Rituximab Use in Elderly Patients Newly Diagnosed with Primary Immune Thrombocytopenia

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Introduction

- Immune thrombocytopenia (ITP) is a rare autoimmune disorder characterized by a low platelet count, which leads to increased risk of bleeding.
- Although it is well recognized that rituximab, a monoclonal anti-CD20 antibody, can be used off-label as a second-line therapy for ITP, data on its use in large real-world ITP patient populations are lacking.
- We described incidence, patient characteristics, and treatment patterns of rituximab use in a population-based cohort of elderly patients with newly diagnosed ITP.

Methods

- **Data source:** 100% Medicare hematologic disease files (2007-2015).
- **Inclusion criteria:** Patients newly diagnosed with primary ITP at age ≥67 years in 2010-2014 who were continuously enrolled in Medicare Parts A and B (FFS) for 24 months before diagnosis.
  - **ITP diagnosis:** ≥1 inpatient or ≥2 outpatient claims ≥30 days apart but within 365 days carrying an ICD-9-CM code for ITP (287.31).
  - **Date of ITP onset:** date of the first ITP claim or, when applicable, the first general thrombocytopenia claim (287.3x, 287.4x, 287.5) within the 12 months before the first ITP claim.
- **Exclusion criteria:** Patients with secondary causes of thrombocytopenia or prior exposure to rituximab in the 12 months before the date of ITP onset.
- **Baseline period:** 12 months before ITP onset.
- **Follow-up period:** from the date of ITP onset until the first of rituximab initiation, death, disenrollment from FFS coverage, or 09/30/15.

Rituximab identification and treatment patterns:

- **Initiation:** first appearance of a claim for rituximab infusion with a diagnosis code for ITP and without codes for chronic lymphocytic leukemia, non-Hodgkin lymphoma, or rheumatoid arthritis (all conditions approved for rituximab use).
- **Treatment course:** consecutive rituximab claims ≤17 days apart ending at the last administration plus 7 days.
- **Number of administrations:** number of claims for rituximab on different service dates.
- **Dose:** 100 mg multiplied by service count reported on the claim.

Statistical Analyses:

- Baseline characteristics at ITP onset were reported using descriptive statistics.
- Cumulative probability of rituximab initiation was estimated using the Kaplan-Meier method with log-rank test to assess differences by baseline characteristics.
- History of bleeding and receipt of other ITP therapies before rituximab initiation and patterns of rituximab use in the first course of treatment were characterized.

Results

Table 1. Baseline characteristics

		Rituximab Initiation	
	Overall n(%)	Yes n(%)	No n(%)
N patients	17,117	1,562	15,555
Age at ITP onset (years)			
mean (SD)	79.1±7.6	79.2±7.7	78.6±7.1
66-69	1,919(11)	165(10)	1,754(11)
70-74	3,646(21)	352(23)	3,294(21)
75-79	3,686(22)	374(24)	3,312(21)
80+	7,866(46)	671(43)	7,195(47)
Sex			
Male	8,475(50)	742(48)	7,733(50)
Female	8,642(50)	820(52)	7,822(50)
Race			
Caucasian	15,252(89)	1,455(93)	13,797(89)
African-American	1,009(6)	49(3)	960(6)
Other	856(5)	58(4)	798(5)
Year of first ITP diagnosis code			
2010	4,016(24)	354(23)	3,662(24)
2011	3,652(21)	299(19)	3,353(22)
2012	3,456(20)	340(22)	3,125(20)
2013	3,122(18)	296(19)	2,826(18)
2014	2,862(17)	273(18)	2,589(17)
Select Conditions at Baseline			
DM	5,596(33)	465(30)	5,131(33)
COPD	3,085(18)	213(14)	2,872(19)
CAD	5,573(33)	396(25)	5,177(33)
CKD	2,758(16)	180(12)	2,578(17)
CHF	3,311(19)	170(11)	3141(20)
Any bleeding	4,160(24)	400(26)	3,760(24)
Specific bleeding			
Intracranial hemorrhage	156(1)	*	^
Gastrointestinal hemorrhage	1,229(7)	97(6)	1,132(7)
Hematuria	1,237(7)	106(7)	1,131(7)
Ecchymosis	367(2)	68(4)	299(2)
Epistaxis	501(3)	58(4)	443(3)

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease ; COPD, chronic obstructive pulmonary disease; DM, diabetes; GI, gastrointestinal; ITP, immune thrombocytopenia; SD, standard deviation.
*Values for cells with ten or fewer patients are suppressed.
^Values are suppressed to avoid deriving cells with ten or fewer patients.
[a]Defined in the 12 months before ITP onset.

