

ORIGINAL RESEARCH REPORT

Omega-3 supplementation to reduce alpha threonine kinase 1 (AKT1) levels in children with acute lymphoblastic leukemia (ALL) in the induction phase of chemotherapy

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ABSTRACT

Background: Omega-3 inhibits tumor growth and progression in various cancers, but the mechanisms involved remain unclear. Omega-3 induces apoptosis, promotes cell cycle arrest, and reduces inflammation through various mechanisms, including reduced AKT phosphorylation. AKT is involved in cell growth, proliferation, and apoptosis. Acute lymphoblastic leukemia is one of the most prevalent malignancies in children with low remission levels. PI3K/AKT pathway mutations are found in acute lymphoblastic leukemia. Omega-3 is known to inhibit leukemogenesis through AKT1 signaling pathways. **Objectives:** To analyze omega-3's role in AKT1 level reduction in children with acute lymphoblastic leukemia (ALL). **Methods:** A randomized open label pre- and post-test control group study was conducted on two groups: a treatment group receiving 1,000 mg of omega-3 orally once a day during the chemotherapy protocol's induction phase; and a control group receiving placebos. AKT1 levels were measured before (day 0) and after the induction phase of chemotherapy was completed (day 43). The statistical analysis included paired t-tests, independent sample t-tests, and chi-square tests. **Results:** Twenty-six subjects included in this study were divided into 13 subjects in the control group and 13 subjects in the treatment group. There was a significant reduction in AKT levels before and after receiving omega-3 supplementation in the treatment group ($p < 0.001$). Meanwhile, there was a significant increase in the control group's AKT1 levels ($p < 0.001$). **Conclusion:** Omega-3 supplementation suppressed AKT1 levels.



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Highlights

1. Acute lymphoblastic leukemia (ALL) is more frequent in male, and the incidence of malnourished (wasted and severely wasted) is high 42.31%.
2. Omega 3 can be supplemented to ALL patients as supportive therapy to increase the appetite, calorie intake and mid-upper arm muscle circumference.
3. Omega 3 reduce AKT levels in patients with ALL.

BACKGROUND

Acute lymphoblastic leukemia (ALL) is a malignancy that affects 43 per 1 million children in the United States (IARC, 2004). In Indonesia, 2,000-3,200 new ALL cases were found yearly (Mostert et al., 2006). Evidence shows that PI3K/AKT/mTOR pathways are activated in ALL (Suppipat et al., 2011). The PI3K/Akt/mTOR activation is linked to the pathogenesis and progression of various human cancers, including ALL. Protein kinase B or AKT is a serine–threonine protein kinase that plays important roles in cell growth, proliferation, transcription, migration, and apoptosis (Gu et al., 2013). It is known that there are three AKT isoforms: AKT1, AKT2, and AKT3. One of AKT1's functions is apoptotic inhibition for cellular survival. However, a recent study showed that the pathway's activation involving AKT is associated with poor prognosis and drug resistance in children with ALL, as well as chemotherapy driven apoptosis *in vitro*. Inhibited PI3K/AKT pathways decreased cell proliferation (Bressanin et al., 2012).

Omega-3 fatty acids are an essential fatty acid with considerable health benefits including anti-inflammatory effects, antioxidant effects (Elbarbary et al., 2016), and chemoprotective effects in cancer. It is known to promote anti-tumour immunity and inhibit cancer cells, tumor angiogenesis, and metastasis. The conceivable mechanisms by which omega-3 fatty acids hinder tumor cell growth may include cell proliferation impairment, an increase in cell death, or a combination of both. This is implicated by many signaling pathways (Sawyer and Field, 2010), including inhibited Wnt/ β -catenin signaling, mitogen-activated protein kinases, inhibited Cox-2/PGE2 signaling, and p53/AMPK/mTOR signaling (Shin et al., 2013). Tumor cell proliferation is inhibited as one of omega-3's chemoprotective effects. In general, it is known that AKT phosphorylation reduction will lead to increased apoptosis. PI3K/AKT pathways are important for leukemogenesis (Park et al., 2010). PI3K/AKT enhancement is found in many kinds of malignancy, including leukemia. In 50-75% of ALL patients, the PI3K/AKT pathway is activated and has negative effect on the patient's outcome (Bressanin et al., 2012).

