Hospitalization for toxicity in patients treated with Rituximab

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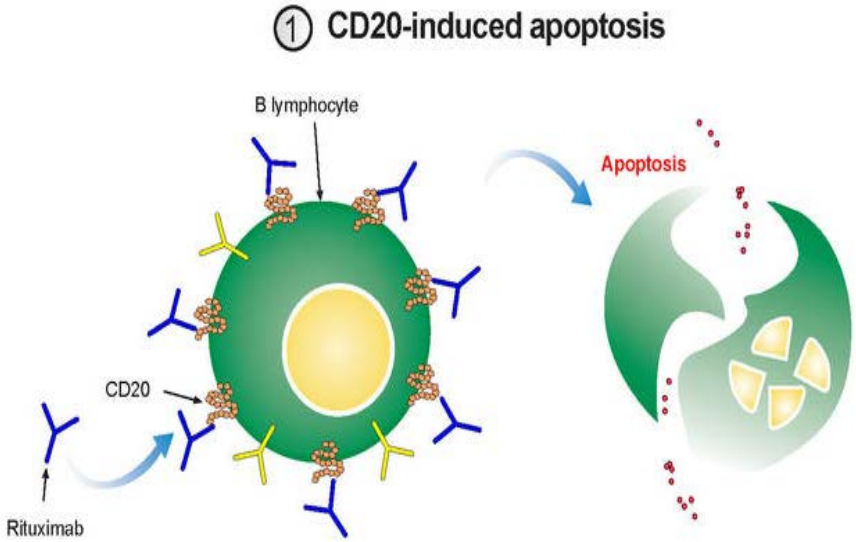
Rituximab

- Chimeric murine/human IgG_1 Kappa monoclonal antibody directed against CD20
- CD 20 expressed in >90% of B cell lymphomas
- Mediates cell lysis probably via complement dependent and antibody dependent cytotoxicity



Rituximab

- First monoclonal antibody to be approved in 1997 in refractory indolent lymphomas
- Now used both in first line and refractory B cell malignancies and autoimmune disorders
- Typical dose 375 mg/m2 weekly for 4-8 weeks
- Also used in combination with other chemotherapy agents
- Used as maintenance therapy in certain lymphomas

Effects of Rituximab

- Depletion of B cells within first 3 weeks with sustained depletion upto 6-12 months after the last infusion
- Decrease in serum IgM and IgG levels from 5 through 11 months following last administration
- Half life can range from 5 to 77.5 days based on the dosage and schedule

Safety of Rituximab

- Considered to be a safe and well tolerated drug even in elderly patients
- Common side effects: Infusion reactions
  - Significant reactions in about 10% patients during first infusion
- Low hematologic toxicity except for neutropenia

Clinical trial experience

- Infections in NHL single arm trials
  - Overall incidence 31%
    - Bacterial (19%),viral (10%),unknown (6%),Fungal (1%)
  - Grade 3 or 4
    - Less than 5 %
  - Rate of infections higher in patients who received prior chemotherapy

Clinical trial experience

- Infusion reactions
  - Typically with first infusion
- Cardiac complications
  - Most trials with <5 % incidence
- Cytopenia
  - Grade 3 or 4 : 40-45%
- All other Grade 3-4 toxicities
  - <5%

Post marketing experience

- Prolonged or late onset neutropenia
- Cardiac arrythmias and fatal cardiac failure
- Autoimmune events
- Increase in grade 3 and 4 infections
  - Progressive multifocal leucoencephalopathy
  - Reactivation of Hepatitis B,CMV,Toxoplasmosis
- Neoplasia
  - Skin tumors,Kaposi's sarcoma
- Bowel obstruction and perforation
- Fatal bronchiolitis obliterans and interstitial lung disease

Infections

- Hepatitis B reactivation
  - Retrospective review of 394 patients with lymphoma who were positive for Anti HBc Ab
  - HBV infection higher in Rituximab treated patients(2.7% vs 0.8 %)
  - Current practice to document Hep B status prior to Rituximab
  - Lamivudine prophylaxis with therapy

Targhetta et al Haematologica 2008;93:951-2

Infections

- Progressive multifocal leucoencephalopathy
  - Reactivation of latent JC polyoma virus
  - Total of 57 cases have been reported from 1197 to 2008 in HIV negative patients after Rituximab
  - Median time from last Rituximab dose to PML diagnosis : 5.5 months
  - Median time to death 2 months
  - Case fatality rate : 90%

