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The use of 5-aminolevulinic acid and its derivatives in photodynamic therapy and diagnosis

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Abstract. 5-aminolevulinic acid (5-ALA) is used as a drug in the photodynamic therapy (PDT) and photodynamic diagnosis (PDD) of cancer. Combined with irradiation at the appropriate wavelength, it is used as a photosensitizer precursor to identify/kill tumour cells. In cells, 5-aminolevulinic acid is converted to protoporphyrin IX (PpIX), which is the precursor of hemin. Internal application of 5-ALA induces the overproduction of the endogenous photosensitizer, PpIX, which can subsequently be activated by light at the appropriate wavelength. 5-ALA can be applied internally to trans-mutated areas or be injected directly into them. Chemical derivatives of 5ALA have the potential to improve bioavailability, enhance stability and lead to better therapeutic outcomes for treated patients. 5-ALA is currently the most commonly used drug in the photodynamic therapy and diagnosis (PDT/PDD) of cancers.
Keywords: photodynamic therapy, photodynamic diagnosis, 5-aminolevulinic acid (5- ALA), esters of 5-aminolevulinic acid, cancer
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List of abbreviations

5-ALA — 5-aminolevulinic acid
PDT — Photodynamic Therapy
PDD — Photodynamic Diagnosis
PpIX — Protoporphyrin IX
MAL — Methyl aminolevulinate
HAL — Hexyl aminolevulinate
AMP — Adenosine monophosphate

AMPK — AMP dependent protein kinase
5'AMP-activated kinase
DMSO — Dimethyl sulfoxide
AK — Actinic keratosis
BCC — Basal cell carcinoma
FD — Fluorescence diagnosis
FDA — Food and Drug Administration
EMA — European Medicines Agency

1. Introduction

5-aminolevulinic acid (5-ALA) is a water-soluble compound in the group of non-protein keto acids and amino acids. It is a straight-chain δ-amino acid with a weak chromophore group (carbonyl group) [1]. 5-ALA molecules are characterised by a simple structure and relatively low molecular weight (167.8 Da). 5-ALA is the most commonly used drug in the photodynamic method of treatment and diagnosis (PDT/PDD) of cancer. In recent years, it has also been used in agriculture as a biodegradable herbicide [2, 3, 4].

5-ALA is the first intermediate in the biosynthesis of heme and precursor of protoporphyrin IX (PpIX) (Fig. 1) — an endogenous compound with a strong photosensitizing effect, widely used in the therapy and diagnosis of cancer and pre--cancer diseases – PDT, PDD (*Photodynamic Therapy*, *Photodynamic Diagnosis*).

Photodynamic therapy is an alternative method of cancer treatment, which has been developing relatively quickly in various fields of medicine since the 1960s.

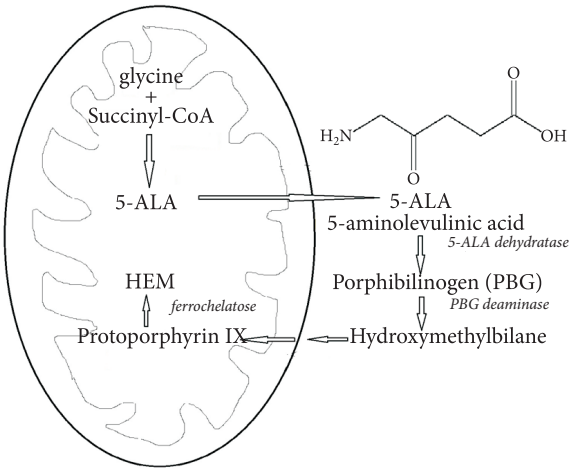

Fig. 1. Heme biosynthesis diagram

Many publications about photodynamic therapy using 5-ALA have been written in the last few years. Two on ALA-PDT were published in 1991, and by 2007 there were already about 4,000 [5]. According to the WoS database, 12,941 publications related to photodynamic therapy were published over the past 5 years, but only 243 of them directly dedicated to ALA-PDT.

