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Research Article

The Effect of Immunonutrition and Chemotherapy-Induced Neutropenia in Advanced Gastrointestinal Cancer Receiving Palliative Chemotherapy, a Pilot Randomized Controlled Trial

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ABSTRACT

Background: Malnutrition affects individual fitness popularity and influences the response to chemotherapy in cancer sufferers. Moreover, chemotherapy may additionally get worse the nutritional popularity in these sufferers and *vice versa*. Consequently, Oral Nutrition Dietary Supplements (ONS), either general or unique system, have been advocated *via* several tips in these settings. Immunonutrition formulas theoretically offer a higher anticachectic and anti-tumor effect to an ordinary weight loss plan or standard formulation. Our take a look at changed into aimed to evaluate the impact of ONS with immunonutrients and standard ONS on grade II-IV neutropenia in Gastrointestinal (GI) cancer that has received palliative chemotherapy.

Methods: We carried out a unmarried-center, double-blind, prospective controlled trial in sufferers with advanced GI cancer who acquired palliative chemotherapy. Patients were randomized into corporations, ONS with Immunonutrients (ONS-IM) and general ONS system (ONS-SF) with 500 kcal/day. The primary endpoint turned into the incidence of neutropenia grade II-IV. Furthermore, frame weight, frame composition, PG-SGA (affected person-generated subjective international assessment) scores, dietary consumption, anti-inflammatory parameters and remedy toxicities were evaluated at baseline and 12 weeks after chemotherapy between two corporations.

Results: A complete of 50 sufferers had been included (24 *vs.* 26 in the ONS-IM *vs.* the ONS-SF, respectively). All sufferers have been recognized with colorectal cancer, 24 (48%) had been men, with a mean age of 65.8 years (IQR 34-84). PG-SGA ≥ 9 was 60%, 46% had ≥ 2 organ metastases and 54% acquired first-line chemotherapy. There have been no statistical variations within the baseline traits among the two businesses. Neutropenia grade II-IV happened less frequently inside the ONS-IM group compared to the ONS-SF institution (16.7% *vs.* 42.3%, P=0.067), mainly in subgroup of patients who received both ONS-IM or ONS-SF greater than 70% (14.3% *vs.* 45.8%, P=0.028). The suggest variations within the PG-SGA rating were extensively higher inside the ONS-IM as compared to ONS-SF institution (6.7; 95% CI: 5.35, 8.14 *vs.* 4.72; 95% CI: 3.09, 6.35, P=0.05). Frame fat mass and the proportion of CD3 be counted had been improved extensively within the ONS-IM organization as compared to the ONS-SF organization. There was no difference in different anti-inflammatory markers among the 2 businesses.

Conclusion: Sufferers who had been supplemented with immunonutrition established a lower in grade II-IV neutropenia, stepped forward PG-SGA ratings, frame fats mass and the proportion of CD3 counts.

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Keywords: Immunonutrition; Chemotherapy-induced neutropenia; Advanced gastrointestinal cancer

INTRODUCTION

Malnutrition isn't always uncommon in most cancers patients. Numerous factors which includes most cancers itself or cancer remedy influenced this sizable condition. During cancer progression, various pro-anti-inflammatory cytokines, inclusive of Tumor Necrosis issue alpha (TNF-α) and Interleukin 6 (IL-6) play the most crucial function in cancer anorexia. Additionally, these might cause protein extraction from the muscle tissues, extended fats breakdown, ensuing in a discount in muscle tissues and frame fats loss. Subsequently, malnutrition impacts unplanned treatment slowing, behind schedule wound recovery, worsening muscle feature and dwindled response to chemotherapy [1].

Now not best chemotherapy and focused therapy, however additionally radiation therapy and surgical treatment may have a negative impact on dietary status in most cancers sufferers. In the course of chemotherapy, more than 50% of patients increase decreased appetite, fatigue, mucositis, nausea, vomiting and specially neutropenia and leucopenia. As a result, behind schedule, reduced or discontinued chemotherapy can arise which then affects inferior scientific consequences. Numerous studies [1-5], mentioned that early nutritional guide without looking ahead to malnutrition development improves dietary status, performance repute and best of existence. It may additionally improve reaction to remedy and decrease headaches. Immunonutrition containing glutamine, arginine and omega-three preferably gives a better anticachectic and antitumor effect that strengthens the immune device of the body. Furthermore, the blessings of immunonutrition had been tested in various researches in a subset of critical unwell patients, most cancers patients undergoing postsurgery or for the duration of chemo radiotherapy treatment. But, immunonutrition dietary supplements for patients with gastrointestinal cancer who get hold of best chemotherapy stays restrained. consequently, the purpose of this observe changed into to compare the efficacy of oral nutrition dietary supplements with immunonutrients formulation to conventional formulation in terms of grade II-IV neutropenia in gastrointestinal cancer receiving palliative chemotherapy. The percentage of alternate in frame weight, frame composition, PG-SGA rating, anti-inflammatory parameters and hematologic and nonhematologic toxicities among two organizations was additionally investigated.