Rituximab maintenance regimens

- Systematic review of randomized trials of Rituximab maintenance
- Maintenance associated with higher grade 3/4 adverse events (RR 1.67 CI 1.29 to 1.99)
- Grade 3 /4 infections: RR 3.55 CI 1.88 to 6.69

Vidal et al JNCI 2011;103

Rituximab : Population based analysis

- Multi institutional study from Canada
- 4021 patients who received chemotherapy with or without Rituximab for DLBCL
- No significant increase in one year hospitalization rates for infections, cardiac, pulmonary, gastrointestinal or neurological diagnoses

Lee et al,British Journal of hematology 2012

Hospitalization for toxicity in patients treated with Rituximab

Aim

- To determine the incidence and cause of hospitalizations for toxicity associated with Rituximab

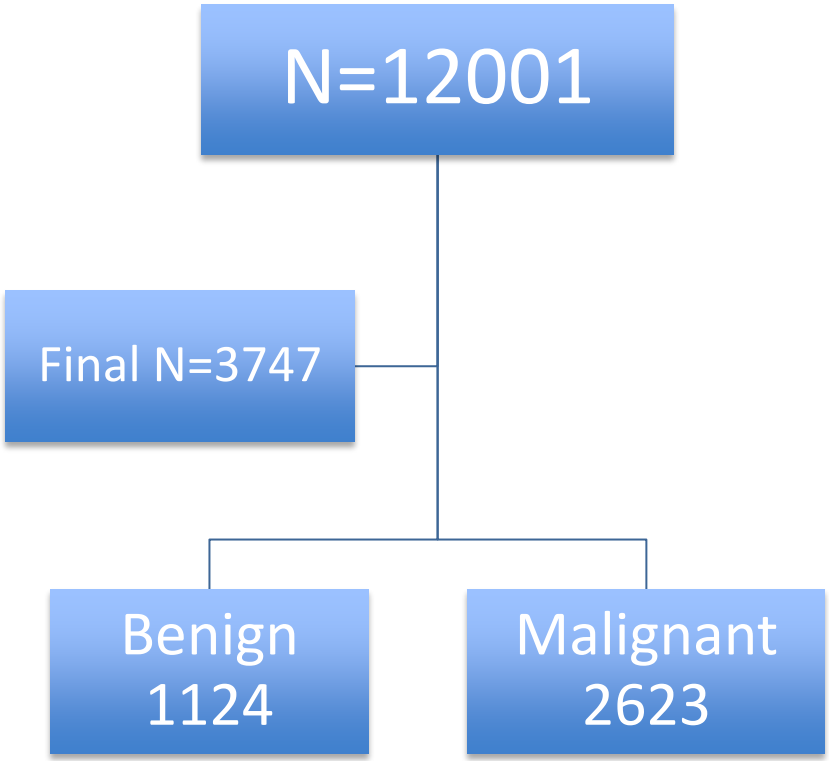
Study population

- 100% Texas Medicare
  - MEDPAR files ,Outpatient standard Analytic file (OUTSAF) and Medicare carrier files
- N= All patients who received first dose of Rituximab between 2001 and 2008
- Patients who were enrolled in HMO and without Medicare coverage in the 12 months prior to Rituximab were excluded

Methods

- Rituximab use identified by HCPCS code J9310
- Claims for other chemotherapy within 3 months prior and 12 months after first Rituximab noted
- Excluded patients who received other chemotherapy agents concurrently
- All patients with any approved diagnoses who have received Rituximab as part of their therapy
- Total number of infusions in the first 8 weeks of initiating Rituximab calculated

Methods



- Exclusions
  - Patients enrolled in HMO
  - No Medicare coverage in 12 months prior to first Rituximab
  - Any other chemotherapy agents along with Rituximab
  - Cases where primary or secondary diagnoses not an approved indication for Rituximab

Methods

- ICD 9 codes used to identify causes for any hospitalizations 12 months prior and 8 weeks post first infusion of Rituximab
- The diagnoses were then stratified using appropriate ICD 9 codes
  - Infection, Neurologic, Cardiac, Pulmonary and Gastrointestinal toxicities
- Rates of hospitalization compared to before and after Rituximab infusion
- ICD 9 code 046.3 was used to look specifically for incidence of Progressive multifocal leucoencephalopathy

