The Immunomodulating Effects of Arabinoxylan Rice Bran (Lentin) on Hematologic Profile, Nutritional Status and Quality of Life among Head and Neck Carcinoma Patients Undergoing Radiation Therapy: A Double Blind Randomized Control Trial

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ABSTRACT

Immunostimulants have been explored to reduce the complications of radiation/chemotherapy. This double blind randomized trial aimed to determine the immunomodulating effects of Lentin among head and neck cancer patients in addressing radiation treatment complications such as anemia, leukopenia, weight loss and improvement of quality of life. Sixty-five (65) patients were enrolled and given either Lentin or placebo - 2 weeks prior, during radiation/chemoradiotherapy and 2 months after. Complete Blood Count, Body Mass Index, percent weight loss and EORTC Quality of Life questionnaires QLQ H&N35 were used to assess the degree of anemia, weight loss and quality of life. Overall CBC results revealed higher values on all parameters in Lentin arm. Upon completion of radiochemotherapy, the Lentin arm showed significantly higher mean hemoglobin by 1.30 g/dL (p=0.010), hematocrit (p=0.001), RBC (p=0.001) and platelets (p=0.017). Also, higher overall BMI (22.69 versus 21.52) and a lower percent weight loss (6.10% versus 6.91%) for Lentin compared to placebo were noted with p-values of 0.199 and 0.571, respectively. Treatment related toxicity using the RTOG grading showed lower severity scores on all parameters (p-values: >0.05) and better QoL scores for patients taking Lentin (p-value: 0.019). Results from this study showed better clinical outcomes for patients taking Lentin. These have led to fewer blood transfusions, treatment delays and hospital admissions, avoidance of treatment mortalities and morbidities, and improved quality of life among head and neck cancer patients undergoing chemoradiotherapy.

INTRODUCTION

Prognostic factors such as anemia and decreasing body mass index correlate well with treatment outcomes in Head and Neck cancer patients undergoing radiochemotherapy[1,2]. Hemoglobin level of less than 12 g/dl during multimodality cancer therapy are associated with decreased local tumor control and survival most often accompanied by decreasing leukocyte counts increasing susceptibility to infection and affecting the quality of life[3-8]. Blood transfusion and diet are the most common practice to improve hemoglobin status and body mass index. However, in our local setting where blood products are scarce and restoring body mass index through proper diet seems to take time, physicians resorted to dietary supplements that would help improve the immune system and combat the common adverse effects of radiochemotherapy that would cause treatment interruptions. However, this custom is not widely practiced due to lack of available data supporting its use.

Arabinoxylan rice bran also known locally as Lentin is a natural blend of hemicellusose product of rice bran that was partially hydrolyzed using shiitake mushroom enzymes (*Lentinus edodes mycelia* extract) wherein the principal ingredient is the arabinoxylan compound or b-1,4 xylophyronase hemicellulose[9]. The immunomodulatory mechanism and antitumor activity has been attributed to its complex structure of heteropolysaccharide (arabinogalactan, arabinoxylan, arabinan, β-1,3:1,4- glucan)[10]. As of this writing, only few articles have been published on the effects of Arabinoxylan rice bran (Lentin) among patients undergoing chemotherapy and lesser for patients undergoing both chemotherapy concurrent with radiotherapy (RT)[11-16].

This study, aimed to determine the effects of the immunomodulating capacity of Arabinoxylan rice bran on hematologic profile more focus on the degree of anemia and leukopenia, nutritional status as reflected by weight loss and differences in Body Mass index (BMI) and quality of life among head and neck cancer patients undergoing radiotherapy or concurrent with chemotherapy.

METHODOLOGY

Study Design

This is a double-blind randomized study of Head and Neck cancer patients seen at the Jose R. Reyes Memorial Medical Center- Department of Radiotherapy from November 2016 to March 2018 and were subsequently enrolled to either Lentin or placebo through random permutation.

Patient Population

Patients were given the treatment description along with explanation of the possible benefits and risks prior to obtaining informed consent. Eligible patients were biopsy proven head and neck malignancy from stages I- IVB undergoing radiotherapy alone or concurrent with chemotherapy with an ECOG performance status $\leq$ 2. Patients were excluded if they were found to have metastasis during CT planning, synchronous malignancy, elevated hepatic and renal enzymes at the onset of treatment, or a case of recurrence.

