Photodiagnosis and Photodynamic Therapy 20 (2017) 276–286

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Treatment of peritoneal carcinomatosis with photodynamic therapy: Systematic review of current evidence

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ARTICLE INFO

Keywords:
Photochemotherapy
Neoplasms
Photosensitizing agents
Peritoneum
Photodynamic therapy
Peritoneal carcinomatosis

ABSTRACT

Background: Peritoneal carcinomatosis results when tumour cells implant and grow within the peritoneal cavity. Treatment and prognosis vary based on the primary cancer. Although therapy with intention-to-cure is offered to selective patients using cytoreductive surgery with chemotherapy, the prognosis remains poor for most of the patients. Photodynamic therapy (PDT) is a cancer-therapeutic modality where a photosensitiser is administered to patients and exerts a cytotoxic effect on cancer cells when excited by light of a specific wavelength. It has potential application in the treatment of peritoneal carcinomatosis.

Methods: We systematically reviewed the evidence of using PDT to treat peritoneal carcinomatosis in both animals and humans (Medline/EMBASE searched in June 2017).

Results: Three human and 25 animal studies were included. Phase I and II human trials using first-generation photosensitisers showed that applying PDT after surgical debulking in patients with peritoneal carcinomatosis is feasible with some clinical benefits. The low tumour-selectivity of the photosensitisers led to significant toxicities mainly capillary leak syndrome and bowel perforation. In animal studies, PDT improved survival by 15–300%, compared to control groups. PDT led to higher tumour necrosis values (categorical values 0–4 [4 = highest]: PDT 3.4 ± 1.0 vs. control 0.4 ± 0.6, $p < 0.05$) and reduced tumour size (residual tumour size is 10% of untreated controls, $p < 0.001$).

Conclusion: PDT has potential in treating peritoneal carcinomatosis, but is limited by its narrow therapeutic window and possible serious side effects. Recent improvement in tumour-selectivity and light delivery systems is promising, but further development is needed before PDT can be routinely applied for peritoneal carcinomatosis.

1. Introduction

Peritoneal carcinomatosis describes the dissemination and growth of cancer deposits within the peritoneal cavity. These most commonly represent secondary metastases from colorectal, ovarian, urogenital, gastric and pancreatic cancers. Less commonly, cancer deposits metastasise from melanomas or malignancies of distant organs such as the breast. Primary tumours originating from the peritoneum (e.g., peritoneal mesothelioma and primary peritoneal carcinoma) are rare [1,2].

The peritoneum has a complex anatomy with a large surface area equivalent to that of the external body [3]. Peritoneal cancer deposits can be extensive [4] and cover vital intra-abdominal structures (e.g., small bowels, liver and great vessels) [3]. Peritoneal carcinomatosis can occur in the absence of haematogenous or lymphatic metastases [5], causing local complications, including ascites and bowel obstruction [4].

The therapeutic modalities and prognosis vary widely depending on the origin of the primary cancer. Whilst some patients are treated with intention to cure, most patients have a poor prognosis and therapies are aimed at palliative symptom control.

Patients with pseudomyxoma peritonei or appendiceal neoplasia with peritoneal metastases can be treated with cytoreductive surgery and heated intraperitoneal chemotherapy with reasonable outcomes (median survival 196 months) [6]. Peritoneal carcinomatosis of ovarian origin can be treated with intention to cure in selected patients who are fit for major surgery with acceptable perioperative morbidity [7,8]. For selected patients, cytoreduction surgery, which aims to resect all macroscopic disease, is performed before or after chemotherapy (median survival 22–64 months) [9]. Peritoneal carcinomatosis secondary to gastrointestinal cancers (e.g. gastric or colorectal) have a poor prognosis even in the selected patients where cytoreductive surgery and heated intraperitoneal chemotherapy is attempted (median survival 8 and 7–19 months for gastric and colorectal, respectively) [10–12]

Photodynamic therapy is a therapeutic anti-cancer modality that

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https://doi.org/10.1016/j.pdpdt.2017.10.021
Received 11 July 2017; Received in revised form 11 October 2017; Accepted 26 October 2017
Available online 27 October 2017
1572-1000/

has been used to treat many cancers, including oesophageal, skin and lung cancers [13]. A photosensitiser is administered that more rapidly accumulates in malignant compared to non-malignant tissue. A ground state photosensitiser is activated to a higher energy active triplet state when exposed to light of a particular wavelength. Decay of the active triplet state releases energy in the form of electrons to generate toxic singlet oxygen ($^1O_2$) and reactive oxygen species. These products mediate tumour cell toxicity, microvascular damage [14] and anti-tumour immune responses [13,15–17].

In 1986, Tochner et al. investigated the use of photodynamic therapy in a peritoneal carcinomatosis murine model. They reported a high cure rate of 85% [18]. This encouraged further research into the use of photodynamic therapy in peritoneal carcinomatosis over the next three decades [13]. Preliminary evidence suggests that photodynamic therapy might improve the outcomes of peritoneal carcinomatosis management and provide an effective modality alongside other therapeutic options.