Supportive therapy can be done in children with ALL by supplementing omega-3 fatty acids, including DHA (Docosahexaenoic Acid) and EPA (Eicosapentaenoic Acid). This has a positive effect on appetite level, calorie intake, and mid-upper arm muscle circumference (Elbarbary et al., 2016). However, the role of omega-3 in AKT1 levels in children with ALL remains unclear.

OBJECTIVE

The purpose of this study was to analyze the effect of omega-3 supplementation on AKT1 signaling pathways in children with ALL in Surabaya.

MATERIAL AND METHOD

Study Design

A randomized pre- and post-test control group study was conducted on two groups: a treatment group receiving oral 1,000 mg Omega-3 once a day during the chemotherapy protocol's induction phase; and a control group receiving placebos. Each group consisted of 13 subjects. The experimental study is shown in **Figure 1**.

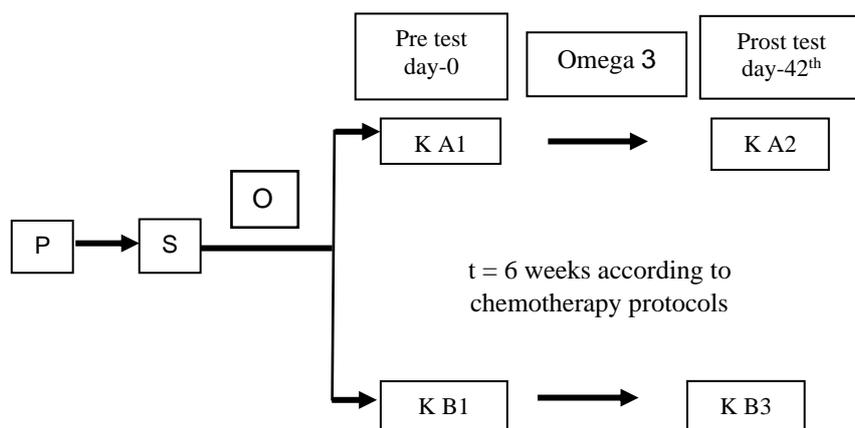


Figure 1. Experimental design

- Notes: P : Population
 S : Sample
 O : Open label
 K A1 : First measurement of AKT1 level in the treatment group
 K B1 : First measurement of AKT1 level in the control group
 K A2 : Second measurement of AKT1 level in the treatment group, 7th week
 K B2 : Second measurement of AKT1 level in the control group, 7th week

Data Collection

The criteria for subjects were children aged 1-10 years old with ALL, underwent the 2013 Indonesian ALL chemotherapy protocol, inpatients at the Hemato-Oncology Pediatric Ward at Dr. Soetomo Distric General District Hospital. Children with ALL in critical condition, children with congenital abnormalities, and children with ALL who could not receive nutritional intervention enterally were excluded. The subjects dropped out if they were in critical condition or passed away. The patients' blood was collected for AKT1 measurement. AKT1 levels were measured before (day 0) and after (day 42) the induction phase was completed. The AKT1 examination method was enzyme-linked immunosorbent assay (ELISA). The omega-3 doses were based on the FAO (2010) and Institute of Medicine of the National Academies (2005) recommendations in soft gel.

At the end of the induction protocol, each patient's results were evaluated by a bone marrow analysis (BMA). Those with lymphoblast counts less than or equal to 5% in the BMA were considered in remission. Those with lymphoblast counts above 5% were considered not in remission (remission failed).

This study was registered with ethical clearance number 151/Panke.KKE/II/2015 issued by the Ethics Committee of Dr. Soetomo General District Hospital on April 15th, 2015.

Data Analysis

A statistical analysis was done using a normality test to distribute the data. Then, if the data were normally distributed, the paired t-test (to compare pre- and post-test results in each group) and independent t-test (to compare between groups) were used. If the data were not normally distributed, the Wilcoxon signed-rank test (to compare pre- and post-test results in each group) and Mann-Whitney U test (to compare between groups) were used. The chi square test was applied on nominal data.

