Effect of Protein and Energy-Dense Nutritional Supplement with Immunonutrients on Cachexia in Cancer Patients: An Open-Label, Single-Arm Study Among Indian Patients

Rachana Bhoite [1,*], Varalakshmi Lalithya Pratti[1], Vinita Satyavrat[1], Rahul Rathod[1]

[1]Dr. Reddy's Laboratories Pvt Ltd., Ameerpet, Hyderabad, Telangana 500016, India

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Corresponding author:

Rachana Bhoite, Lead - Nutrition Sciences India & Emerging Markets, Nutritional Business, Dr. Reddy's Laboratories Pvt. Ltd., Ameerpet, Hyderabad (India).

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Abstract

Background

Cachexia is highly prevalent in cancer patients and is responsible for as much as 20% of all cancer deaths. Nevertheless, there is little emphasis on cachexia in routine clinical practice. This study looks at the efficacy and tolerability of a protein and energy-dense nutritional supplement with immunonutrients on cachexia in cancer patients.

Methods

This was a three-month, prospective, open-label study of patients undergoing radio-therapy and/or chemotherapy for head and neck or gastrointestinal or lung cancer. Efficacy endpoints were mean change in muscle strength, acute phase proteins (albumin and pre-albumin), C-reactive protein (CRP) levels, weight, Glasgow prognostic score (GPS), and nutritional status at the end of the study period.

Results

The study population consists of 47 (79.66%) males and 12 (20.34%) females with a mean age of 47.98 ± 12.16 years. The mean change in muscle strength, albumin, pre-albumin, CRP levels, and weight for the overall study population was 0.17 ± 12.09 kg (P=0.9145), -0.05 ± 0.53 g/dl, (P=0.5888), -0.01 ± 0.09 g/dl (P=0.2951), 0.50 ± 37.41 mg/dl (P=0.9258), -0.59 ± 3.70 kg (P=0.2265), respectively. At the end of the study period, there was a significant improvement in the nutritional status concerning total calories, protein, and fat intake.

Conclusion

Protein and energy-dense nutritional supplement with immunonutrients might help in the improvement of muscle strength, GPS, and dietary intake. The addition of the supplement to the diet regime of patients with cancer cachexia increases their daily consumption of proteins which might translate to multimodal clinical benefits.

Introduction

Nutrition and diet are essential components of cancer treatment to maintain overall wellness and improve tolerability. Cancer Cachexia syndrome (CCS) is a deteriorating condition characterized by a spontaneous reduction in food intake, loss of muscle mass, weight loss, fatigue, anemia, and hypoalbuminemia[1]. It is a serious but often unanswered health concern for cancer patients. Nutritional disruption in cancer patients may be attributed to a variety of factors, including metabolic, and pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α), symptomatic distress, and side effects of cancer treatment [2,3]. Cumulatively all these factors are responsible for suppressing appetite and preventing the efficient use of nutrients. Cachexia prevalence ranges from 50% to 80% in patients with cancer, representing up to 20% of cancer-related deaths[4,5]. CCS incidence is associated with a poor prognosis due to decreased daily activities and quality of life attributed to skeletal muscle weakness. Furthermore, CCS is associated with poor clinical outcomes due to the cancer patient's inability to tolerate cytotoxic chemotherapy[6,7]. Studies that evaluated cachexia during chemotherapy reported unintended weight loss in over 20% and 63% of patients with untreated non-small cell lung cancer and mixed types of cancer, respectively[8,9]. Similarly, studies have also demonstrated an association between baseline cachexia and reduced overall survival in patients with pancreatic ductal adenocarcinoma[10]. In a study by Muscaritoli et al., up to 70% of patients with pancreatic and gastroesophageal cancers had cachexia[11]. A systematic review of 21 studies showed a 30% prevalence of cachexia with the highest rates in the liver (50%), pancreas (45.6%), and head and neck cancers (42.3%), respectively[12].