Drug Administration

Drug preparations were in powder form packed at 1 gram per sachet. They were instructed to dissolve 1 sachet in ½ glass of water to be taken three times a day after meals for a total dose of 3 grams per day, to be administered two weeks before the start of treatment, during radiation/ chemoradiotherapy, and for two months after completion radiotherapy or radio-chemotherapy. Patients were allowed to take iron and multivitamins as food supplement.

Hematologic Parameters and Nutritional Assessment

Complete Blood count (CBC), body weight and BMI were obtained 2 weeks before radiation/radiochemotherapy,

Table 1. Demographic Profile of Patients		
	Placebo	Lentin
Median Age	49	54.5
GENDER		
Male	29	24
Female	4	8
RT dose		
70 Gy	29	27
66 Gy	3	1
60 Gy	1	4
Histology		
SCCA	31	31
Adenoid Cystic Carcinoma	1	1
Malignant Ameloblastoma	1	0
Differentiation		
Undifferentiated	12	6
Well differentiated	1	2
Moderately Differentiated	1	2
Poorly Differentiated	6	3
Anatomic Site		
Nasopharyngeal	22	16
Laryngeal	5	6
Maxillary	3	2
Oropharyngeal	1	1
Salivary Gland	1	0
Oral Cavity	1	7
CHEMO given		
Yes	32	28
No	1	4
Stage		
I	0	0
II	5	5
III	8	7
IVA	15	16
IVB	5	4
Clinical Outcomes		
Mortality	11	0
Blood transfusions	17	1
Hospital Admissions	21	2
Metastasis	5	0
Infection	4	0
Recurrence	2	0

then weekly during treatment, and monthly for 2 months following treatment.

Quality of Life Measures and Treatment Related Side Effects Evaluation

The EORTC Quality of Life Questionnaires for Head and Neck Cancer Patients QLQ H&N35 and RTOG grading system were used for the evaluation of Quality of Life (QOL) and treatment related side effects. Patients were assessed on a weekly basis 2 weeks before and during radiation/ radiochemotherapy, and then once a month for 2 months following treatment.

Statistical Analysis

Means and standard deviations were used to summarize the data in quantitative form, such as age, BMI, weight loss, CBC parameters and WBC differential counts, blood chemistry, and QOL results. Gender was summarized using counts and percentages. To determine homogeneity between the two groups, student's t-test and Fischer's exact test was done for mean age and gender. Student's t-test compared the BMI, weight loss, CBC parameters and WBC differential counts, blood chemistry test results of the two groups, while Mann-Whitney Test compared their QOL. Subset analysis was done for clinical outcomes (disease progression, infection, metastasis, hospital admission, blood transfusion and mortality) using Chi square analysis and Fisher's exact tests. All statistical tests were performed in SPSS version 20.0. P-values less than 0.05 indicated statistically significant differences.

RESULTS

Demographic Profile of Patients

A total of 70 patients were selected and only 65 patients were enrolled in the study from November 2016 to February 2018. Patients were enrolled to either to placebo (n= 32) or Lentin (n= 33). The median age was 52 years old, and majority of the patients were male and the predominant site being the nasopharynx with an undifferentiated squamous cell carcinoma histology. Patients were mostly locally advanced stage and were given concurrent chemoradiotherapy. Majority of the total radiation dose prescribed was 70 Gy.

Table 2. Demographic Profile Statistical Analysis

	ALL	Placebo	Lentin	*p*-value
Age (years)	51.24 ± 10.34	49.38 ± 10.77	53.16 ± 9.68	0.148
Gender: Male	50 (80.6%)	27 (87.1%)	23 (74.2%)	0.335

Values expressed as Mean ± SD.
p-values displayed are based on Student's t-test and Fisher's exact test.

Complete Blood Count

The mean hemoglobin of the two groups did not differ during pre RT (p=0.854) and during RT (p=0.537). But at post RT, the mean hemoglobin of the lentin group was significantly higher (p=0.010) than the placebo group.

Table 3 shows that at post RT, the mean hemoglobin of the lentin group was higher by 1.30 g/dL [$CI_{95\%}$: 0.33 to 2.26] versus the placebo group.

Similarly, the mean hematocrit of the two groups did not differ pre RT (p=0.551) and during RT (p=0.446). But at post RT, the mean hematocrit of the lentin group was significantly higher (p=0.001) than the placebo group.

Table 3 showed that at post RT, the mean hematocrit of the lentin group was higher by 0.05% [$CI_{95\%}$: 0.02 to 0.08] versus the placebo group.

