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New Advances in Aminolevulinic Acid in Urology

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Aminolevulinic Acid (ALA) serves as a precursor and the trigger for porphyrin synthesis in humans, animals and plants which is an important biological function. The research on ALA dates back to the early fifties. In the beginning it was focused specifically on the analysis of the porphyrin synthesis pathway. The first clinical application of ALA-PDD for diagnosis of non-muscle invasive bladder cancer was reported by Kriegmair et al. [1]. Many comparative clinical studies- the effectiveness of ALA *vs* white light endoscopy in diagnosing cancer of the bladder have been performed in the last two decades with a variable degree of sensitivity (100%-90%) and specificity (55%-65%).

The microbial fermentation of 8 molecules of ALA and six different enzymes results in the production of protoporphyrin IX (PpIX) - the vital compound in detection and treatment of cancer of the bladder. Porphyrin biosynthesis is fundamental for humans and any failure or inadequacy in its production leads to porphyria. PpIX possesses high affinity to iron (Fe^{2+}) and subsequently *promotes* heme formation in humans, and magnesium deposits (Mg^{2+}) in plants with the production of chlorophyll. Ogura S et al. [2] in 2011 in BMC Res. Note, stated that the addition of ALA to the iron improves hemo proteins and cytochrome C oxidase, in particular. The enzyme is crucial in aerobic metabolism due to the fact that ferrochaletase regulates the final stage of heme production and expulsion of ALA from the cell. This ability decreases with age leading to accumulation of PpIX in the cell. It has been demonstrated by Okura and Tanakain [3] the book, Aminolevulinic acid Science, technology and application; Tokyo institute of technology press, SBI pharma publication, 2011, that in cancer patients the amount of this enzyme will be reduced significantly and that will result in high levels of PpIX. The level of accumulation of protoporphyrin IX varies in different types of tissue. Photodynamic assessments of active PpIX reveal the highest concentrations in normal and cancerous epithelia. This is due to differences in the metabolic activity of cells, cellular 5-ALA uptake and enzymatic activity during the synthesis and metabolism of PpIX. PpIX synthesized from ALA is a photo reactive substance. It shows sensitivity to blue light of the length: λ=400-410 nm and reaches the fluorescence maximum for λ=635 nm (21-23). The intensity of fluorescence is directly related to the intracellular concentration of PPIX (24). This is the basis of the photodynamic principle of use of PPIX to differentiate types of tissues.

Enzyme Activities

The major cause of selective accumulation of PPIX in different tissues is reduced activity of ferrochaletase. This enzyme catalyses the incorporation of iron into PPIX with the formation of a molecule of heme. Reduced ferrochaletase activity is found in tumour cells and is associated with a disproportionately large accumulation of PPIX. The increased levels of this substance in tumour tissues results in a strong fluorescence signal from these tissues. This property serves as a diagnostic criterion of cancer. Ferrochaletase activity is reduced up to 10 fold in tumours. This results in accumulation of porphyrins in tumour cells and a simultaneous reduction in intracellular heme concentrations. The low metabolic activity of ferrochaletase in cancer cells is probably due to the prevalence of glycolysis rather than the oxidative phosphorylation which is found in normal tissue. Also fast growing tumours show a lower activity of mitochondrial cytochromoxidase. In addition to a reduced ferrochaletase activity, there is an increased activity of porphobilinogen-deaminase (PBGD) and other enzymes that are involved in PPIX synthesis. This is another reason for increased production of PPIX in certain diseases as well as intoxication after an exogenous supply of 5-ALA.

Fluorescence cystoscopy has been in use in the diagnosis and follow-up of Non-Muscle-Invasive Bladder Cancer (NMIBC) for over a decade. Clinical indications are the topic of international and national guidelines published in several countries across Europe. In the Netherlands, for example, the use of fluorescence cystoscopy for Carcinoma *In Situ* (CIS) is strongly advised. However, many of us who specialize in the diagnosis and management of bladder cancer have been confronted by the lack of an overall European consensus on the role of fluorescence cystoscopy.

