Zorin V.P., Zorina T.E.

Biophysical determinants of sensibilization of transformed tissues and cells by chlorin type photosensitizers: kinetic aspects

Belarusian State University, Minsk, Republic of Belarus

Photodynamic therapy (PDT) efficacy strongly depends on the selectivity of photosensitizer (PS) accumulation and distribution in cellular and tissue targets, thus the search for new photosensitizers with optimal photophysical and pharmacokinetic characteristics is considered to be the main direction of PDT development. PS used in PDT accumulate in tumor tissue, although the fundamental mechanisms are less clear. Theoretically, once a molecule used for cancer detection or treatment is injected into blood stream, it encounters the following "resistance" before reaching the intracellular space: distribution through vascular space, transport across microvascular wall, transport through interstitial space, transport across cell membrane. Each of these stages involved into the control of sensitizer location and retention in tumor represents a complex process which depends on numerous parameters.

We have focused our researcher on understanding the physical and chemical parameters governing the distribution of porphyrin sensitizers among protein, cells and tissues structures. This work includes three lines of studies:

1. The kinetics of pigment transfer from protein carriers or biological membranes was analyzed by spectroscopic techniques;

2. The kinetics of porphyrin accumulation and redistribution between blood cells was studied by flow cytometry and fluorescent microscopy;
3. The kinetics of porphyrin accumulation and release from tissue was estimated ex vivo with several fluorescent techniques.

All measurements were carried out with chlorin-type photosensitizers (chlorin e_6, monomethyl ester of chlorin e_6, dimethyl ester of chlorin e6, trimethyl ester of chlorin e_6 and temoporphin).

The results obtained show that the dynamics of the distribution of the studied pigments differs significantly and may be of certain value when the pharmacokinetic behavior of porphyrin sensitizer is analyzed. High capacity of porphyrin binding to blood cells may change the kinetics of pigment uptake by different tissues due to decreasing of pigment activity in plasma. In addition, the parameters of plasma/blood cells partitioning may be translated into blood/vessels endothelium distribution of sensitizer. Therefore, our finding may be helpful in defining the optimal therapeutic protocol for PDT application for malignant and vasculature diseases.

The studied compounds, like most second-generation photosensitizers are insoluble in water, thus requiring special drug formulations for their injection. The developed experimental approaches have been used to compare the rates of chlorins release from lipid vesicles in model systems and in vivo [1-4]. According to the data obtained characteristic values of retention time changes in very wide range, from seconds for chlorin e6 to several hours for meta-tetra(hydroxyphenyl)chlorin. Our recent results show that the recovery kinetics may play significant role in the application of photosensitizer liposomal formulations and make possible to control of sensitizer biodistribution. Pharmacokinetic and fluorescent microscopy studies of photosensitizers distribution in several in vivo and in vitro models confirm this conclusion.

References

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