

Answer 1:

Bibliographic Information

Boundaries and possibilities in fluorescence diagnosis and photodynamic therapy of oral carcinoma. Schleier, P.; Berndt, A.; Voth, M.; Herzau, M.; Kolossa, S.; Zenk, W.; Dietel, W.; Gawellek, M.; Kosmehl, H. Klinik fuer Mund-, Kiefer- und Gesichtschirurgie, Germany. Deutsche Zahnärztliche Zeitschrift (2004), 59(5), 276-283. Publisher: Deutscher Aezrte-Verlag GmbH, CODEN: DZEEA7 ISSN: 0012-1029. Journal written in German. CAN 142:129878 AN 2004:1043691 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Protoporphyrin IX fluorescence diagnosis (PpIX-FD) of oral squamous cell carcinoma (OSCC) has a high sensitivity (96%). The limitations of the method are currently detd. by false pos. findings, the causes of which should be defined and removed prior to wide clin. application. Possible ways of increasing the sensitivity will be investigated. The sensitivity of the method demonstrated by accumulation of the photodynamically active substance protoporphyrin IX (PpIX) in tumor tissue offers the theoretic possibility of selective tumor therapy by photodynamic reactions. The objective was to investigate the effectiveness of the PpIX-based photodynamic therapy (PDT) on OSCC and to define the extent of its effect. Probandes were asked to rinse their oral cavity with 0.4% 5-aminolevulinic acid (ALA) for 20 min. After an interval of 3 h the fluorescence findings were recorded with a special CCD camera. The recorded fluorescence findings were registered in a data bank and processed for statistics. OSCC xenografts in SCID mice were used to perform interstitial ALA-PDT with laser light (water-cooled applicator system). The therapeutic effect was evaluated histol. Furthermore, it was attempted to record the therapeutic effect quant. by means of fluorodeoxyglucose positron emission tomog. (FDG-PET). Almost all oral squamous cell carcinomas exhibited an ALA-induced fluorescence in vivo. However, there were also false pos. findings. As causes the authors identified bacterial fluorescence, radiation consequences of the mucosa after therapeutic irradiation, denture stomatitis, and incorrect patient management. The foundation of photodynamic therapy of OSCC is the reliable accumulation of protoporphyrin in the tumor tissue. Exptl. PDT of OSCC in an animal model was very effective. However, the limitations for a successful use are mainly detd. by the depth of penetration of both 5-aminolevulinic acid and laser light. To achieve an adequate therapeutic success in s.c.

tumors, interstitial application of a laser stray light applicator is necessary. Thermal effects could be excluded by using an applicator system with internal cooling. This facilitates a potential ALA-PDT of invasive portions of OSCC. Up to about 3 mm in depth, necrosis around the puncture channel of the laser fiber could be demonstrated histol., 3 days after ALA-PDT. The OSCC xenografts on SCID mice could be pos. demonstrated with the FDG-PET method. However, quant. detection by means of PET of the cytotoxic effect of ALA-PDT in the early interval of 24 h after therapy was not always successful.

Answer 2:

Bibliographic Information

Macro-microscopic fluorescence imaging of human NPC xenografts in a murine model using topical vs. intravenous administration of 5-aminolevulinic acid. Manivasager, Vanaja; Heng, Paul Wan Sia; Hao, Jinsong; Zheng, Wei; Soo, Khee Chee; Olivo, Malini. Division of Medical Sciences, National Cancer Centre, Singapore, Singapore. International Journal of Oncology (2002), 21(5), 1003-1007. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 138:381505 AN 2002:850832 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The use of 5-aminolevulinic acid to induce endogenous porphyrins for the purpose of detection of epithelial cancers is being studied extensively in many centers around the world. The challenge is to prep. an efficacious formulation of 5-ALA for the purpose of cancer detection. In this study, we compared two formulations of topical 5-ALA applications with i.v. administration in NPC/CNE-2 xenografts on balb/c nude mice. One of the formulations was a gantrez muco-adhesive patch and the other was a polyvinyl-pyrrolidone muco-adhesive patch. The Karl Storz fluorescence endoscopy system was used to obtain macroscopic fluorescence images.

Microscopic fluorescence imaging was done by laser confocal microscopy. The macroscopic images were further analyzed for fluorescence intensity distribution. It was found that between the two formulations of topical application of 5-ALA; there was very little difference in the fluorescence biodistribution. When the topical applications were compared with the i.v. administration, the tumor to normal differential in biodistribution was significantly higher with the topical application compared to the i.v. application.

