Review

Multimodality approach in management of malignant pleural mesothelioma

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Summary

Malignant pleural mesothelioma (MPM) is a solid, locally aggressive tumor, which has been closely linked to asbestos exposure. The survival rate without treatment ranges from 4 to 12 months. Response to chemotherapy and radiation is poor, and surgery is the most effective therapy. There are currently 3000 new MPM cases per year in the United States, with the peak incidence in the United States and Europe expected to occur in the year 2020. The prognosis depends on the stage of the tumor at the time of diagnosis, its histological type, lymph node status, and resection margins. While the diagnosis is often delayed, earlier intervention may improve life expectancy. Single-modality therapy has not been effective in changing the natural history of MPM. As a result, multimodality regimens involving surgery with radiation, chemotherapy, or immunotherapy have been initiated. Multiple modality approach has demonstrated favorable outcome, particularly in patients with epithelial histology, negative resection margins and presence of no metastases to extrapleural lymph nodes. Cisplatin and mitomycin have demonstrated modest efficacy in management of distant tumor recurrence. Cisplatin and gemcitabine regimen as well as cisplatin/pemetrexed followed by 54 Gy of adjuvant hemithorax radiation have been reported to improve the outcome.

Keywords: Multimodality treatment; Chemotherapy; Radiation; Supportive care; Immunotherapy; Gene therapy; PDT; Antiangiogenic therapy

1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive disease of the pleura. This rare tumor affects predominantly men over 50 years of age (male to female ratio 3:1) and is associated with a long latency period (20—40 years) between exposure and expression of the disease. As a consequence of the long latency between the asbestos exposure and tumor manifestation, the incidence of MPM will continue to rise in the next 15 years. Without treatment, it is associated with a poor median survival, ranging from 4 to 12 months [1]. The clinical presentation of MPM is highly variable. It is a unilateral disease in 95% of cases, occurring predominantly on the right side (60% of cases) [2]. Patients in early stages of the disease present with a range of symptoms including dyspnea, chest pain, fever, and pleural effusion. Advanced stages are characterized by weight loss, ascites, or chest wall deformity. The time period between presentation and diagnosis is usually 2—5 months and a delay in establishing a definitive diagnosis reduces the median survival.

Difficulty in diagnosing and staging of the disease in early stages, and the short period of time between diagnosis and death, has thwarted the development of a universally accepted stage-related standard approach [3]. Initial approaches to therapy of MPM with single modality treatment regimens involving surgery versus radiotherapy versus chemotherapy failed to prolong the survival of patients. As a result, different multimodality regimens have been proposed. To date, only multimodality regimens employing extrapleural pneumonectomy (EPP) followed by adjuvant chemoradiation have demonstrated prolonged survival [2,4,5]. The prognosis of disease depends on performance status, age, histology, and hematological parameters [6,7]. However, the mode of treatment and clinical classification are independent prognostic factors for patients with MPM [8].

Although each individual modality has had limited success by itself, a multimodality approach has been reported to improve survival and quality of life [9]. An encouraging 45% 5-year survival rate has been reported by Sugarbaker et al. [5] for a subgroup of patients with early-stage disease, epithelial histology [5]. Efforts to decrease the risk of local recurrence after EPP and pleurectomy/decortication (P/D) have included the use of intrapleural and intravenous chemotherapy, brachytherapy, and external beam radiation therapy. None of these adjuvant treatment trials was randomized. For patients who have undergone EPP, the pattern of recurrence is predominantly a combination of local and distant failure. The recently available chemotherapy agents or other intrapleural...
agents may offer better outcome. Advances in local therapy also may decrease the rate of abdominal recurrences. True distant recurrences remain less common [10]. The lowest rate of local recurrence (13%) with a 4% local-only recurrence rate was seen in the study by Rusch et al. [11] using 54 Gy hemithorax radiation as adjuvant therapy. This is the lowest rate of local recurrence after EPP that has been reported. Baldini et al. [3] reported a 50% local recurrence rate, with a 13% local-only rate, after trimodality therapy. In the study by Rusch et al. [11], distant failures predominate indicating the need for systemic chemotherapy, which should be administered either as neoadjuvant and/or adjuvant therapy. Any review of treatment efficacy based on observed patterns of failure may suffer from treatment selection biases. No randomized trials evaluating the various surgical or adjuvant therapeutic approaches have been performed [10].

