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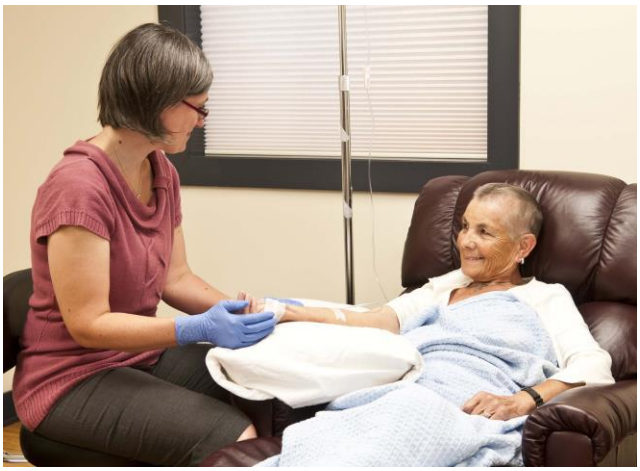
CENTRE DE CANCÉROLOGIE INTÉGRATIVE D'OTTAWA
29 BAYSWATER AVENUE, OTTAWA, ONTARIO, K1Y 2E5 Phone: (613) 792-1222 Toll Free: 1-(855)-546-1244 Fax: (613) 792-1620 www.OICC.ca

Professional Resource: Alpha Lipoic Acid (ALA)



Proper Name

1,2-Dithiolane-3-pentanoic acid

Common Names

Alpha-lipoic Acid; ALA; Thioctic Acid; Lipoic Acid; Acetate Replacing Factor; R-ALA; S-ALA; Thioctacid

Common Uses in Cancer Care

ALA is typically prescribed in cancer care for its antioxidant properties as a means to:

- Stimulate glutathione synthesis
- Strengthen the effects of other antioxidants (e.g., vitamins C and E)
- Enhance insulin signalling
- Manage oral submucous fibrosis
- Prevent and treat chemotherapy induced side effects, such as peripheral neuropathy

Further, there are some reports of ALA being used as an agent with anticancer properties.

ALA is also commonly used in combination with dichloroacetic acid (DCA) to prevent neuropathy that could occur as a side effect of that treatment.

Routes of Administration

Intravenous (IV) and Oral

Pharmacokinetics

ALA is synthesized in humans in small amounts where it plays a role in many important enzymatic reactions (1, 2). In doing so, ALA is reduced to dihydroplipoic acid (DHLA) and eventually re-oxidized in the formation of nicotinamide adenine dinucleotide hydride (NADH). In this way, ALA and DHLA act as a redox couple transferring electrons to and from other substances.

ALA is bound to proteins in the body. Free lipoic acid is not present in the body unless administered therapeutically (1). It is currently believed that only the free, unbound form of ALA is responsible for the many therapeutic properties attributed to this antioxidant. ALA naturally exists in two enantiomeric forms, although the R-enantiomer is the naturally occurring form (3). Synthetic ALA is a racemic mixture of the S- and R-enantiomers, and is the form used therapeutically.

ALA is quickly metabolized in the liver and excreted by the kidneys and therefore has limited bioavailability after oral administration (4). Furthermore, ALA is highly sensitive to heat and light and has reduced bioavailability in its oral form if taken with food (5). Orally (in tablet doses ranging from 50-600 mg), ALA is absorbed within 30 minutes to 1 hour and has a plasma half-life of 30 minutes.

Mechanism of Action

ALA is a powerful antioxidant that functions as a cofactor for several important mitochondrial enzymes (2). The therapeutic activity of ALA is based on its antioxidant properties, four of which have been studied extensively: its metal chelating abilities, its action as a scavenger of reactive oxygen species (ROS), its capacity in regenerating endogenous antioxidants, and its capability to repair oxidative damage (1, 2). We are also beginning to understand how ALA may play a role in the prevention and treatment of neuropathy as well as in cancer.

Metal Chelation

ALA and its reduced form, DHLA, function as direct reactive oxygen species (*ROS*) scavengers in chelating redox-active metals including free iron, copper, manganese and zinc (1, 2). Chelation of free metal ions prevents them from inducing oxidative damage by catalyzing reactions, generating highly reactive free radicals that can lead to a multitude of chronic diseases within the body.