Methods

- Covariates
  - Age
  - Gender
  - Race
  - Ethnicity
  - Medicaid eligibility
- Charleson comorbidity index

Statistical methods

- Chi square statistic for differences in patient characteristics between benign and malignant
- McNeman's test to compare hospitalization rates before and after Rituximab
- Kaplan meier analysis for each patient group
- Log rank test to compare different doses
- Cox proportional hazards for dose response analysis
  - Dose examined as time dependent variable

RESULTS

Diagnoses

Benign Disorders (n=1124)	n	%
Rheumatoid arthritis	550	48.93
Immune thrombocytopenic purpura	189	16.81
Disorders of plasma protein metabolism, macroglobulinemia	146	12.99
Primary Thrombocytopenia	89	7.92
Autoimmune hemolytic anemias	66	5.87
Diffuse diseases of CT	47	4.19
Other benign disorders	37	3.29

Malignant(n=2623)	n	%
Other lymphomas	1381	52.65
Chronic lymphoid leukemia	557	21.24
Nodular lymphoma	361	13.76
Lymphosarcoma and reticulosarcoma	174	6.63
Neoplasm of uncertain behavior of other lymphatic	35	1.33
Hodgkin's disease,unspecified	23	0.88
PTLD	20	0.76
Marginal Zone lymphoma	20	0.76
Other malignancies	52	1.98

