Intrapleural Photodynamic Therapy for Mesothelioma: What Place and Which Future?

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In the surgical multimodal management of malignant pleural mesothelioma, it seems crucial to proceed with an efficient local adjuvant treatment to kill residual tumor cells. Intrapleural photodynamic therapy has recently emerged as a potential candidate in this goal. In this review, we analyzed and classified 16 articles in which patients with malignant pleural mesothelioma received intrapleural photodynamic therapy after maximal surgical resection. The toxicity, effect on survival, and development of the technique were assessed. After two decades of clinical studies, intrapleural photodynamic therapy after surgical resection became a safe treatment that significantly improved the survival of patients.

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Malignant pleural mesothelioma (MPM) is an aggressive serosal tumor of the pleura. Its main etiologic agent is an exposure to asbestos fibers, mostly work-related, and the disease appears after a latency of 30 to 40 years after initial exposure. MPM is considered as a rare tumor; however, its incidence is rising throughout the world because of the increasing use of asbestos until the 1970s and will peak in the next decade. We also fear a pandemic rise of MPM in the future, with developing countries still using asbestos today.

The three main histologic subtypes of MPM are epithelial, biphasic, and sarcomatoid. MPM has a poor prognosis, with a median survival of less than 1 year. This can be explained by the delay of diagnosis due to late clinical symptoms, with a disease already advanced locally, the difficulty of obtaining a confident anatomopathologic diagnosis, and a complex treatment with deceiving outcomes.

Current Treatments for MPM

Treating MPM remains a challenge, and there are two main alternatives: palliative chemotherapy or multimodal treatment including surgical resection combined with chemotherapy or radiotherapy, or both [1]. Surgical resection offers the best chance of survival, and surgical cytoreduction should be performed when macroscopic complete resection is deemed achievable [2]. However, microscopic tumor cells persist after the most complete tumor resection, and resection should be associated with a local adjuvant treatment.

There are two leading types of surgical procedure for the treatment of MPM: extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D) or radical pleurectomy. EPP consists of an en bloc resection of the lung, visceral and parietal pleura, pericardium, and diaphragm, whereas P/D preserves the lung and is therefore less disabling. A modified EPP attempts to preserve the barriers of the peritoneum, pericardium, abdomen, and phrenic nerve to the diaphragm. P/D is defined by the resection of the visceral and parietal pleura, and is referred to "extended P/D" when the pericardium or the diaphragm, or both, are resected [3]. Pleurectomy associated with a lobectomy (P/L) is also a possibility.

Even after an optimal operation and perioperative chemoradiotherapy, local or distant recurrences are inevitable. Many teams have worked on intrapleural therapies, such as hyperthermic cisplatin-based chemotherapy, immunotherapy, or gene therapy, to kill the residual microscopic disease [4]. In search of a more effective and selective adjuvant treatment to resection, and in line with these intrapleural therapies, intraoperative photodynamic therapy (PDT) could be of interest as part of a multimodal treatment for MPM.

Photodynamic Therapy

PDT became acknowledged as an innovative oncologic treatment in the 1970s by Dougherty and colleagues [5]. The effect of PDT requires the interaction of three components: a photosensitizer (PS), oxygen, and light with the specific wavelength activating the PS. None of these are individually toxic, but when combined they induce a tumoricidal photochemical reaction (Fig 1). The PSs used in the treatment of MPM are porfimer sodium Photofrin (Axcan Pharma, Birmingham, AL) and m-tetrahydroxyphenylchlorin (m-THPC) Foscan (Biolitec Pharma Ltd, Vienna, Austria). The effect of PDT depends on the type and dose of the PS used, the light

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Abbreviations and Acronyms

CI = confidence interval
DFS = disease free survival
DLI = drug light interval
EPP = extrapleural pneumonectomy
MPM = malignant pleural mesothelioma
m-THPC = m-tetrahydroxyphenylchlorin
OS = overall survival
P/D = pleurectomy decortication
P/L = pleurectomy and lobectomy
PDT = photodynamic therapy
PS = photosensitizer

dose, and the oxygen concentration in the tissue illuminated. The appeal of PDT as an adjuvant treatment relies on its relative tumor selectivity, depending on a PS able to direct itself and stay longer in the tumor cells than in healthy cells, and an illumination restricted to the cancer superficial zone. Intrapleural PDT is a two-stage process: (1) preoperative intravenous administration of the PS with a specific drug dose and drug-light interval (DLI) and (2) intraoperative illumination of the pleural cavity, after maximal resection of the tumor, by a laser source at an appropriate wavelength and reaching a specific light dose (J/cm^2).