Other therapeutic options including intrapleural chemotherapy, photodynamic therapy, gene therapy, immunotherapy, and vaccination have demonstrated some benefits, but have yet to be evaluated for their efficacy [12].

2. Multimodality treatment

Failure of single modality treatments to increase survival has led to a multimodality approach to treat MPM. Various multidisciplinary approaches, including EPP or P/D with complementary chemotherapy, radiotherapy, and local or systemic immunotherapy have focused on the control of the locoregional recurrence. Radical debulking surgery, radiotherapy, and adjuvant chemotherapy are the corner stones of multimodality treatment [13]. EPP is the most appropriate strategy for providing radical cytoreduction. Adjuvant chemotherapy is currently being administered 4–6 weeks after the operation [14].

In 1999, in a series of 176 patients, Sugarbaker et al. [5] reported that the significant factors influencing survival include histological subtype, lymph node involvement, resection margins, and invasion beyond the pleura [5]. A subgroup of patients with the epithelial histology and stage I disease (according to staging system of Brigham and Women’s Hospital/Dana Farber Cancer Institute) with negative lymph nodes had a median survival of 51 months, while patients with sarcomatous type and N2 disease had a much less favorable prognosis [5]. Baldini et al. [3] reported that the multimodality treatment can reduce systemic recurrence and influence natural history of MPM. In patients who cannot undergo EPP, cytoreduction can be achieved with P/D. These patients receive chemotherapy and eventually radiotherapy regimens similar to those provided after EPP [15].

Historically, the indication for pleurectomy includes early stage disease to spare the lung. However, convincing data showing prolonged survival after EPP made this approach the preferred therapy for MPM in some centers. Pleurectomy is offered to patients with more advanced disease, where a radical debulking will be impossible [16–19]. Further indication for pleurectomy includes diminished performance status, cardiopulmonary compromise, elderly and multimorbid patients with diminished forced expiratory volume in one second (FEV1), who would not tolerate an EPP [20,21]. A preoperative assessment should be performed to evaluate if the patient is a proper candidate for the kind of therapy including pleurectomy, extrapleural pneumonectomy, or supportive/palliative therapy. The overall performance status, predicted postoperative lung function, and preoperative cardiac function affect the therapeutic strategy. A myocardial infarction in the last 3 months and a history of life-threatening arrhythmia are contraindications for an extrapleural pneumonectomy [22] emphasizing the role of pleurectomy in these patients. A preoperative echocardiography can evaluate the left ventricular function, presence of pulmonary hypertension, and mediastinal as well as pericardial invasion. It also assesses the baseline cardiac function, which has to be monitored for possible cardiac toxic effects of some chemotherapy regimens. A PFT and arterial blood gas (ABG) analysis can be helpful to assess the pulmonary reserve. A quantitative ventilation–perfusion scan (VQ), which has been recommended for mesothelioma patients undergoing extrapleural pneumonectomy, can help to assess the postoperative FEV1 [23]. Computed tomography (CT) and magnetic resonance imaging (MRI) are crucial for the staging and evaluation of resectability of the tumor [24]. The technical aspects of EPP has been described in the literature [25]. The goal of this procedure is to remove all structures with any evidence of tumor invasion [23,26]. In some cases, such as with stages Ib, II, and III, a partial removal of the chest wall might be necessary [27]. Despite the aggressive nature of EPP, it is the best palliative approach to improve dyspnea and orthopnea as a result of ventilation–perfusion mismatch in a trapped lung [23]. Further, after removal of the affected portion of the lung, higher doses of radiation can be applied to the hemithorax. However, anatomic differences between the right and left approach should be taken into account. The assessment of the aorta is important, as it can be the determining factor in the resectability of the tumor. After the removal of pericardium on the left side, a reconstruction is not routinely performed. The risk of herniation of the heart to the left side is very low; however, the physicians should be aware about this complication of EPP. Some institutions recommend reconstruction with a biodegradable material; however, there is no published data in the literature. Given the smaller size of the left hemithorax, less air has to be aspirated from it at the end of the operation (500 cc in women and 750 cc in men). The average blood loss is estimated to be between 500 and 750 cc. Hemostasis is critical, as postoperative bleeding is associated with high morbidity [25]. The major disadvantage of EPP is its impact on the cardiopulmonary system, making an adequate preoperative cardiac function as well as high capacity of remaining lung mandatory for this procedure. Patients eligible for this treatment strategy are being evaluated on the basis of spirometry, oximetry, arterial blood gas (ABG), computed tomography (CT), magnetic resonance imaging, ventilation–perfusion scan and echocardiography. The exclusion criteria are predicted postoperative forced expiratory volume in one second of <1 L, preoperative CO2 > 45 mmHg, PaO2 < 65 mmHg, left ventricular ejection fraction (EF) < 45%, Karnofsky performance score < 7, transdiaphragmatic, chest wall, or contralateral invasion of tumor on CT and/or MRI, presence of significant systemic disease or inadequate functional status. Postoperative care is essential to prevent atelectasis, deep vein
thrombosis (DVT)/pulmonary embolus, and fluid overload leading to pulmonary edema (fluid restriction 1 L/day).