Reactive Oxygen Species (ROS) Scavenger

As an antioxidant, ALA functions both endogenously and exogenously due to its ability to act as a direct *ROS* scavenger in both its oxidized and reduced forms (2). Unlike most other antioxidants, ALA is both hydrophilic and lipophilic, enabling it to play an active role in the cytoplasm, lipoproteins, serum and plasma membrane. Oxidative stress results from a wide array of both radical and nonradical reactions, and culminates in the destruction of DNA, lipids and proteins (1). ALA and DHLA each play unique roles in *ROS* scavenging, with ALA scavenging hypochorous acid, oxygen singlets, and hydroxyl radicals and DHLA scavenging superoxide and peroxyl radicals. In this way, DHLA is able to prevent the free radical-mediated peroxidation of proteins and is able to neutralize free radicals without becoming directly involved in the chemical reaction (1, 2).

Regeneration of Endogenous Antioxidants

Once an antioxidant has scavenged *ROS* and especially free radicals, it forms an oxidation product that must be safely regenerated or degraded to prevent itself from exhibiting pro-oxidant activity (1). In order to return to an active antioxidant capable of scavenging additional *ROS*, it must first be reduced (2). DHLA as a potent reducing agent has the ability to reduce and regenerate many crucial antioxidants including vitamin C, vitamin E and glutathione. DHLA may also be efficient in reducing

the oxidized form of tocopherol, the *a*-tocopheryl radical, either directly or indirectly via reduction of vitamin C, which is also a reducer of this radical (1, 2). In addition, DHLA also plays a principal role in the reduction of coenzyme Q10, which also is a reducer of the *a*-tocopheryl radical.

Oxidative Damage Repair

Oxidative stress damages DNA, lipids, and proteins and must be overcome by degradation, renewal and repair; this is particularly important for proteins that exhibit low turnover rates (1). ALA is a potent redox-regulator of proteins such as myoglobin, methionine, prolactin, thioredoxin and NF-κB transcription factor (1, 6). One method by which DHLA is able to participate in oxidative repair is by providing reducing substrates such as NAHD (1). The reduction of sulfhydryl groups by DHLA has also been shown to enhance the regulation of insulin stimulated glucose transport (6).

Treatment and Prevention of Neuropathy

Neuropathy is a painful and debilitating condition that can result in reduced physical abilities as well as quality of life (7). Although neuropathy is a potential complication associated with diabetes, chemotherapy induced peripheral neuropathy (CIPN) is also a common side effect associated with neurotoxic chemotherapeutic agents. Hyperglycemia, commonly seen in diabetes and cancer, potentiates oxidative stress that can inevitably lead to neuronal and endothelial damage (2). Both ALA and DHLA participate in insulin production and ALA can enhance glucose uptake in insulin-sensitive and insulin-resistant muscle tissue (2). ALA also plays a role in treatment and prevention of neuropathy by counteracting the negative effects of lipid peroxidation (8). ALA has been shown to improve both somatic and autonomic neuropathies by regulating endoneural blood flow, improving vascular dysfunction, and reducing oxidative stress (9).

Cancer

Although still in the preclinical stage of investigation for cancer treatment, there are several hypotheses regarding the mechanisms of action by which ALA may prove useful in the treatment of cancer. One idea surrounds ALA's ability to induce hyperacetylation of histones: proteins capable of causing proliferation of many types of cancer cells (10). By inhibiting histones, ALA may be able to drive cancerous cells towards apoptosis. ALA has also been shown to be able to inhibit the protein complex NF-κB (nuclear factor κB). If activated, NF-κB is able to increase the survival of cancerous cells and increase cellular transformation, metastasis, invasion, proliferation, chemo-resistance, radio-resistance, and inflammation (2, 10). ALA exhibits antimutagenic and anticlastogenic properties, classifying it as part of the group of natural antimutagenes (2). By increasing the uptake of oxidizable substrates into the mitochondrion of cancerous cells, ALA is also able to stimulate pro-oxidant driven apoptosis (10). Another mechanism of action is ALA's ability to increase homocysteine levels in cancer cells lines to toxic concentrations for these malignant cells. Finally, ALA is being investigated for its ability to correct functional defects in peripheral blood mononuclear cells in advanced cancer patients (11).

<u>Clinical Evidence related to Effectiveness</u>

Although there are numerous preclinical studies looking at the use of ALA alone or in combination with other agents for the treatment of cancer, the human intervention literature is limited. There

are a small number of randomized and non-randomized trials, some observational studies, and a few case studies that support the use of ALA in cancer and/or in the treatment of chemotherapy-induced peripheral neuropathy.

ALA Monotherapy

In a recent open-label non-randomized study looking at the use of several antioxidants in the treatment of various cancers, patients were divided into various arms, each receiving a single antioxidant (11). Six patients were given ALA alone, and this group showed an overall 22% ($p=0.05$) decrease in *ROS*, and an overall non-significant 35% ($p=0.08$) increase in glutathione peroxidase 1 (GPx) after treatment. In this study, responses to ALA treatment in terms of *ROS* levels and GPx activity were comparable to other antioxidants studied in the trial.

