Original Article

Fish oil supplementation is beneficial on caloric intake, appetite and mid upper arm muscle circumference in children with leukaemia

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A randomised trial was carried out to determine the effect of supplementation of fish oil among 51 children with leukaemia aged 4 to 12 years on appetite level, caloric intake, body weight and lean body mass. They were randomly allocated into the trial group (TG) and the control group (CG). At baseline, 30.8% of TG subjects and 44.0% of CG subjects were malnourished and 7.7% of subject from TG and 28.0% from CG were classified as stunted. The majority of subjects from TG and CG were in the mild malnutrition category for mid upper arm muscle circumference (MUAMC)-for-age. The TG group showed significant increment in MUAMC (0.13 cm vs -0.09 cm) compared with CG at 8 weeks (p<0.001). There was a significant higher increase for appetite level (0.12±0.33) (p<0.05) and an increasing trend on energy and protein intake in the TG group (213±554 kcal; 3.64± 26.8 g) than in the CG group. In conclusion, supplementation of fish oil has a positive effect on appetite level, caloric intake and MUAMC among children with leukaemia.

Key Words: fish oil, MUAMC, appetite, caloric intake, leukaemia

INTRODUCTION

Malnutrition and weight loss are common among cancer patients and are due to a variety of mechanisms involving the tumour, the host response to the tumour, and anticancer therapies.[1] It is a major cause of morbidity and mortality.[1,2] Symptoms may occur at all stages of the cancer during treatment.[3] Nausea, vomiting, diarrhoea, anorexia, taste changes, and increased metabolic rate are the most common side effects of chemotherapy and contribute to patients voluntary limitation of their food intake to prevent the symptoms.[4] In addition, treatment itself for example chemotherapeutic agents may adversely affect growth and body composition in children.[5] Compared with adults; children have decreased caloric reserves because of their particular body composition (higher water content and decreased fat), these making them susceptible to malnutrition sooner than adults.[6]

By maintaining adequate dietary intake, it may help to prevent the weight loss and reduce the risk of malnutrition in patient with cancer.[4] However, studies have reported that by increasing protein and energy intake alone in patient with cancer may provide little impact on patients' overall of body weight and lean body mass.[7,8] Although caloric intake needs has been increased in cancer patients, it seems quite difficult to gain in lean body tissue unless the underlying metabolic abnormalities are improved.[9] Thus, nutritional support can be beneficial to patients with malnutrition or patients at risk for malnutrition. The provision of nutritional support for patients with cancer is to stabilize or improve nutritional status, maximize quality of life and improve clinical outcome.[10]

One possible approaching for nutritional support is to include the use of eicosapentaenoic acid (EPA). EPA, a polyunsaturated fatty acid (PUFA) found in fish oil, has been shown to inhibit inflammation in vivo and has been associated with weight gain, better response to therapy, fewer complications and even improved survival in patients with cancer.[11-14] Furthermore, the effect of fish oil rich in EPA on maintaining, stabilizing or gaining body weight have been found in studies in patient with pancreas cancer,[14-16] healthy men,[18,19] and even among pediatric malignant disease.[4]

Despite overwhelming evidence showing the beneficial effects of fish oil in EPA on patient with cancer improves nutritional status and QOL which reviewed in adult patients with cancer. To date there is currently insufficient evidence to recommend supplementation of fish oil in paediatric with cancer. Therefore, the present study was