MATERIALS AND METHODS

A prospective unmarried-middle, double-blind, randomized managed trial turned into finished in advance in gastrointestinal cancer patients who obtained palliative chemotherapy at King Chulalongkorn Memorial sanatorium. The observe become authorised with the aid of the institutional evaluation board of the Chulalongkorn college faculty of medicine in compliance with international pointers for the protection of human research inclusive of declaration of Helsinki, Belmont report, CIOMS guiding principle and worldwide convention on harmonization in correct clinical exercise. (COA No. 1076/2021; IRB No. 362/64) The take a look at changed into registered and has been authorised in Thai scientific Trials Registry (TCTR20210723001) date July 23, 2021.

Patients in this take a look at, patients with superior gastrointestinal most cancers two decades or older who have been deliberate to get hold of palliative chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, irinotecan) or CapeOX (capecitabine and oxaliplatin) with a standing of Japanese Cooperative Oncology organization (ECOG) of 0-2, PG-SGA rating ≥ 4 [6,7] and able to eat through oral route have been enrolled. Sufferers had been required to have good enough laboratory effects, no previous use of granulocyte colony stimulating agents (G-CSF) and a lifestyles expectancy of greater than 6 months. All members signed inform consent before joining the examine.

Randomization and treatment regimen

Trial design and treatment: All patients were randomly assigned to a 1:1 ratio by using six permutation blocks that apply a sequential series of sealed numbered envelopes containing computer generated random assignments. Patients were stratified by age (<65 or 65) and PG-SGA score (score 4-8 or ≥ 9) to receive the standard ONS formula (ONS-SF (Blendera®); control group) with 500 kcal/day, while or isocaloric ONS with immunonutrients (ONS-IM (Neomune®); experimental group) which was starting in the first day of chemotherapy. Both packages were sealed and sachets were provided every 2-3 weeks following the chemotherapy schedule in a total of 12 weeks.

Assessment: Scientific traits, body weight, body composition, PG-SGA ratings, nutritional consumption and inflammatory parameters have been evaluated, no more than 7 days prior to chemotherapy management and 12 weeks after chemotherapy in all patients. The prevalence of grade II-IV neutropenia and different toxicities become recorded and assessed every 2-3 weeks at some point of the chemotherapy time table consistent with the common terminology standards for unfavorable activities quantity 4.03 (CTCAE v4.03). PG-SGA patients were classified as extreme or mild malnutrition (B or C) or nicely-nourished (A). To display compliance, sufferers ought to whole food diary. Affected person compliance turned into evaluated by way of telephone inquiry that evaluated the amount of patient's oral dietary aid every 2 weeks. Compliance of as a minimum 70% turned into expected in our take a look at. Approximately frame composition, Body Fat Mass (BFM), Lean Frame Mass (LBM), Skeletal Muscular Tissues (SMM) and hand grip strength had been determined using Inbody 770 for bioimpedance analysis. Concerning inflammatory parameters, whole blood mobile count, serum albumin, prealbumin, C-Reactive Protein (CRP), IL-6 concentrations and percentage of CD3, CD4 and CD8 count had been examined at baseline and 12 weeks after chemotherapy. Facts from valid cycles earlier than

discontinuation were blanketed in analysis according to the purpose-to-deal with (ITT) precept.

Statistical analysis

The primary endpoint was the incidence of grade II-IV neutropenia between two groups. No previous study has investigated these unanswered questions. Therefore, a randomized pilot study with a comparative control group was planned. The sample size in this study to be able to calculate various mental values was 25 subjects per group, for a total of 50 patients, which included a total dropout rate of approximately 20% per group. The 95% confidence interval was established. Data were analyzed using IBM SPSS Statistics for Windows, Version 28.0 (released 2021; IBM Corp, Armonk, NY). Summary statistics were reported as percentages for categorical values. Means+SD were calculated for continuous variables with normal distribution. Fisher's exact test or the *chi-square* test was used to compare incidence of grade II-IV neutropenia between the experimental and control groups, as appropriate. All analyzes were tested two-sided and significant differences were applied when $p<0.05$.

