Successful pericardial sclerosing using bleomycin in pulmonary adenocarcinoma with massive recurrent pericardial effusion

Ivana Purnama Dewi[1, 2, 3], Ismail Damanik[1, 3], Dita Aulia Rachmi[1, 3], Kristin Purnama Dewi[1, 4], Rochmad Romdoni[1, 3]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Faculty of Medicine, Duta Wacana Christian University, Yogyakarta, Indonesia
[3]Department of Cardiology and Vascular Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia
[4]Department of Pulmonology and Respiratory Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia

Introduction: Malignant pericardial effusion (MPE) is a serious complication in several cancers. MPE may give rise to cardiac tamponade, a life-threatening condition that requires urgent drainage. Although simple pericardiocentesis enables symptom resolution, MPE often recurs unless further procedures are done. Among the most frequently considered ones are sustained drainage, talcage with antineoplastic agents, or surgical creation of a pleuro-pericardial window.
Case report: A 53-year-old male patient complaining of shortness of breath for two weeks before hospital admission. He said that his complaints had even increased the day before admission. The patient has a history of pulmonary adenocarcinoma, undergoing chemotherapy for the past 1.5 months. The patient also had previously been hospitalized with the same complaint and underwent pericardiocentesis. On physical examination, there were decreased heart sounds, increased jugular venous pressure, and decreased blood pressure. On echocardiography, there was a massive pericardial effusion. We performed pericardiocentesis followed by bleomycin injection. After nine days of hospitalization, the patient was discharged from hospital.
Conclusion: We report a patient with a history of lung cancer and recurrent MPE. We performed immediate pericardiocentesis with fixed drainage. Pericardial sclerosis with bleomycin is a safe and effective method of preventing recurrent MPE and repeated invasive procedures.

Klíčová slova: malignant pericardial effusion, pericardiocentesis, bleomycin, sclerosis, lung cancer.

Úspěšná sklerotizace perikardu bleomycinem u plicního adenokarcinomu s masivním recidivujícím perikardiálním výpotkem

Úvod: Závažnou komplikací u několika typů rakoviny je maligní perikardiální výpotek (MPV). Ten může mít za následek srdeční tamponádu, život ohrožující stav s nutností urgentní drenáže. I když prostá perikardiocentéza přináší úlevu od příznaků, pokud nepodnikneme další kroky, dochází často k recidivě MPV. Nejčastěji zvažovanými postupy jsou trvalá drenáž, talkáž antineoplastickými léky nebo chirurgické vytvoření pleuroperikardiálního okénka.
Popis případu: Muž, 53 let, stěžující si na dušnost dva týdny před přijetím do nemocnice. Den před příjmem se jeho obtíže údajně ještě zhoršily. Pacient má v anamnéze plicní adenokarcinom a během posledního 1,5 měsíce je léčen chemoterapií. Už dříve byl hospitalizován se stejným problémem a podstoupil perikardiocentézu. Fyzikální vyšetření odhalilo tlumené srdeční ozvy, zvýšenou nálpň krčních žil a pokles krevního tlaku. Echokardiografické vyšetření ukázalo masivní perikardiální výpotek. Provedli jsme perikardiocentézu s následnou injekcí bleomycinu. Po devíti dnech hospitalizace byl pacient propuštěn z nemocnice.
Závěr: Popisujeme případ pacienta s anamnézou rakoviny plic a recidivujícím MPV. Provedli jsme okamžitou perikardiocentézu s fixní drenáží. Sklerotizace perikardu bleomycinem je bezpečná a účinná metoda prevence recidivy MPV a opakovaných invazivních zákroků.

Klíčová slova: maligní perikardiální výpotek, perikardiocentéza, bleomycin, sklerotizace, rakovina plic.

KORESPONDENČNÍ ADRESA AUTORKY: Ivana Purnama Dewi, MD, dr_ivanapd@staff.ukdw.ac.id
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya, Jl. Mayjen Prof. Dr. Moestopo No. 6–8, 60286, Surabaya Indonesia

Cit. zkr: Interv Akut Kardiol 2021; 20(2): 116–120
Článek přijat redakcí: 20. 10. 2020
Článek přijat po přepracování: 30. 12. 2020
Článek přijat po druhém přepracování: 20. 1. 2021
Článek přijat k publikaci: 3. 2. 2021

Pericardial malignancy is detected in 2–15 % of autopsies and 0.1 % of patients with a history of cancer. Primary tumors that often involve the pericardium are lung cancer followed by breast cancer, leukemia, esophageal cancer, and lymphoma (1). The clinical features of pericardial malignancy may include pericarditis, malignant pericardial effusion (MPE), cardiac tamponade, or constrictive pericarditis. In patients with a history of malignancy, MPE was associated with a mean survival < 4 months. The prognosis was also influenced by the primary site and patient history (2).