3. Perioperative mortality

Some of published series have demonstrated a high perioperative morbidity and mortality [12]. Butchart et al. [12] reported a mortality of 30% for EPP; other studies in the 1970s had similar results. Since then, several series at large academic centers have established that the operation can be done with mortality rates of less than 10%. Rusch and Venkatraman [28] studied the factors influencing the outcome after resection of malignant pleural mesothelioma in 174 patients; 115 patients had extrapleural pneumonectomy and 59 pleurectomy/decortication. Among patients having EPP or P/D, 142 received adjuvant therapy. The median survival for stage I tumors was 29.9 months, for stage II 19 months, for stage III 10.4 months, and for stage IV 8 months. The authors did not differentiate between pleurectomy and extrapleural pneumonectomy with regard to overall survival; however, they concluded that there is no difference in survival between the two surgical approaches. The stage of disease, histology, gender, and adjuvant therapy had an impact on survival (Table 1) [28]. Martin-Ucar et al. [29] reported a mortality rate of 7.8% in his series of 51 patients and Maggi et al. [30] reported a perioperative mortality of 6.25 in 32 patients. Sugarbaker et al. [14] reported in 1992 an operative mortality of 45%; however, the difference was not statistically significant. Postoperative radiation was found to provide any effective palliation, while higher doses can be palliative [36]. The Joint Center for Radiation Therapy in Boston confirmed that a dose of at least 40 Gy is necessary for palliation [37]. After pleurectomy, the dose of radiation must be limited to 20 Gy unless it will affect the remaining lung.

Following EPP, most recurrences (67%) occur in the ipsilateral hemithorax [3]. Radiation following pneumonectomy reduces the local recurrence rate. Baldini et al. demonstrated that 31% of patients treated with radiation had a local recurrence, while the recurrence rate without radiation was 45%; however, the difference was not statistically significant. Postoperative radiation was found to benefit patients with positive resection margins, while those with negative margins did not show any decrease in local recurrence after postoperative radiation [3]. Higher doses of radiation have been recommended by Yajnik et al.

4. Radiation therapy

The radiosensitivity of mesothelioma cells is modest [34]. The effectiveness of radiation therapy in the treatment of MPM is limited by the diffuse nature of the tumor and by the radiosensitivity of adjacent vital structures. Radiation limit of adjacent vital structures includes lung (20 Gy), liver (30 Gy), spinal cord (45 Gy), heart (45 Gy), and esophagus (50 Gy). Radiation pneumonitis and esophagitis are not infrequent complications, while myelitis and hepatitis are less common [35].

Successful palliation with radiation only has been demonstrated in small groups of patients. An effective palliation generally requires the application of greater than 40 Gy to the hemithorax. A radiation of less than 40 Gy does not provide any effective palliation, while higher doses can be palliative [36]. The Joint Center for Radiation Therapy in Boston confirmed that a dose of at least 40 Gy is necessary for palliation [37]. After pleurectomy, the dose of radiation must be limited to 20 Gy unless it will affect the remaining lung.