RESULTS

From August 2021 to April 2022, a total of 50 patients were randomly assigned to receive the experimental group (ARM A ONS-IM; N=24) or the control group (ARM B ONS-SF; N=26) and all patients were included in the intention-to-treat analysis (Figure 1). At the date of the data cutoff, only 41 patients (82%), 19 from ONS-IM group and 22 from ONS-SF group, completed the treatment protocol.

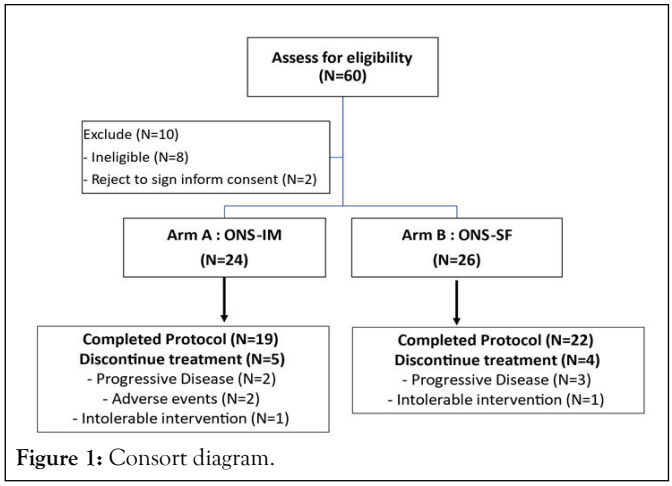

Figure 1: Consort diagram.

The 50 patients in this study were patients with colorectal cancer, including 24 men (48%) and 26 women (52%), with a mean age of 65.8 years (IQR 34-84). PG-SGA equal to or greater than 9 was 60%, 46% had equal to or greater than 2 organ metastases and 54% received first-line chemotherapy. Targeted EGFR monoclonal Ab, Panitumumab was administered only 1 patient in ONS-SF group whereas 10 patients (20%), 4 in ONS-IM and 6 in ONS-SF group, received anti-VEGF monoclonal Ab, bevacizumab. A higher percent of two or more organ metastases and first line setting in the ONS-IM group than the ONS-SF group were reported, but there were no statistical differences in baseline characteristics between the ONS-IM group and the ONS-SF group. Other baseline characteristics were summarized in Table 1.

Table 1: Baseline characteristics between the ONS-IM group *vs.* the ONS-SF group.

	ONS-IM (N=24)	ONS-SF (N=26)	Total (N=50)	p-value
Age (years; mean)	65.5	66.04	65.8 (34-84)	0.85¶
Age<65 years	10 (41.7%)	10 (38.5%)	20 (40.0%)	>0.999‡
Age ≥ 65 years	14 (58.3%)	16 (61.5%)	31 (60.0%)	
BMI mg/m^2 (mean)	21.9	22.4	22.1 (14.9-33.8)	0.62¶
Sex				
Male	15 (62.5%)	9 (34.6%)	24 (48.0%)	0.05‡
Female	9 (37.5%)	17 (65.4%)	26 (52.0%)	

ECOG				
0	1 (4.2%)	3 (11.5%)	4 (8.0%)	0.63‡
1	22 (91.7%)	22 (84.6%)	44 (88.0%)	
2	1 (4.2%)	1 (3.8%)	2 (4%)	
Comorbidity				
No	12 (50.0%)	12 (46.2%)	24 (48.0%)	>0.999‡
Yes	12 (50.0%)	14 (53.8%)	26 (52.0%)	
Charlson comorbidity index (mean ± SD)	8.21 ± 1.4	8.46 ± 1.1 (6-11)	8.34 ± 1.2 (6-11)	0.48‡
PG-SGA score	10.04	8.88	9.44 (4-19)	0.77‡
PG-SGA 4-8	9 (37.5%)	11 (42.3%)	20 (40.0%)	
PG-SGA ≥ 9	15 (62.5%)	15 (57.7 %)	30 (60.0%)	
Number of organ metastases				
1	11 (45.8%)	16 (61.5%)	27 (54.0%)	0.27‡
≥ 2	13 (54.2%)	10 (38.5%)	23 (46.0%)	
Line of CMT treatment				
1L	15 (62.5%)	12 (46.2%)	27 (54.0%)	0.25‡
2L	9 (37.5%)	14 (53.8%)	23 (46.0%)	
Chemotherapy regimen				
FU+Oxaliplatin	13 (54.2%)	11 (42.3%)	24 (48.0%)	0.40‡
FU+Irinotecan	11 (45.8%)	15 (57.7%)	26 (52.0%)	