Photodynamic therapy was developed as a method for antineoplastic treatment based on a tumour-specific accumulation of photosensitizer, which induces cell death after irradiation with light at the appropriate wavelength in line with the maximum absorption of the photosensitizer.

The activity of the enzymes in the heme synthesis pathway in cancer cells, unlike healthy cells, leads to an increased accumulation of PpIX. After application of an exogenous 5-ALA preparation, cancer cells synthesize 10 times more PpIX than healthy cells, and is used in the PDT process [6].

Depending on the intercellular location of the photosensitizer, the photodynamic process may trigger different signalling cascades and induce cell death resulting from a number of possible processes, such as: apoptosis, autophagy and necrosis. The results of research by Hong-Tai Ji et al show that photodynamic therapy involving 5-ALA induces autophagic cell death mediated by AMP-activated protein kinase. The authors clearly emphasize that this is the activation of AMPK (AMP dependent protein kinase) rather than MAPK (mitogenactivated protein kinase). These observations indicate the importance of the AMPK pathway in the cell death mechanism induced by 5-ALA [7].

The selective accumulation of porphyrin IX (PpIX) in cancer tissue after topical application of 5-ALA has been used in the diagnosis of cancerous lesions, including in the mouth, bladder, endometrium and cervix. Through the use of PDD it is possible to detect preclinical diseases that are usually not detected by conventional diagnostic methods [8].

Initially, for almost two decades, research focused on discovering and explaining the mechanisms of ALA-PDT and improving the therapeutic efficacy of the photodynamic method. In recent years solutions have been created for problems related to improving the administration and penetration of 5-ALA to the tissue, increasing PpIX synthesis in cells after the application of 5-ALA, as well as improving the fluorescence, as used in ALA-PDD [9].

2. Bioavailability of 5-ALA and its derivatives

One of the more serious issues of the photodynamic method using 5-ALA is its poor bioavailability. Problems limiting the use of ALA-PDT were related to low permeability of 5-ALA through the stratum corneum. The 5-ALA molecule is polar and in physiological pH is present mainly as a charged zwitterion, and hence related

to low lipid solubility and reduced bioavailability. The hydrophilic character of 5-ALA significantly impedes the penetration of the drug through the highly hydrophobic stratum corneum. The n-octanol/water ratio for 5-ALA is only 0.03 [10]. This is not only the main barrier in the transport of the drug to the cell, it is also an obstacle in obtaining the required 5-ALA concentration in the affected tissue. The results of research on cell lines indicate that to achieve a high level of cytotoxicity against cancer cells (> 90%), the interstitial concentration of 5-ALA should be 0.01-0.17 mg/ml [11-13].

However, in cancer tissues there are accidental disturbances of the stratum corneum and damage to epidermal membranes caused by disease lesions, which in turn makes it easier for penetration into the cell to occur and allows its concentration to be increased in the lipid intracellular structures.

Research has been also carried out on the use of DMSO, glycolic and oleic acid to improve 5-ALA penetration [14-16].

The next step in solving the issue of 5-ALA bioavailability was the use of nanocarriers. They must be designed to accumulate mainly in the target tissue. Several types of nanoparticles for PDT application have been developed so far, mainly based on liposomes. The use of liposomes to enclose the 5-ALA particles results in increased PpIX biosynthesis in the tumour compared to healthy tissue [17-19].

Another advantage of liposomes is the improved penetration and the ability to use a lower drug concentration while maintaining the optimal results of PDT [20].

Recently, silica nanoparticles have emerged having such desirable properties as: small pore size, large surface area and volume, and lack of toxicity. Their porous structure makes them a perfect carrier for hydrophobic photosensitizer molecules. An additional advantage is their good oxygen permeability, which plays a very important role in the photodynamic process [21, 22]. Other nanocarriers used in ALA-PDT are: ALA-dendrimers, niosomes, conjugated gold nanoparticles, polymer and fullerene nanoparticles, and carbon nanotubes [23].

Corporations engaged in nanotechnology, especially namomedicine, must still consider the additional problem of the toxicity that can occur when using a drug carrier. Therefore, the use of carriers (nanoparticles) to improve the "biotransport" of drugs has been carefully investigated.