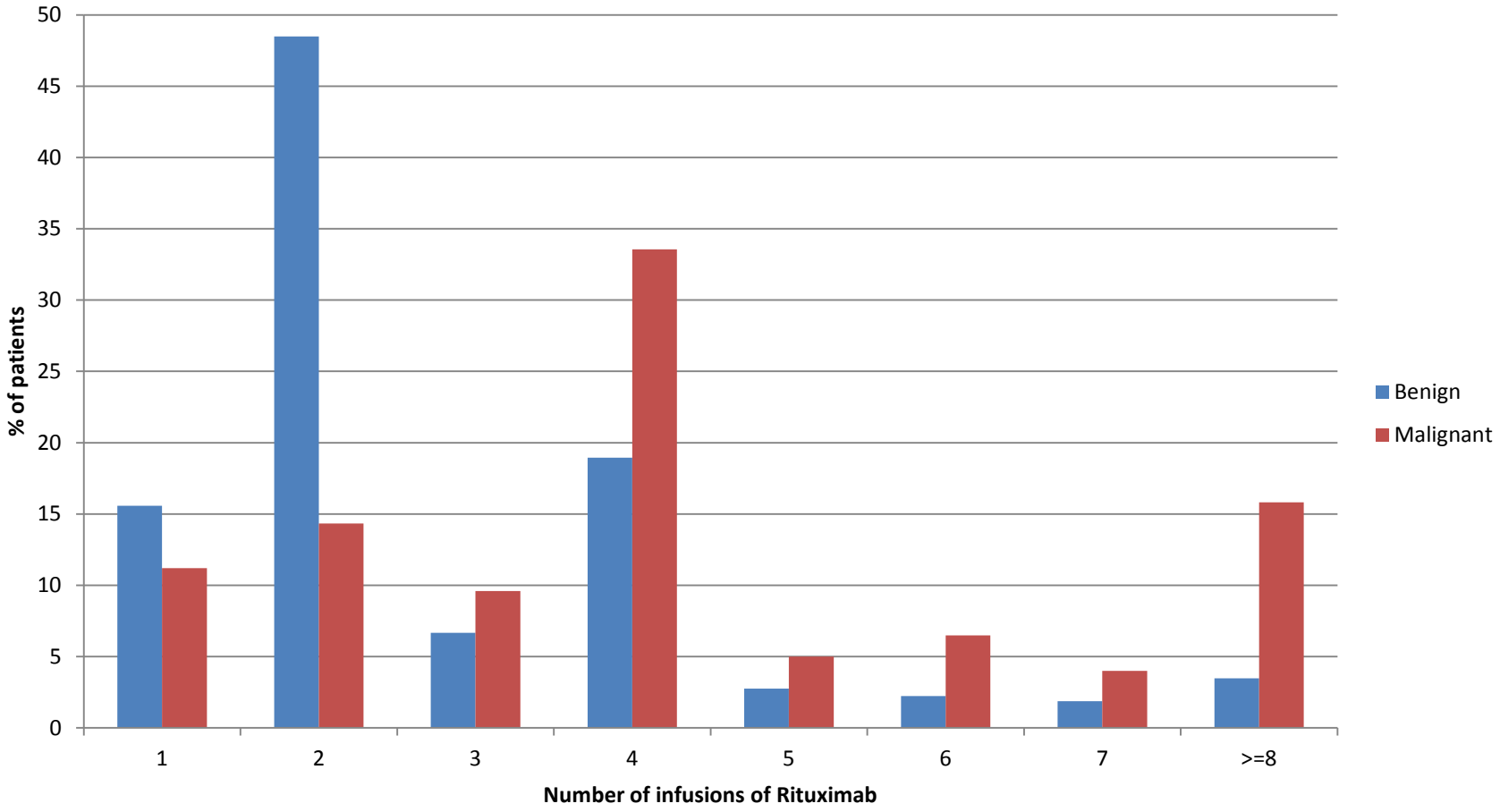
Patient characteristics

Characteristics	Category	All Patients n (%)	Benign n(%)	Malignant n(%)
Number	**Total**	3747(100)	1124(30)	2623(70)
Age	<65	469(12.52)	308(27.40)	161(6.14)
	65 - 69	563(15.03)	229(20.37)	334(12.73)
	70 - 74	568(15.16)	189(16.81)	379(14.45)
	75 - 79	712(19.00)	188(16.73)	524(19.98)
	>= 80	1435(38.30)	210(18.68)	1225(46.70)
Gender	Male	1483(39.58)	326(29.00)	1157(44.11)
	Female	2264(60.42)	798(71.00)	1466(55.89)
Ethnicity	White	3301(88.10)	945(84.07)	2356(89.82)
	Black	218(5.82)	92(8.19)	126(4.80)
	Hispanic	160(4.27)	57(5.07)	103(3.93)
	Others	68(1.81)	30(2.67)	38(1.45)
Medicaid Eligible	Yes	523(13.96)	217(19.31)	306(11.67)
	No	3224(86.04)	907(80.69)	2317(88.33)