RESULT

There were 26 subjects involved in this study, divided into 13 in the treatment group and 13 in the control group. The subjects' characteristics were their gender, age, nutritional status, and hematological profile as shown in **Table 1**.

Table 1. Subject's characteristics (n=26)

Characteristics	Treatment n = 13 x ± SD	Control n = 13 x ± SD	p-value
Sex, (n, %)			0.691 ¹
- Male	7 (53.8)	8 (61.5)	
- Female	6 (46.2)	5 (38.5)	
Age, months	69.33 ± 49.51	59.23 ± 38.46	0.565 ¹
Nutritional Status (n, %)			0.501 ²
- Normal	7 (53.8)	8 (61.5)	
- Wasted	4 (30.8)	5 (38.5)	
- Severely wasted	2 (18.2)	0	
Hemoglobin (g/dl)	9.70 (1.85)	10.9 (3.51)	0.269 ³
Leucocyte (/mm ³) (mean/min-max)	8,123 (2,100-27,100)	10,707 (1,400-78,000)	0.671 ³
Thrombocyte (/mm ³) (median/min-max)	135,846 (40,000-267,000)	119,923 (15,000-20,500)	0.579 ³

¹Fischer exact test; ²Chi square test; ³Independent sample t-test. Significant if p>0.05

There was a total of 15 boys and 11 girls across both groups. The sex ratio between males and females was 1.4:1, distributed homogenously in both groups (p = 0.691). The average age in the treatment group was 69.38 months (about 5.5 years old), with subjects ranging from 12 to 164 months old. In the control group, the average age was 5.23 months (about 4.9 years), with subjects ranging from 17 to 151 months old. There was no significant difference between the groups (p = 0.565).

Approximately 42.31% of subjects were malnourished (wasted and severely wasted), while 57.69% were normal. This category was distributed homogenously among both groups, and there were no significant differences between the groups (p = 0.501).

Hemoglobin (Hb), leucocytes, and thrombocytes levels had no significant difference in both groups. There were 21 anemic subjects (80.77%) with an Hb of below 10 g/dl. Leukocytes numbers varied from 1,400 to 78,000/mm³. Thrombocytes ranged between 15,000/mm³ to 267,000/mm³ in all groups.

The AKT1 levels are displayed in Table 2 and Figure 2. There was a significant difference in AKT1 levels before (pre) and after (post) the induction phase in the treatment and control groups. The pre-data and post-data AKT1 differences (Δ AKT1) were calculated, and there was a significant difference between groups (p = 0.000). The pre-data and post-data in each group were also compared. It was found that AKT1 levels in the pre- and post-induction phase were significantly different in each group (p < 0.001).

Based on the bone marrow analysis (BMA) after the induction phase, the patients' outcomes were significantly different between groups (p = 0.027) (Figure 3). AKT1 levels increased in subjects with non-remission outcomes, while AKT1 levels decreased in subjects in remission. The treatment with omega-3 had a better effect. Hence, there was no intolerance or side effects during omega-3 supplementation in the treatment group.

Table 2. AKT1 levels before and after chemotherapy protocol induction phase in both groups (n = 26)

AKT1 level	Treatment group x ± (SD)	Control group x ± (SD)	p-value
Before induction phase (day 0) (ng/ml)	4.415 (2.055)	6.977 (2.497)	0.227 ¹
After induction phase (day 42) (ng/ml)	2.808 (1.250)	8.008 (1.820)	< 0.001 ¹
Deviation	-1.608 (1.215)	1.031 (1.855)	< 0.001 ¹

¹Independent sample t-test

AKT1 levels increased in subjects with non-remission outcomes (deviation 2.3 ng/ml), and decreased in subjects in remission (deviation = -1.24 ng/ml). There was a significant relationship between AKT1 levels after the induction phase with chemotherapy outcomes, as well as remission or non-remission in the induction phase ($p = -0.046$).