3. 5-ALA ester derivatives

In physiological conditions, more than 90% of 5-ALA molecules are in the form of zwitterions, with a positive charge at the amino terminus and a negative charge at the carboxyl terminus. Compounds structured this way have limited capability of reaching the target cell in a biological environment. To improve cellular permeability, achieve greater stability in physiological pH, increase the selectivity

of accumulation in cancer tissue and reduce side effects, attempts have been made to modify the 5-ALA molecule, through obtaining a number of derivatives. The introduction of lipophilic derivatives of 5-ALA occurring naturally in the body to photomedicine has led to a revival in this area of research [24].

The presence of the amino and carboxyl group in the 5-ALA molecule gives great opportunities to obtain numerous derivatives. 5-ALA ester derivatives are usually obtained by esterification with aliphatic alcohols (methyl, propyl, butyl, hexyl) in the presence of thionyl chloride or hydrogen chloride, and with aromatic alcohols such as benzyl alcohol. Stability tests have also been carried out in aqueous solutions of 5-ALA tyrosine ester [25].

A major achievement in improving the bioavailability of 5-ALA was the use of its esters, especially the methyl (MAL) and hexyl (HAL) esters, which have made it possible to significantly extend the clinical application of ALA-PDT. The longer carbon chain in the 5-ALA ester molecule results in increased lipophilicity, for much greater permeability through the cell membranes and skin, which facilitates the transport of the drug into the cell. In addition, the production of photoactive compounds in the target area is increased [26]. The literature data show that the use of 5-ALA aliphatic esters causes the non-specific distribution of 5-ALA in all cell types, but with increased production of PpIX in cancer cells [27, 28].

The production of 5-ALA-induced PpIX in cells is highly dependent on the lipophilicity of 5-ALA esters [29]. Longer chain esters, such as butyl and hexyl ester, have higher PpIX production efficiency than 5-ALA. On the other hand, although MAL methyl ester is more lipophilic than the parent compound, it induces lower PpIX production in cells. This can be explained by the de-esterification of MAL methyl ester to 5-ALA before the ester can overcome the lipophilic barriers. The metabolism of 5-ALA derivatives to PpIX *in vivo* must be preceded by a de-esterification reaction, i.e. the release of the parent form of 5-ALA. The results of some studies indicate that the production of PpIX from ALA esters depends on the esterase activity in cells [30, 31].

Studies conducted by Lee et al. show that the butyl, pentyl and hexyl esters of 5-ALA induce higher PpIX production in the target area than 5-ALA or its methyl ester. To obtain a comparable concentration of PpIX, the required concentration of HAL hexyl ester is about a hundred times lower than 5-ALA [32].

The use of 5-ALA esters allows the use of lower drug concentrations and shorter application times, compared to the parent hydrophilic 5-ALA. The esterification of 5-ALA improves the bioavailability of the drug, but not its stability. To improve the stability, the 5-ALA molecule is modified by blocking the amino group that causes the dimerization of molecules. Such derivatives are obtained through condensation of the 5-ALA molecule or its ester with acetic anhydride or acetyl chloride [33].

Thirteen new derivatives were introduced by the team of Wei Zhu [34]. Several show high cytotoxicity of cancer cells after irradiation with 600 nm wavelength light.

The results of studies carried out *in vivo* indicate that the greatest therapeutic efficacy has been found for the preparation: 5-(2'-acetamide-3'-phenylpropanoid)--benzyl 4-oxopentanoate [34] (diagram below).

Work on obtaining new 5-ALA derivatives is continuing, and new 5-ALA-derived drugs for the treatment and diagnosis of many diseases have emerged.