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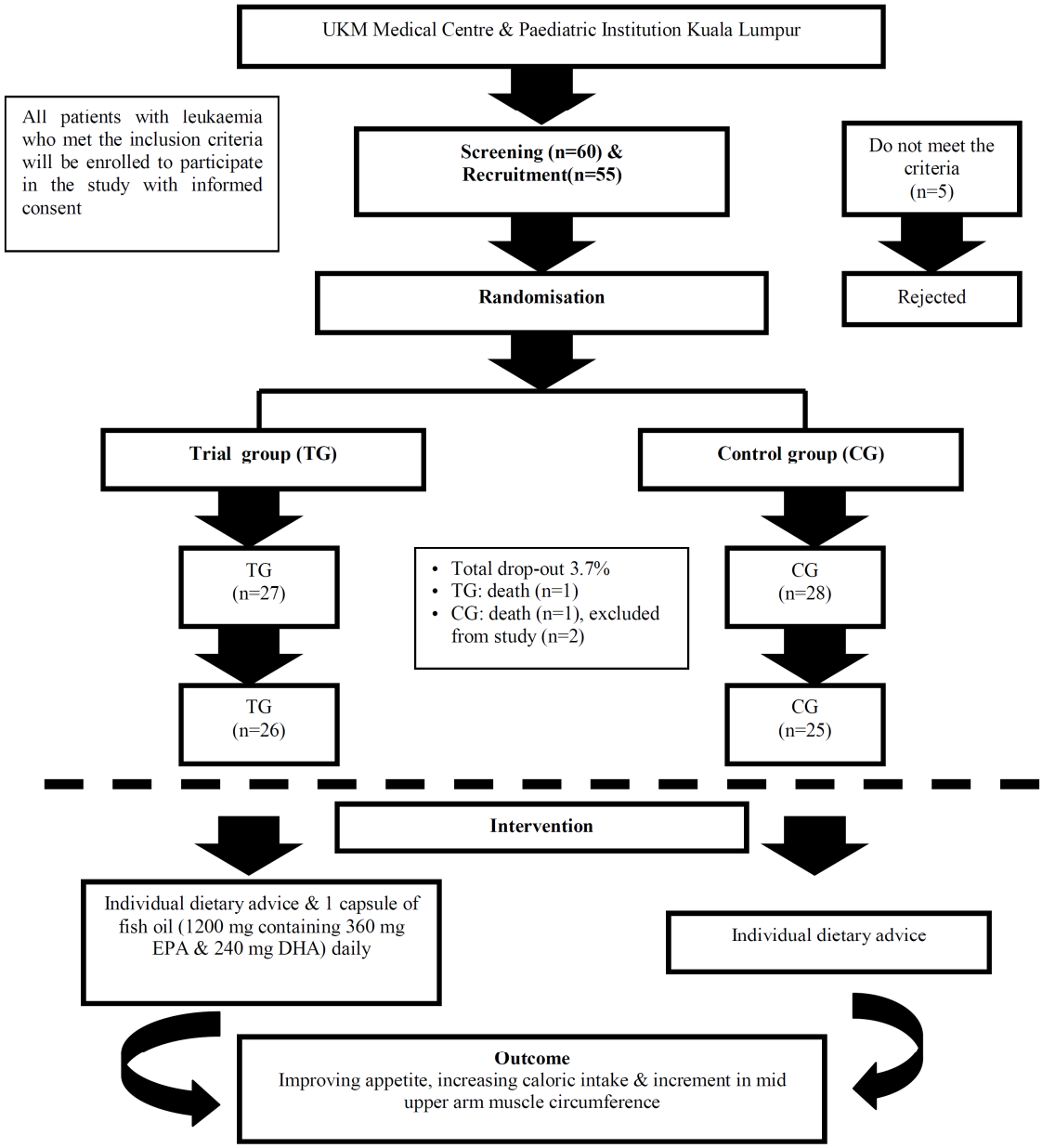

Figure 1. Recruitment of subjects and study design

performed to investigate the effect of supplementation of fish oil among children with leukaemia in increasing their appetite level, caloric intake and body weight.

MATERIALS AND METHODS

Study design and participants

This study was a randomised controlled trial in children with leukaemia (Figure 1). The study was performed in the Haematology & Oncology Paediatric Ward of the Universiti Kebangsaan Malaysia Medical Centre and Paediatric Institute of Kuala Lumpur. The study protocol was approved by the ethics committee of the Universiti Kebangsaan Malaysia Medical Centre (Project Code: FF-045-2005). Permission to conduct the study was obtained from the director of Universiti Kebangsaan Malaysia Medical Centre and Hospital Kuala Lumpur, Malaysia.

Fifty one children with leukaemia (32 boys and 19 girls) aged 4 to 12 years were enrolled in this study. Inclusion criteria were children with leukaemia aged 4 to 12 years old and able to consume diet orally. Patients were excluded from this study if they were involved in another research project or those were receiving nutrition support on tube feeding or parenteral nutrition or those on nutrient supplementation. The study was explained to the carers and patient when they agreed to participate in the study. An informed consent was obtained from subjects and carers.