Major nutrition organizations have published guidelines recommending nutritional screening as part of the baseline assessment for all cancer patients[13,14]. European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines have recognised malnutrition and associated weight loss to be linked with an unfavourable prognosis in cancer patients[15]. The guidelines recommend nutritional support to improve clinical outcomes in cancer patients who are moderately or severely malnourished or incapable of meeting their oral nutritional needs[14,15]. The European Palliative Care Research Collaborative (EPCRC) has come up with the three diagnostic criteria for cancer cachexia namely: (i) weight loss in excess of 5% in the last 6 months, (ii) weight loss in excess of 2%, and body mass index (BMI) of <20 kg/m^2 in the last 6 months, or (iii) weight loss in excess of 2% and diagnosis of sarcopenia in the last 6 months[16]. Zhou T et al. proposed a new cachexia staging score (CSS), that classifies patients into four groups: non-cachexia, pre-cachexia, cachexia, and refractory cachexia, respectively[17]. The European Society of Medical Oncology (ESMO) also published clinical practice guidelines for cancer cachexia patients in 2021[18]. Despite this, there is little attention to CCS in routine clinical practice, and specific risk factors and management strategies are not yet well characterized. This study examines the efficacy and tolerability of a protein and energy-dense nutritional supplement with immunonutrients on cachexia in cancer patients undergoing chemotherapy and/or radiotherapy.

Materials and Method

Study Design and Eligibility Criteria

This was a three-month, prospective, multi-centre, open-label, single-arm study to evaluate the efficacy and tolerability of protein and energy-dense nutritional supplement with immunonutrients on cachexia in cancer patients. The eligibility criteria included male and female patients undergoing radiotherapy and/or chemotherapy for head and neck or gastrointestinal or lung cancer, aged ≥ 18 years, BMI ≥ 17.0 to ≤ 24.9 kg/m^2, history of weight loss in the past 6 months based on subjective global assessment score, the Eastern Cooperative Oncology Group (ECOG) performance status of ≤ Grade 2, acceptable hematologi-

cal, hepatic and renal state and no history of substance abuse. Women of reproductive age were expected to practice an acceptable method of contraception during the study period. Patients were excluded if they were unable or unwilling to provide informed consent and comply with the protocol procedures, had a current or past history of severe hepatic or renal impairment, or the presence of any uncontrolled systemic disease, were pregnant or lactating women, had central nervous system metastases or another malignancy, were taking prescription medications intended to increase appetite or muscle mass or treat weight loss and were unable to take medication orally. Patients were also excluded if they had participated in a clinical study within 90 days before the first dose of the study product and had active coronavirus (COVID-19) infection. The study was carried out in accordance with the ethical principles outlined in the latest version of the Declaration of Helsinki, and the applicable guidelines for good clinical practice (GCP). Ethics committee approval was taken for this study and the study was registered at the Clinical Trials Registry of India portal vide registration number CTRI/2020/11/029409.

Study Intervention

Patients who met the eligibility criteria were included in the study and underwent baseline assessments and laboratory testing. During the study period, patients received nutritional support through protein and energy-dense nutritional supplement with immunonutrients over and above their normal diet. The protein and energy-dense nutritional supplement powder is high in protein, and omega-3 fatty acids and fortified with antioxidant and immunonutrients nutrients (vitamin C, vitamin A, vitamin E, zinc, and selenium). Patients were required to take one sachet (33 gm) of the protein and energy-dense nutritional supplement powder with 200 ml of lukewarm water twice daily for 90 days. The idea was to fill their dietary requirements and see any change in biomarkers for the anti-oxidative and immuno-booster activity for a faster immune response, strengthening the immune system, enhancing antibody production, and protecting the immune cells against oxidative stress. At the end of the study period, patients had to undergo laboratory tests and assessments to evaluate the impact of the study intervention on cachexia.