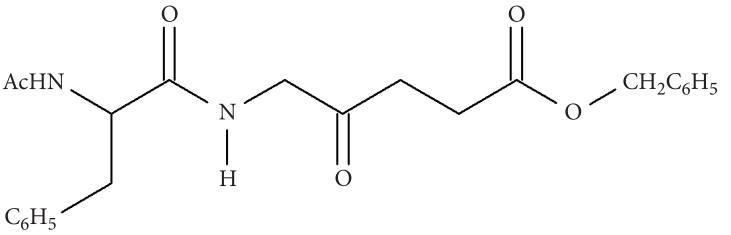

Fig. 2. Structure 5-(2'-acetamide-3'-phenylpropanoid)-benzyl 4-oxopentanoate [34]

4. The mechanism of action of ALA-PDT

The application of exogenous 5-ALA induces the biosynthesis of PpIX and then heme with the participation of the ferrochelatase enzyme, which catalyses the last stage of the heme biosynthesis pathway (Fig. 1). The photodynamic method is based on the photosensitizing effect of protoporphyrine IX, so it is important that its concentration in the cell is sufficient. Unlike heme, PpIX is a photosensitive substance (with a singlet oxygen yield of approx. 56%) and with sufficiently high fluorescence quantum yield. The results obtained so far suggest that any improvement in ALA-PDT effectiveness depends mainly on PpIX production. To improve the therapy outcome, all actions have to be aimed at increasing the production of protoporphyrin IX at the point of 5-ALA application, or at inhibiting the conversion of PpIX to heme.

The inhibition of the conversion of protoporphyrin IX to heme can be obtained by using ferrochelatase inhibitors and iron ion chelators, for example [35, 36]. Iron ion chelators have the ability to inhibit the activity of ferrochelatase, which further hinders the formation of heme, and therefore increases the protoporphyrin concentration in the cells. Clinical trials have shown that the use of such iron chelators as: EDTA, 2-allyl-2-isopropylacetamide or 1,10-phenanthroline causes the accumulation of PpIX in cancer cells after 5-ALA application.

However, the results of clinical trials show that the long-term use of iron chelators for therapeutic purposes may cause highly toxic effects. This is related to the fact that iron chelators inhibit the activity of ribonucleotide reductase, a critical enzyme in the synthesis of DNA. It has been demonstrated that the compounds that strongly chelate iron reduce

oxidative cell damage and their necrosis caused by labile iron under the influence of UVA. Long-term use of such chelators may lead to systemic iron deficiency and inhibition of enzymes that require iron, necessary for the proper functioning of the body [37]. The problem has been solved by applying 'cage chelators'. Iron chelators closed in a cage remain secure and inactive. They are only released and activated under the influence of appropriate doses of UVA radiation. Cage chelators should show: high lyophilicity and easy cell penetration, no toxicity, no possibility of iron chelating under normal conditions, and high affinity with iron after UVA irradiation. Strong PIH (pyridoxal isonicotinoyl hydrazine) (Fig. 3) and SIH (salicylaldehyde isonicotinoyl hydrazone) (Fig. 4) chelators were used to develop prototype cage iron chelate compounds [38, 39].