Table 3. AKT1 level's relationship with remission outcomes (n = 26)

AKT1 level	Non-remission (n = 7) (1 treatment + 6 controls)	Remission (n = 19) (12 treatment + 7 controls)	p-value
Before induction phase (ng/ml)	4.98 (2.21)	5.45 (2.71)	0.408 ¹
After induction phase (ng/ml)	7.28 (4.76)	2.34 (3.05)	0.046
Deviation	2.3 (1.73)	-1.24 (1.11)	< 0.001

¹Independent sample t-test

DISCUSSION

ALL accounts for around 80% of leukemia cases among children aged 0-14 years in Europe, with incidence peaking in early childhood (WHO Europe, 2009). ALL incidence in Indonesia is lower. For instance, in Yogyakarta, Indonesia the average annual incidence rate (AAIR) of childhood ALL was 20.8 per million per year between 1998-2009 (Supriyadi et al., 2011). Dr. Soetomo General District Hospital, Surabaya, Indonesia had 544 patients with ALL between 2005-2013 (Haematology & Oncology Center of Dr. Soeteomo District Hospital, unpublished data). The event-free survival (pEFS) of children with ALL has been significantly associated with age (Möricke et al., 2005). In Yogyakarta, Indonesia, the 3-EFS rate was 20% in pediatric patients with ALL (Sitaresmi et al., 2013).

The youngest age at which subjects were diagnosed with ALL was 12 months old (one year) in the treatment group and 17 months old in the control group. A sharp peak of ALL incidence was observed at 2-5 years of age (Rana et al., 2009). A study by Moricke et al. (2005) stated that the most unfavorable outcome of chemotherapy was found in infancy, while the best results were achieved at toddler and pre-school age. Beyond five years old, survival probability decreased (Möricke et al., 2005).

Malnutrition is one of the risk factors affecting the outcome of chemotherapy treatment in children with ALL (Lobato-Mendizábal et al., 1989). Bayram et al. (2009) discovered that, at the time of diagnosis, approximately 75% of cancer patients were malnourished, and between 20% and 40% of these patients died due to malnutrition and related complications (Bayram et al., 2009). This study recorded that 42.31% of subjects were malnourished (wasted and severely wasted), while 57.69% were not. Lobato-Mendizábal et al. (1989) presented similar results with 37.21% of subjects being undernourished; they had significantly worse chemotherapy treatment outcomes than the well-nourished subjects (62.79%). This outcomes regarding malnutrition can be attributed to poor tolerance in maintaining myelosuppressive chemotherapy (Lobato-Mendizábal et al., 1989).

There were significant reductions in AKT1 levels after omega-3 supplementation in the treatment group, while the control group showed a significant rise in AKT1 levels. Several studies have shown that Akt, a downstream kinase of PI3K, is involved in malignant transformation (Chang et al., 2003). The AKT1 is constantly activated in hematological malignancy or solid tumors and supported by tumorigenesis (Aggarwal et al., 2004). The PI3K/AKT and mammalian target of rapamycin (mTOR) pathways are activated in 50-75% of T-ALL (T-cell acute lymphoblastic leukemia) cases (Terwilliger and Abdul-Hay, 2017). Many components of this pathway are overexpressed in leukemia (Martelli et al., 2011). Many upstream AKT regulators have been found to be responsible for this activation (Wilder, 2015).

PI3K is activated by receptor tyrosine kinases (RTKs), integrins, B- and T-cell receptors, cytokines or G-protein coupled receptors (GPCRs) at the surface of the cell that produces phosphatidyl 3,4,5 inositol phosphate (PIP3). The PIP3 serves as a second messenger and a docking site for proteins with pleckstrin-homology (PH) domains, including phosphoinositide-dependent kinase 1 (PDK1) and its downstream target, protein kinase B (Akt) (Sanchez et al., 2019). PIP3 initiates Ser/Thr kinase Akt activation. PIP3 recruits PDK1 and AKT to the plasma membrane, where PDK1 phosphorylates Akt on

Thr308 in the kinase domain's activation loop. AKT's phosphorylation on Ser473 by PDK2 acts as a "gain control" for AKT, and regulates its degree of activation (Park et al., 2010). Pro survival signalling cascades are initiated when AKT binds and activates, leading to the reduction of apoptosis while increasing cell motility, survival, and growth (Serhan and Chiang, 2008).