Efficacy Endpoints

The study efficacy endpoints were mean change in muscle strength, acute phase proteins (albumin and pre-albumin), weight, C-reactive protein (CRP) levels, and Glasgow prognostic score (GPS) at the end of study period. The primary endpoint was a mean change in muscle strength measured by hand grip dynamometer/strength to evaluate individual muscle strength at baseline day 30, 60, and 91, respectively. The GPS score was calculated based on CRP level to reflect the systemic inflammation status and serum albumin levels to reflect the nutritional status and characterized patients into three groups, namely 0, 1, and 2 [19]. The GPS score was recorded at baseline day 30, 60, and 91, respectively. Other efficacy end-points were patient satisfaction as measured by the tolerability testing of the protein and energy-dense nutritional supplement powder on day 30 and day 60, respectively, and mean change in nutritional status (24-hour dietary recall) for one week before the treatment period and one week before the end of the study period.

Statistical Analysis

The statistical analysis of the continuous variables was summarized by the arithmetic mean, and standard deviation (SD). A paired sample t-test or repeated measure ANOVA (as appropriate) was used to compare the changes in mean parameter values at the end of the study. Categorical variables were summarized in terms of frequencies and percentages. The Chi-square test was used to compare the difference in proportions between two different time points. A two-sided $P<0.05$ was considered

significant. The last observation carried forward (LOCF) method was used to impute missing values, if any, to the follow-up assessments. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., North Carolina, USA).

Results

Baseline characteristics of participants

A total of 132 patients were screened, and 101 eligible patients were included in the study. Of these 101 patients, 42 could not adhere to protocol procedures due to the COVID-19 pandemic, and the results were analyzed in 59 patients. There were 47 (79.66%) males and 12 (20.34%) females with a mean age of 47.98 ± 12.16 years. The baseline characteristics of the study participants are presented in (Table 1).

Table 1. Baseline Characteristics of the Study Subjects

Parameters	**N=59**
Age, mean ± SD, year	47.98 ± 12.16
Gender, n (%) Male Female	 47 (79.66) 12 (20.34)
Weight, mean ± SD, kg	55.39 ± 9.02
BMI, mean ± SD, kg/m^2	20.31 ± 2.49
Performance status, n (%) 0 1 2	 15 (25.42) 40 (67.80) 4 (6.78)

Change in muscle strength

Compared to the pre-intervention level, there was a marginal increase in muscle strength for the overall study population (27.72 ± 14.93 vs. 27.89 ± 13.09 kg mean difference 0.17 ± 12.09 kg, P=0.9145), but the difference was not statistically significant (Table 2).

Table 2. Change in muscle strength (kg)

Timepoint	**Overall study population (N=59)**		
	mean ± SD	**Difference**	**P value**
Baseline	27.72 ± 14.93	-	-
Day 30	28.35 ± 13.27	0.63 ± 10.96	0.6605
Day 60	27.69 ± 12.52	-0.03 ± 11.34	0.9846
Day 91	27.89 ± 13.09	0.17 ± 12.09	0.9145

Change in acute phase proteins, CRP levels, and weight

Compared to baseline levels, there was a marginal decrease in albumin (mean difference -0.05 ± 0.53 g/dl, P=0.5888), pre-albumin (mean difference -0.01 ± 0.09 g/dl, P=0.2951), and weight (mean difference -0.59 ± 3.70 kg, P=0.2265) at the end of the study period for the overall study population (Table 3). However, the difference was not statistically significant. Similarly, a marginal increase in the CRP levels (mean difference 0.50 ± 37.41 mg/dl, P=0.9258) was noted at the end of the study period (Table 3).

Table 3. Change in acute phase proteins, CRP levels, and weight

Parameters	Baseline	Day 91		
	Mean ± SD	Mean ± SD	Difference	P value
Acute phase proteins (albumin), g/dl (N=50)*	4.22 ± 0.51	4.17 ± 0.51	-0.05 ± 0.53	0.5888
Acute phase proteins (pre-albumin), g/dl (N=50)*	0.21 ± 0.09	0.20 ± 0.06	-0.01 ± 0.09	0.2951
CRP levels, mg/dl (N=50)*	13.75 ± 21.20	14.25 ± 29.71	0.50 ± 37.41	0.9258
Weight, kg (N=59)	55.39 ± 9.02	54.80 ± 8.96	-0.59 ± 3.70	0.2265

* For 9 patients, values of laboratory tests are not available

Change in GPS score

The number of patients with a GPS score of 0 at baseline grew, while the number of patients with GPS scores of 1 and 2 at baseline declined at the end of the study period. However, neither the rise nor decline was statistically significant (Table 4).