The researcher had screened 60 patients but only 55 subjects were eligible to enter the study. Patients had been excluded because they did not meet the study's criteria (n=5). Figure 1 show the subject enrolment and study design. Fifty-five eligible subjects were equally randomised into the two groups: the trial group (TG) and control group (CG). At the end of 8 weeks, 51 subjects completed the study, two subjects died (TG=1; CG=1) and two subjects (CG=2) withdrawn from the study.

Data collection

Demographic information including age, gender, ethnic group, number of siblings was obtained from subjects and

their caregiver through an interview and also extracted from patients' medical record. Socio-economic data such as parent's education level, occupation and household income were also gathered during the interview. In the study of Simons *et al.*, a numerical scale ranging from 0 (absolutely no appetite) to 10 (extremely good appetite) and in the study of Bruera *et al.*, a visual analogue scale (VAS) of 0 to 100 mm (0 mm=best, 100 mm=worst) was used for appetite rating. However, appetite rating using VAS in our study was modified because it was hard for children to rate their appetite with the original scale and appetite rating was obtained using a modified hedonic scale ranging from 0 (less appetite) to 4 (most appetite).

Dietary intake was also assessed using a combination of 24-hour dietary recalls at baseline and 2 day-24-hour dietary records (one weekday and one weekend) at 30-days and 60-days. The 24-hour dietary recalls was carried out through interview with the mother or directly with an older child (age group 9-12 years old). Each interview lasted 15 to 20 minutes. The children or their families were instructed on how to record their food and drink consumption in a notebook provided for the 2-day-24-hour dietary records using standard portion or household measures (examples: 1 cup of milk, 2 teaspoonful of jam, etc). A food album on commonly consumed food was used to help subjects and their care-givers to recall and estimate the portion/serving size of their food and drink that were consumed. Then the quantity of food intake were changed into gram based on the Food Composition Malaysia Book,[22] Atlas Food: Exchange Size & Portion,[23] and Singapore Food Composition.[24] Mean energy and macronutrient intake were determined using computerized software Nutritionist Pro version 2.0. Total energy requirement was estimated using the Seashore equation,[25] depending on the children's age, their body weight, a activity factor and a stress factor. Estimated protein requirement was 1.0 -1.2 g/kg.[26]

The anthropometric measurements were assessed by body weight, height, triceps, and the circumference of the mid upper arm. The same investigator collected all the measurements to avoid interobserver error, and for maintaining uniformity and accuracy in techniques. Height of the children were measured by using SECA Stadiometer Model 220 (Germany). The reading was taken to the nearest 0.1 cm. The electronic scale (SECA, Germany) was used to measure weight of the children wearing minimum clothing and it was recorded to the nearest 0.1 kg. The anthropometric indices were calculated using WHO Anthro software and classified according to standard deviations units (z-scores) based on WHO Child Growth Standards.[27] Children who were less than two standard deviation below the reference median (< -2 SD) were considered as underweight (weight-for-age), stunted (height-for-age) and wasted (weight-for-height) respectively.

The method of Durnin and Rahaman,[28] was used to measure triceps skin fold using the Harpenden calliper. The investigator measured the subject's skin fold by grasping a length-wise double fold of skin and fat (using thumb and forefingers) about 1 cm above the designated midpoint of the upper arm of the right and pinching the midpoint with the callipers. This was repeated three times, and the triceps skin fold measurement was obtained by averaging the three values. A non-stretchable tape made of fibreglass was used to measure the circumference of the mid upper arm. The circumference was measured at the midpoint of the upper left arm between the acromion process and the tip of the olecranon. After locating the midpoint, the left arm is extended to hang loosely by the side with the palm facing inwards. The tape is wrapped gently but firmly around the arm at the midpoint and the measurement were recorded.[29] This was repeated three times, and the mid upper arm circumference was obtained by averaging the three values.