Cardiac tamponade is a life-threatening condition. The pressure from the pericardial effusion will compress the ventricles, resulting in ventricular diastolic collapse and decreased cardiac output (3). In symptomatic patients with unstable hemodynamics, effusion fluid should be drained immediately to prevent cardiogenic shock and relieve symptoms. While pericardiocentesis effectively relieves symptoms and enhances hemodynamics, it is still very important to prevent recurrences (3). Recent literature states that the recurrence rate is as much as 40 % (4).

Bleomycin, a complex glycopeptide, is of a highly water-soluble nature resulting from Streptomyces verticillus. We report a patient with a history of pulmonary adenocarcinoma with recurrent pericardial effusions. We performed pericardiocentesis followed by an injection of bleomycin, obtaining a good result.

Case report

A 53-year-old man, was admitted to a general hospital through the emergency room with the chief complaint of shortness of breath. The complaint had been present for two weeks before admission. His shortness of breath got worse two days before admission, especially during activities and sleep. It was relieved by sitting. The patient had a diagnosis of lung adenocarcinoma and had been on chemotherapy for two months.

On physical examination, the general condition was weak, blood pressure 107/70 mmHg, pulse rate 71 bpm, respiratory rate 24 breaths per minute, and body temperature 36.8 °C. On head and neck inspection, there was dyspnea with increased jugular venous pressure (JVP). Two heart sounds were present with a distant sound, without murmur or gallop. On lung examination, there were decreased breath sounds, faint in the basal lung area, and there were basal rhonchi in both lungs. Edema was found in the lower extremities. Electrocardiography showed a sinus rhythm of 99 bpm, normal axis, and low voltage (Fig. 1).

Fig. 1. *Electrocardiography showed a sinus rhythm 99 bpm, normal axis, and low voltage*

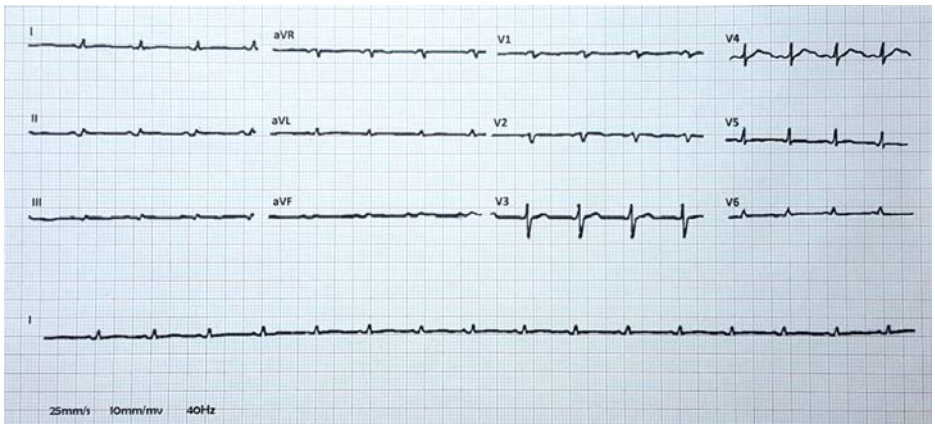
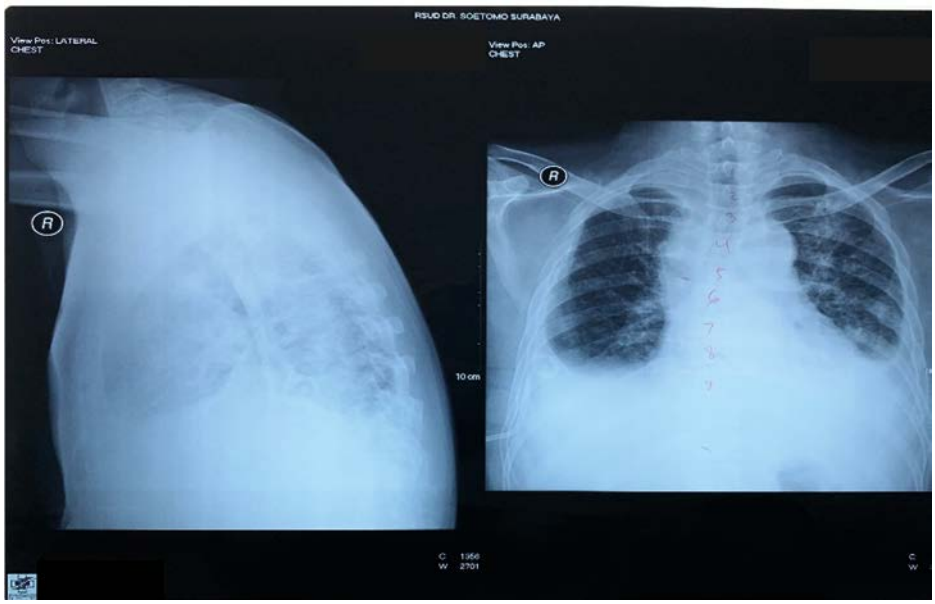