Note: BMI: Body Mass Index, ECOG: Eastern Cooperative Oncology Group, PG-SGA; Patient-Generated Subjective Global Assessment, CMT; Chemotherapy, FU; Fluorouracil, ‡P value was derived from the Fisher's exact test between the ONS-IM group *vs.* ONS-SF group, ¶: P value was derived from independent T test

Neutropenia grade II-IV and other toxicities

Among 50 sufferers who acquired the treatment protocol, neutropenia grade II-IV took place in three (12.5%) and eleven (42.3%) patients inside the ONS-IM and ONS-SF organizations, respectively, p=0.019 (Table 2). There has been a fashion towards a higher charge of febrile neutropenia within the ONS-SF group than in the ONS-IM institution, but, there have been no massive differences (8.3% *vs.* 8.5%, P=0.999). Table 2 shows the neutropenia and febrile neutropenia costs in sufferers who obtained the ONS-IM group and the ONS-SF institution with extra than 70% compliance.

Table 2: Hematologic toxicities between the ONS-IM group *vs.* the ONS-SF group.

All population (N=50)	ONS type			p-value
	ONS-IM	ONS-SF	Total	
Neutropenia	N=24	N=26	N=50	0.067
Grade 0-I	20 (83.3%)	15 (57.7%)	36 (72.0%)	
Grade II-IV	4 (16.7%)	11 (42.3%)	14 (28.0%)	
Febrile neutropenia	N=24	N=26	N=50	>0.999
No	22 (91.7%)	23 (88.5%)	45 (90.0%)	
Yes	2 (8.3%)	3(11.5%)	5 (10.0%)	
Patients with compliance >70% (N=45)	**ONS type**			**p-value**
	ONS-IM	**ONS-SF**	**Total**	
Neutropenia	N=21	N=24	N=45	0.028*
Grade 0-I	18 (85.7%)	13 (54.2%)	36 (71.1%)	
Grade II-IV	3 (14.3%)	11 (45.8%)	13 (28.9%)	
Febrile neutropenia	N=21	N=24	N=50	0.611
No	20 (95.2%)	21 (87.5%)	41 (91.1%)	
Yes	1 (4.8%)	3 (12.5.0%)	4 (8.9%)	

Note: p-value was derived from the Fisher's exact test between the ONS-IM group *vs.* ONS-SF group, *Statistically significant P value<0.05

There was a fashion for a higher frequency of dose discount within the ONS-SF group compared to the ONS-IM organization, but it become no longer statistically considerable (53.8% *vs.* 29.2%, respectively). Different chemotherapy dose modifications are proven in Supplementary Table 1.

For nonhematologic toxicities, diarrhea, nausea and mucositis had been not statistically large variations among two groups in intention-to-treat evaluation. Mucositis turned into observed 0% as opposed to 3.8% within the ONS-IM and ONS-SF corporations, respectively (P=0.999). Diarrhea became observed to be 4.2% within the ONS-IM institution and 3.8% inside the ONS-SF group respectively (P=0.999). Nausea become found 8.3% inside the ONS-IM and 3.8% in the ONS-SF institution, respectively (P=0.999).

Body weight and PG-SGA scores

In terms of body weight, neither organization confirmed significant changes between baseline and after 12 weeks of ONS-IM or ONS-SF. The PG-SGA ratings improved appreciably after 12 weeks of treatments in each agencies. in the ONS-IM group, the PG-SGA rankings reduced from 9.6 ± 4.1 to 3.3 ± 2.1 (p<0.001), at the same time as inside the ONS-SF institution, the PG-SGA rankings reduced further from 8.4 ± 3.6 to 4.2 ± 2.8 (p<0.001). Additionally, a better change in PG-SGA ratings was stated inside the ONS-IM group as compared to the ONS-SF organization (6.3 ± 2.86, 4.1 ± 3.70; ONS-IM *vs.* ONS-SF, p=0.05). Those results imply, oral nutritional supplements showed better dietary repute on the end of the have a look at. Summarized effects were proven in Table 3 and Supplementary Figure 1.