Table 4. Change in GPS, N=50

	n (%)	Chi-square	P value
Baseline			
0	9 (18.00)	-	-
1	39 (78.00)		
2	2 (4.00)		
Day 30			
0	2 (4.00)	17.1750	**0.0018***
1	43 (86.00)		
2	5 (10.00)		
Day 60			
0	11 (22.00)	8.7251	0.0684
1	33 (66.00)		
2	6 (12.00)		
Day 91			
0	12 (24.00)	7.5254	0.1106
1	32 (64.00)		
2	6 (12.00)		

* Significant value

Change in nutritional status

Of the 59 patients, the change in the nutritional status could only be assessed in 22 patients, as the remaining patients could not record the 24-hour dietary recall for one week before the end of the study period (Table 5). There was a significant improvement in nutritional status in the overall intake of calories (1020 ± 307.55 vs. 1300 ± 227.14 Kcal, mean difference = 280 ± 163.80, P<0.0001), proteins (29.01 ± 9.68 vs. 60.98 ± 7.06 gm, mean difference = 31.97 ± 8.63, P<0.0001), and fats (25.96 ± 11.09 vs. 40.99 ± 9.09 gm, mean difference = 15.03 ± 11.70, P<0.0001) at the end of the study period. Likewise, carbohydrate intake has improved (167.70 ± 51.66 vs. 174.51 ± 55.42 gm, mean difference = 6.81 ± 27.92, P=0.2658), but the outcome has not been statistically significant.

Table 5. Change in nutritional status, N=22

Endpoints	Total Calories, mean ± SD, Kcal	Carbohydrates, mean ± SD, gm	Proteins, mean ± SD, gm	Fats, mean ± SD, gm
Baseline	1020 ± 307.55	167.70 ± 51.66	29.01 ± 9.68	25.96 ± 11.09
Day 91	1300 ± 227.14	174.51 ± 55.42	60.98 ± 7.06	40.99 ± 9.09
Difference	280 ± 163.80	6.81 ± 27.92	31.97 ± 8.63	15.03 ± 11.70
P value	**<0.0001***	0.2658	**<0.0001***	**<0.0001***

* Significant value

Patient satisfaction

The protein and energy-dense nutritional supplement powder was very well tolerated, and 57 (96.61%) of 59 patients reported being satisfied on day 30 and day 60, respectively.

Discussion

Cachexia is widespread in cancer patients, and affects 50–85% of all patients, depending on tumor type, treatment, patient characteristics, individual sensitivities, and assessment method [4,5]. It often necessitates early nutritional intervention targeted at protein supplementation. Several studies have shown that protein supplements can improve a patient's nutritional status and help maintain body weight and lean body mass, ensure better treatment tolerance, improve the quality of life, and enhance overall survival [14,15]. The ESMO Clinical Practice Guidelines recommend a multimodal approach involving oral nutritional supplements to treat cancer cachexia in adult patients[18]. Various approaches, including dietary supplements and oral nutritional supplements with or without nutritional counselling, are currently being explored to accomplish this goal. However, some studies contradict the role of oral nutritional supplements in managing cachexia in cancer patients [20,21]. The main objective of this study is to examine the effectiveness and tolerability of a protein and energy-dense nutritional supplement powder on cachexia in cancer patients undergoing chemotherapy and/or radiotherapy. At the end of the study period, our study found a marginal improvement in muscle strength, and a significant improvement in nutritional status regarding overall intake of calories, proteins, and fats. The number of patients having a GPS score of 0 also increased at the end of the study period.

