Review Article

Malignant pleural effusion in lung cancer: focus on treatment—through a review of literature

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Abstract: Malignant pleural effusion (MPE) is frequently associated with lung cancer and often the treatment is palliative. However, in some cases, an improvement in survival is possible. We evaluated the therapeutic options of MPE patients in lung cancer through a review of the literature. We have seen how, in addition to palliative treatments, surgery improves survival in selected cases. In patients destined for medical treatment, we noticed that the biomolecular characteristics and receptor structures are fundamental to achieve targeted and personalized therapy. It is now possible an effective treatment for the patients in which palliative cares were the only therapeutic possibility until a few years ago.

Keywords: Non-small cell lung cancer (NSCLC); malignant pleural effusion; chemotherapy; surgical treatment

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Introduction

Malignant pleural effusion (MPE) is often associated with advanced lung cancer. About 15% of non-small cell lung cancer (NSCLC) patients shows a MPE; adenocarcinoma is the most frequently associated histology with negative impact on the prognosis (1). In fact, the average survival is approximately 4.3 months (2). The differential diagnosis with paraneoplastic pleural effusions due to the association of cancer with pulmonary embolism, thoracic duct obstruction, superior cava vein compression, pericardial infiltration, hypoalbuminemia, obstructive pneumonia, or atelectasis (3,4) must be done. Many studies proposed different treatment strategies to improve outcomes although it is difficult to establish the best approach in terms of tolerability and survival. The purpose of this review is to evaluate the various proposals of treatment in order to establish the best strategy program in the management of MPE patients. We evaluated the different types of treatment and we found that most of these have only palliative purposes. However, the cytoreductive therapy in patients with the first discovery of MPE during pulmonary resection and the hyperthermic intrathoracic chemotherapy (HITHOC) improve survival. Moreover, the biomolecular characteristics of neoplasms allow the new frontier treatment development although the prognosis for these patients remains poor yet.

Discussion

Diagnosis of MPE

MPE is characterized by the presence of neoplastic cells in the pleural fluid and it shows an incidence of around 150,000 cases per year. Lung cancer with a percentage rate of 8–15% followed by breast cancer and lymphomas are the most frequent etiologies of MPE (5,6). Chest X-ray is the first level investigation in case of MPE doubt that allows to detect the pleural cavity effusion greater than 200 cc. However, patients with MPE display an effusion between

500 and 2,000 cc. Computed tomography (CT) scan of the thorax seems to be characterized by a high false negative rate, equal to 70%, in the identification of malignant lesions determining MPE (1). Sensitivity of CT scan is improved by integration with the 18 fluorodeoxyglucose positron emission tomography (FDG-PET), that allows to reach 93% of sensitivity and 75% of specificity (1). Diagnosis is made through histological and/or cytological (50 cc of effusion are sufficient) evaluation. The predominant characteristics of MPE are the presence of lymphocytes among nucleated cells (50–70%), eosinophils, erythrocytes with PH <7.3 and glucose <60 mg/dL. Regulatory T cells (Treg) assist immune suppression towards malignant agents in MPE and a significantly higher rate of these was found in comparison with non-malignant effusions, causing a worse survival trend (7). However, the diagnosis is linked to the evidence of neoplastic cellularity and the search for this showed a variable range of positivity (from 50% to 90%) (8-11). In case of negative cytology, it is advisable to perform a pleural biopsy by video-assisted thoracoscopy or less invasive methods under radiological guidance (12-15). Psallidas *et al.* (16) proposed the study of biomarkers in order to establish a score scale for therapeutic management based on survival. No biomarkers were identified for pleurodesis while 8 biomarkers were found for survival score. Moreover, biomarkers in pleural fluid allow molecular analysis linked to appropriate targeted therapies. More concrete results were obtained using the ratio of biomarkers (CEA, CA19.9, CA15.3, CA72.4) in the pleural fluid and serum (F/S), with low cut-offs. CEA showed a specificity of 100% but a sensitivity of 37.8% in serum and 19.8% in pleural fluid (17-19).

Treatment

Thoracentesis is the first approach in symptomatic pleural effusion, causing a vicious cycle between protidemic depletion and electrolyte balance (20,21). Cattapan *et al.* (22) evaluated the tumor dissemination related to the procedure performed in lung cancer with malignant pleural effusion. Data confirmed that an invasive pleural procedure increases the risk of tumor dissemination with rate of 22.4% and a higher risk of death (HR: 3.35, 95% CI: 1.87–6.01). Currently, malignant pleural effusion is generally treated with combined systemic chemotherapy approaches, diuretics, and injection of drugs into the pleural cavity such as talc after thoracoscopy or as cisplatin and bleomycin for pleurodesis after closed thoracic drainage (23,24).

