Trainee Research-in-Progress Submission Example

Title: *Lack of Adequate Pneumococcal Vaccination Response in Chronic Lymphocytic Leukemia Patients Receiving Ibrutinib*

Category of Presentation: *Clinical Research*

Topic of Presentation: *Supportive Care*

Abstract Text:

Background

Chronic lymphocytic leukemia (CLL) is characterized by a dysfunction of innate and adaptive mediated immunity and subsequently infections are commonly incurred by patients. The CDC recommends CLL patients to receive the 13-valent pneumococcal conjugated vaccination (PCV13) to reduce the risk of infection. Ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase (BTK), has been associated with the development of pneumonia in 4-18% of patients. BTK is essential for B cell function and development as well as Toll-like receptors which are involved in innate and adaptive immunity.

Objective

This study evaluated the effectiveness of PCV13 vaccination between CLL patients treated with ibrutinib and active surveillance (control) by assessing anti-pneumococcal antibody generation following vaccination. Secondarily this study investigated BTK and SAMSN1 (hematopoietic adapter containing SH3 and SAM domain 1) expression following vaccination.

Methods:

This IRB approved, prospective, single-center, non-blinded study evaluated immunization response of PCV13 in 2 study cohorts (ibrutinib or control). All eligible patients provided written consent. At Day 0 (vaccination) both study cohorts received a single dose (0.5mL) of PCV13. Peripheral blood samples (8mL) were collected on day 0 and 30. Serum pneumococcal antibody generation was assessed with microsphere photometry for antibody specific serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23) and analyzed by Lumniex 200 instrument. Adequate immunization response was defined by a ≥ 2-fold increase of ≥ 3 of pneumococcal serotypes. Mononuclear cells were isolated using Ficoll-Hisotpaque 1077 density gradient and CD19+ B-lymphocyte isolation was performed using Dynabeads® CD19 pan B. Subsequently, Western blot analysis was performed to identify BTK and SAMSN1 expression at day 0 and 30.

Results:
Eight patients (n=4 ibrutinib, n=4 control) were enrolled with a median patient age of 69 yo (75% > 65yo). All CLL control patients (4/4) generated an adequate immunological response, whereas (0/4) of ibrutinib patients generated an adequate immune response to PCV13 (p=0.029; post-hoc Fisher exact). Five PCV serotypes: 1 (p=0.03), 3 (p=0.03), 5 (p=0.01), 6B (p=0.009), and 18C (p=0.03) were significantly increased at Day 30 in control patients. Overall there was a significant increase in the median change of specific pneumococcal antibody titers in the control group (p<0.0001; CI 90.9-124.7). Elevated SAMSN1 expression was identified in pre-vaccination ibrutinib patients (p<0.0115) and mechanistically could explain impaired immunization response.

Conclusions:
PCV13 vaccination in CLL patients receiving ibrutinib does not induce an adequate vaccination response. Given These results, additional evaluation to improve immunogenicity of pneumococcal vaccination in ibrutinib patients is warranted.

See ePoster here

Trainee Research-in-Progress Submission Example

Title: *Characterization of Marijuana Use in Cancer Patients Receiving Chemotherapy*

Category of Presentation: *Practice Management*

Topic of Presentation: *Supportive Care*

Abstract Text:

Background

Marijuana has been suggested as a supportive care agent to manage side effects associated with chemotherapy. As legalization of medical and recreational marijuana increases throughout the United States, it is possible that use amongst cancer patients will increase. Previously, little was known regarding the prevalence and demographics of those who choose to use marijuana for side effect management while receiving chemotherapy.

Objective

Primary outcome: The primary outcome of this research will thoroughly characterize the demographics and health status of patients who use and do not use medical marijuana as adjunctive therapy in treating chemotherapy induced side effects. Secondary Outcome: The secondary outcome will further characterize those who choose to use medical marijuana to treat their chemotherapy induced side effects.

Methods:

An anonymous, self-administered, and voluntary survey was provided to patients in the infusion center at the University of Colorado Cancer Center. The survey included questions on marijuana use history, reasons for using or abstaining, clinical characteristics and demographics.

