

Photodynamic therapy with aminolevulinic acid: a novel therapeutic target in the management of gastrointestinal malignancies

Abstract

Surgery combined with chemoradiotherapy is the mainstay for the management of gastrointestinal malignancies. Ultimate goal is to eliminate locoregional recurrences, to prolong survival and to prevent morbidity and mortality associated with traditional treatment modalities in management of gastrointestinal malignancies. In this respect, Photodynamic Therapy (PDT) seems to be a good alternative treatment option for gastrointestinal malignancies because of its promising results in precancerous, cancerous and noncancerous lesions. Studies support the complete response with PDT in recurrent and advanced cases with gastrointestinal malignancies. Aminolevulinic acid (ALA) is a heme precursor leading to accumulation of the photosensitizer protoporphyrin IX (PpIX) in tissues that makes ALA useful target for PDT. Thus, PDT using ALA seems to be promising novel, advanced, an efficient, convenient approach in management of patients with gastrointestinal malignancies. This review highlights the principles of action mechanism of PDT with ALA, applications in gastrointestinal malignancies and limitations and its future directions in this field.

Keywords: 5-aminolevulinic acid, Photodynamic therapy, Gastrointestinal cancers, Gastric cancer, Colorectal cancer, Hepato-pancretico-biliary cancer

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Introduction

The concept of photodynamic therapy (PDT) has initiated after Raab, a medical student and his teacher Von Tappeiner discovered that certain dyes could cause cell death in the presence of light source.¹ Even though, first clinical trials were conducted in dermatological disease, PDT did not have an enough attention until 1970s.² Then, PDT has increasingly studied as therapeutic modality in precancerous, cancerous and non-cancerous lesions in humans.

Here, we describe basic principles of action of PDT with ALA, applications in gastrointestinal malignancies and limitations and its future directions in this field.

Principles of photodynamic therapy and ala as a photo synthesizer

PDT requires three essential components: a photosensitizer, a light source and oxygen. The photosensitizer is a molecule that localizes to the target cells or tissues. When the photosensitizer is exposed to specific wavelengths of light, it becomes activated from the ground state to excited state and causes the production reactive oxygen species (ROS) including singlet oxygen (1O_2) which trigger the destruction of tumour cells via apoptosis and necrosis.³

Recently, aminolevulinic acid (ALA) has been used as photosensitizer for PDT.^{4,5} ALA is first committed intermediate in the heme synthesis pathway (Figure 1).⁶ A heme synthesis pathway has two rate limiting enzymes that are, ALA synthase and ferrochelatase.⁷ Ferrochelatase is responsible for converting protoporphyrin IX (PPIX) into heme. Exogenous ALA administration saturates ferrochelatase, resulting in PPIX accumulation.⁵ ALA is not a photosensitizer but its end product PpIX is photoreactive substance.

Preferentially uptaken of ALA is resulted with PpIX accumulation in malignant cells.⁵ Excess accumulation of PpIX may occur because of low activity of ferrochelatase which catalyses the insertion of

an iron atom into PpIX or higher activity of hydroxymethylbilane synthase in malignant cells.⁸ Beside this, there is an accumulating evidence suggests that membrane transport systems of ALA and porphyrin play very important role in accumulation of PpIX.^{9,10}

The wavelength of the light source must correspond to a maximal absorption peak of the photo synthesizer in order to achieve proper cell death. A light source with high fluence rate and capable of delivering a large dose of light in a short time is also important.¹¹

The presence of oxygen in a tumour cell is also important for success of PDT, since oxygen is required for photochemical reactions to occur, and hypoxic regions tend to be not responsive to photo synthesizer.¹²

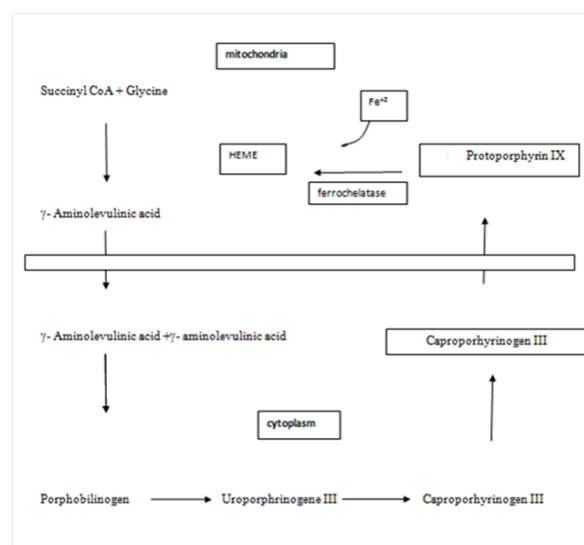


Figure 1 Heme synthesis.