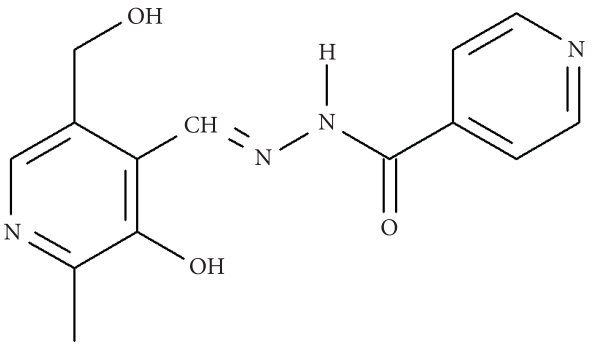

Fig. 3. PIH — pyridoxal isonicotinoyl hydrazone

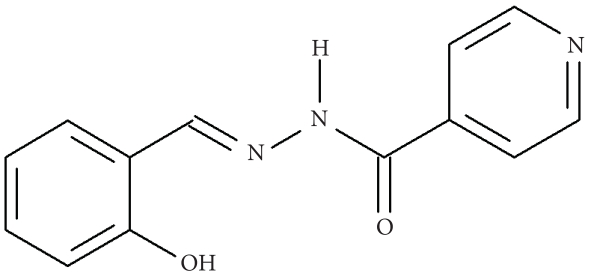

Fig. 4. SIH — salicylaldehyde isonicotinoyl hydrazine

Literature data indicate that exogenous administration of 5-ALA leads to selective accumulation of PpIX in cancer tissues, particularly in the case of superficial skin cancer. Yamamoto et al. have shown that apart from the reduction of ferrochelatase activity and the increase of porphobilinogen deaminase activity in cancer cells, an important role in PpIX accumulation is played by nitric oxide, leading to a decrease in its intracellular concentration by interacting with iron [40, 41].

One of the reasons for the selective accumulation of 5-ALA-induced PpIX in cancer tissue is the abnormal function of the stratum corneum. The activity of enzymes in the heme synthesis pathway in cancer cells compared to in healthy cells, and the limited availability of iron, seem to be the main reasons for greater PpIX accumulation within cancer cells. A significant improvement in 5-ALA permeability to the skin can be achieved through: iontophoresis, intradermal injection or fractionated light irradiation (using a fractionated laser). The fractionated light irradiation method involves double exposure of the affected tissue: four hours after application of the 5-ALA preparation, 20% of the calculated dose of red radiation is applied, followed by the remaining 80% of the red light dose after two hours of incubation [23].

5. Pre-clinical and clinical trials of 5-ALA and its derivatives

The ALA-PDT method has a wide application in both the therapy and diagnosis of cancer and pre-cancer conditions, as well as in cosmetology and aesthetic medicine. The first reports on excessive accumulation of PpIX and the high photosensitivity after the administration of 5-ALA appeared in 1956 as the result of work by Berlin et al. In 1987, 5-ALA was used for the first time in photodynamic therapy for the selective elimination of erythroleukemia cells (di Guglielmo disease). In 1990, Kennedy and Pottier used the 5-ALA preparation for the first time for clinical purposes, mainly in the treatment of superficial skin cancers (mainly basal cell carcinoma), applying 5-ALA to the affected surface and then irradiating it with white light. Reguła et al. were some of the first researchers to present the results of the successful ALA--PDT treatment of pancreatic cancer. The research was carried out on an animal model - a Syrian hamster [9]. In 1999, in the US, the ALA-PDT method was used for the first time on a broader scale in the treatment of actinic keratosis (AK) using Levulan®Kerastic and blue light. Levulan®Kerastic (5-ALA hydrochloride) has been widely accepted for use in the ALA-PDT method as a 20% solution for topical application to the skin [42].

A non-invasive treatment with ALA-PDT appears to be an attractive method, especially in the treatment of patients with co-existing diseases or a high risk of surgery. PDT therapy is especially recommended for patients who do not tolerate other treatment methods and for lesions in areas that are difficult to access. Currently, numerous clinical trials are carried out on the use of the ALA-PDT method in the treatment of non-melanotic skin cancers and cutaneous T-cell lymphoma. The efficacy of treatment for basal cell carcinoma is estimated at 50-100%. Positive results of ALA-PDT treatment have also been obtained in the treatment of invasive squamous cell carcinoma [43, 44]. Compared to cryotherapy, the ALA-PDT method was more effective and better tolerated by the patients [45]. In addition,

clinical trials on multiple actinic keratoses of the face and scalp showed treatment efficacy through the topical application of ALA-PDT. The ALA-PDT method has also proven to be effective in the treatment of head and neck cancer, especially surface lesions, as well as oral, pharyngeal and throat cancers and cervical cancer. Good results for the treatment of precancerous conditions of the gastrointestinal tract have been demonstrated [46-50].