Table 3. Complete Blood Counts of Patients at Pre RT, during RT and at Post RT

Parameters	Group	Pre RT Mean ± SD	*p*-value	RT Mean ± SD	*p*-value	Post RT Mean ± SD	*p*-value
Hb (g/dL)	Placebo	14.06 ± 1.72	0.854	12.55 ± 1.29	0.537	10.59 ± 1.53	0.010
	Lentin	14.14 ± 1.56		12.74 ± 1.21		11.89 ± 1.73	
Hct (%)	Placebo	0.42 ± 0.05	0.551	0.37 ± 0.04	0.446	0.31 ± 0.05	0.001
	Lentin	0.41 ± 0.05		0.38 ± 0.04		0.35 ± 0.05	
RBC (x 10^9/uL)	Placebo	4.86 ± 0.51	0.330	4.29 ± 0.43	0.196	3.47 ± 0.53	0.004
	Lentin	4.71 ± 0.66		4.46 ± 0.61		4.2 ± 0.93	
WBC (x 10^3/uL)	Placebo	9.57 ± 3.67	0.951	9.18 ± 5.25	0.124	6.15 ± 2.23	0.374
	Lentin	9.51 ± 4.3		7.56 ± 2.44		6.72 ± 2.19	
Platelets (x 10^3/ uL)	Placebo	326.43 ± 90.58	0.404	271.37 ± 60.26	0.739	215.96 ± 78.11	0.017
	Lentin	305.01 ± 104.3		276.96 ± 71.79		271.43 ± 73.36	

p-values based on Student's t-test.

Likewise, the mean RBC of the two groups did not differ pre RT (p=0.330) and during RT (p=0.196). But at post RT, the mean RBC of the lentin group was significantly higher (p=0.004) than the placebo group. Table 3 shows that at post RT, the mean RBC of the lentin group was higher by 0.73 x10^9/µL [$CI_{95\%}$: 0.25 to 1.21] versus the placebo group. However, the mean WBC of the two groups did not differ pre RT (p=0.951), during RT (p=0.124) and at post RT (p=0.374) (table 3).

On the other hand, the mean platelet counts of the two groups did not differ pre RT (p=0.404) and during RT (p=0.739). But at post RT, the mean platelet counts of the lentin group was significantly higher (p=0.017) than the placebo group. Table 3 shows that at post RT, the mean platelet counts of the lentin group was higher by 0.73 x10^9/µL [$CI_{95\%}$: 0.25 to 1.21] versus the placebo group.

White Blood Cell Differential Counts

The mean neutrophils of the two groups did not differ pre RT (p=0.578) and during RT (p=0.659). But at post RT, the mean neutrophils of the lentin group was significantly higher (p=0.007) than the placebo group. Table 4 shows that at post RT, the mean neutrophils of the Lentin group was higher by 0.18 [$CI_{95\%}$: 0.05 to 0.31] versus the placebo group.

Similarly, the mean lymphocytes of the two groups did not differ pre RT (p=0.928) and during RT (p=0.204). But at post RT, the mean lymphocytes of the lentin group was significantly higher (p=0.045) than the placebo group. Table 4 shows that at post RT, the mean lymphocytes of the lentin group was higher by 0.08 [$CI_{95\%}$: 0.01 to 0.14] versus the placebo group. However, the mean eosinophils of the two groups did not differ pre RT (p=0.276), during RT (p=0.264) and at post RT (p=0.315).

The mean basophils of the two groups did not differ pre RT (p=0.195), during RT (p=0.254) and at post RT (p=0.354). The mean monocytes of the two groups did not differ pre RT (p=0.469), during RT (p=0.275) and post RT (p=0.541).

Nutritional status of patients

Both arms had a mean BMI of 22.10 (range, 12.7 to 31.2; figure 1) with a weight loss of 6.51% (range, 15.0 to 17.0). The two groups had significant percentage weight loss (Placebo: 6.91 ± 5.61 p<0.001; Lentin: 6.10 ± 5.72, p<0.001; figure 2), the placebo group had a mean weight loss of 6.91% [$CI_{95\%}$: 4.9 to 8.9] while the Lentin group had a mean weight loss of 6.1% ($CI_{95\%}$: 4.0 to 8.2), the difference did not differ significantly (p=0.571).