Results:

Fifty-three (28.6%) of the 185 patients surveyed reported use of marijuana within the past 6 months. Forty-three (23.3%) patients reported former use and 89 (48.1%) reported having never used marijuana. Forty-one of the current users (77.4%) reported using marijuana to manage the side effects of chemotherapy with the most common reason to use marijuana being to nausea and vomiting (n=29, 54.7%). Current marijuana use was associated with younger age ($p=0.002$), use of complementary and alternative medicine ($p<0.001$) and higher side effect frequency scores ($p<0.001$). Of all respondents, 41 (22.16%) reported that their oncology provider asks about marijuana use.

Conclusions:

The results of this survey demonstrate that cancer patients who use marijuana are not representative of marijuana users in the general population with cancer patients having higher use. Additionally, there are very few demographic and clinical differences between oncology patient marijuana users and non-users, with age being the only difference. Education level, employment, income, and gender were similar between groups. Of those who choose to use marijuana, it is most commonly used to manage side effects associated with chemotherapy and users have higher side effect frequency scores compared to non-users. With legalization increasing throughout the country and high prevalence rates in cancer patients, providers should increase discussions surrounding safe and appropriate use of marijuana.

See ePoster Here

Pneumococcal Vaccine Response in Chronic Lymphocytic Leukemia Patients Receiving Ibrutinib

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INTRODUCTION

- Chronic lymphocytic leukemia (CLL) patients have impaired immunocompetence due to accumulation of non-functional B-cells
- The Centers for Disease Control and Prevention (CDC) and Advisory Committee on Immunization Practices (ACIP) recommend CLL patients receive the pneumococcal 13-valent conjugate vaccine (Prevnar 13®) for protection against *S. pneumonia*[1]
- Ibrutinib, a Bruton's tyrosine kinase inhibitor (BTK), inhibits B-cell signaling and has demonstrated impressive clinical improvements in CLL patients.[2] However, the effect of this agent on vaccination response is unknown.
- Increased SLy2 (HACS1) mRNA expression has been correlated with impaired pneumococcal vaccine response through inhibition of B-cell proliferation and differentiation[3]

OBJECTIVES

- Determine whether concurrent administration of pneumococcal 13-valent vaccine with ibrutinib generates a ≥ 2 fold increase in ≥ 3 of the 6 pneumococcal antigens
- Evaluate HACS1 and BTK expression in lymphocytes in patients concurrently receiving ibrutinib therapy compared to non-treatment patient controls
- Determine if changes in HACS1 correlates to attenuated pneumococcal vaccine response

STUDY DESIGN

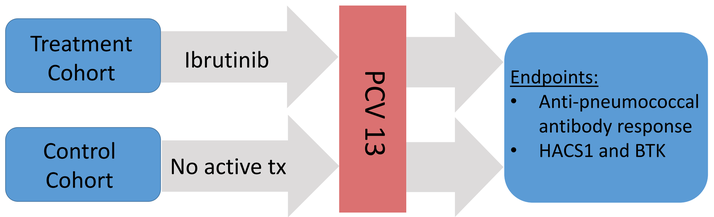


Figure 1: Assignment of eligible patients to their respective cohort. All study participants receive PCV13 and return at Day 30 for assessment.

PATIENT ELIGIBILITY

Inclusion

- No prior therapy for CLL (*Control cohort)
- Actively receiving ibrutinib 420mg orally once daily (*Treatment cohort)
- ECOG PS ≤ 2
- Normal renal & hepatic function

Exclusion

- Vaccinated with PCV13 in past 2 years
- Received anti-CD20 monoclonal antibody in previous 6 months
- Corticosteroid use in previous 14 days (except for maintenance therapy which may not exceed 20mg/day prednisone equivalent)
- Concurrent systemic immunosuppressant therapy
- Recent infection requiring systemic treatment in past 14 days