The muscle circumference of the mid upper arm is derived from measurements of both mid upper arm circumference and triceps skin fold. The mid upper arm muscle circumference was computed using the following formula[30]

MUAMC = MUAC – [(π x TSF)], where,
MUAMC = mid upper arm muscle circumference in cm
MUAC = mid upper arm circumference in cm
TSF = triceps skin fold thickness in cm

Triceps skin fold and MUAMC values were expressed in percent range according to age and sex. Percentiles used for triceps skin fold and mid upper arm muscle circumference were reference from Frisancho.[30] The values below the 15th percentile were classified as inadequate and the value with equal to or greater than the 15th percentile were classified as adequate.

No established toxicity questionnaire for dose-limiting fish oil related side effects are available,[31] therefore we used the question of tolerability and new symptoms to assess the toxicity. On day 30, subjects' tolerability on consuming the capsule was measured on a scale of 1 to 4 (1=no difficulty, 4=extremely difficult). Patients were also asked whether they experienced any symptoms during the intervention.

Data collection was carried out for the patients in all the two groups to obtain baseline data. With the exception for socio-demography questionnaire which was used once at baseline only and difficulty to consume the capsule questionnaire which was started at day-30. The same methods and instruments were used repeatedly at day-30 and day-60.

Intervention

Subjects in TG were asked to consume one capsule of fish oil per day. Each capsule provided 1200 mg containing 360 mg EPA and 240 mg docosahexaenoic acid (DHA). Each subject was provided 1 bottle/10 capsule every week. To check the compliance of the patient, they were asked to record each time they have had their supplementation and to return the empty bottle to the researcher during the visit. If the compliance of the patient were above 80%, they remained with the study. In order to increase their dietary intake, both groups were asked to consume full cream milk (197 kcal/serving, twice a day) throughout 60 days of the study.

Both groups of subjects were given detailed advice on their usual daily food intake at baseline, day-30 and day-60. The advice included more fruit, vegetables, and low-fat dairy products and less saturated fat, total fat, and cholesterol. The recommended diets also contained more

Table 1. Demographic and socioeconomic background of the subjects and caregivers in the trial group (TG) and control group (CG) at baseline

Characteristics	TG (n=26)		CG (n=25)	
	n	% of subjects	n	% of subjects
Gender				
Male	19	37.3	13	25.5
Female	7	13.7	12	23.5
Age group, years				
4-6	10	19.6	9	17.6
7-9	7	13.7	7	13.7
10-12	9	17.7	9	17.7
Ethnicity				
Malay	17	33.3	19	37.3
Chinese	4	7.8	3	5.9
Indian	5	9.8	3	5.9
Household income, RM				
<500	2	3.9	2	3.9
501-1000	2	3.9	7	13.7
1001-2000	16	31.4	9	17.6
2001-3000	6	11.8	4	7.8
>3001	0	0	3	5.9
Father's occupation				
Unemployed	0	0	2	4.0
Self-employed	11	21.6	6	11.8
Government staff	3	5. 9	5	9.8
Private staff	12	23.5	10	19.6
Others	0	0	2	3.9
Mother's occupation				
Unemployed	22	43.1	19	37.3
Self-employed	0	0	1	2.0
Government staff	1	2.0	1	2.0
Private staff	3	5.9	4	11.8
Others	0	0	0	0

Independent t-test and Chi-square analysis where appropriate, showed that the baseline results were comparable for demographic and socioeconomic background between the two groups ($p>0.05$)

whole grains and fewer refined grains, sweets, and red meats. The advice also focused on healthy and balanced meals as well as strategies/tips on preparation of healthy food and eating out, to the patients and parents. It emphasized increasing physical activity in patients. Problems and concerns in complying with the advice were also discussed.

Statistical analysis

Descriptive and statistical analyses were done using SPSS, version 13.0 (SPSS Inc, Chicago, IL, USA). Values were expressed as percentage and mean±SD. Baseline values were compared using an independent t-test and categorical data were analysed by using Pearson's chi-square analysis. Repeated-measures analysis of variance was used with the supplementation period as the within-subject factor and with the supplementation intervention as the between-subject factor and adjusting for respective baseline means for age, sex and ethnicity. Data were of normal distribution using Kolmogorov-Smirnov. The differences were considered statistically significant if the $p<0.05$.