In diagnoses, 5-ALA has been used mainly for the visualization of cancer tissues during surgical procedures. The patient is administered a specific dose of 5-ALA and the surgical field is lit during the surgery. The photosensitizer particles are then excited, which during their return to the ground state radiate some of the energy, causing a red fluorescence. This phenomenon is used in photodynamic diagnosis (PDD). Through the use of a CCD camera, it is possible to visualize the tumour foci, which to a large extent allows the precise determination of the size of the tumour and other areas with cancer cells present [51]. The fluorescence of 5-ALA-induced porphyrins may help in detecting the early stages of some malignant tumours [52]. Fluorescence has been clinically used in the detection of brain, oesophageal, bladder, uterine and skin cancers. The method of fluorescence induced by exogenous 5-ALA is called FD (fluorescence diagnosis) or PDD (photodynamic diagnosis). Fluorescence surface analysis helps in estimating the preoperative states or the size of the postoperative residual tumour. It is often difficult to distinguish between healthy and cancerous tissue, and the results of FD or PDD make it possible to accurately remove tumours, such as gliomas, which can significantly extend the survival of patients with glioblastoma. Clinical data indicate that the resection of malignant gliomas under FD control significantly improves progression-free survival [52]. ALA-PDD is used for diagnosing such abnormalities as high dysplasia or early adenocarcinoma in the Barrett's oesophagus, as well as in gynaecology — in the diagnosis of pre-cancerous changes to the cervix, and in ovarian cancer [8]. ALA-PDD allows the definition of resection margins narrower than those in a conventional mapping biopsy. The 5-ALA photodynamic method has also been used in neurosurgery for the intraoperative imaging of brain tumours [53].

In recent years, ALA-PDT therapy has increasingly used 5-ALA derivatives, especially its esters, because of their good properties related to bioavailability, preparation stability and good therapeutic results.

5-ALA methyl ester (MAL) has been approved in the United States, New Zealand and Australia, as well as some European countries in the treatment of basal cell carcinoma (BCC) and actinic keratosis (AK) [54-55]. The research shows that it is more selective towards cancer cells than 5-ALA, and the therapy is less painful and more effective [56-57].

Among the tested esters, the hexyl ester HAL has proved to be the most effective. Currently, the hexyl ester is undergoing clinical trials in the treatment and diagnosis of bladder cancer. Its great advantage is that it can be administered in a concentration

lower than for 5-ALA [9]. This year, it was registered in Poland, under license number 11910. The entity responsible is Ipsen Pharma, and the drug strength is 8 mmol/L. It currently receives no public funding in Poland.

In addition, the clinical and preclinical trials of ALA/MAL-PDT have shown great potential in the treatment of mycosis fungoides, papilloma, viral skin diseases, lymphocytoma, leishmaniasis, alopecia areata, erythroplasia of Queyrat and mild pemphigus [58-59].

In 2008, the ALA-PDT method was approved in the US for the treatment of moderate acne vulgaris. In addition, thanks to good cosmetic effects, 5-ALA and its esters are now widely used in dermatology.

Recent reports have shown a growing interest in 5-ALA photodynamic therapy in the treatment of non-cancerous skin diseases, including actinic keratosis, acute inflammatory acne, purulent inflammation of the sweat glands and sebaceous gland hypertrophy [41]. ALA-PDT has proven to be an effective method in treating non--malignant vulval diseases and infections caused by some bacteria, fungi, protozoa and viruses, including inflammation of the foreskin and penile glans. This method of treatment is very useful, especially for strains resistant to traditional antibiotic therapies [60]. Recently, cosmetic treatments using the ALA-PDT method have become quite popular for patients with aging symptoms and sun-induced damage, such as: actinic keratosis, discoloration, rosacea, and widened blood vessels. In aesthetic medicine, ALA-PDT is used in photorejuvenation [61-63].

6. 5-ALA preparations used in clinical practice

Registered preparations of 5-ALA and its derivatives are collected and shown in Table 1. The individual preparations are discussed below.

The Food and Drug Administration approved a 20% solution of 5-ALA hydrochloride (Levulan® TM, Dusa Pharma) with a blue light source for the treatment of actinic keratosis (early stage of skin cancer).