METHODS

- Peripheral blood samples (~15 mL) at Day 0 (prior to PCV13 administration) and Day +30
- Pneumococcal Antibody Panel Test (Mayo Medical Laboratories®) - Microsphere Photometry to identify the presence and concentration of anti-pneumococcal IgG titers against serotypes 1, 3, 4, 5, 9, 12F, 14, 19F, 23F, 6B, 7F, 18C
- Separation and peripheral blood mononuclear cell (PBMC, lymphocytes) isolation via Ficoll followed by cryopreservation.
- B-lymphocyte isolation - Dynabeads CD19 Pan B®
- Western Blot analysis
  - Anti-SAMSN1 (HACS1) rabbit polyclonal antibody (Abcam® ab139735)
  - BTK rabbit monoclonal antibody (Cell Signaling Technology® 82B8)

ENDPOINTS

Data analysis:

- Satisfactory immune responses for anti-pneumococcal antigen generation defined as ≥2-fold titer increase post-vaccination in ≥ 3 serotypes[4]
- Pre and post-vaccination expression of HACS1 and BTK will be evaluated with densitometry using NIH Image J software

Statistical analysis:

- Pneumococcal serotypes – Chi Square
- HACS1 and BTK – Student's two-sided t-test

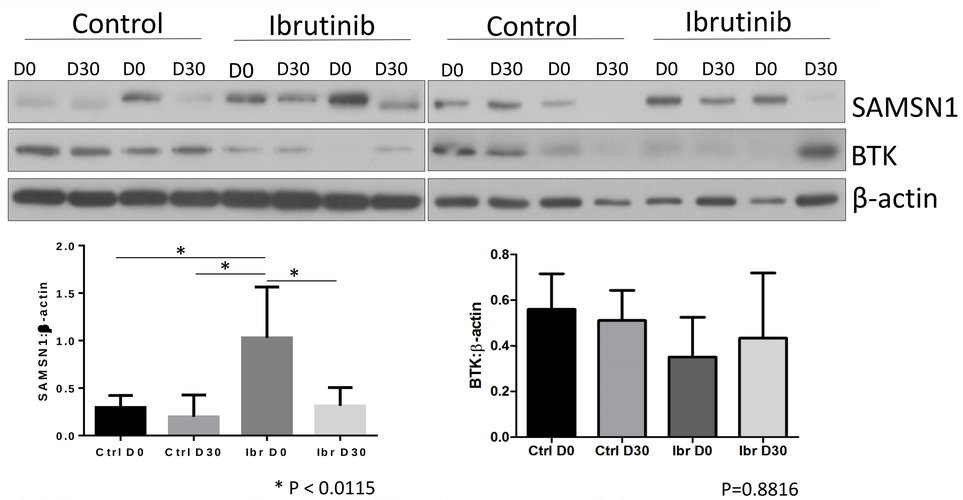
RESULTS

Table 1: Patient Demographics

Subject	Gender	Age	Rai Stage	Cytogenetics/Mutations	Previous Treatments	Last anti-CD20 mab
Ibrutinib Treated						
1	M	53	IV	11q del, 13q del, trisomy 12, IgVH unmutated	FCR, R-CVP, rituximab, ofatumumab + idelaslisib, ibrutinib X 17 months	52 mo
2	F	77	III	Trisomy 12	FCR, R-CVP, ofatumumab, ibrutinib X 13 months	29 mo
3	M	69	IV	13q del, 17p del, P53	FCR, ibrutinib X 5 months	11 mo
4	F	71	I	IgVH mutated	Rituximab, ibrutinib X 7 motnths	12 mo
Control						
1	F	53	I	Trisomy12	Bendamustine and rituximab	36 mo
2	M	72	I	13q	None	N/A
3	F	72	I	T(11;14)	FCR	73 mo
4	M	59	0	13q	None	N/A

FCR= Fludarabine, cyclosphosphamide, rituximab; **R-CVP**= rituximab, cyclophosphamide, vincristine, prednisone; **GS-1101** = idelalisib