Omega-3 has anticancer properties against different kinds of malignancies, including leukemia. This is possible through omega-3 affecting many steps of the tumorigenic process, including initiation, promotion, latency, growth, and metastasis (Sam et al., 2017). Omega-3 is also selectively toxic toward cancer cells, but has little to no toxicity to normal cells (D'Eliseo and Velotti, 2016). Proposed molecular mechanisms of omega-3's anticancer properties via PI3K/AKT/mTOR are mediated by several mechanisms. A study conducted by Gu et al. (2013) showed that DHA supplementation inhibits PDK1 activity by translocating PIP3 and reducing its phosphorylation at the S241 position. Consequently, phosphorylation of AKT is reduced at T308 (Gu et al., 2013). Sam et al. (2017) proved that omega-3 fatty acid DHA mediated the accumulation of p53, down-regulated survivin and caspase-3, and induced apoptosis in acute lymphoblastic leukemia cells (Sam et al., 2017). Omega-3 has many cyclooxygenase-2 products which act as anti-inflammatories. Serhan and Chiang (2008) state that autocoids called resolvins or prostaglandin H₃ (PGH₃) have anti-inflammatory properties and exhibit comparable affinity toward PG receptors at the cell's surface. Hegde et al. (2011). Their study discovered that Δ 12-PGJ3 (Δ 12-prostaglandin J3) produced cyclooxygenase-derived cyclopentenone prostaglandin (CyPG) from omega-3 and eicosatetraenoic acid (EPA) alleviate leukemia development in two well-studied murine models of leukemia.

AKT1 levels in subjects with non-remission outcomes increased significantly. Adhering ALL cells to bone marrow stroma cells triggers intracellular signals to regulate cell-adhesion-mediated drug resistance (CAM-DR). Active AKT are needed for stromal cell protection of ALL cells (Sanchez et al., 2019). Piovan et al. (2013) proposed that glucocorticoid resistance is a major factor of therapeutic failure in T-ALL. Their study found out that AKT1 kinase is a major negative regulator of NR3C1 glucocorticoid receptor protein activity, causing glucocorticoid resistance in T-ALL. Phosphorylated AKT (pAKT1) interacts directly with NR3C1 by altering glucocorticoid-induced gene expression. This directly induces phosphorylate of NR3C1 at position S134 and inhibits glucocorticoid-induced NR3C1 translocation to the nucleus (Piovan et al., 2013). Impaired nuclear activity of NR3C1 leads to impaired apoptosis; therefore, AKT1 is an important indicator of therapeutic failure in ALL (Fransecky et al., 2015).

Activated Akt supports a number of metabolic functions, such as maintaining protein translation, glucose metabolism, and inhibiting autophagy and apoptosis (Altman and Rathmell, 2012). Akt is highly antiapoptotic and requires glucose to protect cells from death, meaning Akt activation promotes glucose metabolism and inhibits other metabolic pathways. This leads to a glycolytic phenotype in growth-factor-stimulated cells and the aerobic glycolysis characteristic of cancer cells (Elstrom et al., 2004). This is known as the Warburg effect, in which 90% of glucose is converted to lactate. This proves that oxidative capacity is damaged (DeBerardinis et al., 2008).

PI3K and Akt stimulate expression of lipogenic genes and lipid synthesis in numerous cell types because of TCA cycle alteration. This also suppresses the catabolism of intracellular components, such as fatty acids that would be used to support cell growth (DeBerardinis et al., 2008). AKT activation is mediated by phosphorylation at Thr308 by PDK1 and Ser473 by mTORC2 (Dan et al., 2016).

Strengths and Limitations

Further studies are needed to explore other pathways such as PI3K.

CONCLUSION

Omega-3 supplementation reduced AKT1 levels significantly and improved chemotherapy outcomes.

Acknowledgment

None.

Conflict of Interest

All authors have no conflict of interest.

Funding

None.

Author Contribution

The author contributed to all processes in this study, including preparation, data gathering and analysis, drafting, and approval for the manuscript's publication.

Ethics Consideration

The study was registered with ethical clearance number 151/Panke.KKE/II/2015 issued by the Ethics Committee of Dr. Soetomo General District Hospital on April 15th, 2015.

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