Table 3: Body weight and PG-SGA between the ONS-IM group *vs.* the ONS-SF group.

	ONS-IM (N=24)		ONS-SF (N= 26)		Pa[a]	Pb[b]	Pc[c]
	0 weeks	12 weeks	0 weeks	12 weeks			
BW change (kg± SD)	57.51 ± 1.86	58.28 ± 2.00	55.89 ± 2.44	56.07 ± 2.26	0.246	0.71	0.255
	0.77 (95% CI -1.82, 0.28)		0.17 (95% CI -1.23, 0.86)				
PG-SGA scores	9.90 ± 0.91	3.25 ± 0.46	8.68 ± 0.75	4.05 ± 0.52	<0.001*	<0.001*	0.050*
	-6.7 (95% CI 5.35, 8.14)		-4.72 (95% CI 3.09, 6.35)				

Note: Value means ± SE change after 12 weeks of experimental. Pa value between 0 weeks and 12 weeks in ONS-IM group, Pb value between 0 weeks and 12 weeks in ONS-SF group, Pc the change value of two groups. BW: Body Weight. *Statistically significant P value<0.05

Body composition and inflammatory parameters

About body composition and inflammatory parameters, BFM and CD3 percentage were significantly improved in the ONS-IM group compared to the ONS-SF group. But both groups did not show significant changes in albumin, prealbumin, IL-6, CRP, the percentage of CD4, the percentage of CD8 fat free mass, soft lean mass and skeletal muscle mass at 12 weeks of intervention. However, BFM, prealbumin, the percentage of CD3 and CD8 increased significantly from baseline in the ONS-IM group after 12 weeks of treatment. Other body composition and inflammatory parameters were reported in Tables 4 and 5.

Table 4: Body composition between the ONS-IM group *vs.* the ONS-SF group.

	ONS-IM (N=10)		ONS-SF (N=10)		Pa	Pb	Pc
BFM (kg)	15.25 ± 2.34	17.78 ± 2.40	19.48 ± 3.44	19.66 ± 3.26	0.028*	0.944	0.026*
	2.53 (95% CI -4.28, -0.78)		0.17 (95% CI -1.98, 1.63)				
FFM (kg)	42.90 ± 2.24	42.28 ± 2.56	40.88 ± 3.42	41.06 ± 3.38	0.515	0.888	0.36
	-0.61 (95% CI -4.14, 5.36)		0.17 (95% CI -1.19, 0.84				
SLM (kg)	39.76 ± 1.89	39.61 ± 2.44	38.47 ± 3.25	38.46 ± 3.20	0.575	0.944	0.359
	-0.15 (95% CI -0.396, -4.26)		-0.01 (95% CI -6.41, 0.66)				
SMM (kg)	22.70 ± 1.25	22.24 ± 1.49	21.80 ± 2.04	21.43 ± 2.00	0.441	0.201	0.499
	-0.45 (95% CI -2.37, 3.28)		-0.36 (95% CI -1.52, 0.87)				
Hand grip, left (kg)	20.46 ± 3.43	23.41 ± 3.35	19.20 ± 2.18	22.24 ± 3.14	0.139	0.31	0.751
	2.94 (95% CI -7.14, 1.25)		3.04 (95% CI -9.09, 3.00)				
Hand grip, right (kg)	20.91 ± 3.23	23.41 ± 4.30	21.08 ± 2.51	22.38 ± 3.67	0.204	0.6	0.628
	2.5 (95% CI -6.42, 1.42)		1.3 (95% CI -6.51, 3.91)				

Note: Value is mean ± SE change after 12 weeks of experimental, 95% Confidence Interval (CI) of difference lower, upper a=Pa value was derived from the Wilcoxowasgned rank test between 0 weeks and 12 weeks in ONS-IM group, b=Pb value was derived from the Wilcoxon signed rank test between 0 weeks and 12 weeks in ONS-SF group, c=Pc value was derived from the Mann-Whitney test between the change value of two groups. BFM: Body Fat Mass; FFM: Fat Free Mass; SLM: Soft Lean Mass; SMM: Skeletal Muscle Mass, *Statistically significant P value<0.05

Table 5: Inflammatory parameters between the ONS-IM *vs.* ONS-SF.