ALA in Combination with Standard Care

Oral submucous fibrosis is a highly potent, irreversible precancerous condition that has been linked to oral cancer. In a recent RCT trial, 18 patients with this painful condition were given either ALA in combination with the standard treatment of betamethasone and hyaluronidase, or standard treatment alone (12). Patients in the ALA plus standard treatment group exhibited better relief of symptoms such as burning sensation of the mucosa and improved mouth opening, as compared to the controls, as well as the reversal of higher clinical stages to lower ones.

In a single case report completed in follow up to a study using mouse cancer models, an elderly female with primary gastric adenocarcinoma that had metastasized was treated with a combination of ALA, hydroxycitrate, and gemcitabine (13). The patient continued on this regime for an 8 month period and observed increased quality of life, increased survival beyond expectancy, increased weight, regression of tumor on CT scan and improved biochemical markers.

ALA in Combination with Low-dose Naltrexone (LDN)

There are several published case reports documenting improved symptoms and longer than expected survival following treatment with ALA and low-dose naltrexone (LDN). One case report describes treatment of a 46 year old male with poorly differentiated adenocarcinoma of the pancreas with metastases to the liver, who had previously failed chemotherapy and had continued to have disease progression even while receiving standard treatment. (14). This patient had immediate improvement in symptoms after starting the ALA /LDN protocol, and 78 months after initially beginning treatment with this protocol, he was back at work, free from symptoms, and without progression of his disease. In another publication by the same authors, case studies are presented of three patients with metastatic and non-metastatic pancreatic cancer all with poor prognosis who were treated with an IV ALA/LDN protocol (10). One person followed this protocol without any additional standard therapies and was still alive and free of any signs and symptoms 39 months after initial diagnosis (at the time of publication). A second person was treated for six months and observed an increased quality of life, improvement of all symptoms, and no signs of disease recurrence through a PET scan. A third person exhibited immediate improvement in symptoms after starting the ALA/LDN protocol, and felt well enough to undergo surgery. Finally, a third case report by the same authors describes a 61 year old man with follicular lymphoma who

was first treated with a series of IV ALA therapies followed by six months of LDN (15). Upon initial physical examination and PET/CT scans, this patient was shown to have multiple large, metabolically active, pathologic lymph nodes that revealed complete resolution within 6 months of therapy and remained at bay one year later at the time of publication.

ALA in Combination with other Natural Health Products

In an open, non-randomized study involving 28 advanced stage cancer patients with tumors at various sites, patients were divided into five groups, with each group receiving a combination of two antioxidants (16). Three of the groups received a combination that included ALA alongside carboxycysteine-lysine salt sachets, amifostine, or GSH. Among these combinations, ALA with carboxycysteine and ALA with GSH were both effective in reducing *ROS* while ALA with amifostine was effective in increasing GPx. In addition, the antioxidant combinations were able to reduce serum levels of IL-6 and TNFa.

In a single case report, a 71 year old male with poorly differentiated carcinoma with metastases to the right leg and liver was treated with dichloroacetic acid (DCA) and ALA and experienced an increase in quality of life and significant pain reduction following initiating this therapy (17). After 5 months of treatment, this patient was able to completely stop all pain medications.

ALA for Neuropathy

There has been limited clinical research exploring the use of ALA within cancer care; however, numerous studies have been have been published supporting the safe and effective use of ALA in diabetic neuropathy. In an open, uncontrolled trial aimed at investigating the therapeutic potential of ALA in combating oxaliplatin induced peripheral neuropathy, fifteen patients with colorectal cancer were treated with a combination of ALA and oxaliplatin (9). Eight out of the fifteen patients demonstrated a reduction in the severity of neurologic symptoms, improving by at least one grade. The seven patients that did not demonstrate a significant improvement all had clinically advanced stages of peripheral neuropathy. A separate uncontrolled study by the same authors, using a protocol of ALA combined with docetaxel and cisplatin (18) included 14 patients of whom 8 demonstrated an improvement in neurological symptoms.