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A median radiation dose of 54 Gy (range: 45–54 Gy) after extrapleural pneumonectomy demonstrated excellent local control. The radiation therapy targeted the entire hemithorax, including the pleural folds, the thoracotomy, and chest tube incision sites. The authors concluded that EPP followed by high-dose radiation of hemithoracic can be well tolerated by patients with malignant mesothelioma [11,38]. The major complications were fatigue and esophagitis, as well as an esophageal fistula in one case. For the patients undergoing extrapleural pneumonectomy (n = 75), the sites of recurrence were locoregional in 2, locoregional and distant in 5, and isolated distant recurrence in 30. Considering the high rate of distant recurrence, the authors recommended that systemic chemotherapy should follow resection and radiation [11]. Rosenzweig et al. [39] reported in their phase II trial about high-dose-rate intra-operative radiation therapy (HDR-IORT) in seven patients after extrapleural pneumonectomy and six patients after pleurectomy/decortication. A median of three sites were treated with a dose of 1500 cGy to each site, with 1000 cGy delivered to the mediastinum followed by postoperative external beam radiation therapy 3–5 weeks later. Serious complications requiring further intervention occurred in 50% of patients in EPP group and 20% of patients in pleurectomy group. The authors did not recommend HDR-IORT due to its toxicity [39].

Most recently, the intensity-modulated radiation therapy (IMRT) has been suggested by some authors, which might have the potential to overcome the geometric/dosimetric constraints [40,41]. In a small series of seven patients, the radiation was applied with intensity-modulated radiation therapy to the hemithorax following extrapleural pneumonectomy. No serious toxicity was observed during the therapy [40,41]. Radiation is also effective in prevention of local recurrence after thoracenteresis or thoracoscopic biopsy. A prospective randomized trial of radiation, delivered to needle biopsy and thoracoscopy port sites, showed that none of the 20 patients after radiation had site metastases, while 8 of the 20 control patients developed such metastases. Treatment within 15 days of the procedure was required [42].

5. Chemotherapy

Sensitivity of mesothelioma to chemotherapy is modest. No single agent has been shown to have an effect on overall survival. As single agents, some of the antimetabolites, anthracyclines, and platinum compounds appear to be active. Solheim et al. [43] demonstrated in a phase II study (n = 63) a response rate of 37% for antimetabolite methotrexate given at a dose of 3000 mg every 10 days combined with leucovorin. Toxicity was observed in 58% of patients. The platinum-based agents, cisplatin and carboplatin, have response rates of 14 and 11%, respectively. Carboplatin at a dose of 400 mg/m² every 4 weeks is better tolerated than cisplatin without any difference in response rate [44]. A trial combining three of the more active chemotherapeutic agents (cisplatin, doxorubicin, and mitomycin C) resulted in a response rate of 21%, which is not better than any of the single agents alone. In a Cancer and Leukemia Group B (CALGB) randomized trial of combined cisplatin and doxorubicin versus cisplatin and mitomycin, each combination demonstrated a response rate of only 13% [45]. Gemcitabine, a pyrimidine antimetabolite, achieves no response if applied as a single agent, while its combination with cisplatin shows increased response. A regimen of cisplatin 100 mg/m² followed by gemcitabine at 1000 mg/m² for a total of six cycles resulted in an initially promising response rate of 48%. Major side effects included nausea and vomiting in 21% and leucopenia in 36% [46]. The combination of cisplatin and irinotecan (CPT-11) showed a modest 1-year overall survival rate of 38.5% [47]. Pinto et al. [48] introduced MMM regimen (n = 22 patients) including mitoxantrone, methotrexate, or mitomycin in alternate cycles. They reported an overall response rate of 31.8%. The dyspnea improved in 68.4% of patients, and pain in 33.3%. Decreased pleural effusion was observed in 15 of the 19 patients (78.9%), who presented with pleural effusion at the time of diagnosis [48]. A combination of interferon and doxorubicin showed a response rate of 29%. Severe side effects such as myelosuppression, anemia, and thrombocytopenia may limit application of this regimen [49].

