Review Article

The role of intracavitary therapies in the treatment of malignant pleural mesothelioma

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Abstract: Surgery is one of the steps of multimodality approach for the treatment of MPM. Due to anatomical features, microscopically radical (R0) resection is never possible and a Macroscopic Complete Resection (R1) is considered the target for mesothelioma surgeons. Recently, intracavitary therapies have been described with the aim of extending the loco-regional effect of surgery. Different agents might be administered intrapleurally: chemotherapy drugs are the most widely used, but also photodynamic therapy (PDT) showed to lead to satisfactory long-term outcomes; furthermore, immunotherapies and gene therapies have been also reported. Despite promising results, no high-quality evidences are currently available and controlled randomized trials are required to establish the exact role of intracavitary therapies and to standardize the technique.

Keywords: Malignant pleural mesothelioma (MPM); multimodality treatment; surgery; intracavitary therapy

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Introduction

Malignant pleural mesothelioma (MPM) is a rare disease with a frequently fatal prognosis, strictly related to asbestos exposure (1). To date, there is not a standard of care that might lead to satisfactory long-term outcomes; the association of cisplatin and pemetrexed as systemic therapy showed to give a survival advantage in a prospective randomized trial, while the MARS trial demonstrated a possible detrimental effect of ExtraPleural Pneumonectomy (EPP) after neoadjuvant chemotherapy compared with chemotherapy alone (2). Nevertheless, results are still based on a large quantity of low-quality and retrospective evidences that make conclusions inconsistent. Consequently, to date, several different multimodality approaches combining surgery, chemotherapy and/or radiotherapy in different setting are commonly used in the treatment of MPM (1).

Surgery can play different roles in the management of MPM; it can be used for staging or palliative purpose or it might be performed as a part of a multimodality treatment (1,3) with radical intentions, while the use for recurrence is anecdotal and reserved to highly selected patients(4).

Recently, the use of lung sparing approaches (extended pleurectomy decortication, EPD; or pleurectomy decortication, P/D) is gaining more and more consensus (5) as it allows to considerably reduce postoperative complications and can extend the possibility of a surgical approach also for older people or those with a partially impaired lung function (1). Nevertheless, anatomical borders of the pleura prevent the possibility of a microscopically radical resection with disease-free margins (R0), and Macroscopic Complete Resection (R1) is to date considered the target of a surgical resection (6).

Intrathoracic therapies

With the aim of improving the local effect of surgery, additional intraoperative loco-regional treatments have been proposed. The rationale behind these intracavitary therapies is to spread drugs on the tumor surface, with a possible more direct and therefore stronger and more efficient effect; concurrently, local delivery might have a lower impact in terms of systemic toxicity and adverse reactions.

Chemotherapeutic agents and hyperthermia

The first reports using intracavitary chemotherapy are dated back in the 80s mainly in the field of abdominal surgery, while later in the 90s the first experiences reporting the use of this technique for MPM were published (7). Together with chemotherapy agents, hyperthermia is often used to increase the effects of intracavitary therapies; in fact, hyperthermia has a key role in increasing drugs penetration in the tissues and enhance their cytotoxic effects by modifying cells' membrane permeability increasing radio-chemo-sensitivity (8). Schaaf *et al.* (9) reported the results of *in vitro* effects of temperature on tissues during hyperthermic intraperitoneal chemotherapy, confirming that 40 ℃ should be considered the ideal temperature threshold in order to have a benefit in terms of OS and DFI; Ratto *et al.* (8) and Matsuzaki *et al.* (10) confirmed the adjuvant effect of hyperthermia; nevertheless a recent *in vitro* study (11) questioned its role, stressing the importance of the use of a combination of drugs.

Cisplatin is the most common drug that was used in intracavitary setting. Sugarbaker *et al.* (12) retrospectively compared oncological outcomes of patients affected by MPM treated with EPP or P/D with and without the use of HITHOC after surgery; patients treated with HITHOC had a significant better survival (35.3 *vs.* 22.8 months) and this difference was significant also in patients with nodal involvement. Concurrently, Ishibashi (13) compared DFI after different surgical approaches for surgery for MPM (EPP or P/D both associated with HITHOC with cisplatin) and he noticed a significant better DFI after P/D. Concurrently, different studies explored the pharmacokinetic of HITHOC using cisplatin alone or in association with other drugs as Anthracyclines (8,14-17), confirming its feasibility and its low systemic exposure; doxorubicin was reported to have a low penetration into the tissues compared to cisplatin; moreover, direct cardiac toxicity of doxorubicin has been discussed, but no clear evidences are available. Nevertheless, there is no consensus on the correct doses of drugs used for HITHOC which usually change in every institution's protocols; cisplatin has been administered intracavitary at a dose of up to 225 mg/m^2 when used alone and doxorubicin is usually administered at a dose of 80 mg/m^2 (18). Chan (7) also reported a phase I study in a cohort of 141 patients analysing the use of gemcitabine together with cisplatin (1,000 and 175 mg/m^2 respectively) after EPP and P/D with interesting long term results.