New generations of ALA as a photosensitizer with spectrums of absorption at higher wavelengths such as 650-740nm have allowed deeper tissue penetration and more extensively studied in worldwide. Methyl ester derivative of ALA is approved for treatment of basal cell carcinoma of the skin and actinic keratosis.^{13,14} ALA is administered topically or systemically via oral, intravenous and intradermal routes. When ALA administered systemically, it distributes to virtually all tissues preferentially in liver and tissues with elevated metabolic rates.¹⁵ Side effects of systemic and oral administrations are nausea, vomiting, photosensitization in skin and urinary frequency, alterations of liver function, hypotension in 4-6 hours and resolving within 24 hours.^{16,17} Currently, 5-ALA is only cleared for use dermatologic, malignant glioma, urogenital applications,⁵ but is used for gastrointestinal and other systemic applications.¹⁸

ALA photodynamic therapy (ALA-PDT) in gastrointestinal cancers and peritoneal carcinomatosis

ALA-PDT in upper gastrointestinal system

The use of ALA-PDT in superficial and early lesions of upper gastrointestinal system diseases shows great promise as an alternative to invasive techniques. Evidence for these options is discussed below. Premalignant lesions such as Barrett's oesophagus with high grade dysplasia are theoretically ideal for treatment with PDT.¹⁹ These are superficial and large mucosal areas easily accessible for light. Dysplasia may arise in the setting of Barrett's oesophagus and that can lead to the development of adenocarcinoma. A phase I study showed that high grade dysplasia can be eradicated 89% with free from cancer rate 96% after 36 months follow up in patients treated with red light after 60mg/kg ALA.²⁰ The first study of ALA-PDT in the human gastrointestinal tract organs; oesophagus, duodenum and colorectal tumours was described as a pilot study in 1995.²¹ They reported that ALA-PDT is promising technique for the treatment of small tumours located to mucosa such as Barrett's oesophagus. However, in a phase II study demonstrated the poor response to ALA-PDT in respect for residual disease and progression of disease with recurrence²² Dunn and Lovat.²³ systematically reviewed and synopsis was given from the literature for PDT-ALA for treatment of dysplasia in Barrett's oesophagus. They reported that ALA-PDT is both safe and effective for the treatment of dysplasia and early cancer in Barrett's oesophagus. Further studies are required to demonstrate the comparative effectiveness of PDT-ALA in the treatment of oesophageal and cardia lesions.

Studies investigating the role of ALA-PDT in gastric cancer are very limited. Both reports *in vivo* and *in vitro* were from China.^{24,25} ALA-PDT was reported to be an effective and promising therapy for gastric cancer following *in vitro* study on human gastric cancer cells²⁴ and *in vivo* study with human gastric cancer cell lines injected to nude mice skin.²⁵ A clinical experience of using ALA in combination with in chemo-immune-hyperthermia in patients with Stage IV gastric cancer was reported from Japan.²⁶ They conclude that ALA can exert good palliation in combination with other therapies in late stages of gastric cancer. Hino et al.²⁷ studied ALA-PDT using light emitting diodes (LED) light in different wavelength in a mouse model of peritoneal dissemination of gastric cancer. They reported ROS generation and cytotoxic effects of ALA-PDT were the highest at 410nm and lowest at 635nm. Differences in light source indicate that optimal wavelength is one of the essential parameters in development of strategy with ALA-PDT. Again, ALA was found to be feasible and safe in biopsy-proven early gastric carcinoma without visible lesions.²⁸ Even studies these suggested great promise regrettably were not followed by

randomized clinical trials. Beside these studies, researchers have a great effort to understand ALA specific accumulation in cancer cells to increase effectiveness of ALA-PDT *in vitro* gastric cancer cell line.¹⁰ They have found that higher expression of peptide transporter PEPT1 (ALA influx transporter) and low expression of ATP-binding cassette transporter (ABCG2) (porfirin efflux transporter) determined ALA-induced PpIX production and photosensitivity *in vitro*.

Beside this, Porfimer Sodium has been used as a photo sensitizer in treatment of 113 patients with esophageal cancer after local failure following chemo radiotherapy.²⁹ Complete remission rate was 58.4% (66/113) and 5-year progression free survival was 22.1% with overall survival was 35.9%. Treatment related death was 1.8% in recurrent cases of esophageal cancer. Porfimer sodium is also curative option for superficial cases with esophageal cancer.^{30,31}

ALA-PDT in small bowel cancers

ALA-PDT has been also applied to duodenal and ampulla Vateri tumours,²¹ and patients with polyps in duodenum due to familial adenomatosis polyps.³² that indicating promising results. However, further studies are required to optimize the ALA-PDT.

ALA-PDT in hepato-pancreatic biliary cancers

ALA-PDT studies in hepatocellular carcinoma have been mostly limited to *in vitro* studies in cultured cell lines and *in vivo* murine studies. The accumulation of PpIX after administration of ALA was higher in tumoural tissue than that in non tumoural tissue in hepatocellular cancer model.³³ ALA-PDT has been found to be decreasing tissue oxygenation 10-fold in rat liver.³⁴ ALA-PDT has been found to be yielded with apoptosis in 70% of HepG2 cells following 18 hours of ALA incubation.³⁵ ALA-PDT has been resulted also cell death in hepatoblastoma cell lines.³⁶ PDT within pancreatico-biliary system cancers has been extensively studied with comparatively little focus to ALA-PDT. Tumour growth was significantly decreased in *in vitro* and *in vivo* studies with ALA-PDT and with other photo synthesizers.^{37,38} Little attention to ALA-PDD in hepatopancreaticobiliary cancers may due to a report showed no effect in bile duct cancer in 2001.³⁹ However, hexyl aminolevulinic acid form successfully expressed higher concentration of PpIX in cholangiocarcinoma cell lines expressing H⁺ peptide co transporter PEPT1 suggesting PEPT1 and other forms of ALA may be very effective in PDT approach of cholangiocarcinoma.⁴⁰