A hexaminolevulinate hydrochloride intravesical solution for instillation was approved by the FDA in 1991 as a tool for the diagnosis of bladder cancer. The disadvantage of its use is the poor tolerance of patients, i.e., they have to hold the solution for a period of 2 hours with the inserted catheter. This instigated research for more effective and tolerable methods. In 1994 we started our first use of photodynamic diagnosis PDD in superficial bladder cancer [3]. The results published in 1996, in the 'Journal of the Baghdad Faculty of Medicine' revealed the high degree of sensitivity (94%) in detection of superficial bladder cancer and carcinoma in situ compared to white light cystoscopy - 71%. This leads to an important question of the effectiveness of photodynamic diagnosis with regard to postsurgical tumor recurrences. As we all know, the recurrence rate is high in superficial bladder cancer and most of our resections are incomplete! In our clinic we have been using blue light guided transurethral resection of the bladder since 2000. But the problem of tolerability of the substance in the bladder by 30% of my patients was disappointing.

Improvements in biotechnology and the production of ALA as an oral supplement opened the way to comparative studies on the use of oral and intravesical administration of 5-ALA for non-muscle invasive forms of bladder cancer. It was demonstrated that there was no difference in the strength of fluorescence signal after oral administration or instillation of the compound. The possibility of oral administration has opened new hopes in the utilization of ALA to explore more cancers in urology. ALA is not only used for the diagnosis of bladder cancer, but also plays an important role in surgical resection. The surgeon can use blue light technique during a procedure to identify any incompletely removed areas of a tumour that cannot be seen by regular white light. Thus, Dr. Inoue of Kochi University in Japan has shown that the tumour retention rate after conventional TURBT for non-muscle invasive bladder cancer under white light was 20-50%, but decreased to 20% after ALA-PDD-guided TURBT [4-8]. Denzinger et al. [9] compared the recurrence rate of

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SBT after TURBT over a long-term follow-up for 8 years involving 191 patients. The recurrence-free-survival rates after TURBT with conventional white light were 90.9 -78.6% after 12 months and 71.0-45.0% after 96 months, respectively. The rate was significantly better with PDD-guided–TURBT. The proportional-hazards model, in which the hazard ratio of PDD-TURBT was 0.29 showed that PDD-TURBT was an independent prognosis-improving factor related to intravesical recurrences of bladder tumours.

This led us to reevaluate our position on recurrent tumours. Are we talking about recurrence or incomplete resection? Are the facts that blue light explored many hidden areas of the same tumour or CIS or will it show up again in a short period of time? Another point is the margins of the tumour, is the tumor completely resected or not? Many problems concerning accuracy of diagnosis remain to be solved. Perhaps they will be resolved with the development and improvement in light sources.

Radical prostatectomy is another nightmare for the urologist when lymph nodes are not completely removed or the margins are not completely free of cancer. With 5-ALA given to a patient 4 hours before surgery blue light can also be used for open, laparoscopic or robotic prostatectomy to check for margin free resection and to detect any hidden metastatic lymph nodes. In the case of renal cancer, when a local tumour removal is indicated, blue light can identify safe margins and involved lymphatics. Other possible applications include colon cancer and gynaecological cancers. GI tumours will also benefit from the use of this amazing technology.

Amazing results have been achieved in the treatment of unresectable malignant glioma. The application of ALA with intraoperative excitation of PpIX with blue light and the application of PDT by sterotactic interstitial laser photo-illumination resulted in programmed cell death for a localized area within the brain tissue that is not accessible to the surgeon. These results have unlocked the expectation of using ALA not only in the diagnosis of bladder cancer but also PDT. We, in the Arab World, are conducting a study on the use of ALA on bladder cancer with cell death induction using an external source of energy after excitation of the tumour cell loaded with ALA. The preliminary results are promising and the source can be applied in many ways to induce apoptosis of malignant cells. This can be very helpful in the future for treatment of SBT and will add a new armamentarium to our current strategies.

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