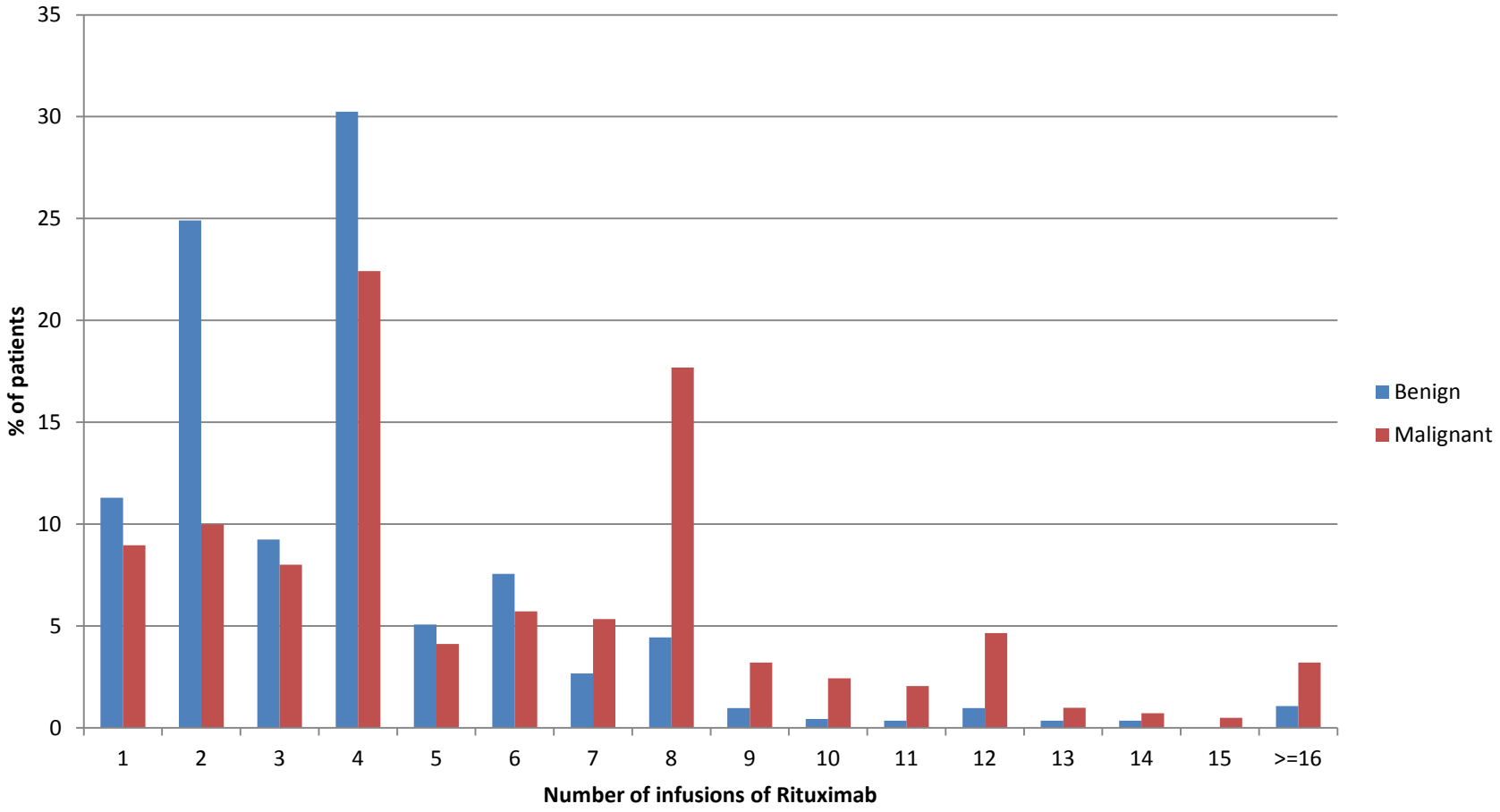
Patient Characteristics

Characteristics	Category	All Patients n (%)	Benign n(%)	Malignant n(%)
Year of initial Rituximab	2001	276(7.37)	14(1.25)	262(9.99)
	2002	321(8.57)	24(2.14)	297(11.32)
	2003	415(11.08)	54(4.80)	361(13.76)
	2004	448(11.96)	101(8.99)	347(13.23)
	2005	438(11.69)	96(8.54)	342(13.04)
	2006	616(16.44)	250(22.24)	366(13.95)
	2007	618(16.49)	287(25.53)	331(12.62)
	2008	615(16.41)	298(26.51)	317(12.09)
Comorbidity	0	1412(37.68)	203(18.06)	1209(46.09)
	1	1114(29.73)	432(38.43)	682(26.00)
	2	591(15.77)	242(21.53)	349(13.31)
	>=3	630(16.81)	247(21.98)	383(14.60)
Hospitalizations 12 months prior receiving initial Rituximab	0	1911(51.00)	596(53.02)	1315(50.13)
	1	904(24.13)	257(22.86)	647(24.67)
	2	470(12.54)	143(12.72)	327(12.47)
	3	217(5.79)	55(4.89)	162(6.18)
	≥4	245(6.54)	73(6.5)	172(6.57)
Hospitalizations 12 months post receiving initial Rituximab	0	1976(52.74)	639(56.85)	1337(50.97)
	1	865(23.09)	258(22.95)	607(23.14)
	2	414(11.05)	93(8.27)	321(12.23)
	3	226(6.03)	59(5.25)	167(6.37)
	≥4	266(7.1)	75(6.67)	191(7.27)

Number of infusions of Rituximab received in the first 8 weeks



Total number of infusions of Rituximab received within 12 months after the first infusion