Recently, Bertoglio and colleagues (19) reported results of a protocol of surgical pleurectomy and partial decortication followed by hyperthermic intrathoracic chemotherapy using cisplatin (80 mg/m^2) and doxorubicin (25 mg/m^2) and adjuvant chemotherapy (cisplatin and Permetrexed) for early stage (I–II) MPM; among 26 patients that were treated with this protocol, results showed a median OS of 36.5 months for the entire cohort of interesting 46-month for patients in stage I. Concurrently no high grade postoperative morbidity were registered nor any case of 30- or 90-day mortality after surgery.

Povidone iodine

Povidone iodine is a molecule which is often used as antiseptic. *In vitro* studies showed that povidone iodine have possible antitumor effects (20) by stimulating inflammatory response; similar results on MPM cells were observed by Fiorelli and his colleagues (21).

Alongside *in vitro* studies, the largest cohort of patients treated with pleurectomy/decortication and intraoperative povidone-iodine hyperthermic lavage and postoperative prophylactic radiotherapy was reported by Lang-Lazdunski *et al.* (22,23); in the latest report of his experience, among 102 patients treated with the same protocol, the majority were in stage III and had an epithelioid histology. Median overall survival of the entire cohort was 32 months and he observed a low rate of comorbidities with no postoperative death.

Photodynamic therapy (PDT)

PDT is a light-based intraoperative treatment; a photosensitizing agent (usually porfimer sodium Photofrin or meta-tetra hydroxyphenyl chlorin Foscam) is administered to the patient and a source of light of a specific wave-length is located in the pleura. After surgery, light detectors are fixed into the chest cavity to monitor light dose, and a laser fiber is subsequently inserted by the mean of a specific tool filled with light-dispersing intralipid

solution and it is then moved around the chest until all light detectors register the planned light dose. When the light source is switched on in the presence of oxygen, it starts an instant reaction that produces singlet oxygen, a very reactive form of oxygen, which is also supposed to be the main cell-killer mechanism of PDT; more in details, the effect on tumor cells are a direct damage on cell membranes, an antiangiogenetic effect and a triggering of antitumor immune response. All these effects are strongly dependent on many factors related to photosensitizing agent and the modalities of its administration (24,25). PDT in the treatment of MPM carries two main advantages; firstly, the cytotoxic effects have a relatively deep penetration in to the tissues; secondly, it has no cumulative toxic effect, so that it can be therefore administered several times and it can be associated to the others traditional systemic or loco-regional treatments such as chemotherapy or radiotherapy (7,25,26).

Friedberg and his colleagues reported the use of a protocol of PDT in the treatment of MPM; recently they reported a 36-month (27) median overall survival in the whole cohort, and an overall survival of more than 7 years for N0 patients. The authors stated "*The potential value of intra-operative PDT is again raised, a question that should be answered by an ongoing randomized trial. This study demonstrates a complicated multimodal treatment plan can be safely executed with teamwork. Analysis and critical review of this study reveals areas where generalized improvements can be made in surgery-based trials for MPM.*"

Intrapleural immunotherapies

Based on preliminary clinical evidences, immunotherapy has been proposed as a valuable option for intrapleural treatment of MPM (28). Both interferons (IFNs) and IL-2 have been used as intrapleural agents.

Boutin *et al.* (29) described intracavitary administration of gamma-IFN for MPM; IFN was administered twice a week for two months with a complete response in 4 patients among 19, but in 2 cases they observed severe complications. The use of intrapleural IL-2 for MPM was reported by Astoul *et al.* (30) who showed a response in 12 out of 22 patients, all of them in early stage; conversely Goey *et al.* (31) did not find any correlation between intracavitary IL-2 and survival. More recently, Lucchi and his colleagues reported the use of a multimodality protocol (32) accounting for pleurectomy and decortication with intrapleural administering of IL-2 (both preoperative and postoperative) and doxorubicin (only postoperative); all patients underwent adjuvant chemo-radiotherapy and additional postoperative subcutaneous IL-2; survival data were promising, but the real role of IL-2 on the disease control has not been established.