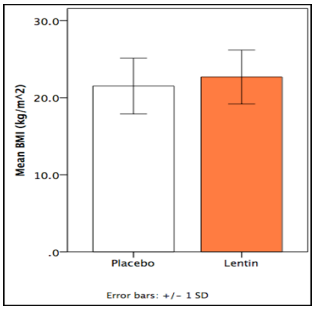

Figure 1: Mean BMI

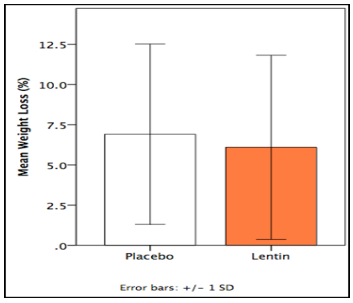

Figure 2: Mean percent weight loss

Treatment Related Side Effects

The mean skin (p=0.102), mucous membrane (p=0.808), eye (p=0.523), ear (p=0.500), saliva (p=0.124), pharynx (p=0.188) and larynx (p=0.073) side effects of the two groups did not differ.

Table 5. RTOG Severity Grading of Radiation Toxicities

	Placebo	Lentin	*p*-value
Skin	0.95 ± 0.34	0.81 ± 0.31	0.102
Mucous Membrane	0.65 ± 0.43	0.62 ± 0.42	0.808
Eye	0.05 ± 0.12	0.03 ± 0.1	0.523
Ear	0.23 ± 0.31	0.17 ± 0.33	0.500
Saliva	1.14 ± 0.47	0.96 ± 0.47	0.124
Pharynx	0.75 ± 0.41	0.62 ± 0.39	0.188
Larynx	0.56 ± 0.45	0.37 ± 0.36	0.073

Values expressed as Mean ± SD. *p*-values displayed based on Student's t-test.

Quality of Life

The QoL of Patients treated with Lentin was significantly better (p=0.019) than patients under the placebo group.

Table 6. Quality of Life Scores of Patients

Group	Mean QoL scores	*p*-value
Placebo	1.72 ± 0.33	0.019
Lentin	1.53 ± 0.24	

Values expressed as Mean ± SD. *p*-values based on Mann-Whitney test.

Table 4. WBC Differential Counts of Patients at Pre RT, during RT and at Post RT

Parameters	Group	Pre RT Mean ± SD	*p*-value	RT Mean ± SD	*p*-value	Post RT Mean ± SD	*p*-value
Neutrophils	Placebo	0.64 ± 0.10	0.578	0.72 ± 0.08	0.659	0.51 ± 0.31	0.007
	Lentin	0.65 ± 0.11		0.71 ± 0.08		0.69 ± 0.12	
Lymphocytes	Placebo	0.28 ± 0.10	0.928	0.22 ± 0.09	0.204	0.19 ± 0.14	0.045
	Lentin	0.28 ± 0.10		0.25 ± 0.11		0.26 ± 0.11	
Eosinophils	Placebo	0.03 ± 0.02	0.276	0.03 ± 0.02	0.264	0.04 ± 0.06	0.315
	Lentin	0.04 ± 0.04		0.05 ± 0.08		0.02 ± 0.03	
Basophils	Placebo	0.01 ± 0.02	0.195	0.02 ± 0.02	0.254	0.01 ± 0.02	0.354
	Lentin	0.01 ± 0.02		0.03 ± 0.06		0.00 ± 0.01	
Monocytes	Placebo	0.07 ± 0.12	0.469	0.06 ± 0.06	0.275	0.04 ± 0.04	0.541
	Lentin	0.05 ± 0.04		0.09 ± 0.16		0.06 ± 0.11	
Stabs	Placebo	0.00 ± 0.00	-	0.000 ± 0.000	0.200	0.00 ± 0.00	-
	Lentin	0.00 ± 0.00		0.001 ± 0.010		0.00 ± 0.00	

Clinical Outcomes

Table 7 presents the clinical outcomes of the patients in the study.

Table 7. Clinical Outcomes

Outcome	Placebo	Lentin	P-value
Mortality	11	0	0.000339377
Blood transfusions	17	1	0.00001
Hospital Admissions	21	2	0.000001
Metastasis	5	0	0.028733562
Infection	4	0	0.06043956
Progression	2	0	0.253846154

p-values displayed are based on Chi square test and Fisher's exact test.