Indwelling pleural catheter (IPC)

A method proposed by many authors is the IPC tunneled subcutaneously, mostly in patients with recurrent MPE and trapped lung and contraindication to thoracoscopy. Messeder *et al.* (25), using this technique, revealed a favorable symptom management and physiological pleurodesis with low risk of complications (16% of cases). Boshuizen *et al.* (26), in a randomized controlled trial comparing the IPC with talc pleurodesis (TP), displayed no differences in dyspnea and pain management although the reduction in length of hospital stay and in number of re-treatment (0.21 *vs.* 0.53, P=0.05) were observed.

TP

Chemical pleurodesis plays a fundamental role in the treatment of MPE and the talc, inducing an inflammatory reaction, is the mainly used drug. In fact, the modern purified talc preparation is considered safe, effective, and economically advantageous with low-grade of adverse reactions (27). This view is also supported by an important evaluation extrapolated from the Cochrane Database (28) but it is in disagreement with other studies that revealed a high percentage of adverse effects due to the use of talc (29-32). Korsic *et al.* (33), comparing TP and thoracentesis in pulmonary and breast MPE, highlighted a better control of symptoms and a better average survival (21.5 *vs.* 9 weeks, P<0.001) by chemical pleurodesis. Saka *et al.* (34) displayed 83.3% of MPE control at 30 days with minimal adverse effects and absence of ARDS and infections. Arellano-Orden *et al.* (35) evaluated the systemic effects of this procedure. Two hundred twenty-seven cancer patients undergone, after evacuation of the pleural effusion, to pleurodesis with 5 grams of sterile talcum powder [$Mg_3Si_4O_{10}(OH)_2$] free of asbestos. Two groups of treatment were identified: small-particle talc (ST, 103 patients) and large particle talc (LT, 124 patients).

Subsequently, pleural and serum levels of proinflammatory cytokines such as Interleukin-8 (IL-8), tumor necrosis factor (TNF-α), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were assessed after 3, 24, 48 and 72 hours. ST patients showed higher serum and pleural levels of proinflammatory cytokines than LT patients in the first 72 h (the average levels of serum IL-8 at 48 h were 241 and 53 pg/mL respectively; 24 h pleural TNF-α levels were 98 and 47 pg/mL, respectively). In addition, a considerable early mortality rate (<7 days) was found in ST Group (8 out of 103 patients). Authors concluded

that the treatment with ST determines a strong systemic inflammatory reaction associated with a high mortality rate. Demmy *et al.* (31) compared two talc techniques in the treatment of MPE. Fifty-seven patients underwent TP, 29 through drainage (TP) and 28 through tunneled catheter daily drainage (TCD). There were no differences in terms of maximum lung re-expansion (79% *vs.* 73%). In terms of outcomes, patients treated with TCD displayed a disease free survival higher than patients treated with TP (82% *vs.* 52%). However, pleurodesis was obtained in 86.2% of TP patients unlike 68% of TCD patients but the dyspnea score was better in patients treated with TCD (8.5 *vs.* 6.1). In conclusion, TCD treatment compared to TP showed better overall success (62% *vs.* 46%). The same considerations regarding the effectiveness of talc spray pleurodesis and the high risk of respiratory complications were also reported for the injection into the pleural cavity of anti-tumor drugs as demonstrated by Dresler *et al.* (36) which showed positive results up to 97%, but burdened by 14% of complications and 4% of respiratory failure.

Intrapleural infusion of drugs

New generation drugs like lobaplatin are currently being tested in order to improve the adherence of pleura, reducing hospitalization and costs (37-40). Hsu *et al.* (41) highlighted that MPE patients who underwent pleurodesis by minocycline, with and without previous urokinase treatment, had longer control of effusion and better survival. In fact, pleurodesis seems to induce inflammatory response after pulmonary reexpansion counteracting the tumor invasion and metastasis. Wang *et al.* (42) tested on 2.292 MPE patients the elemene, turmeric extract with likely anti-tumor activity. Authors achieved an excellent overall response rate particularly in lung carcinomas (RR 1.20, 95% CI: 1.07–1.34; P<0.05) where it was better than in other cancers (RR 1.14, 95% CI:1.05–1.23; P<0.05), without significantly increasing complications and pain. Lee *et al.* (43), analysing the Helixor-M (Mistletoe extract) in 52 MPE patients, noticed 48% of relapse, 25% of pain and 15% of fever. Xu *et al.* (44) tested in 55 MPE patients the association of systemic chemotherapy and the instillation of lobaplatin plus erythromycin in the pleural cavity. Authors experienced 35.7% of low-grade chest pain, considering this association a safe and effective option in malignant effusion related to NSCLC. Bagheri *et al.* (45) carried out a randomized study on 60 cancer patients with MPE, demonstrating the efficacy and safety of iodopovidone compared to bleomycin with 83.3% of positive response. Same considerations on the use of iodopovidone have been reported by Ibrahim *et al.* (46). Many Authors (47-49) proposed the pleural infusion of avastin (monoclonal antibody against VEGF) and paclitaxel in advanced NSCLC with MPE, based on the improvement of symptoms with a low and mild toxicity comparable to the chemotherapy only. Studies on angiogenesis and tumor growth (50-54) have pushed the randomized control trials evaluating the use of the intracavitary endostar (a novel modified recombinant human endostatin), associated or not with other drugs (pemetrexed, platinum), that allowed an excellent control of effusion. Koyama *et al.* (55) studied 26 MPE patients with NSCLC IIIb–IV treated by the combined use of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus carboplatin (CBDCA). Twenty-one patients showed a response (80.8%); 6 patients (23.1%) obtained a complete control of MPE while 15 (57.7%) a partial control, increasing median free survival (P=0.009) and overall survival (P=0.047).