This article is the first attempt to systematically review all existing evidence concerning the use of photodynamic therapy in treating peritoneal carcinomatosis. Given the limited evidence in human disease, we included animal studies to create an overview of the entire knowledge base.

2. Methods

2.1. Criteria for study inclusion

2.1.1. Studies

All original peer-reviewed comparative and non-comparative studies of any type were included. Conference proceedings were excluded.

2.1.2. Participants

Patients or animal models with peritoneal carcinomatosis of any origin were included. Peritoneal carcinomatosis was defined by having more than one intraperitoneal nodule (disseminated model). Animal models where only one solid mass was obtained and those where seeding was performed outside the peritoneal cavity (e.g., flanks) were excluded.

2.1.3. Interventions

All studies that used any type of photodynamic therapy, with or without other modalities, to treat cancerous nodules within the peritoneum were considered. In vitro studies were excluded.

2.1.4. Primary outcomes

- Survival
- Adverse effects

2.1.5. Secondary outcomes

These outcomes measured the local pathological tumour response to the treatment:

- *Nodule necrosis*: this represents the proportion of tumour mass which is found to be necrotic. A = mild (< 1/3 of the tumour mass), B = moderate (1/3–2/3 of the tumour mass), C = strong (> 2/3 of the tumour mass).
- *Tumour size*: in order to estimate the tumour size, some studies used bioluminescence imaging which assesses the luciferase activity in cancer cells that stably express luciferase. Other studies tagged cancer cells with green florescent protein before seeding them into animal models. The fluorescence intensity was used to estimate tumour size.
- *Mean percentage of tumour burden*: this equals the mean tumour burden of the treatment group divided by the mean tumour burden of the control group (mean tumour burden per group was calculated by subtracting the weight of organs in a third group of healthy animal from the weight of organs in the tumour animal model).
- *Experimental peritoneal cancer index*: this index divides the abdominal cavity into four quadrants and each quadrant is given a score of 0–5 based on the size of tumour in it (0: no tumour is visible, 1: tumour is 0–0.5 cm, 2: tumour is 0.5–1 cm, 3: tumour is 1–2 cm, 4: tumour is 2–3 cm, 5: tumour > 3 cm). The results of all four quadrants are summated giving an experimental peritoneal cancer index score of 0–20.
- *Necrosis value*: this is determined by the depth of the necrotic area in the specimen in relation to the full tumour thickness (score = 0: no necrosis, score = 1: necrosis up to 33%, score = 2: necrosis is 33–66%, score = 3: necrosis is 66–99%, score = 4: necrosis is 100%) for each sample of the illuminated peritoneum [19]. 'Response' is defined as having a necrosis value of 3 or 4. 'Insufficient response' is defined as having a necrosis value of 0–2.

2.1.6. Search strategy

Literature searches were performed in both MEDLINE and EMBASES databases (June 2017) to identify both animal and human studies investigating the use of photodynamic therapy in peritoneal carcinomatosis of any origin. The used search terms were ("photodynamic" OR "photochemotherapy" OR "phototherapy" OR "photoradiation" OR "photoimmunotherapy" OR "fluorescen*") AND "peritone*", in any field. The search was restricted to articles written in English.

2.1.7. Study selection

The selection process was divided into two phases. In the initial phase, the titles and abstracts of all citations located through the electronic search were scanned to identify potentially relevant articles to the eligibility criteria. The full texts of the relevant articles were obtained in the second phase and assessed for inclusion or exclusion. The selection process was performed independently by two authors (MQA and GG). Only studies that fulfilled the eligibility criteria were included. In cases of disagreement, a consensual decision was made following discussion of the full manuscript. The references of the 'relevant articles' were checked for any additional relevant articles.

2.1.8. Risk of bias assessment

The risk of bias in the included studies was determined using an assessment tool modified from the Cochrane Collaboration assessment tool for interventional studies [20,21]. This included 10 elements (i. randomisation, ii. concealment of allocation, iii. blinding of assessors, iv. sample size calculation, v. statistical model description, vi. description of subjects, vii. disclosing financial support, viii. incomplete outcome data, ix. detailed description of intervention and x. description of housing and nutrition conditions for animals in preclinical studies). The answers to the above elements were either 'yes' if the area was well covered in the article or 'no' if the element was not reported.

3. Results

3.1. Description of studies

Fig. 1 summarises the process for identifying studies. Twenty eight studies were included in this review: three human studies (11 citations) [3,22–29] and 25 animal studies [18,19,30–52].

Twenty seven studies were excluded. Reasons for exclusion were: non-tumour bearing animal model [27,53–58], no disseminated peritoneal carcinomatosis model (tumour cells injected in the flanks [59] or subcutaneously [60,61] or only a single intraperitoneal tumour [62]), no photodynamic therapy given (photosensitiser only [53,63] or light only [64]), no useful clinical outcomes [64–70], conference abstracts (no full texts) [71–76] and mixed populations and interventions (results are not broken down by intervention) [77].