Table 2. Cumulative probability of rituximab initiation after ITP onset (%)

	Time from ITP onset				
	6 months	1 year	3 years	5 years	*P* value
Overall	6.7	8.7	10.6	11.2	
Age at ITP onset, years					0.2822
66-74	6.1	8.3	10.2	10.9	
≥75	6.9	8.9	10.7	11.3	
Sex					0.103
Male	6.4	8.3	10.2	10.7	
Female	7.0	9.1	10.9	11.7	
Race					<.0001
White	7.0	9.1	11.0	11.6	
African American	3.1	4.4	5.8	6.7	
Other	4.6	6.1	8.1	8.5	
Select comorbid conditions					
DM					0.0431
Yes	6.2	8.2	9.7	10.2	
No	6.9	9.0	10.9	11.6	
COPD					0.0006
Yes	6.0	7.3	8.4	8.4	
No	6.8	9.0	11.0	11.7	
CAD					<.0001
Yes	5.4	6.9	8.6	9.1	
No	7.2	9.5	11.5	12.1	
CKD					0.0005
Yes	5.5	6.9	8.3	8.6	
No	6.9	9.0	10.9	11.6	
CHF					<.0001
Yes	4.7	5.8	6.4	6.7	
No	7.1	9.3	11.4	12.0	

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes; ITP, immune thrombocytopenia.

Table 3. History of bleeding and use of specific ITP therapies among rituximab users (%)

	Time before rituximab initiation		
	prior 4 weeks	prior 6 months	all history[a]
History of any bleeding	25.2	46.3	59.3
History of specific bleeding			
Intracranial hemorrhage	2.0	3.4	4.2
Gastrointestinal hemorrhage	7.6	13.8	19.4
Hematuria	3.3	7.6	13.6
Ecchymosis	7.8	13.6	17.2
Epistaxis	6.6	11.2	13.4
History of specific therapy			
IV Anti-D	1.5	2.6	3.1
IVIg (excluding Anti-D)	26.0	35.2	39.4
IV steroids	8.6	22.0	32.1
Platelet transfusion	23.8	36.7	41.0
Splenectomy	1.3	2.9	3.0

Ig, immunoglobulins.
[a]From the start date of baseline period to rituximab initiation

Table 4. Rituximab use in the first course of treatment

	Mean(SD)	5th PCTL	Median(IQR)	95th PCTL
No. of administration	3.6 (1.4)	1	4(3-4)	6
Course duration, weeks	3.7 (1.6)	1	4(3-4)	6
Avg. days b/w administrations	7.2 (0.8)	6.8	7(7-7)	8.8
Avg. weekly dose, mg	715 (136)	500	700(630-800)	900
Avg. dose per administration, mg	732 (126)	600	700(700-800)	900

IQR, interquartile range; PCTL, percentile; SD, standard deviation.
Note: Of 1562 rituximab-treated patients, 9% received only one dose.

Summary

- We identified 17,117 elderly patients with newly diagnosed ITP in 2010-2014; of these, 1562 (9%) received rituximab with a median (IQR) time to rituximab of 3 (1-8) months.
- Overall, cumulative probability (95% CI) of initiating rituximab at 3 years was 10.6% (10.1%-11.1%). White patients and those without select comorbid conditions were more likely to receive rituximab than their counterparts (Table 2).
- Among rituximab-treated patients, at initiation, 59% had a history of any bleeding, 4% were splenectomized, and 32%-41% received IV immunoglobulins, IV steroids, or platelet transfusions (Table 3).
- The median number of infusions during the 1st course of rituximab was 4 (IQR, 3-4) over a median duration of 4 weeks (IQR, 3-4); 9% of patients received only 1 dose, while 66% received ≥4 doses (Table 4).

Conclusions

- About one in ten elderly patients with newly diagnosed ITP received rituximab.
- White patients and those without select comorbid conditions were more likely to receive rituximab, while older patients (age ≥75 years) had similar incidence of rituximab use as their counterparts.
- Data suggest that weekly rituximab infusion for 4 weeks is the standard schedule for the first course of treatment in this setting.
- Further studies assessing the potential factors associated with rituximab initiation and its benefits and risks are warranted.

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