In our study, the ECOG performance status at baseline was 0 and 1 in 25.4% and 67.8% of patients, respectively. The mean BMI of 20.31 ± 2.49 kg/m^2 at baseline in our study is closer to the value of 21.83 ± 3.22 kg/m^2 reported in a previous study [17]. The median BMI at baseline reported in other studies also

ranged between 21.7 and 24.2 kg/m^2 [22,24]. In a phase II trial of a multimodal intervention in 46 patients of lung and pancreatic cancer by Solheim TS et al. [22], patients in the intervention group demonstrated a significant increase in body weight relative to the control group (1.29 ± 3.42 vs. -3.19 ± 3.67, P<0.001). However, no significant differences were observed in grip strength, subjective global assessment, and CRP levels. Another phase II study involving 39 cancer patients reported increased weight, lean body mass, and appetite with antioxidants, vitamins, omega-3 fatty acids, medroxyprogesterone acetate, and celecoxib supplementation[25]. In a study by Yeh KY et al.[26], 68 head and neck cancer patients with a BMI of <19 kg/m^2, receiving an Ethanwell/Ethanzyme (EE) regimen for a period of 3 months showed a significantly increased (P<0.05) body weight along with higher serum albumin and prealbumin levels relative to the control group. While Ethanwell is a protein-dense oral nutritional supplement enriched with omega-3 fatty acids, glutamine, selenium, and CoQ10, Ethanzyme comprises multiple probiotics and vitamins. In a study of 32 patients with stage IV solid tumors, oral supplementation with a combination of β-hydroxy-β-methyl butyrate (HMB), arginine, and glutamine demonstrated a significant improvement (P <0.05) in the body mass and the fat-free mass compared to the isonitrogenous control mixture of nonessential amino acids over a period of 4-24 weeks [27]. However, in another study of 472 patients with advanced cancer, administration of a mixture of HMB, glutamine, and arginine showed no statistical difference in lean body mass compared to an isonitrogenous, isocaloric control over a period of 8 weeks [20]. In our study also, we did not find any statistical difference regarding muscle strength, weight, serum albumin and prealbumin levels, and CRP levels. Our study showed a marginal increase in muscle strength at the end of the study period (mean difference 0.17 ± 12.09 kg, P=0.9145). The possible explanation for not achieving a significant improvement in muscle strength could be a lack of response to systemic chemotherapy or the peripheral neuropathy associated with the pharmacological class of systemic therapy or a lack of compliance to the nutritional intervention. However, in the absence of data on the types of therapy used as well as treatment response or objective measures to assess compliance, it is hard to establish a conclusive association.

In a randomized multicentre trial, 72 participants with advanced pancreatic cancer taking L-carnitine showed increased BMI, reduced hospital stay, and increased overall survival compared to the control group [28]. In another randomized controlled trial of 166 advanced cancer patients, the administration of whey protein isolate supplementation (20 g/day) along with nutritional counselling showed more favourable outcomes concerning muscle strength and toxicity compared to counselling alone over a period of 3 months [29]. Although, our study showed a marginal improvement in the muscle strength, data pertaining to toxicity and overall survival was not captured. A study on 297 advanced cancer patients [17] showed that patients with more severe cachexia stages exhibited significantly lower skeletal muscle indexes, severe symptom burden, higher rates of sarcopenia, poor quality of life, and shorter survival times (P<0.001). A scoping review of 14 studies by Zanetti M et al. [30], showed the impact of protein or amino acid supplementation on improving muscle mass and strength with reduced oral intakes. In a randomized controlled trial by Baldwin C et al. [21], the simple nutritional intervention did not improve clinical outcomes or quality of life in patients with advanced cancers of the gastrointestinal tract (n = 277), and lung (n = 81) receiving weight loss chemotherapy. The mean change in weight and hand grip strength was small at 6 weeks and 26 weeks, respectively. However, the difference was statistically insignificant among the groups. Compliance with the nutritional intervention declined to 48% by week 6. A systematic review of 21 studies by Mochamat et al. [31], made no positive recommendation on the role of vitamins, minerals, proteins, or other supplements in the treatment of cachexia in cancer patients. In our study, although there was a non-significant reduction in the weight, serum albumin, and pre-albumin

levels, CRP levels showed a non-significant increase over the baseline values. Compared to the baseline values, the number of patients with a GPS score of 0 at baseline increase at the end of the study period (18% vs. 24%). With respect to improving muscle and grip strength and CRP levels, the results of our study are consistent with previously published reports [21, 22, 29, 30]. However, the results are contrary to previously published reports with respect to improvements in weight, BMI, serum albumin, and pre-albumin levels [20, 22, 25-27]. Baldwin C et al. [21], reported a 48% decline in compliance with nutritional intervention by week 6. This could be a possible explanation for the fact that we did not obtain favourable outcomes for the overall study population in our study.