Figure 1: SAMSN1 and BTK Expression Pre- and Post-PCV13 Vaccinations



* P < 0.0115 P=0.8816

Figure 3 (A) Western blot analysis for difference of SAMSN1 and BTK expression from CD19+ isolated lymphocytes from peripheral blood. Ibrutinib and control CLL patients from baseline (D0) and post-vaccination (D30). **(B)** Baseline (D0) and post PCV13 vaccination (D30) SAMSN1 expression (mean ± SEM; n=8) normalized to β-actin between the control (Ctrl) and ibrutinib (Ibr) cohorts. **(C)** Baseline (D0) and post PCV13 vaccination (D30) BTK expression (mean ± SEM; n=8) normalized to β-actin between the control (Ctrl) and ibrutinib (Ibr) cohorts.

Table 2: Anti-Pneumococcal IgG Seroprotective Titers

	Ibrutinib Cohort (n=4)			Control Cohort (n=4)		
Serotype	**Day 0**	**Day 30**	**Difference**	**Day 0**	**Day 30**	**Difference**
1	1.1	1.3	0.2	22.6	112.2	89.6
3	0.7	0.6	-0.1	2.2	18.9	16.7
4	0.4	0.3	-0.1	5.9	12.1	6.2
5	1.7	1.6	-0.1	6.1	112.8	106.7
14	2.4	1.6	-0.1	6.1	112.8	106.7
19F	3.2	5.1	1.9	7.1	12.4	5.3
23	4.3	3.6	-0.7	9.8	33.3	23.5
6B	3.1	3.3	0.2	4.4	30.8	26.4
7F	1.6	2.1	-0.4	7.0	13.1	6.2
18C	0.9	0.6	-0.3	2.2	21.4	19.2
19A	2.5	2.3	-0.1	9.2	31.5	22.3
9V	3.4	3.0	-0.4	6.2	4.7	-1.5

Table 2: Difference in anti-pneumococcal IgG pre- and post-vaccination serotiters following PCV13 administration

DISCUSSION

- All control patients (4/4) generated an adequate immune response versus (0/4) ibrutinib patients (p=0.029)
- Significant increase in the median change of specific pneumococcal antibody titers in the control vs ibrutinib group (p<0.0001; CI 90.9-124.7)
- Ibrutinib therapy results in a *decrease* or no change in antibody generation versus baseline
- SAMSN1 pre-vaccination expression was elevated for pts on ibrutinib

Conclusions

- In this pilot study, CLL patients receiving ibrutinib were unable to mount an adequate immune response to PCV13
- Highlights need to address vaccinations before initiating novel oral oncolytic therapies

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Marijuana Use in Cancer Patients Receiving Chemotherapy

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Introduction

- Marijuana is used by cancer patients to manage side effects associated with chemotherapy
- As legalization of medical and recreational marijuana increases throughout the United States, it is possible that use amongst cancer patients will increase. Colorado is a unique environment to study marijuana use due to the recreational and legal status in the state
- Little is known about the prevalence, demographics, reasons for using and sources of information regarding use of marijuana in cancer patients

Objectives

- *Primary Outcome*: The primary outcome of this research is to characterize the demographics and health status of patients who use and do not use medical marijuana as adjunctive therapy in managing chemotherapy induced side effects
- *Secondary Outcome*: The secondary outcome of this research is to further characterize those who choose to use medical marijuana

Methods

- Voluntary, anonymous survey of patients in the outpatient infusion center at the University of Colorado Cancer Center
- Surveys were collected from August 2015 – December 2016
- The survey is a 34 question instrument, which can be completed in 5-10 minutes
- The survey was created based on previous literature assessing complementary and alternative medicine (CAM) use in cancer patients[1].
- This study was approved by the Institutional Review Board at University of Colorado Hospital and the Protocol Review and Monitoring System at the University of Colorado Cancer Center
- Data was collected and stored in REDCap
- Statistical Analysis
  - Data was analyzed using SPSS software
  - Chi-squared or paired t-test was used to analyze categorical or difference of means respectively
- A symptom frequency score was determined from the following
  - Sum of how often patients reported experiencing nausea/vomiting, diarrhea/constipation, hair loss, fatigue, pain and anorexia/weight loss on a scale from 1-5