Surgery in patients with MPE

Role of surgery in MPE patients with NSCLC is still debated (56,57). Ried *et al.* (8) proposed complete surgical removal of the parietal pleura. This approach was indicated only in selected cases (patients with potentially better prognosis), exposing patients to a high complications index rate (25%) and a significant mortality rate (19%). Ren *et al.* (58) analyzed patients treated for NSCLC in which were found "unexpected" macroscopic malignant pleural nodules (MPN) with and without MPE. The overall 3- and 5-year survival rates were 36.1% in the absence of minimum MPE group and 16.8% in the MPE group; median survival time (MST) after surgery was 36.8 *vs.* 22.4 months (P=0.005) respectively. Okamoto *et al.* (59), analyzing 100 stage IV NSCLC patients undergone pulmonary resection, noticed poor survival outcomes in case of malignant pleural disease (MPD). Seventy-three patients displayed MPD (32 with MPE and 41 with MPN). Two patients showed contralateral metastasis (M1a) and 25 distant metastases (M1b). MPE patients compared to M1b patients had a better survival (P=0.015) while patients with MPN had a more favorable prognosis (P=0.054). Among MPD patients, MPE Group in comparison with MPN Group experienced an overall MST of 26.1 *vs.* 25.9 months, 3-year survival rate of 43.1% *vs.* 39.9% and 5-year survival rate of 37.7% *vs.* 14.8%. In addition, Authors highlighted that N0–N1 patients had better survival than N2-N3 patients although in both groups MPE patients had a better outcomes than MPN

patients. In fact, 5-year survival in patients with MPE N0–N1 compared to patients with MPN N0-N1 was 63.6% *vs.* 27.3% respectively. Finally, none of patients with N2–N3 MPN survived 5-years after surgery. In conclusion, the primary tumor resection can be considered in patients with MPE N0–N1, also improving survival in MPN N0–N1 patients. Le Pimpec Barthes *et al.* (56) believe that complete surgical resection can improve survival only in case of M1a patients. Authors, studying 164 NSCLC patients (70 M1a and 94 M1b), observed that in M1b patients treated with resection there was no improvement in 5-year survival compared to patients treated without resection (16.7% *vs.* 15%). Conversely, in M1a patients the 5-year survival increased from 9% to 16.2% after surgery. Therefore, Authors consider that surgery is overestimated in M1b patients and underestimated in M1a patients. The treatment with hyperthermia is based on the less resistance of cancer cells to high temperatures (lethal effect for exposure at 43 ℃ for 4–8 hours). Furthermore, many chemotherapy drugs at higher temperatures have a greater cytotoxic power (60). Işık *et al.* (61) analyzed outcomes in three lung cancer groups patients, with pleural but without distant metastases, based on treatment: (I) Group 1 (19 patients) underwent cytoreduction and subsequent intrapleural hyperthermic perfusion chemotherapy (HIPEC) at 42 ℃ with 0.9% sodium chloride isotonic solution and cisplatin; (II) Group 2 (13 patients) underwent TP; (III) Group 3 (12 patients) underwent pleurectomy/decortication in VATS. All groups also underwent systemic chemotherapy. The median survival of the three groups was 15, 6 and 8 months respectively; 1-year survival was 54.7%, 0.6% and 0.8%. According to the authors, the association between surgery and HIPEC must to be considered as therapeutic option in MPE patients. Yamaguchi *et al.* (62), analyzing the "trimodality treatment" (chemotherapy, extrapleural pneumonectomy and hyperthermia) in stage IV NSCLC and MPD patients, highlighted 1-year, 3-years and 5years disease free survival rates of 77.8%, 11.1% and 11.1% respectively and 1-year ,3years and 5-year overall survival rates of 100.0%, 33.3% and 22.2% respectively. Also, Moon *et al.* (63) proposed the simple intrapleural hyperthermia (SIH) as safe and advantageous treatment. In 34 cancer patients with MPE treated by SIH, the response rate was 82.4% and 3-month and 7-month recurrence-free rates were 86.9% and 73.9%, respectively. Furthermore, no postoperative respiratory complications occurred.