In our study, there was a significant improvement in the nutritional status of the study population in terms of daily intake of calories (mean difference = 280 ± 163.80, P<0.0001), proteins (mean difference = 31.97 ± 8.63, P<0.0001), and fats (mean difference = 15.03 ± 11.70, P<0.0001) at the end of the study period. Although not statistically significant, there has been an increase in daily carbohydrate intake (mean difference = 6.81 ± 27.92, P=0.2658) as well. To the best of our knowledge, these parameters were not investigated earlier and this study might be the first to our knowledge to report on these findings. The protein and energy-dense nutritional supplement powder used in our study was very well tolerated and 96.61% of patients reported being satisfied on day 30 and day 60, respectively. A significant improvement in the nutritional status of the study population in terms of daily intake of calories can be considered a notable finding for designing more robust studies with the study product in the future.

Conclusion

Given the protein-energy malnutrition of cancer cachexia and its degenerative state due to chemotherapy/ radiotherapy, protein-energy levels would have further deteriorated without nutritional intervention. Thus, the addition of protein and energy-dense nutritional supplement powder along with their daily diet might positively impact the improvement of muscle strength, GPS, and dietary intake, especially protein in patients with cancer cachexia when used for a longer duration. The encouraging results of our study provide a ground for undertaking larger studies in specific patient populations to address the unavoidable need to recommend an optimal oral nutritional strategy for managing cancer cachexia.

Limitations of the Study

This was a proof of principle study to understand the impact of nutritional supplements on cancer patients. A study with a larger sample size would be beneficial for the future. Because of the Covid wave 1 and 2, there were too many dropouts from the study. This could be further improved in the next study.

Abbreviations

ANOVA: Analysis of Variance; BMI: Body Mass Index; CCS: Cancer Cachexia Syndrome; CRP: C-reactive Protein; CSS: Cachexia Staging Score; ECOG: The Eastern Cooperative Oncology Group; EE: Ethanwell/Ethanzyme regimen; EPCRC: The European Palliative Care Research Collaborative; ESMO: The European Society of Medical Oncology; GCP: Good Clinical Practice; GPS: Glasgow Prognostic Score; HMB: β-Hydroxy-β-Methyl Butyrate; LOCF: The Last Observation Carried Forward; SD: Standard Deviation

Ethics Approval and Consent to Participate

Ethics approval for the study was obtained at each participating centre. The institutional ethics committees at each of the following centres approved the study:

• HCG Manavata Cancer Centre, Nasik

• HCG Cancer Centre, Vishakhapatnam

• Kailash Cancer Hospital & Research Centre, Vadodara

• Sanjeevani CBCC USA Cancer Hospital, Raipur

Consent for Publication

The author consents to Editorial Board to publish the paper. The author(s) accept responsibility for publishing this material in his own name, if any.

Availability of Data and Materials: The data analysed is available with the corresponding author and could be available on reasonable request.

Conflicts of interest

Dr. Rachana Bhoite, Varalakshmi Lalithya Pratti, Dr. Vinita Satyavrat and Dr. Rahul Rathod, these authors are employees of Dr. Reddy's Laboratory India.

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Authors' Contributions

RB conceptualized, supervised, and approved the final draft of the study. VLP supervised and monitored the study. VS helped in securing and monitoring the funding for the study. RR helped in the interpretation of the data. All authors critically reviewed all manuscript drafts and provided comments. All authors gave their approval for the final version to be published. RB is the guarantor of this work and, as such, takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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