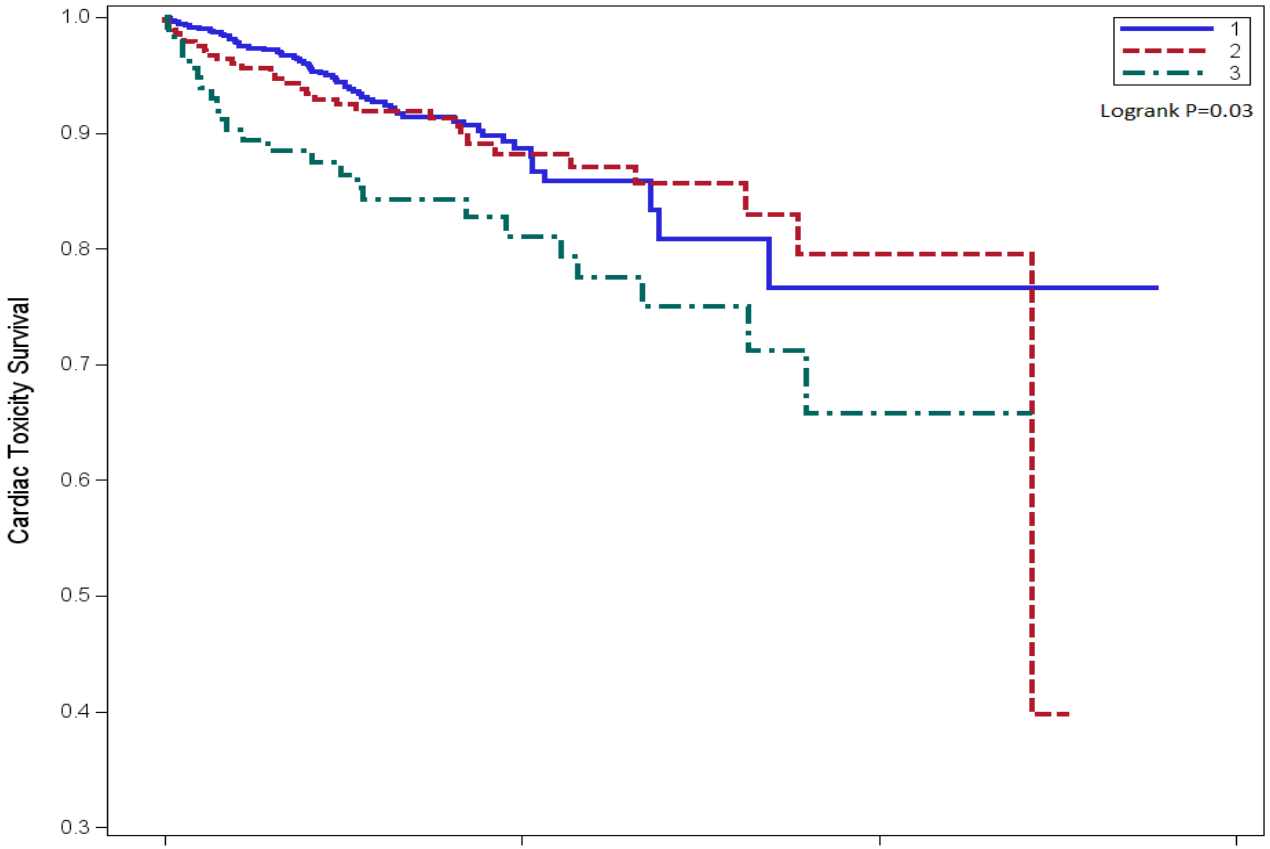
Hospitalization rates

Primary diagnosis for patients hospitalized (ICD-9 code)	Diagnosis	12 mo before initial Rituximab		12 mo after initial Rituximab		P-value*
		No.	%	No.	%	
Any cause	Benign	528	46.98	485	43.15	0.03
	Malignant	1308	49.87	1286	49.03	0.48
Cardiac	Benign	49	4.36	56	4.98	0.44
	Malignant	148	5.64	184	7.01	0.02
Neurologic	Benign	11	0.98	15	1.33	0.41
	Malignant	38	1.45	61	2.33	0.02
Infection	Benign	81	7.21	108	9.61	0.03
	Malignant	198	7.55	311	11.86	<0.001
Pulmonary	Benign	18	1.60	26	2.31	0.21
	Malignant	27	1.03	64	2.44	<0.001
GI	Benign	5	0.44	6	0.53	0.76
	Malignant	8	0.30	12	0.46	0.37