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

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Results

Comparison of Users and Non-Users

Table 1. Demographics of Marijuana Users and Non-Users

	Total	User	Non-User	P-Value
	n=185 (% of Total)	n=53 (% of Users)	n=132 (% of Non-Users)	
Age				
20-49	40 (21.6%)	18 (24.5%)	22 (16.7%)	**0.002**
50-69	110 (59.5%)	32 (60.4%)	78 (59.1%)	
>70	35 (20.0%)	3 (5.7%)	32 (24.2%)	
Gender				
Female	115 (62.2%)	32 (60.4%)	83 (62.9%)	0.705
Male	69 (37.3%)	21 (39.6%)	48 (36.4%)	
Race				
White/Caucasian	169 (91.4%)	47 (88.7%)	122 (92.4%)	0.413
Other	16 (8.6%)	6 (11.3%)	10 (7.6%)	
Education Level				
GED or High School Degree	29 (15.8%)	10 (18.9%)	19 (14.4%)	0.376
Some College or Bachelor's	104 (56.2%)	32 (60.4%)	72 (54.5%)	
Masters or Higher	51 (27.6%)	11 (20.8%)	40 (30.3%)	
Employed				
Yes	75 (40.5%)	18 (34.0%)	57 (43.2%)	0.248
No	110 (59.6%)	35 (66.0%)	75 (56.8%)	
Income (of those employed)				
<$60,0000	16 (23.2%)	4 (23.5%)	12 (23.1%)	0.908
>$60,0000	53 (76.8%)	13 (76.5%)	40 (76.9%)	

Table 2. Clinical Characteristics of Users and Non-Users

	Total	Users	Non-Users	P-Value
	n=185 (% of Total)	n=53 (% of Users)	n=132 (% of Non-Users)	
Cancer Stage				
1	9 (4.9%)	4 (7.7%)	5 (3.8%)	
2	19 (10.4%)	8 (15.4%)	11 (8.4%)	
3	42 (23.0%)	12 (23.1%)	30 (22.9%)	0.395
4	83 (45.4%)	22 (42.3%)	61 (46.6%)	
Not Sure	30 (16.3%)	6 (11.5%)	24 (18.3%)	
Length of Diagnosis				
<1 year	90 (49.5%)	27 (52.9%)	63 (48.1%)	
1-2 years	26 (14.3%)	8 (15.7%)	18 (13.7%)	
2-3 years	22 (12.1%)	7 (13.7%)	15 (11.5%)	0.787
4-5 years	21 (11.5%)	4 (7.8%)	17 (13.0%)	
>5 years	23 (12.6%)	5 (9.8%)	18 (12.7%)	
Side Effect Frequency Score	13.9	17.3	12.5	**<0.001**
CAM Use During Chemotherapy				
Yes	56 (30.6%)	33 (62.3%)	23 (17.7%)	**<0.001**
No	127 (69.4%)	20 (37.7%)	107 (82.3%)	
Provider Asks About Marijuana Use				
Yes	41 (22.5%)	16 (30.8%)	25 (19.2%)	0.070
No	141 (77.5%)	36 (69.2%)	105 (80.8%)	

Characterization of Users

Table 3. Characterization of marijuana use

	Users
	n=53 (% of Users)
Method of Marijuana Use	
Edible	35 (66.0%)
Smoke	26 (49.1%)
Vaporizer	12 (22.6%)
Tincture	11 (20.8%)
Applied to Skin	6 (11.3%)
Cannabis Strain Used	
THC	25 (47.2%)
CBD	11 (41.5%)
Don't Know	12 (22.6%)

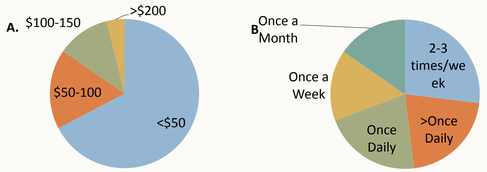

Figure 1. Usage trends amongst marijuana users (A) average monthly spending (B) frequency of using marijuana