RESULTS

Out of 51 subjects, 62.7% of the subjects were males (Table 1). The age group was divided into three groups from 4 to 6 years, 7 to 9 years and 10 to 12 years. Majority of the subjects in TG (23.5%) and CG (17.6%) were in the age group of 4 to 6 years. The majority of subjects in TG and CG were Malays (70.6%) followed by Indian (15.7%) and Chinese (13.7%). Regarding the father's profile in both groups, most of them were working in the private sector (23.5% and 19.6%). Almost half of the mothers were unemployed (43.1% and 37.3%). Overall, the mothers had worked before their children being been diagnosed, they made a decision to quit temporarily from work because they knew that their child needs full attention and support.

More than half of TG (61.5%) had mild difficulty in tolerating the capsule as shown in Table 2. This is because the size of the capsule is quite big and the children had difficulty swallowing the capsules. However the caregiver made an initiative to break the capsule so the

Table 2. Difficulty levels in consuming the capsule in the TG group (n=26)

Difficulty levels consuming the capsule	n (%)
No difficulty	10 (38.5)
Mild difficulty	16 (61.5)
Moderate difficulty	0 (0)
Extremely difficulty	0 (0)

Table 3. Percentages of malnutrition (z-score) among children with leukaemia at baseline

Gradation of nutritional status	TG		CG	
	n	%	n	%
Weight-for-age				
< -2 z-score†	8	30.8	11	44.0
≥ -2 z-score to median	11	42.3	8	32.0
≥ median to 2 z-score	7	26.9	6	24.0
≥ 2 z-score‡	0	0	0	0
Total	26	100	25	100
Height-for-age				
< -2 z-score§	2	7.7	7	28.0
≥ -2 z-score to median	10	38.5	5	20.0
≥ median to 2 z-score	14	53.8	12	48.0
≥ +2 z-score	0	0	1	4.0
Total	26	100	25	100
Weight-for-height				
< -2 z-score¶	7	26.9	9	36.0
≥ -2 z-score to median	10	38.5	7	28.0
≥ median to 2 z-score	5	19.2	3	12.0
≥ 2 z-score††	4	15.4	6	24.0
Total	26	100	25	100
MUAMC-for-age				
≤5ψ	0	0	0	0
>5-≤15ʃ	23	88.5	21	84.0
>15-≤85	3	11.5	4	16.0
>85-≤95§	0	0	0	0
>95††	0	0	0	0
Total	26	100	25	100

†underweight; ‡overweight; §stunted; ¶wasted; ††obese; ψsevere malnutrition; ʃmild malnutrition.
Independent t-test and Chi-square analysis where appropriate, showed that the baseline results were comparable for gradation of nutritional status between the two groups (p>0.05)

Table 4. Effects of supplementation of omega-3 (fish oil) fatty acids

Anthropometric measurement‡	TG (n=26)			CG (n=25)			ANCOVA (p value)†		
	Baseline	Day-30	Day-60	Baseline	Day-30	Day-60	$F(p)_{group}$	$F(p)_{time}$	$F(p)_{group\times time}$
Weight (kg)	20.0±6.45	20.7±6.35	21.1±6.33	21.7±10.1	21.7±10.1	21.8±10.2	NS	p<0.000	NS
Height (cm)	119 ±14.2	120±14.2	119±13.5	122±17.7	122±17.6	122±17.7	NS	NS	NS
MUAMC (cm)	6.12±1.13	6.16±1.16	6.29 ± 1.00	5.72±0.86	5.25±1.06	5.16±0.89	NS	p<0.000	p<0.001

†Repeated-measure analysis of covariance (ANCOVA)
‡Adjusted for respective baseline means age, sex and ethnicity
NS – not significant

children could swallow without having any difficulty. All of the patients (100%) did not experience any symptoms like vomiting, diarrhoea, constipation, nausea or headache during the intervention.

Of subjects from TG, 30.8%- and 44.0% of subjects from CG were malnourished (z score < -2 for indices weight-for-age), and 7.7% of subjects from TG and 28.0% of subject from CG were classified as stunted for height-for-age (z-score < -2) according to WHO (1995) at baseline (Table 3). The majority of subjects from TG (92.3%) and CG (68.0%) were in normal category (≥ -2 z-score to median and median to 2 z-score for indices height-for-age) respectively. The result indicated for indices weight-for-height, 26.9% of the subjects from TG and 36.0% of the subjects from CG were in the underweight category, respectivley. Only a few subjects (15.4% from TG and 24.0% from CG) were in the obese category based on weight-for-height indices(≥ 2 z-score). The majority of subjects from TG (88.5%) and CG (84.0%), respectively, were in the mild malnutrition category (>5th to ≤15th percentile) for MUAMC-for-age at baseline.