Dose Response

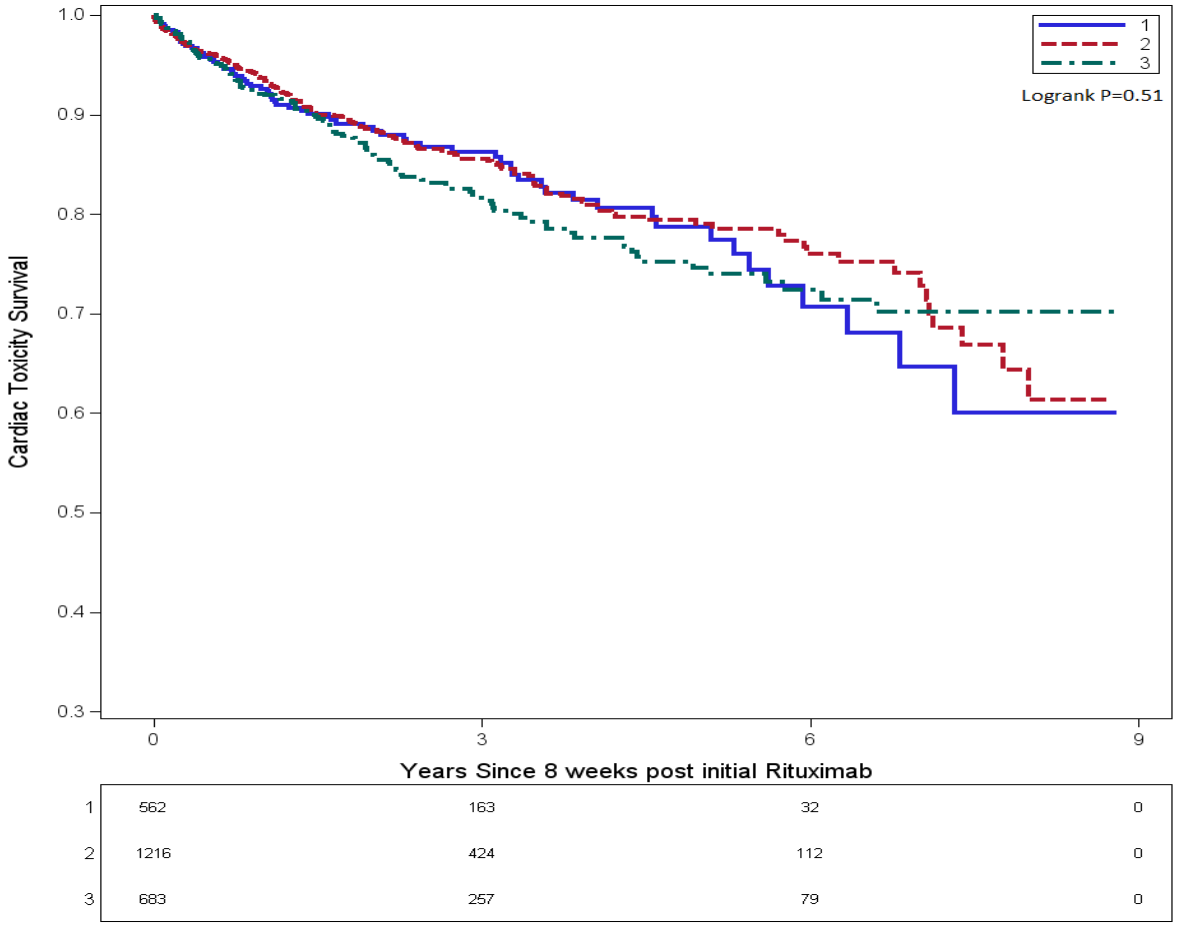
Toxicity	Rituximab dose	Benign			Malignant		
		HR	95% CI		HR	95% CI	
Infections	1 -2	1.00			1.00		
	3-4	0.94	0.66	1.32	0.74	0.60	0.92
	>5	0.72	0.44	1.18	0.68	0.53	0.87
Cardiac	1-2	1.00			1.00		
	3-4	1.11	0.67	1.83	0.84	0.62	1.14
	>5	2.59	1.49	4.51	1.09	0.80	1.48
Neurologic	1-2	1.00			1.00		
	3-4	2.67	1.16	4.16	1.68	0.95	2.99
	>5	0.18	0.02	1.55	1.31	0.69	2.49
Pulmonary	1-2	1.00			1.00		
	3-4	0.85	0.40	1.81	0.97	0.57	1.65
	>5	1.72	0.76	3.91	1.15	0.65	2.03

Cardiac toxicity benign patients



1	701	147	5	0
2	285	99	13	0
3	115	47	8	0

Cardiac toxicity malignant patients



Results

- Increase in rates of hospitalizations observed in patient with malignant disorders in the 12 months after Rituximab;but not in patients with benign conditions
  - Likely disease related in cancer patients
- Higher rate of infections in both benign and malignant patients
  - No dose response noted

Limitations

- Toxicity in the first year
- Prolonged follow up needed for toxicity related to maintenance regimens
- Only serious toxicities that resulted in hospitalizations were captured

Conclusions

- No overall increase in toxicity related hospitalizations from Rituximab
- Possible increase in infections; further studies needed

Acknowledgements

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