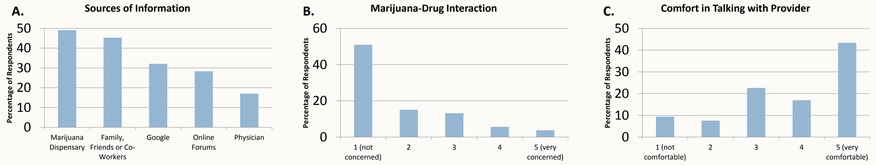

Figure 2. Current marijuana user responses to questions about (A) sources of information regarding marijuana use (B) concerns about marijuana-drug interaction and (C) comfort level in talking with provider about marijuana use

Results, Continued

Table 4. Characterization of marijuana use

	Users
	n=53 (% of Users)
Use Marijuana to Manage Side Effects Associated with Chemotherapy	
Yes	41 (77.4%)
No	11 (20.8%)
Use Marijuana For the Following Reasons:	
Relieve Nausea/Vomiting	29 (54.7%)
To Relax	28 (52.8%)
Improve Appetite	27 (50.9%)
Improve Sleep	25 (48.2%)
Relieve Pain	25 (47.2%)
To Treat the Cancer Itself	10 (18.9%)
Side Effects from Marijuana	
Slower Reaction Time	14 (26.4%)
None	14 (26.4%)
Paranoia	8 (15.1%)
Anxiety	6 (11.3%)
Poor Coordination	5 (9.4%)

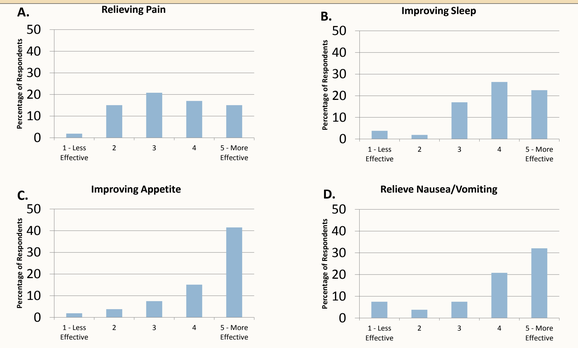

Figure 1. Perceived Efficacy of Marijuana to Manage Side Effects of Chemotherapy. Patients were indicated on a scale from 1 to 5 how effective they felt marijuana was in improving or relieving (A) pain, (B) sleep (C) appetite or (D) nausea/vomiting

Discussion

- Fifty-three (28.6%) of the 185 patients surveyed reported use of marijuana within the past 6 months, where only 12.9% of Coloradans 21 years or older are current users[2]
- Cancer patients who are marijuana users are:
  - more likely to use CAM products (<0.001) and experience chemotherapy side effects more frequently (p<0.001)
  - more likely to be 20-49 years old and are less likely to use if they are 70 years or older
- Providers do not frequently ask about marijuana use
- The most common sources of information is from the dispensary or family and friends.
- Most patients use marijuana to manage side effects associated with chemotherapy and not for treating the cancer itself
- Poor coordination is reported as the most common side effect with an equal amount of respondents reporting no side effects

Conclusion

- Cancer patients who use marijuana are not representative of marijuana users in the general population, they have a higher rate of use and less predictors of use[2]
- Younger age, more frequent side effects, and CAM use are associated with those who choose to use marijuana during chemotherapy treatment
- Use of marijuana was reported to be tolerable and the side effects did not seem to be additive to chemotherapy or supportive care medication side effects, however more research regarding the efficacy and safety of marijuna is required
- Pharmacists and other health care providers should look for opportunities to provide evidence based information regarding marijuana use during chemotherapy
- The next steps for this work include:
  - Surveying health care providers about their willingness to discuss marijuana use with patients and barriers to communications
  - Analysis of how to best disperse information to patients who use marijuana
  - Survey cancer patient populations at hospitals throughout Colorado with different demographics to investigate various prevalence levels throughout the state

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