DISCUSSION

The results of this study showed that upon completion of radiochemotherapy (2 months post RT/CRT), patients who were treated with Arabinoxylan rice bran (Lentin) showed significantly higher mean hemoglobin (p=0.010), hematocrit (p=0.001), RBC (p=0.001) and platelets (p=0.017) and this was accompanied with significantly higher neutrophil count (p=0.007) and lymphocyte count(p=0.045). Both groups had significant weight loss (p<0.001). Lastly, patients treated with Lentin had better quality of life (p=0.019) and lower treatment related toxicities compared to the placebo group.

Combining treatment modalities of radiation and chemotherapy in the management of certain head and neck malignancies have been proven to improve outcomes in local control and survival but these come at the expense of increased treatment toxicity rates. Patients who were unable to tolerate the combined regimen have suffered treatment delays that resulted to poorer outcomes with hematopoietic tissues (which are most sensitive to ionizing radiation) suffering the immediate effects of exposure. [6-8]

In this study, based on overall complete blood count results, there were higher values on all hematologic parameters in the Lentin arm. The pre-treatment (2 weeks loading dose) CBC values showed higher hemoglobin, hematocrit, RBC, neutrophilic, lymphocytic, eosinophilic and basophilic counts in the Lentin arm compared to placebo. During radiotherapy/ chemoradiotherapy, patients given Lentin had higher values in all parameters except for the decrease in WBC, however, this was not statistically significant. While on post-treatment hematologic assessment (2 months), Lentin treated patients had better results in all parameters which were statistically significant based on its ability to maintain the hemoglobin, hematrocit, RBC count, platelet count, neutrophil and lymphocyte counts within normal range compared to the placebo counterpart where a marked decreased in neutrophil and lymphocyte count was predominant. These RBC indices, more specifically the hemoglobin values, were of paramount importance as higher values coincided with better tumoricidal property in radiation therapy resulting to superior local control and overall survival. Ghoneum et al reported on the protective effect of Lentin on the overall maintenance of hematopoietic tissues in mice after exposure to gamma irradiation and found out that Lentin could be used as a radioprotector against gamma irradiation induced depletion of WBC, RBC indices including hemoglobin, hematocrit, RBC count and platelet count by preventing immune system dysfunction[17].

On the nutritional status, recorded weight and BMI on follow-ups showed higher overall BMI for Biobran/RBAC (22.69) compared to placebo (21.52) and a lower percent weight loss on Biobran/RBAC (6.10%) versus placebo (6.91%). Treatment related toxicity using the RTOG grading showed lower severity scores on all parameters in Biobran/ RBAC compared to placebo. Quality of Life scores using EORTC H&N35 were worst in placebo compared to Lentin. Deaths during the course of treatment were significantly higher in placebo (11) compared to the Lentin with no recorded treatment related mortality. A study done by Masood et al who evaluated the effects of Lentin among breast cancer patients in reducing chemotherapy induced side effects observed that patients taking Lentin had significant reduction in tiredness, fatigue, anorexia, nausea and hair fall. These patients were unlikely to need anti-emetics, appetizers or food supplements as they reported improved quality of life[13]. The same findings were reported by Petrovics et al among cancer patients who were suffering from chronic fatigue syndrome and

were treated with Lentin and oncothermia concluded that these patients had reduced pain and better quality of life through enhance NK cell activity[18].

A subgroup analysis done showed that patients taking Lentin had lower rates of blood transfusion and hospital admission and no incidence of tumor progression, infection and metastases as compared to placebo. These have led to lesser treatment delays, avoidance of treatment mortalities and morbidities, more patients completing the treatment and improved quality of life among head and neck cancer patients undergoing radiotherapy/chemoradiotherapy.

LIMITATIONS AND RECOMMENDATIONS

The number of participants in this double-blind randomized pilot study was low, however the results were promising - revealing significant improvement in clinical outcome after Lentin administration. Certain medications such as those for pain were not withheld and were given upon the discretion of the attending physician and the patients' symptoms. Based on the data, performing a study on different cancer sites with the same treatment modality would corroborate with our findings. Also, the results obtained did not immediately translate to improved outcomes in terms of local control, overall survival, disease free survival and recurrence free survival. These parameters are best obtained with 5 to 10 years of follow up, of which we believe could be a prospect for future studies.

CONCLUSION

The study showed better clinical outcomes based on hematologic parameters, nutritional status, treatment-related toxicities and quality of life in Arabinoxylan rice bran (Lentin) compared to placebo undergoing radiochemotherapy. This suggests that Lentin might be a potential adjunct in preventing radiation induced side effects among head and neck cancer patients.

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