ALA-PDT in colorectal cancer

ALA-PDT again understudied in colorectal cancer. PDT with other photosensitizer was used in the treatment of villous adenoma⁴¹ and polyps⁴² of colorectum. More recently, it has been reported that ALA-PDT using blue and white LED light demonstrated greater antitumour effects *in vitro* and *in vivo*.⁴³ It has been reported that selective inhibition of H⁺-coupled aminoacid transporter PAT1 and increased H⁺-coupled di/tripeptide transporter PEPT1 could contribute to ALA-PDT as an underlying mechanism in accumulation of PpIX in colon cancer patients.⁴⁴

ALA-PDT in peritoneal malignancies

ALA-PDT has not been studied in peritoneal surface malignancies even ALA guided diagnosis has been reported in primary peritoneal serous carcinoma⁴⁵ and peritoneal malignancies of ovarian cancers.⁴⁶ Peritoneal malignancy management using CRS and HIPEC has been evolved in past years.⁴⁷ Promising results in management of peritoneal malignancies with PDT have been reported from the

most of the previous studies carried out using photofrin in peritoneal surface malignancies with severe side effects such as capillary leak syndrome.^{48,49}

Several studies have shown that ALA-mediated photodynamic diagnosis (PDD) is a promising tool for diagnosing peritoneal metastasis in gastric cancer. ALA-mediated PDD was used in addition to diagnostic laparoscopy for 52 patients with advanced gastric cancer. Of these patients, peritoneal metastasis has been detected in 5 of 24 (20.8%) patients with no evidence of peritoneal metastasis using ALA-mediated PDD.⁵⁰

Photodynamic therapy can be even preventive effect to development of peritoneal metastasis. Talaporfin as a second generation photosensitizer mediated photodynamic therapy (PDT) has been reported to have a more accumulation in metastatic nodules and an anti-tumor effects resulted with longer survival rates in mice model developed peritoneal metastases.⁵¹

Combination of photodynamic therapy with immunotherapy

Even though cancer immunotherapy has shown promising results, high proportion of patients may relapse or given limited response. PDT can reduce tumor burden and increase the secretion of tumor antigen from the cancer cells. Combination of PDT with immunotherapy might have better outcomes in cancer therapy. Indeed, PDT can be combined with tumor specific immunotherapy with long peptide vaccination.⁵²

Further studies will be required for effect of ALA-PDT in peritoneal surface malignancies.

Five year view

Studies of PDT with ALA in other gastrointestinal malignancies and peritoneal carcinomatosis are limited to few phase I and II clinical and *in vitro/in vivo* studies. Photodynamic Therapy (PDT) represents the method of choice for some of the diseases including minimally invasive therapeutic procedure to treat oesophageal cancer with high cure rates, low side effects. Increasing uptake of photosensitizer into the cells with appropriate light source and wavelength need to be investigated will improve the effects of PDT in cancerous cells. Furthermore, combination of PDT with immunotherapy has shown promising results in the treatment of advanced cancers.

Key issues

1. Studies of Photodynamic Therapy (PDT) with alanine (ALA) are aimed to improve oncologic treatment option
2. ALA may serve for better target therapy and better patient outcomes due to its ability to selectively accumulates in cancerous cells
3. Studies of PDT with ALA are limited in gastrointestinal cancers and peritoneal carcinomatosis
4. *In vitro* and *in vivo* studies significantly vary with regard to protocols, duration and outcome measurements
5. Technical aspects such as delivering light source, increased sensitivity and specific activity of photosensitizers and dosing strategies need to be clarified with further studies
6. Well controlled studies are necessary to determine whether PDT with ALA may add value to traditional treatment approaches

7. PDT with ALA deserves further investigation to elucidate ALA's role in the surgical therapies

Expert commentary

ALA-PDT is considered to be a novel and promising antitumor strategy. It promise to be targeted accurately and selectively in earlier and advances lesions. It can be used repeatedly with comparatively limited side effects. Disadvantages of ALA-PDT are limited tissue penetration, not selective to tumour cells and tissues. Beside this, its potential has not been fully demonstrated. Furthermore, its applications and in combination with other approaches are also not defined. The fact that PDT definitely reduces morbidity compare to surgery and in combination with chemo radiotherapy. PDT also can be repeated without compromising the efficacy.

Further studies including the cellular mechanism of ALA-PDT and using nanotechnology to increase the sensitivity and specificity of photo sensitizers (third generation of photosensitizer, etc.) and to develop accurate dose and light source for selective treatment certainly will develop our understanding and produce more effective therapy for not only gastrointestinal but also for other malignancies.

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Conflicts of Interest

Author declares there are no conflicts of interest.

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