There was significant group and time interactions for MUAMC (p<0.001) as shown in Table 4. This indicator showed a greater increment in the TG group than in the CG group. There was no significant group and time interaction for body weight. However, this outcome showed positive time effects when the interaction term was removed, body weight (p=0.001) increased in both groups over time. There was no significant difference over time between groups for height.

There is significant higher increase for appetite level in the TG group (0.12±0.33) than in the CG group (0.04± 0.35) (p<0.05) as shown in Figure 2. In Figure 3, there was an increasing trend on energy and protein intake in the TG group (213 ± 554 kcal; 3.6 ± 26.8 g). While the

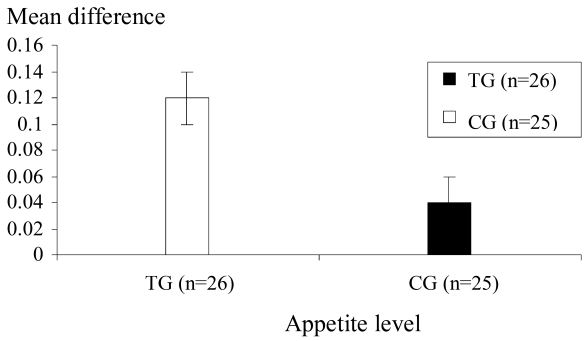

Figure 2. Effect of supplementation of omega-3 (fish oil) on changes in appetite level at 8 weeks in children with leukaemia. Average mean baseline and day 60 appetite level (mean ± SD); Means difference = values on 60 day – values at baseline

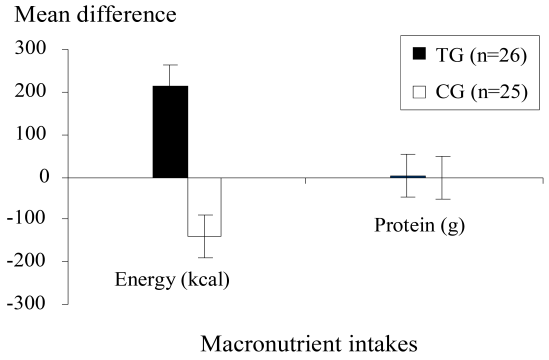

Figure 3. Effect of supplementation of omega-3 (fish oil) on changes in macronutrients intake (total energy and protein intake) at 8 weeks in children with leukaemia. Average mean baseline and day 60 macronutrients intake (mean±SD); Mean difference = values on 60 day – values at baseline

CG group showed a reduction on enegry and protein intake (-139±699 kcal; -0.5±22.3 g).

DISCUSSION

Growth failure and poor nutritional status are common in children with cancer and chronic disease. It also can be an early sign for undiagnosed cancer. Malnutrition will lead to low response to therapy, and descreased survival rate of the patients. Thus, it is important for the patients to maintain body weight. Recent studies have reported that increasing energy and protein intake may have little impact of the patients.[7,8] One approaches that shows significant weight increases compared with controls is omega-3 (fish oil) fatty acids.[4]

This randomised study using supplementation of omega-3 (fish oil) fatty acids has a positive effect in increasing MUAMC among children with leukeamia. Eventhough there were no significant effect in group and time interaction on body weight, there was an increasing trend on body weight in both groups compared with baseline. The results were comparable to the study done among pancreatic cancer patients,[31,32] and children with β-thalassaemia major.[33] The increment in MUAMC are consistent with those of other studies among pancreatic cancer patients,[32,34] gastrointestinal cancer patients,[35] and children with β-thalassaemia major.[36]

Increasing the caloric intake of children with leukeamia for eight weeks, was associated with significant improvement of appetite level and increment of MUAMC. Growth improvement and increasing caloric intake after supplementing fish oil proved that part of the growth impairment of these patients is correctable by proper nutritional intervention to compensate for their hypermetabolic status of these patients. It has been reported that supplemention of fish oil has a beneficial effect in gaining body weight[3] and increasing energy and protein intake among pancreatic cancer patients.[8,34,36] Thus, it is recommended that this supplementation should be considered in every treatment protocol for these patient.