Astoul and colleagues reported that intrapleural IL-2 administration produced objective clinical responses in 12 of 22 (54%) patients with MPM, with all responders having early-stage epithelioid histology (4). Median survival for responders was 28 months, compared with 8 months for non-responders (4). Clinical outcomes using other routes of IL-2 administration, however, are conflicting.

Gene therapy

Gene therapy is the ultimate frontier of intrapleural therapies and it is thought to assist patient's immune system in reacting against the cancer. Sterman and his colleagues reported the results of a phase I study using adenovirus vector with a suicide gene; despite interesting results, the role of gene therapy seemed to be only marginal in affecting long term outcomes. The same group reported a phase I clinical trial using a vector with an IFN used as immune stimulant in patients with pleural malignancies, with promising results (33-35).

Conclusions

Additional intracavitary therapies in the treatment of MPM have shown to have a potential role in increasing the radicality of surgery. The main advantages of these techniques should be to allow a less aggressive surgical resection, preserving lung function and quality of life possibly resulting in an increased adherence to further adjuvant or recurrence treatment and therefore a better overall survival; as a matter of fact, multimodality treatment and care to patients' quality of life are two main issues in the future development of mesothelioma surgery (36) and intrapleural technique will possibly play an important role. Unfortunately, data are based on retrospective or small prospective and single-institution studies that prevent from clearly establishing the role of intracavitary therapies and therefore to standardize their use in the treatment path; randomized trials are urgently needed to validate the impact of intrapleural therapies and to prove their potential.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bertoglio P, Waller DA. The role of thoracic surgery in the management of mesothelioma: an expert opinion on the limited evidence. Expert Rev Respir Med 2016;10:663-72.
2. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763-72.
3. Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v31-9.
4. Bertoglio P, Fanucchi O, Ricciardi S, et al. Chest wall resection for mesothelioma recurrence after surgery. Asian Cardiovasc Thorac Ann 2016;24:893-5.
5. Flores RM. Pleurectomy decortication for mesothelioma: The procedure of choice when possible. J Thorac Cardiovasc Surg 2016;151:310-2.
6. Sugarbaker DJ. Macroscopic complete resection: the goal of primary surgery in multimodality therapy for pleural mesothelioma. J Thorac Oncol 2006;1:175-6.
7. Chan WH, Sugarbaker DJ, Burt BM. Intraoperative adjuncts for malignant pleural mesothelioma. Transl Lung Cancer Res 2017;6:285-94.
8. Ratto GB, Civalleri D, Esposito M, et al. Pleural space perfusion with cisplatin in the multimodality treatment of malignant mesothelioma: a feasibility and pharmacokinetic study. J Thorac Cardiovasc Surg 1999;117:759-65.
9. Schaaf L, van der Kuip H, Zopf W, et al. A Temperature of 40 °C Appears to be a Critical Threshold for Potentiating Cytotoxic Chemotherapy In Vitro and in Peritoneal Carcinomatosis Patients Undergoing HIPEC. Ann Surg Oncol. 2015;22 Suppl 3:S758-65.
10. Matsuzaki Y, Tomita M, Shimizu T, et al. Induction of apoptosis by intrapleural perfusion hyperthermo-chemotherapy for malignant pleural mesothelioma. Ann Thorac Cardiovasc Surg 2008;14:161-5.
11. Cameron RB, Hou D. Intraoperative hyperthermic chemotherapy perfusion for malignant pleural mesothelioma: an in vitro evaluation. J Thorac Cardiovasc Surg 2013;145:496-504.
12. Sugarbaker DJ, Gill RR, Yeap BY, et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg 2013;145:955-63.
13. Ishibashi H, Kobayashi M, Takasaki C, et al. Interim results of pleurectomy/decortication and intraoperative intrapleural hyperthermic cisplatin perfusion for patients with malignant pleural mesothelioma intolerable to extrapleural pneumonectomy. Gen Thorac Cardiovasc Surg 2015;63:395-400.
14. van Ruth S, van Tellingen O, Korse CM, et al. Pharmacokinetics of doxorubicin and cisplatin used in intraoperative hyperthermic intrathoracic chemotherapy after cytoreductive surgery for malignant pleural mesothelioma and pleural thymoma. Anticancer Drugs 2003;14:57-65.
15. Bogliolo GV, Lerza R, Bottino GB, et al. Regional pharmacokinetic selectivity of intrapleural cisplatin. Eur J Cancer 1991;27:839-42.
16. de Bree E, van Ruth S, Schotborgh CE,et al. Limited cardiotoxicity after extensive thoracic surgery and intraoperative hyperthermic intrathoracic chemotherapy with doxorubicin and cisplatin. Ann Surg Oncol 2007;14:3019-26.
17. Ried M, Lehle K, Neu R, et al. Assessment of cisplatin concentration and depth of penetration in human lung tissue after hyperthermic exposure. Eur J Cardiothorac Surg 2015;47:563-6.
18. Gomez D, Tsao AS. Local and systemic therapies for malignant pleural mesothelioma. Curr Treat Options Oncol 2014;15:683-99.
19. Bertoglio P, Ambrogi MC, Chella A, et al. Is less also better? A single-institution experience on treatment of early stage Malignant Pleural Mesothelioma. Eur J Surg Oncol 2017;43:1365-71.
20. Opitz I, Sigrist B, Hillinger S, et al. Taurolidine and povidone-iodine induce different types of cell death in malignant pleural mesothelioma. Lung Cancer 2007;56:327-36.
21. Fiorelli A, Pentimalli F, D'Urso V, et al. Antineoplastic activity of povidone-iodine on different mesothelioma cell lines: results of in vitro study. Eur J Cardiothorac Surg 2014;45:993-1000.
22. Lang-Lazdunski L, Bille A, Papa S, et al. Pleurectomy/decortication, hyperthermic pleural lavage with