	ONS-IM (n=15)		ONS-SF (n=18)		Pa[a]	Pb[b]	Pc[c]
Albumin (g/L)	3.60 ± 0.10	3.45 ± 0.09	3.74 ± 0.06	3.66 ± 0.08	0.12	0.263	0.568
	-0.15 (95% CI -0.02, 0.33)		-0.08 (95% CI -0.05, 0.21)				
Pre-albumin (mg/dL)	17.23 ± 2.36	21.50 ± 2.05	20.61 ± 1.58	21.82 ± 1.24	0.008*	0.32	0.17
	4.26 (95% CI -7.32, -1.20)		1.21 (95% CI -4.43, 1.99)				
IL-6	16.6 ± 5.34	11.4 ± 3.38	9.18 ± 2.17	7.46 ± 1.57	0.14	0.744	0.649
	-5.2 (95% CI -5.38, 15.79)		-1.72 (95% CI -3.94, 7.40)				
CRP (mg/L)	25.74 ± 10.30	8.92 ± 4.02	14.64 ± 7.05	7.67 ± 2.86	0.311	0.495	0.455
	-16.81 (95% CI -4.91, 38.53)		-6.96 (95% CI -4.74, 18.67)				
%CD3	65.15 ± 2.71	70.46 ± 2.51	66.11 ± 2.58	64.88 ± 2.99	0.023*	0.736	0.036*

	5.3 (95% CI 9.61, -1.00)		-1.23 (95% CI-2.85, 5.32)				
%CD4	35.76 ± 1.90	37.15 ± 3.04	37.58 ± 2.52	35.82 ± 2.80	0.418	0.477	0.313
	1.38 (95% CI 6.76, 3.99)		-1.76 (95% CI 2.79, 6.32)				
%CD8	25.76 ± 2.39	29.84 ± 2.55	25.35 ± 2.01	26.35 ± 2.19	0.009*	0.183	0.888
	4.07 (95% CI-6.70, -1.44)		1.00 (95% CI -2.61, 0.61)				

Note: Value is mean ± SE change after 12 weeks of experimental, 95% Confidence Interval (CI) of difference lower, upper a=Pa value was derived from the Wilcoxon signed rank test between 0 weeks and 12 weeks in ONS-IM group, b=Pb value was derived from the Wilcoxon signed rank test between 0 weeks and 12 weeks in ONS-SF group, c=Pc value was derived from the Mann-Whitney test between the change value of two groups. *Statistically significant P value<0.05, IL-6: Interleukin-6, CRP: C-reactive protein, *Statistically significant P value<0.05

DISCUSSION

Oral nutritional support in standard formula or especially immunonutrient formula provides better nutritional status, performance status and quality of life compared to regular diet intake in cancer patients receiving treatment. Based on the benefit of immunonutrition in terms of anti-inflammatory that strengthens the immune system of the body, a low rate of neutropenia or febrile neutropenia during chemotherapy or chemoradiotherapy has been previously reported. Our study demonstrated that advanced colorectal cancer patients receiving ONS-IM significantly reduced the incidence of grade II-IV neutropenia compared to ONS-SF (12.5% *vs.* 42.3%; p=0.019). However, there was a trend to reduce febrile neutropenia in ONS-IM compared to ONS-SF (8.3% *vs.* 11.5%; p=0.99), respectively. Furthermore, the mean differences in the PG-SGA scores were significantly better in the ONS-IM group (6.3 ± 2.86 *vs.* 4.1 ± 3.70, p=0.05). Prealbumin and CD3 percentage were significantly improved in ONS-IM compared to ONS-SF. However, there were no differences in other inflammatory markers between the two groups [8].

Cancer patients receiving palliative chemotherapy required adequate nutritional intake to maintain body weight and to prevent treatment-associated toxicities, which subsequently impacted better clinical outcomes. The rate of neutropenia grade II-IV after chemotherapy was associated with delayed administration or dose reduction and subsequently inferior survival outcomes. According to the study by Chitapanarux I and her colleagues in head and neck cancer patients receiving concurrent chemoradiotherapy population, a higher rate of III-IV hematologic toxicity has been described in the blenderized diet compared to the immunonutrient diet (23% *vs.* 5%; p=0.035). However, the differences in primary cancer types, chemoradiotherapy treatment and duration of ONS and severity of toxicities between our study and the previous study reflect the different rate of hematologic toxicities.

