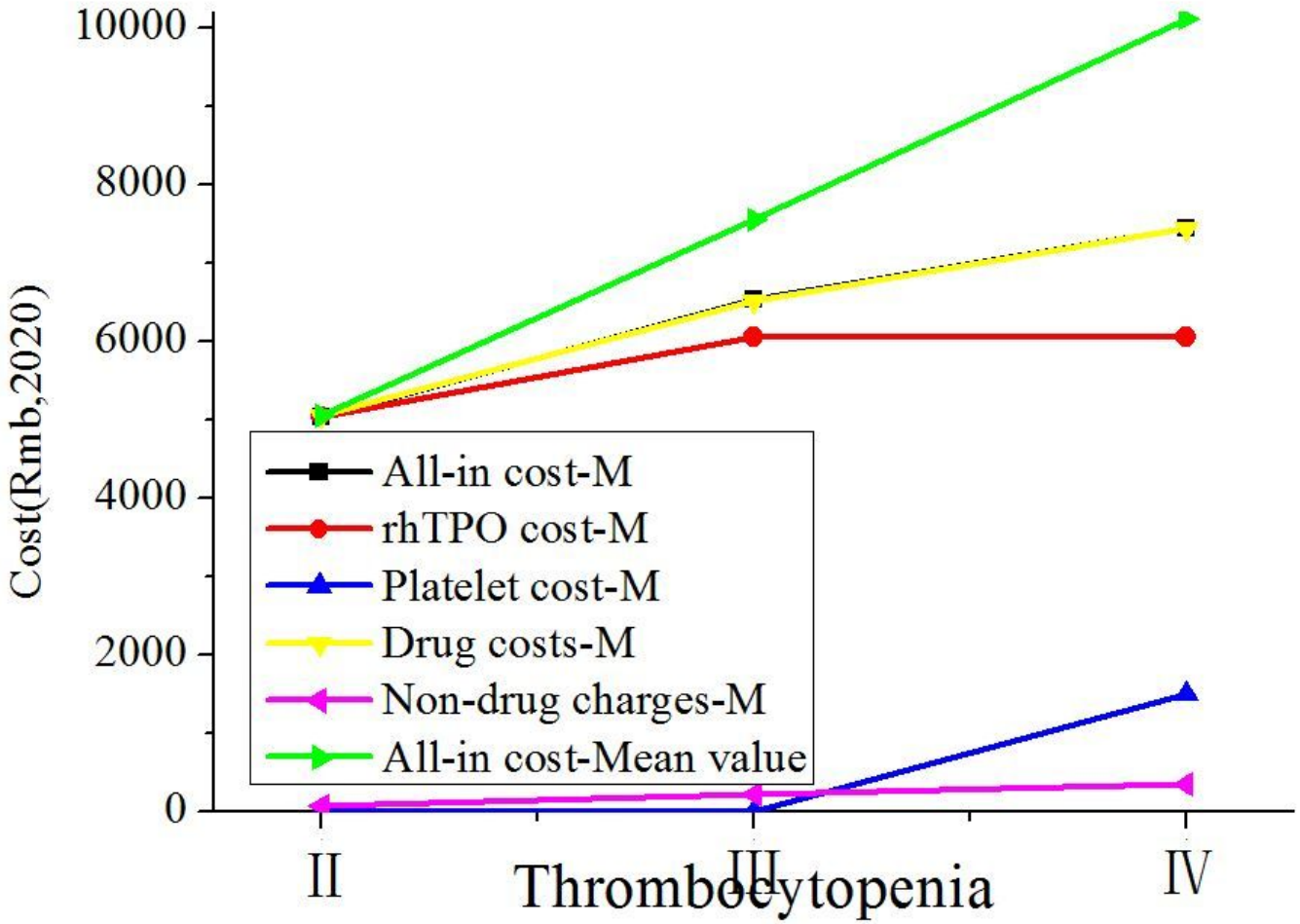

Figure 2

Information about the expenses of patients