povidone-iodine, prophylactic radiotherapy, and systemic chemotherapy in patients with malignant pleural mesothelioma: a 10-year experience. J Thorac Cardiovasc Surg 2015;149:558-65; discussion 65-6.
23. Lang-Lazdunski L, Bille A, Lal R, et al. Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma. J Thorac Oncol 2012;7:737-43.
24. Wang HW, Rickter E, Yuan M, et al. Effect of photosensitizer dose on fluence rate responses to photodynamic therapy. Photochem Photobiol 2007;83:1040-8.
25. Friedberg JS. Radical pleurectomy and photodynamic therapy for malignant pleural mesothelioma. Ann Cardiothorac Surg 2012;1:472-80.
26. Simone CB, Cengel KA. Photodynamic therapy for lung cancer and malignant pleural mesothelioma. Semin Oncol 2014;41:820-30.
27. Friedberg JS, Simone CB, Culligan MJ, et al. Extended Pleurectomy-Decortication-Based Treatment for Advanced Stage Epithelial Mesothelioma Yielding a Median Survival of Nearly Three Years. Ann Thorac Surg 2017;103:912-9.
28. Wong RM, Ianculescu I, Sharma S, et al. Immunotherapy for malignant pleural mesothelioma. Current status and future prospects. Am J Respir Cell Mol Biol 2014;50:870-5.
29. Boutin C, Viallat JR, Van Zandwijk N, et al. Activity of intrapleural recombinant gamma-interferon in malignant mesothelioma. Cancer 1991;67:2033-7.
30. Astoul P, Picat-Joossen D, Viallat JR, et al. Intrapleural administration of interleukin-2 for the treatment of patients with malignant pleural mesothelioma: a Phase II study. Cancer 1998;83:2099-104.
31. Goey SH, Eggermont AM, Punt CJ, et al. Intrapleural administration of interleukin 2 in pleural mesothelioma: a phase I-II study. Br J Cancer 1995;72:1283-8.
32. Lucchi M, Chella A, Melfi F, et al. A phase II study of intrapleural immuno-chemotherapy, pleurectomy/decortication, radiotherapy, systemic chemotherapy and long-term sub-cutaneous IL-2 in stage II-III malignant pleural mesothelioma. Eur J Cardiothorac Surg 2007;31:529-33; discussion 33-4.
33. Sterman DH, Recio A, Carroll RG, et al. A phase I clinical trial of single-dose intrapleural IFN-beta gene transfer for malignant pleural mesothelioma and metastatic pleural effusions: high rate of antitumor immune responses. Clin Cancer Res 2007;13:4456-66.
34. Sterman DH, Recio A, Haas AR, et al. A phase I trial of repeated intrapleural adenoviral-mediated interferon-beta gene transfer for mesothelioma and metastatic pleural effusions. Mol Ther 2010;18:852-60.
35. Sterman DH, Haas A, Moon E, et al. A trial of intrapleural adenoviral-mediated Interferon-α2b gene transfer for malignant pleural mesothelioma. Am J Respir Crit Care Med 2011;184:1395-9.
36. Bertoglio P, Lucchi M, Mussi A. New Keywords in the Treatment of Malignant Pleural Mesothelioma. Ann Thorac Surg 2017;104:1434.

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