In ALA-PDT therapy, the preparation is applied as a 20% cream or 20% gel about 3-5 hours before irradiation. There are reports of the use of ointments and gels with lower concentrations of 5-ALA. The drug known as BF-200ALA is a gel preparation containing 7.8% of 5-ALA. Used in the treatment of actinic keratosis, it has proved more effective than the parent 5-ALA because of its better solubility and skin penetration. The 5-ALA is also administered as a hydrochloride solution, orally or in the form of infusions, as well as in the form of inhalations, e.g. during the diagnosis of throat and larynx cancers [61, 64]. In 2008, the use of Gliolan® (5-ALA hydrochloride) at a concentration of 30 mg/ml was approved for the treatment of brain glioma. Kajimoto et al. described the usefulness of 5-ALA-induced fluorescence to detect atypical meningioma cells and also indicated the possibility of using 5-ALA for the resection

of Grade II meningioma. Atypical meningiomas have a high relapse rate of 41% in 5 years, probably because the actual size of the neighbouring tissue infiltration is not distinguishable and the residual tumour material omitted during surgery. Therefore, 5-ALA-derived tumour fluorescence (Gliolan®) is useful in detecting these regions of residual infiltration in the dura mater and, more importantly, in the neighbouring brain, which could be the source of further relapses. 5-ALA-derived tumour fluorescence may help to improve the diagnosis of patients with invasive but benign meningiomas as well as patients with atypical or anaplastic meningiomas [65].

Since 2001, MAL methyl ester has been registered in the USA, New Zealand and Australia as a drug, under the name Metvix® or Metvixia®. It is administered as a cream and activated with red light three hours after application.

The European Medicines Agency (EMA) in Europe and the USFDA approved the 5-ALA ester derivative (hexyl ester, HAL) — Hexvix TM, Photocure — to diagnose bladder cancer using fluorescent cystoscopy. In 2010, it was admitted for the diagnosis and treatment of bladder tumours [51, 62]. Recent reports indicate that Hexvix® has been approved in 27 European Union countries, as well as in Norway and Iceland.

Table 1

5-ALA preparations currently used in PDT/PDD [66]

Drug name	Components
Metvix® (Photo Cure, ASA, Oslo, Norway)	16% 5-ALA methyl ester hydrochloride
Metvixia® (Galderma, Fort Worth, Texas)	Cream containing 16.8% of 5-ALA methyl ester for topical application only
LevulanKerastic® (Dusa Pharmaceuticals, Wilmington, USA)	20% ALA 5-ALA hydrochloride
Magistral preparation	20% 5-ALA gel/ cream/ emulsion
Alacare® (Medac, Hamburg, Germany)	4 cm^2 patch containing 8 mg of 5-ALA hydrochloride
BF - 200 ALA (Biofronter Bioscence GmbH, Leverkusen, Germany)	5-ALA nanoemulsion containing 7.8% of 5-ALA
Hexvix® (Ipsen Pharma Polska)[1]	5-ALA hexyl ester
Benzvix® (Ipsen Pharma Polska)	5-ALA benzyl ester

[1] Agency for Health Technology Assessment and Tariff System, Department of Health Care Services, 22/08/2018, No. WS.430.6.2018.

Moan et al. proposed the topical application of bioadhesive patches, which additionally increase the selectivity of PpIX accumulation in the target tissue. Each 4 cm^2 Alacare® patch contains 8 mg of 5-ALA hydrochloride. They are used mainly in the treatment of mild actinic keratosis [67-68].

7. Advantages and disadvantages of the ALA-PDT method

Current clinical trials have proven that ALA-PDT is an effective treatment method, more beneficial than standard therapies such as chemotherapy or cryotherapy, considering the cosmetic outcome of the treatment. ALA preparations show little toxicity. Clinical trials conducted on glioblastoma patients have demonstrated the following ALA-specific side effects: arrhythmias, hypertension, gastrointestinal disorders, nausea, skin reactions, hypersensitivity to light and photodermatosis. It is suggested that the frequency of each of these effects is from 1:1000 to 1:100 [8].

In addition, like any treatment method, alongside its advantages the ALA-PDT photodynamic method is also characterised by specific disadvantages. The most serious are those associated with hypersensitivity to light, lack of efficacy in the treatment of large or metastatic tumours and pain during the treatment. The pain is more intense in the treatment of large areas (> 130 nm^2), and its degree is often related to the patient's age [69].

