Inflammation as a Prognostic Biomarker to Evaluate the Effects of Medical Cannabis on Breast Cancer Patients' Short- and Long-Term Outcomes

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Abstract

Despite the increasingly prevalent use of medical cannabis (MC) in cancer patients as a treatment strategy for symptom management, few studies have examined the underlying biological mechanisms such as inflammation in predicting patient outcomes after MC use. This abstract aimed to bridge recent literature and our own data to illustrate how cannabis use may impact inflammation measured by C-reactive protein (CRP), which may subsequently predict treatment responses, quality of life (QOL), and clinical outcomes among cancer patients. A review of the literature was conducted to explore applications of C-reactive protein (CRP) as a potential prognostic biomarker in breast cancer patients initiating MC. We also capitalized on our laboratory's pilot data measuring high-sensitivity C-reactive protein (hsCRP) levels in pain, radiotherapy (RT)-induced skin toxicity, and survival outcomes in breast cancer patients. Recent literature suggests that cannabis usage promotes an anti-inflammatory response with growing evidence that cannabinoid activation affects inflammation/ inflammatory biomarkers, such as C-reactive protein (CRP). All these findings suggest cannabis use may reduce inflammation measured by CRP. On the other hand, findings from our study found CRP to be significantly associated with patient outcomes including pain (p=0.002), radiotherapy-induced skin toxicities (p=0.028) and survival (p=0.005) in a multi-ethnic breast cancer population (n=63), suggesting CRP can be a prognostic biomarker for cancer patient outcomes. Bridging the two pieces of evidence together, we hypothesize that CRP may have clinical significance as a prognostic biomarker in breast cancer patients initiating MC. Future research characterizing the longitudinal relationship between cannabis and C-reactive protein could provide insight into molecular mechanisms and effects on treatment responses, QOL and clinical outcomes in breast cancer patients initiating MC.

Methods

Study Design: A review of the literature was conducted to explore applications of C-reactive protein (CRP) as a potential prognostic biomarker in breast cancer patients initiating MC. We also capitalized on our laboratory's pilot data from three NCI-funded projects (2010-2023) measuring high-sensitivity C-reactive protein (hs-CRP) levels in pain, radiotherapy (RT)-induced skin toxicity, and survival outcomes in breast cancer patients.

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Methods: PubMed and Medline databases were utilized with search terms 'Cannabis', 'Marijuana', C-Reactive Protein', 'Medical Cannabis, 'Medical Marijuana', and Breast Cancer'. In our pilot study, we explored inflammation biomarkers in breast cancer patient populations receiving radiotherapy (RT) (n=63) to assess clinical outcomes including pain, RT-induced skin toxicities, and survival.

Results

- A review of the literature suggests that cannabis usage, specifically cannabinoid-2 receptor activation, promotes an anti-inflammatory response. There is growing evidence that inflammation/ inflammatory biomarkers, such as C-reactive protein (CRP), are affected by cannabinoid activation.
- Multiple studies reported alterations in CB1R and CB2R expression levels in breast cancer and previous small studies associated MC usage with lower CRP levels.
- Findings from recent studies have reported associations between medical cannabis usage and reductions in CRP levels in conditions including chronic pain and fibromyalgia.
- CBD and THC have demonstrated anti-inflammatory activities in vitro and in vivo models. Recent studies suggest CBD reduced the expression of inflammatory mediators such as IL-6, TNF-α, COX-2, and iNOS, while also inhibiting TNF-α production via the p38 MAPK pathway. While other findings reported THC may decrease myeloid immune cell infiltration and downregulate pro-inflammatory cytokines.
- Findings from our pilot study in a multi-ethnic breast cancer population (n=63) found CRP to be significantly associated with the following patient outcomes in breast cancer:
  1. pain (p=0.002)
  2. radiotherapy-induced skin toxicities (p=0.028)
  3. survival (p=0.005)

Variables Mean (SD)	RT-Induced Skin Toxicity			Pain Score			Vital Status		
	1 (n=20)	2-3 (n=43)	p-value	<4 (n=36)	4+ (n=22)	p-value	Alive (n=47)	Dead (n=16)	p-value
ASC	7.42 (0.91)	7.73 (0.69)	0.13	7.47 (0.89)	7.89 (0.39)	**0.017**	7.61 (0.68)	7.7 (1.02)	0.749
Caspase-1	0.14 (0.54)	0.46 (0.31)	**0.023**	0.31 (0.4)	0.48 (0.26)	0.064	0.32 (0.47)	0.49 (0.19)	**0.043**
IL-18	7.24 (0.79)	7.62 (0.63)	**0.04**	7.5 (0.84)	7.52 (0.48)	0.892	7.44 (0.68)	7.68 (0.76)	0.234
IL-6	1.45 (1.09)	1.87 (1.17)	0.218	1.39 (0.9)	2.18 (1.36)	**0.022**	1.56 (1.09)	2.28 (1.2)	**0.03**
hsCRP	1.48 (2.04)	2.51 (1.58)	**0.028**	1.55 (1.7)	2.98 (1.53)	**0.002**	1.79 (1.69)	3.14 (1.72)	**0.005**

Table 1 Inflammation Biomarker Levels and Breast Cancer Clinical Outcomes from Study Team's Pilot Data

Variable		Pre-RT Pain (N = 349)				Post-RT Pain (N = 335)				RT-related Pain (N = 262)				
		No (< 4)		Yes (≥ 4)		P value	No (< 4)		Yes (≥ 4)		P-Value	No		Yes		P-Value
		N	%	N	%	P [3]	N	%	N	%	P [3]	N	%	N	%	P [3]
Total		290	83	59	17		233	70	102	30		203	77	59	23	
Total RT dose (Gy)	< 60	92	89	11	11	**0.045**	74	80	19	20	0.014	66	84	13	16	0.123
	≥ 60	198	80	48	20		159	66	83	34		137	75	46	25	
Pre-RT CRP (mg/L)	< 10	256	85	45	15	**0.006**	210	73	79	27	**0.001**	183	79	48	21	0.056
	≥ 10	30	68	14	32		20	48	22	52		17	63	10	37	
Post-RT CRP (mg/L)	< 10	234	83	47	17	0.410	203	71	82	29	0.077	175	78	49	22	0.373
	≥ 10	32	78	9	22		23	58	17	43		22	71	9	29	
RT-related CRP change (mg/L)	≤ 1	192	82	41	18	0.992	170	72	67	28	0.140	151	82	34	18	**0.006**
	> 1	70	82	15	18		53	63	31	37		43	65	23	35	

[1]P values were from the chi-square test or Fisher's exact test excluding missing

Table 2 CRP Status in Pre-RT, Post-RT, and RT-related Pain for Breast Cancer from Study Team's Findings (Lee et. al, 2019)

Conclusions

Bridging our pilot data and evidence from the literature review together, we hypothesize that CRP may have clinical significance as a prognostic biomarker in breast cancer patients initiating medical cannabis. While research on the effects of medical cannabis on CRP levels is still limited, the available evidence suggests that it may have potential as an anti-inflammatory agent. Future longitudinal research characterizing the relationship between cannabis and C-reactive protein could provide insight into molecular mechanisms and effects on treatment responses, quality of life, and clinical outcomes in breast cancer patients initiating medical cannabis.

Acknowledgments

We would like to thank all participants who participated in the pilot study and the clinical staff who provided support. Study findings were supported by the National Cancer Institute award numbers R01CA135288 and R03CA195643.

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