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REVIEW ARTICLE

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Methods for Treatment of Malignant Pleural Effusion

Alexei L. Charyshkin, PhD, ScD[1*]; Ekaterina A. Kuzmina[2];
Bulat I. Khusnutdinov[1,3]; Evgeniy A.Toneev[1,3]; Vladimir I. Midlenko, PhD, ScD[1]

[1]*Ulyanovsk State University, Ulyanovsk, Russia*
[2]*Pirogov Russian National Research Medical University, Moscow, Russia*
[3]*Regional Clinical Oncology Center, Ulyanovsk, Russia*

Abstract

This brief review provides up-to-date information on the management of malignant pleural effusions (MPE). In general, selection of the most appropriate treatment approach should be individualized. Management of MPE relies on tumor type, pulmonary re-expansion, performance status, symptoms, and life expectancy. Pleurodesis and IPC placement are two effective treatments recommended for recurrent MPE, both of which can effectively improve dyspnea and quality of life of patients. Other options such as intrapleural therapies, radiation therapy, and pleuroperitoneal shunting are alternative treatments. However, most of these treatments are temporary, and MPE would recur soon. Hence, further palliative treatments to effectively control pleural effusions and relieve symptoms are necessary. (**International Journal of Biomedicine. 2020;10(1)16-19.**)

Key Words: malignant pleural effusions • thoracentesis • pleurodesis • indwelling pleural catheters

More than 300,000 patients in the Russian Federation die every year from malignant neoplasms, which thus occupy the third place in the mortality structure of the country's population and remain the most important medical and social problem.

One of the most common complications of tumor diseases is malignant pleural effusions (MPE). In the structure of the general incidence, the proportion of pleurisy reaches 4%, while the oncological etiology accounts for 63% of all exudative pleurisy.

The majority of MPE is caused by metastatic disease: most commonly lung cancer in men and breast cancer in women.[1] These two cancers combined account for 50%–65% of all MPE.[2-5] Mesothelioma is the most common type of primary pleural tumor and is associated with MPE in more than 90% of cases.[3] In 12% of patients with MPE, it is not possible to establish the nature of the primary tumor. The presence of MPE indicates an advanced stage of the disease with a median life expectancy of 3 to 12 months, depending on the stage and type of underlying malignancy.[6] There are more than 100,000 new cases of MPE yearly in Russia.

***Corresponding author**: Prof. Alexei L. Charyshkin, PhD, ScD, Head of the Faculty Surgery Department, Institute of Medicine, Ecology and Physical Education, Ulyanovsk State University. Ulyanovsk, Russia. E-mail:* charyshkin@yandex.ru

Although the first randomized trial for MPE treatment methods was performed in 1977,[7] the optimum management of the disease remains under debate and research. In MPE patients, dyspnea is the most common presenting symptom followed by chest discomfort and cough.[3,8,9] The quality of life is improved by local treatment methods, which not only help reduce the symptoms of pleurisy, but also extend the life of patients from several months to 1-3 years. Prior to considering any definitive treatment intervention, all patients with MPE should undergo a therapeutic aspiration to assess symptomatic improvement and rate of fluid reaccumulation.

During the past two decades, there has been a change in direction in MPE research and management.[1] Historically, studies were focused on halting pleural fluid accumulation and often employed aggressive surgical methods (pleurectomy);[10-12] and most clinical trials[13,14] aimed at identifying the best agent that would achieve obliteration of the pleural space (pleurodesis). The most common end-point of these early studies was radiological improvement at 1-3 months post-pleurodesis, without consideration of the patients' symptoms.[15] Currently, the treatment approach for patients with MPE is mainly aimed at alleviating their symptoms and improving quality of life indicators, which is a key goal of treatment.[16]

In general, selection of the most appropriate treatment approach should be individualized. Management of MPE relies on tumor type, pulmonary re-expansion, performance

status, symptoms, and life expectancy. Asymptomatic patients with a known tumor type who are responding well to systemic therapies should be under observation.[3] Some cancers, such as small cell lung cancer, lymphoma, breast cancer, prostate, and ovarian cancer, may respond well to chemotherapy.[3,17-19]

Patients who have a life expectancy of more than 3 months or are resistant to chemotherapy should be given palliative treatments,(20) such as observation, thoracentesis, indwelling pleural catheters (IPCs), pleurodesis, intrapleural therapies, radiation therapy, and pleuroperitoneal shunting (PPS).[3,20-22]

Thoracentesis is generally safe, especially if it is performed with ultrasound guidance.[23] Thoracentesis is a good choice for patients with advanced disease and a short life expectancy (1-3 months), slow pleural fluid reaccumulation, or poor performance status that precludes the patient from other interventional therapies.[21,24] The amount of fluid evacuated by pleural aspiration will be guided by patient symptoms and should be limited to 1.5L on a single occasion. [3,25] Pneumothorax is one of the most common complications associated with thoracentesis, with an incidence rate as high as 20%-39%.[26] Re-expansion pulmonary edema occurs rapidly if the removed fluid is more than 1.5L.[27,28] As known, almost all patients experience recurrence of symptoms and effusions within 1 month.[3,29] Although thoracentesis does not improve survival, it can significantly improve the patient's condition and avoid hospitalization.