However, these effects were seen predominatly in the patients who were diagnosed with leukeamia rather than solid tumours as reported by Bayram *et al.*[4] This is probably because the enrichment with polyunsaturated fatty acids makes leukeamia cells more susceptible to lipid peroxidation and more sensitive to drug therapy.[37] Eventhough, mechanisms of cancer-associated mal-nutrition are complex, studies have shown that patients with cancer experience an increased elevated acute-phase protein response and high level of pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6).[14,38] and have been subsequently shown to be associated with the development of cancer-associated malnutrition in patients with cancer.[11,39] Studies suggest that supplementation with EPA suppresses IL-6,[14] and the acute phase protein response,[9] which attenuate cancer-induced weight loss. These findings suggested that supplementation of omega-3 (fish oil) fatty acids may be promising in treating cancer-associated malnutrition.

Results of a number of small trials have been reported in which oil, or the main omega-3 fatty acids that contains EPA has been demonstrated to reduce the high rates of weight loss in adult cancer patients.[41,42] There was a line-ar relationship between change in lean body mass and enrichment of plasma phospholipids with EPA, indicating that the greater the intake of omega-3 fatty acids, the greater the protein accretion in the patients. Thus, con-suming omega-3 fatty acids which provide extra protein and energy would allow net deposition of lean tissue.[32]

However, this study has some limitations that could impact the study findings. The small number of subjects may not allow the findings to be generalised to other population such as the elderly. The findings may not be representative as only two hospitals took part in the study. Therefore, further studies are encouraged to be conducted in multiple institutions to achieve a big sample size and represent the nutritional status of children with cancer in general. Even though, compliance of the patients could be checked for the supplementation using plasma EPA levels, it would useful for further studies to focus on methods of optimising compliance (for example, patient record sheets) both within and outside the context of randomised studies. A randomised, double blinded, placebo controlled study should also be considered in the future.

Although there are limitations, our study suggested that supplementation of omega-3 (fish oil) fatty acids along with individual dietary advice had a positive effect on increment of MUAMC, and improved appetite level and caloric intake outcomes when compared with subjects

receiving standard care alone. It would suggest that consuming fish oil supplementation can be beneficial and as a safe to malnutrition or at risk malnourished children with cancer.

Conclusion

In summary, the present study suggest that supplementation of omega-3 (fish oil) fatty acids had a beneficial effect on increasing caloric intake, MUAMC measurements and improving appetite among children with leukaemia. It is, therefore, recommended that omega-3 (fish oil) should be considered as a possible nutritional support approach as part of overall care for children with cancer.

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AUTHOR DISCLOSURES

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Original Article

Fish oil supplementation is beneficial on caloric intake, appetite and mid upper arm muscle circumference in children with leukaemia

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白血病兒童補充魚油有助增加熱量攝取、食慾及上臂肌肉環圍

以隨機試驗評估 51 名 4 至 12 歲患有白血病的兒童，補充魚油對於食慾、熱量攝取、體重及淨體重(去脂體重)的影響。他們被隨機分派為試驗組及對照組。在基線，30.8%的試驗組病童及 44.0%的對照組為營養不良；有 7.7%的試驗組及 28.0%的對照組研究對象被歸類為發育不足。兩組大部份病童在上臂肌肉環圍(MUAMC)年齡比項目被歸為輕度營養不良。在魚油補充至第 8 週時，試驗組的上臂肌肉環圍增加(0.13 公分)比起對照組(-0.09 公分)，顯著較高(p<0.001)。試驗組比起對照組有顯著較高的食慾量增加(0.12±0.33；p<0.05)以及增加熱量及蛋白質攝取(213±554 卡；3.64±26.8 公克)的趨勢。本研究之結論是，白血病兒童補充魚油對於食慾量、熱量攝取及上臂肌肉環圍有正向影響。

關鍵字：魚油、上臂肌肉環圍、食慾、熱量攝取、白血病