The many studies assessing ALA treatment for diabetic peripheral neuropathy have been summarized in several systematic reviews. In one systematic review and meta-analysis, fifteen randomized control trials were included (19). People in the treatment groups were administered 300-600 mg IV ALA per day, following which nerve conduction velocities were observed to increase substantially without any serious adverse effects. A separate systematic review and meta-analysis included a sample of over 1,250 diabetic patients with peripheral neuropathy who were treated with 600 mg of IV ALA and concluded that as little as three weeks of treatment reduced the chief symptoms of diabetic polyneuropathy and that longer treatment times of 4-7 months with oral ALA was sufficient to improve neuropathic deficits and reduce cardiac autonomic neuropathy (20). Another systematic review explored the use of ALA for diabetic peripheral neuropathy when ALA was administered alongside chemotherapy (21). Overall results from the four included studies revealed that IV administration of ALA resulted in a significant and clinically relevant improvement

of neuropathic pain. This review suggested that ALA might have greater efficacy when administered intravenously (21).

Adverse Events and Side Effects

In the majority of published studies, ALA has been well tolerated with minimal and mild side effects when compared to control and placebo groups (5). Side effects are rare but possible and usually occur only at doses greater than 600mg. Possible side effects include nausea, gastric pain, vomiting, and vertigo (5, 18). In IV administration, local pain during infusion and redness are common. Various long term studies using both oral and IV administration have not resulted in any significant adverse effects when compared to placebo (2). There have been some cases of spontaneous hypoglycemia due to the development of insulin autoimmune syndrome associated with the administration of ALA (22). These cases were all reported in Japanese patients and 12 of the 17 patients tested positive for either the DRB1*0406 or the DRB1*0403 gene. In a single case report, a type 2 diabetic male with comorbidities including hypertension, hyperthyroidism and stage 2 chronic renal failure was started on ALA to help combat diabetes induced peripheral neuropathy (23). This patient developed severe cholestatic hepatitis as a result of the ALA. It was later determined using two separate scales that his probability of developing drug induced liver damage was high. Recently, a clinical trial looked at the safety profile of ALA administration in patients with hepatic impairment and found no difference when compared to healthy subjects (20).

Interactions with other Therapies, including Drugs and Natural Health Products

Positive Interactions

One *in vitro* study suggests that ALA may enhance the cytotoxic effect of IV vitamin C and that co-administration of these agents may be beneficial (24). Research also suggests that administration of ALA with platinum chemotherapy agents such as cisplatin and oxaliplatin may protect otic (inner ear) and neural tissue from oxidative damage (25). ALA may also have a protective role against kidney, liver, and inner ear tissue damage caused by aminoglycoside-induced free-radical generation and lipid peroxidation as seen with the administration of antibiotics such as gentamycin and amakacin. ALA protects against oxidative stress and hydrogen peroxide generation when administered alongside haloperidol. Finally, ALA has a synergistic role when co-administered with angiotensin II receptor antagonists such as irbesartan.

Negative Interactions

There is a theoretical risk of hypoglycemia when using oral hypoglycemic agents along with ALA due to the supportive effect of ALA on glucose and insulin metabolism (25). Diabetic patients taking ALA should closely monitor their blood glucose levels particularly if just starting with ALA and if insulin is required.

Cautions and Contraindications

In animal studies using ALA, doses greater than 20 mg/kg proved to be fatal in severely thiamine-deficient rats: an effect that was prevented when ALA was administered simultaneously with thiamine hydrochloride (5). There are no documented cases of fatal overdose in humans, and high

doses of ALA have been studied in numerous clinical trials (e.g., 18, 19, 21). As a precautionary measure, however, many treatment protocols include thiamine along with ALA.

There is not enough research to guarantee the safety of ALA in pregnancy or lactation at this time and there has been one report of miscarriage in a pregnant woman participating in a trial involving ALA; thus, all pregnant and lactating women should avoid the use of ALA (5, 8).

Due to the risk of potentiating hypoglycemia in diabetic patients, ALA should be administered with caution in patients with diabetes or other endocrine disorders that may have an impact on glycemic regulation.

Dosing, frequency and length of treatment

At the OICC, ALA is most often prescribed orally for its antioxidant properties, to enhance the effectiveness of IV vitamin C, and to counteract chemotherapy or other drug (e.g., DCA) induced peripheral neuropathies. The typical therapeutic oral dosages of ALA range from 600-1800 mg daily (8). IV doses are most commonly used in the 300-600 mg range to reduce the risk of adverse effects (5, 8, 9, 21).

Disclaimer

The OICC has prepared this monograph, as part of a series of monograph development, to share results of a review of the scientific research evidence related to common therapies and products used within patient care at our centre. It therefore reflects therapies and products used within the defined scope of practice for our practitioners in Ontario, Canada. The information in this monograph should not be interpreted as medical advice nor should replace the advice of a qualified healthcare provider.

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