Patients over 70 years old experience stronger pain effects, although local anaesthetics can be used to relieve the sensation of pain (burning, stinging, itching). Local skin cooling and nerve blocking by electrical stimulation of the skin can also be applied. The issue of pain relief is essential when using ALA-PDT therapy [70].

ALA-PDT therapy may result in occasional changes in pigmentation, which are usually transient. Other rare side effects in connection with the administration of ALA preparations are nausea, paraesthesia, fatigue and headache [9].

The advantages of using the ALA-PDT method in comparison with traditional treatment methods such as surgery, chemotherapy or radiotherapy are the lack of internal resistance mechanisms, the possibility of repeated application and no risk of immunosuppression.

In addition, the main advantage of using 5-ALA and its derivatives compared to other photosensitizers is the short half-life of its photosensitizing effects, which according to various literature sources is no longer than 48 hours [71]. The ALA-PDT method appears to be a very effective treatment method in clinical oncology. However, it still requires additional clinical and preclinical trials, including on the molecular mechanisms of cytotoxicity, to better understand the therapeutic outcomes and increase their effectiveness [71].

8. Conclusion

Photodynamic therapy mediated by 5-ALA (ALA-PDT) and fluorescence photodetection (FD) is probably one of the most selective methods of cancer treatment in oncology. In addition to the good selectivity of 5-ALA induced porphyrin IX for cancer, it has several additional advantages compared to conventional

photosensitizing agents, including limited systemic toxicity and low skin photosensitivity after application of ALA. Clinical trials show that the use of 5-ALA derivatives in PDT may guarantee higher generation of photoactive compounds, improved depth of tissue penetration, more homogeneous distribution of photoactive porphyrins, shorter application time, lower drug doses, improved stability and reduction in undesirable side effects. 5-ALA preparations must be selected carefully with regard to the medical indications.

5-ALA derivatives may have therapeutic indications in the treatment of bacterial infections. The results of the preliminary tests showed their high effectiveness in photodynamic deactivation of Gram-positive and Gram-negative bacteria and in adjuvant treatments to improve the healing of wounds and in bacterial infections of the oral cavity.

As we can see, the PDT-ALA method seems to be a very promising alternative for the treatment and diagnosis of cancer and pre-cancer conditions. ALA-PDT combines safety, limited side effects and good cosmetic outcomes along with good drug tolerance.

The Institute of Optoelectronics at the Military University of Technology has been working for several years on obtaining effective photosensitizers for PDT, including 5-ALA derivatives, and suitable light sources for PDT/PDD.

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Zastosowanie kwasu 5-aminolewulinowego i jego pochodnych w terapii i diagnostyce fotodynamicznej

Streszczenie: Kwas 5-aminolewulinowy (5-ALA) jest stosowany jako lek w terapii fotodynamicznej (PDT) i diagnostyce fotodynamicznej (PDD) raka. Wraz z promieniowaniem o odpowiedniej długości fali jest używany jako prekursor fotouczulacza w celu identyfikacji lub/i zabicia komórek nowotworowych. W komórkach 5-ALA przekształca się w protoporfirynę IX (PpIX), która jest prekursorem heminy. Miejscowe zastosowanie 5-ALA indukuje nadprodukcję endogennego fotouczulacza PpIX, który może być następnie aktywowany światłem o odpowiedniej długości fali. 5-ALA można podawać zewnętrznie na leczone zmiany lub wstrzykiwać bezpośrednio do nich. Pochodne 5-ALA mogą poprawić biodostępność, zwiększyć stabilność i prowadzić do lepszych wyników terapeutycznych leczonych pacjentów. 5-ALA jest obecnie najczęściej stosowanym preparatem w fotodynamicznej terapii i diagnostyce (PDT/PDD) nowotworów.

Słowa kluczowe: terapia fotodynamiczna, diagnoza fotodynamiczna, kwas 5-aminolewulinowy (5-ALA), estry kwasu 5-ALA, choroby nowotworowe

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