Pleurodesis refers to the process of chemically or mechanically inducing pleural inflammation to the visceral and parietal pleura to obliterate the area and prevent the accumulation of air or liquid in the pleural space. Instillation of the sclerosing agent is thereafter followed by a profound inflammatory response between the layers, which, in turn, result in fibrin accumulation and pleural fibrosis. Pleurodesis is a better option for recurrent MPE than thoracocentesis unless the patient has a very poor performance status, a short life expectancy, or a trapped lung.[27] A variety of different chemicals (e.g. talc, bleomycin, tetracycline, iodopovide) and bacterial products (Corynobactum parvum, Streptococcus pyogenes, Staphylococcus aureus, and others) have been used in clinical studies to achieve pleurodesis.[30-33] The profound inflammatory response they may result in adverse events, such as pain and fever, but it is believed that the level of inflammation correlates with the likelihood of successful pleurodesis.[34] Chest pain and fever are the most common complications of chemical pleurodesis. Other complications include a cough, empyema, local site infection, trapped lung, and acute respiratory distress syndrome.[29] The type of sclerosant, the method of administration and the method of selecting patients to be treated with pleurodesis are still unclear. Talc is the most effective sclerosant available for pleurodesis, especially graded talc, which can be delivered as slurry via an intercostal catheter or by dry-powder poudrage during a thoracoscopy.[3] Talc was first used for pleurodesis in 1935.[35] It has been proven that graded preparations (as opposed to small particle talc) should be used to minimize systemic dissemination of talc particles and the risk of acute respiratory distress syndrome.[36,37]

Results from the largest randomized trial in MPE revealed that the success rates of talc slurry and talc poudrage are not significantly different.[38,39-41] A subgroup analysis of patients with lung and breast cancer suggested a better success rate for talc poudrage.[38] On the contrary, a metanalysis performed by Xia H et al.[42] demonstrated that talc poudrage was superior to talc slurry in pleurodesis success. According to Zhestkov& Iaduta,[43] in a series of 132 patients, the effectiveness of the method was 97.7%, pleurisy recurrence was diagnosed in only 3 patients, and no serious postoperative complications were recorded. Domestic authors recommend talc pleurodesis with daily exudation of pleural effusion up to 300 ml, bleomycin pleurodesis with daily exudation up to 700 ml and combined pleurodesis at more than 700 ml; in case of failure, pleurodesis by videothoracoscopy is recommended.

IPCs have gained popularity during the last decade as they offer ambulatory management, thereby minimizing hospital stay and healthcare costs.[44] An IPC is a silicone tube placed in the pleural cavity and tunneled subcutaneously. The proximal end of the exposed tube has a one-way valve, which connects to drainage bottles. Drainage is guided by symptoms and is patient-driven, offering a sense of control to most patients. The optimal schedule of MPE drainage through an IPC is still not clear. This system provides the patients, or people who care for them, complete control over the removal of fluid from the pleural cavity. Such systems are rarely used in Russia; domestic scientific literature on this issue could not be found. The British Thoracic Society Pleural Disease Guideline recommends the use of IPCs in those patients with MPE that have failed pleurodesis or in those with trapped lung (unsuitable for pleurodesis).[3] A meta-analysis of 1348 patients with MPE treated with IPCs revealed that 95.6% had symptomatic improvement and 45.6% achieved spontaneous pleurodesis after a median of 52 days.[45] The TIME2 randomised controlled trial showed that IPCs achieved control of breathlessness and quality of life comparable to talc pleurodesis, median length of hospitalization was significantly shorter in the IPC group than talc group (0 vs. 4 days; $P<0.001$). Fewer patients with IPCs required further pleural procedures than talc group (6% vs. 22%, $P=0.03$).[16] Another prospective multicenter study achieved the same results.[46] There is ongoing research on possible combinations of IPC with sclerosant agents in order to enhance pleurodesis success.[47] Recent data also provide reassurance on the safety of IPC use, with a risk of death from pleural infection below 0.3%.[48] As IPCs offer long-term access to the pleural cavity, they represent ideal potential portals for local drug delivery.

There is another method proposed by Plaksin and Farshatova[49] for effective control of pleural effusions and obliteration of the pleural cavity: Through a drainage tube installed during thoracoscopy or during drainage of the pleural cavity, 50 ml of a 1% lidocaine solution is injected into the pleural cavity for pain relief, after which the tube is closed for 20 minutes. After that, 40-80 ml of a previously prepared mixture consisting of 1% iodopyron solution and 40% glucose solution in a 1:4 ratio is injected into the drainage tube using a syringe. The drainage is closed for 2 hours. At this time, the patient repeatedly changes the position of the body

so that the drugs get into all parts of the hemithorax. Then the drainage is opened and active aspiration is continued. Drainage is removed from the pleural cavity with a decrease in the volume of exudation to ≤100 ml of effusion per day. The disadvantages of this method of treatment are (1) insufficient analgesia; since there is no premedication (anesthesia before surgical procedures), anesthetic (lidocaine) is administered once; and (2) the use of a standard drainage tube of the same diameter without through holes, which does not allow effective irrigation of the pleural cavity with drugs, thereby reducing their effectiveness.

In conclusion, pleurodesis and IPC placement are two effective treatments recommended for recurrent MPE, both of which can effectively improve dyspnea and quality of life of patients. Other options such as intrapleural therapies, radiation therapy, and PPS are alternative treatments. However, most of these treatments are temporary, and MPE would recur soon. Hence, further palliative treatments to effectively control pleural effusions and relieve symptoms are necessary.

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