MPM is essentially confined to the hemithorax at diagnosis, which would make an efficient surgical treatment all the more valuable. PDT is a preoperative local treatment, used successfully in other medical fields, so it seems legitimate to consider intrapleural PDT as a valid candidate to eradicate the microscopic tumor cells remaining after surgical resection. For a few decades, PDT has been the subject of many studies as part of a multimodal treatment of MPM with resection. A review by Moghissi and Dixon [6] reported the results of 10 of these studies, published between 1994 and 2004. They considered PDT as a treatment with potential but needing

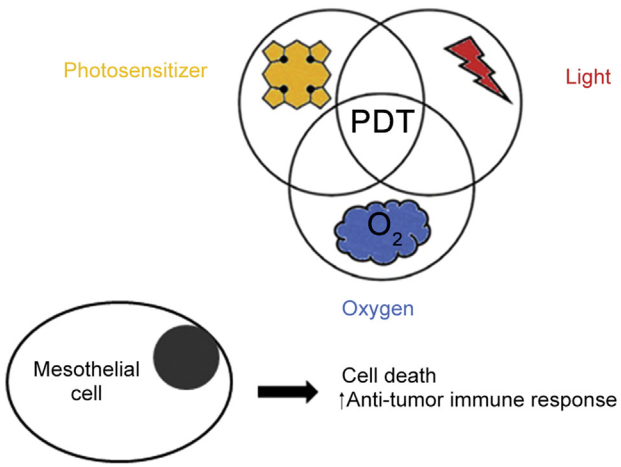

Fig 1. Photochemical reaction of photodynamic therapy (PTD).

further improvement and clinical investigation. The aim of our review was to get a wider overview of this developing technique from its early days up to the present day by exposing its various clinical applications in the surgical management of MPM as well as its evolution through the years regarding toxicity and effect on survival.

Material and Methods

Articles were researched on PubMed, EM-Premium, and ScienceDirect, using the key words "malignant pleural mesothelioma," "pleural malignancies," "photodynamic therapy," "multimodal treatment," "surgery," "pneumonectomy" and "pleurectomy." Exclusion criteria were letters, editorials, case reports, experimental studies on animals, and studies without enough specific data on PDT or surgical treatment. The inclusion criteria were clinical studies focusing only on intrapleural PDT after surgical resection, studies with results on the toxicity of this treatment or posttreatment survival, and articles written in English. These studies were classified between two categories: "feasibility and toxicity studies" and "survival studies." Further research was made when general information was considered useful to the reader.

Results

Sixteen articles published between 1991 and 2012 were selected for this review and are reported in Table 1. Eleven studies were described as "feasibility and toxicity studies" and aimed at finding the most optimal dose of PS, DLI, and light dose. Five studies were classified as "survival studies," among which there were two phase III studies and three retrospective studies with a focus on survival.

The studies included 337 patients. Treatment consisted of a debulking operation of variable degree, after administration of m-THPC (20% of patients) or a hematoporphyrin (80% of patients), followed by intraoperative PDT. Surgical treatment consisted of EPP, P/L, and P/D for, respectively, 41.5%, 5%, and 53.5% of patients. All causes of morbidity and death in these studies during thoracic operations and intrapleural PDT are listed in Table 2.

Feasibility and Toxicity Studies

Between 1991 and 2001, a Swiss and Dutch team published four studies [7–10] using m-THPC Foscan and a light at a 650-nm wavelength. The first study [7] included 4 patients with MPM. Preliminary PDT was performed in 2 patients under different PDT conditions, and biopsies of tumor were taken after 5 days. A 10-mm-deep tumor necrosis was observed at a Foscan drug dose of 0.3 mg/kg, given 2 days before PDT and at a light dose of 10 J/cm^2. Resection and intraoperative PDT were then performed: light was delivered through a bare optical fiber directly into the cavity at a light dose of 10 J/cm^2 to the diaphragm and costophrenic sulcus. A dose of 5 J/cm^2 was applied to the rest of the cavity. One patient died of aspiration