Answer 3:

Bibliographic Information

Antitumor effect of 5-aminolevulinic acid-mediated photodynamic therapy can be enhanced by the use of a low dose of Photofrin in human tumor xenografts. Peng, Qian; Warloe, Trond; Moan, Johan; Godal, Aslak; Apricena, Fabio; Giercksky, Karl-Erik; Nesland, Jahn M. Department of Pathology, The Norwegian Radium Hospital, Institute for Cancer Research, University of Oslo, Oslo, Norway. Cancer Research (2001), 61(15), 5824-5832. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 135:285075 AN 2001:584381 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Practically all of the exogenous photosensitizers used for clin. photodynamic therapy (PDT) target mainly vasculature. Although effective in tumor destruction, they also, unavoidably, induce phototoxicity of normal tissues. Porphyrins synthesized endogenously from 5-aminolevulinic acid (ALA) accumulate within cells. Tumor eradication would be more efficient if both cellular components and vascular stroma of a tumor could be targeted. Thus, PDT with a mixt. of ALA and Photofrin (Pf, a vessel-targeted sensitizer) may simultaneously destroy the two elements. Using chem. extn. assays, pharmacokinetics of ALA and ALA-induced porphyrins were studied in the plasma and tumors of nude mice bearing human WiDr and KM20L2 colonic carcinomas after an i.p. injection of 250 mg/kg body wt. of ALA. Subsequently, PDT efficacy of the two tumor models with ALA, Pf, or with the two drugs in combination was evaluated. The phototoxic effects on tumor cells in vitro with the combined drugs was also detd. Moreover, histol. and ultrastructural alterations of the treated tumors were investigated, and tumor cell clonogenicity was assessed as a function of time after in vivo PDT using an in vitro colony formation assay. Finally, the photosensitivity of normal skin tissue treated according to various protocols was compared. The amts. of ALA peaked at 0.5 h after administration in both plasma and WiDr tumor. The rates of ALA clearance seemed to follow a one-compartment model with half-lives of .apprx.18 and 58 min in the plasma and tumor, resp. About 100 and 60 times higher concns. of ALA were needed to induce a given concn. of porphyrins in the plasma and tumor, resp., although the plasma porphyrins may not only be released from blood cells but also from other organs. Similar kinetics of distribution patterns of ALA- and ALA methylester-induced porphyrins were found in the plasma and tumors, and the elimination rates were consistent with a two-compartment model.

ALA induced much more porphyrins than ALA methylester in both plasma and tumors. Tumors PDT-treated with ALA plus Pf at a low dose (1 mg/kg) grew significantly more slowly than those treated with either of the drugs in both WiDr and KM20L2 models. However, the enhanced antitumor effect was not found in the tumor cells under in vitro conditions. Morphol. studies demonstrated that PDT with the combined regimen resulted in necrosis of neoplastic cells and severe disruption of tumor microvasculature. This was supported by the findings obtained from the studies of in vivo PDT and in vitro clonogenic assay that showed a progressive redn. in tumor cell viability with times following PDT. Such a combined PDT protocol did not induce any phototoxicity in normal skin tissue. These data indicate that targeting both neoplastic cells and stroma with ALA and Pf (a low dose) can potentiate antitumor PDT effect with no risk of prolonged skin photosensitivity.

Answer 4:

Bibliographic Information

The effect of folic acid on porphyrin synthesis in tumors and normal skin of mice treated with 5-aminolevulinic acid or methyl 5-aminolevulinate. Ma LiWei; Steindal Arnfinn E; Juzeniene Asta; Iani Vladimir; Moan Johan Department of Radiation Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo, Norway. ma.li-wei@labmed.uio.no Photochemical & photobiological sciences : Official journal of the European Photochemistry Association and the European Society for Photobiology (2006), 5(8), 755-9. Journal code: 101124451.

ISSN:1474-905X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16886091 AN 2006462579 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

5-Aminolevulinic acid (ALA) or its derivative methyl 5-aminolevulinate (MAL) combined with folic acid was applied in nude mice bearing human colon adenocarcinoma. The aim of the study is to see whether folic acid may increase biosynthesis of porphyrins in tumor tissue after systemic or topical administration of ALA or MAL. The production of porphyrins was determined by spectrofluorometric measurements with an optical fibre probe. It was found that the porphyrin production after i.p injection of 200 mg kg⁻¹ ALA or MAL was significantly increased by i.p injection of 100 mg kg⁻¹ folic acid. However, in the case of topically applied 20% ALA, folic acid had no effect. In the case of topically applied 20% MAL, folic acid (i.p or topically applied) reduced the porphyrin synthesis. This might be used for the protection of normal skin against photosensitization. The effects of folic acid were similar in tumors and normal skin. Two mechanisms may explain the results: enhancement of the efficiency of the rate-limiting enzyme porphobilinogen deaminase by folic acid or interference of folic acid with the transport of ALA and MAL to and into the cells synthesizing porphyrins in the tissues. The present data seem to favour the latter mechanism. Folic acid may have a role as an adjuvant in photodynamic therapy with systemically administered ALA and its derivatives.