

REVIEW ARTICLE

Photodynamic therapy of cholangiocarcinoma

T. ZOEPF

*Department of Gastroenterology and Hepatology, University Hospital Essen, Essen, Germany***Abstract**

Photodynamic therapy (PDT) is a local photochemical tumor treatment that consists of a photosensitizing agent in combination with laser irradiation of a distinct wavelength. In some case reports and small non-randomized pilot studies, PDT has proved feasible in patients with hilar bile duct cancer. Those studies showed an astonishing long survival time of the treated patients. In the yet published two randomized controlled studies, PDT showed a significant extension of survival compared to sole bile duct stenting. A possible explanation for this improved survival is a suspected anti-tumor immunological effect induced by PDT. PDT reaches the same level of survival time as incomplete resection. The main complication is a high risk of severe bacterial cholangitis and liver abscesses requiring peri-interventional antibiotics. Skin phototoxicity, which at the beginning of PDT was the most dreaded potential complication, seems to play an ancillary role using mild light protection. As the available photosensitizers, mainly hematoporphyrin derivative (HPD), are not very effective in terms of depth of tumor necrosis, newer photosensitizers with light absorption in the near infrared spectrum and therefore deeper penetration depth are currently under investigation.

Key Words: *Biliary drainage, Klatskin tumor, laser, palliative therapy, photosensitizer*

Technical aspects of photodynamic therapy

Photodynamic therapy (PDT) is a local ablative method of treating dysplasia or neoplasia. It is more or less selective accumulation of a photoactive drug (photosensitizer) in tumor tissue followed by light activation of the retained photosensitizer using an adequate wavelength. The resulting tumor necrosis is based on disturbance of the microvasculature and degradation of membranes and lysosomes mediated by cytotoxic radicals, mainly singlet oxygen [1]. Hematoporphyrin derivatives (HPD; e.g. Photosan-3[®], Photofrin II[®]) have been the most commonly used photosensitizers. The depth of the ablative effect is limited by the absorption characteristics of the photosensitizer used and by the resulting penetration depth of the appropriate wavelength. The depth of tumor necrosis after HPD-PDT is therefore limited to 4–6 mm. Light activation is performed in the time frame between 48 and 96 h after systemic administration of HPD (2 mg/kg b.w.) by a quartz fiber mounted with a cylindrical diffuser tip of 2–7 cm length coupled to a dye laser or, more recently, diode laser emitting a wavelength of 630 nm. The energy

density applied varies between 180 and 240 J/cm². Light activation can be done by transpapillary access performing an ERCP or by percutaneous access performing PTC. Photosensitizers are also retained by the skin, thus leading to a certain light sensitivity and potential phototoxicity as the only known specific side effect of PDT. Using HPD, the phototoxicity lasts for 4–6 weeks in decreasing intensity. 5-Aminolevulinic acid (5-ALA) is a precursor of the endogenous photosensitizer Protoporphyrin IX, which is generated in the heme pathway. 5-ALA PDT exhibits phototoxicity of only 24–48 h with a limited tumor necrosis depth of 2 mm [2].

Clinical studies

The first report on successful PDT in bile duct cancer was a case report of a patient receiving 7 PDT treatment sessions over a survival period of 4 years [3]. Subsequent pilot studies using HPD as photosensitizer showed feasibility of PDT in patients with non-resectable bile duct cancer according to facilitate endoscopic stenting and relieving jaundice and, what is more, improvement of survival was suspected [4–6].

In a small pilot study, 5-ALA failed to show any significant effect on tumor necrosis and, therefore, in contrast to esophageal neoplasia, was judged as ineffective in bile duct cancer [2]. FDG-PET, which was thought to be an effective tool for assessing the anti-tumor effect of PDT in bile duct cancer, failed to show efficiency [7]. In a retrospective study, patients receiving PDT were compared with a historical group of patients treated with self-expandable metal stents and/or plastic prostheses. There was a trend of improved survival in the PDT group which missed statistical significance [8]. In a long-term follow-up study, patients with distant metastases showed reduced survival compared to patients without distant metastases, and most patients died due to tumor progression after stable disease initially [9]. A non-randomized study comparing percutaneous PDT + stenting with mere percutaneous stenting showed a significantly longer survival of the PDT group [10]. There are two prospective randomized controlled studies comparing PDT with biliary stenting. Ortner et al. showed superior median survival in the PDT group (493 versus 98 days; $p < 0.0001$) and improvement of Karnofski performance status [11]. This study included mainly patients who showed unsuccessful relief of bile duct obstruction with mere stenting and was therefore criticized on the grounds of potential bias [12]. Our own group confirmed the positive effect on median survival of PDT (630 versus 210 days; $p = 0.019$) in the second prospective randomized study [13], in which all non-resectable patients were randomized, especially with successful biliary drainage. Performance status did not improve, but held over the entire period of observation in the PDT group. The only specific complication of PDT is phototoxicity of the skin. In the published clinical studies, the rate of phototoxicity ranges between 0% and 25% [2,4–6,8–11,13–18]. Another reported complication is an increased risk of bacterial cholangitis and liver abscess. As this is also a potential complication of mere stenting, it is difficult to measure the extent of PDT's contribution to that complication. In our randomized study, there is a significantly higher proportion of cholangitis in the PDT group in contrast to the results of Ortner et al. [11,13].

PDT has been tried as neoadjuvant therapy to reduce preoperative local tumor extent, which showed complete tumor necrosis within a layer of 4–6 mm, but viable tumor cells in the deeper surroundings [17]. Newer photosensitizers with an absorption in the near infrared spectrum and therefore deeper necrosis, e.g. meso-tetrahydroxyphenyl chlorine (mTHPC) and bacteriochlorins, are currently under investigation [19–21]. In an uncontrolled study, adjuvant PDT of residual tumor after surgical resection in 8 patients was promising [15].

Recently, the combination of PDT with stenting showed comparable survival rates to R1 resection, but with a considerably lower complication rate [18].

Consensus statements

- Palliative PDT in bile duct cancer improves survival.
- PDT increases the risk of cholangitis and liver abscess.
- Phototoxicity of the skin is of ancillary importance.
- PDT should be confined to patients without distant metastases.
- PDT should be confined to patients with a tumor extent of ≤ 3 cm in diameter.

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