Recently, pemetrexed (Almita) has been introduced for the treatment of malignant mesothelioma. This antifolate agent inhibits the enzymes, thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase [50]. Toxic side effects of the drug can be minimized with simultaneous supplementation of folic acid and Vitamin B12. This supplementation does not diminish the drug efficacy, and in many cases, may improve clinical outcome [50]. The combination of pemetrexed and cisplatin showed a significant response rate of approximately 50% in patients with the epithelial subtype of MPM [51]. Hughes et al. [52] reported the maximum tolerated dose for pemetrexed to be 500 mg/m². The combination of pemetrexed with carboplatin was well tolerated with a good response rate. The major toxicity was short lasting neutropenia [52]. In a phase III trial [53], comparing the efficacy of pemetrexed and cisplatin combination versus cisplatin alone, 456 patients with no prior therapy were enrolled; 226 patients received pemetrexed and cisplatin, 222 patients received cisplatin alone, and 8 patients did not get any therapy, serving as the control group. Median survival varied from 12.1 months after pemetrexed/cisplatin therapy versus 9.3 months in the control group. The pemetrexed/cisplatin combination achieved a response rate of 41.3%, significantly higher than the response of 16.7% in control group.

Weder et al. [54] enrolled 19 patients with potentially respectable MPM in a neoadjuvant protocol with cisplatin and gemcitabine followed by extrapleural pneumonectomy with or without radiation. Neoadjuvant chemotherapy consisted of three cycles of cisplatin 80 mg/m², given every 28 days. The response rate to neoadjuvant chemotherapy was 32%. The median survival time was 23 months. EPP could be safely performed after neoadjuvant chemotherapy in 16 of the 19 patients [54]. However, the authors did not report about the histological type, which could be assumed to be epithelial. The survival in their series is not significantly better than any series without any neoadjuvant therapy; however, the benefit of neoadjuvant therapy deserves further investigation. Further, the neoadjuvant chemotherapy might be associated with postoperative acute lung injury and mediastinal shift [32]. Recently, Fennell et al. [7] evaluated the efficacy of
vinorelbine and oxaliplatin in 26 patients without any prior therapy, who received this regimen for up to six cycles. The overall response rate was 23% and the overall survival was 8.8 months. There was no survival benefit, and the regimen was associated with significant toxicity. Porta et al. [55] evaluated 14 patients in a phase II trial with raltitrexed—oxaliplatin combination. The median survival was only 14 weeks and the trial was terminated because of poor objective responses [55].

In a recent phase II multicenter study conducted by Cancer and Leukemia Group B, the efficacy of irinotecan was evaluated. Thirty-three percent of patients had stable disease and 52% were shown to have progressive disease at the first reassessment with no complete or partial responders. Median survival was 9.3 months, and 1-year survival was estimated to be 46%. Toxicity was moderate to severe in 28% of patients, including lymphopenia in 43% and diarrhea in 18%. Three patients died because of treatment-related toxicities. The authors concluded that irinotecan as a single agent has considerable toxicity in patients with malignant mesothelioma with no anti-tumor activity [56].

6. Conclusion

Malignant pleural mesothelioma remains a diagnostic and therapeutic problem. The aggressive and diffuse nature of this disease makes it difficult for a single modality treatment to result in a significant improvement in survival. Cell type, nodal involvement, and transdiaphragmatic invasion are important prognostic factors. Multimodality treatment for MPM is becoming a more common, safe and effective approach, and provides a significant benefit and better outcome in selected patients. On the other hand, the disease continues to demand new and more effective alternatives in a combination multimodality treatment. Novel therapeutic options such as chemoimmunotherapy, angiogenesis inhibitors, and vaccines need further investigation before they can be included in adjuvant regimens. These potential strategies may show some improvement in clinical outcomes and prolong the mean survival. At the present time, a multimodality approach including aggressive cytoreduction followed by chemo/radiation is the best approach. However, the appropriate multimodality approaches most likely will differ based on disease stage, histology, and patient performance status.

References