PG-SGA scores have been applied to evaluate nutritional status in cancer patients. The score can classify and predict patients for potential malnutrition. Our study demonstrated that the administration of both Oral Nutrition Support (ONS) significantly improved PG-SGA scores from baseline to 12 weeks of treatment, especially in the ONS-IM group (9.6 ± 4.1 to 3.3 ± 2.1; p<0.001). Similarly, Kim SH et al. compared ONS to non-ONS in pancreatic and bile duct cancer who undergo chemotherapy. Significantly decreased PG-SGA scores and increased in fat mass were identified after 8 week of intervention [9]. Therefore, these results confirmed that the ONS standard or immunonutrient formula reduced fatigue and appetite loss, maintained body weight and improved nutritional status.

The advantage of immunonutrition usually enhances the inflammatory parameters of immune responses and maintains the ratio of CD4/CD8 T lymphocyte counts and the expression of the CD3 membrane [10]. The improvement of immune cell function in postsurgical patients resulting in reduction in complication, length of stay and morbidity. Our study reported a significant improvement in prealbumin and the percentage of CD3 in the ONS-IM group and trended to increase the percentage of CD4 and CD8 from baseline to 12 weeks of intervention. Unlike body composition, there were no statistically significant differences in the ONS-IM group. Other cytokine markers such as CRP and IL-6, our study reported an insignificant reduction in CRP and IL-6 in the ONS-IM group, while no significant differences in CRP and IL-6 were observed in the ONS-SF group. Similar to various studies, no significant changes in serum albumin and CRP were observed in immunonutrients group. Compared to the standard formula, improvements in these parameters were rarely observed in the ONS-SF group. According to these findings, immunonutrition might be effective in helping cellular immunity and maintaining the immune system.

To our knowledge, this is the first randomized controlled trial to evaluate the benefits of immunonutrition, especially in lower grade II-IV neutropenia in patients with colorectal cancer who received palliative chemotherapy. Furthermore, in our study 12 weeks of oral nutritional supplement was investigated which effect on positive results. These positive findings encourage our clinical practice about immunonutrition supplement during receiving chemotherapy in various cancer types. In addition to the double-blind study design, all patients were evaluated by the same investigator throughout the study period; therefore, interpersonal variation did not occur [11].

There were some limitations in our study. First, higher rate of irinotecan-based chemotherapy in ONS-SF compared to ONS-IM was observed even with randomization and stratification

(57.7% *vs.* 45.8%, respectively). Therefore, not only immunonutrition but also chemotherapy regimen might be influenced to higher rate of grade II-IV neutropenia in ONS-SF group. Second, the experimental group received more protein than the control group, so it may be difficult to distinguish whether the lower neutropenia rate comes from a high-protein diet or immunonutrients in the experimental group. However, immunonutrition might reduce the rate of chemotherapy induced neutropenia in advanced gastrointestinal cancer after receiving palliative chemotherapy. Thirdly, in body composition and inflammatory parameters, a large number of patients in both groups did not perform these analyzes. Despite such factors, we observed a significant improvement in prealbumin, % CD3 and an insignificant improvement in body fat mass in ONS-IM after a 12-week period. Lastly, overall treatment response and long-term survival outcomes between immunonutrition and standard formula need to be further investigated [12].

CONCLUSION

Cancer patients who received immunonutrition significantly reduced grade II-IV neutropenia compared to the standard formula. Furthermore, the immunonutrition supplement increased the percentage of CD3 counts, the prealbumin level and the decreased PG-SGA score.

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AUTHORS' CONTRIBUTIONS

R.I., N.S. and N.P. contributed to review conception and design. Search strategy was devised by R.I., N.S., T.R. and N.P. Literature search, data collection and analysis were performed by R.I., T.R., N.S. and N.P. The first draft of the manuscript was written by R.I., N.S., T.R. and N.P. critically revised previous versions of the manuscript. All authors, which included N.T., V.S. and S.T., read and approved the final manuscript.

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DATA AVAILABILITY

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Chulalongkorn University Faculty of Medicine (COA No. 1076/2021; IRB No. 362/64). The study was registered and has been approved in Thai Clinical Trials Registry (TCTR20210723001). This study was also performed based on the declaration of Helsinki and good clinical practice guidelines. The informed consent form was completed for all the patients.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare no competing interests.

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