Molecular targeted therapy

The VEGF seems to determine the development of MPE, increasing the vascular and mesothelial permeability and capillary fluid leak (9,64,65). Use of human monoclonal antibody specific for VEGF receptor-2 (VEGFR-2) such as Ramucirumab and Bevacizumab was recently approved for patients with advanced NSCLC (66,67). Bevacizumab need the careful evaluation of VEGF levels in the plasma and pleural effusion. In fact, high levels of VEGF showed a reduction in overall survival and progression-free survival compared to low VEGF levels (68). The efficacy of Bevacizumab was studied by Usui *et al.* (69) in 30 NSCLC patients with MPE. Pleural effusion was controlled without pleurodesis in 93% of patients after 8 weeks. After 12.8 months, 78.6% of patients not required pleurodesis. Median progression-free survival and overall survival were 8.2 months and 18.6 months, respectively. The angiogenetic action of VEGF was also confirmed by Qi *et al.* (70), in a cohort study on 34 NSCLC with MPE. The combined use of paclitaxel and Avastin compared to single paclitaxel treatment reduced MPE level with a success rate of 29% and a survival rate of 25% ($P<0.05$). Du *et al.* (71) analyzed 70 patients underwent intrapleural therapy with Bevacizumab, cisplatin or both. Authors noted that patients treated with Bevacizumab had lower VEGF levels in pleural effusion than patients treated with cisplatin ($P<0.01$), associating with greater therapeutic efficacy in the first group (83.33% *vs.* 50.00%). Also, the combined therapy increased the therapeutic efficacy in patients with high VEGF expression in the pleural liquid ($P<0.01$).

The evolution of the disease is also important. Dosage of tumor markers was used for monitoring the progression or regression of the disease. Then, different new molecular targets were identified in order to set personalized therapies (72-75). Tang *et al.* (72) on 106 NSCLC patients with MPE noted that conventional markers such as carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), squamous cell carcinoma (SCC) antigen and cytokeratin 19 (CK19) were not reliable prognosis indices. Conversely, the Lung specific X protein (Lunx) mRNA can be associated with the degree of disease. Then, Authors compared in 106 NSCLC patients the expression of Lunx mRNA, cast-off cells and CEA in the pleural fluid and they displayed a positive test in 83, 68 and 73 cases respectively. Eighty-two out of 106 patients underwent chemotherapy, obtaining in 12 patients a complete remission (CR), in 48 patients a partial remission (PR), in 10 patients no change (NC)

and in 12 patients a disease progression (PD). Moreover, Authors experienced that in cases of positive response to therapy the expression of Lunx mRNA was reduced; on the contrary, in case of worsening of the disease the same marker increased. Regarding survival linked to the therapy, it is very important to evaluate the epidermal growth factor receptor (EGFR) mutations in NSCLC patients in order to optimize the treatment based on the high response to EGFR-tyrosine kinase inhibitor (TKI) (76). Wu *et al.* (14) studied 1,400 pleural effusion, 890 of which with MPE. Seven-hundred thirteen specimens from 448 patients with adenocarcinoma were examined. Authors revealed that patients with MPE at moment of the first diagnosis in comparison with patients in which MPE appeared during the progression of disease showed: (I) a lower survival (14.3 *vs.* 21.4 months); (II) a higher level of EGFR mutations (68.2% *vs.* 56.6%) associated with a higher average survival compared to patients with wild-type EGFR (17.4 *vs.* 10.9 months). Also, patients with wild-type EGFR treated with TKI displayed a survival of 6.8 months while patients with EGFR mutation treated with TKI displayed a survival equal to 16.8 months. The latter considerations demonstrated that cancer therapies must be personalized according to the genetic characteristics of patients. Wu *et al.* (77) studied wild-type EGFR and echinoderm microtubule-associated protein like 4anaplastic lymphoma kinase (EML4-ALK) fusion in patients with adenocarcinoma. Authors analyzed 116 patients with wild-type EGFR; of these, 39 patients (34%) showed EML4ALK fusion gene. Treatment was the same in patients with and without EML4-ALK fusion gene but the overall survival was better in the first Group compared to the second Group (14.7 *vs.* 10.3 months).

Conclusions

In conclusion, in most patients the treatment of MPE is palliative. Many authors consider pleurodesis with talc an effective and safe approach. However, the role of surgery in selected cases was recognized. Hyperthermia showed the survival improvement in MPE patients. Pulmonary resection in association with HIPEC/HITOC may be considered in patients with stage IV disease but without extrathoracic metastasis (M1a, N0–1). About the concentration of VEGF and the expression of EGFR, it seems evident that the future of cancer treatments is linked to biomolecular characteristics of the patients.

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