Fig. 2. *Chest X-ray showed cardiomegaly impression, right pericardial consolidation, and bilateral pleural effusion*



Laboratory tests found a low albumin level 2.9 g/dl and blood gas analysis revealed the following: pH 7.39, PaO_2 118 mmHg, pCO_2 25 mmHg, HCO_3 13.8 mmol/l, BE – 11.8 mmol/l, SO_2 99 %. A chest X-ray showed a lack of inspiration and cardiomegaly impression. An examination of the lungs revealed right pericardial consolidation and bilateral pleural effusion (Fig. 2).

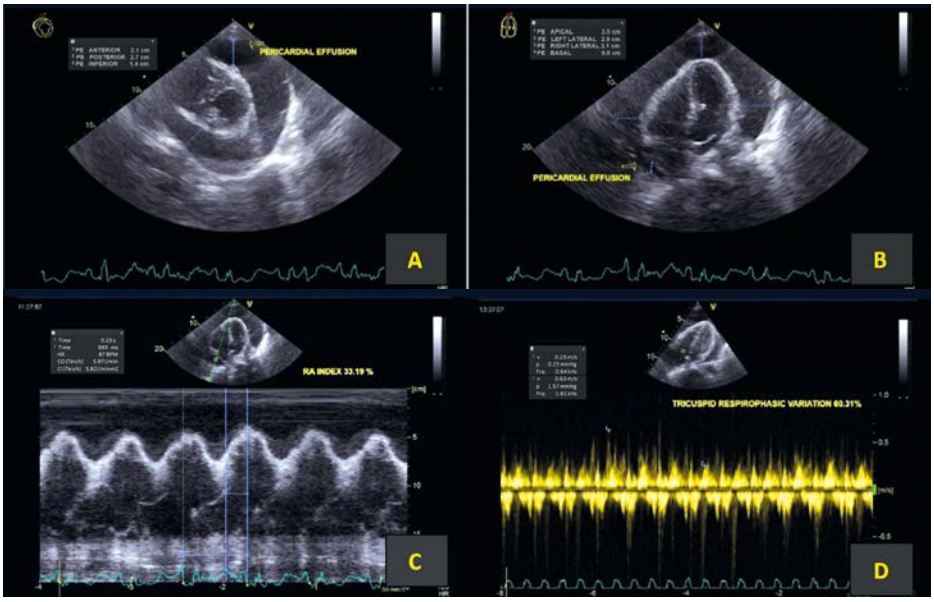
The patient underwent initial transthoracic echocardiography (TTE) (Fig. 3) with a pericardial effusion:

- massive at posterior (2.7 cm), anterior (2.1 cm), apical (2.5 cm), left lateral (2.9 cm), right lateral (2.1 cm),
- moderate at inferior (1.4 cm),
- mild at basal (0.8 cm),
- there were signs of right atrium (RA) and right ventricle (RV) collapse (RA index 33.19 %, tricuspid respirophasic variation 60.31 %).

The patient was then subjected to immediate pericardiocentesis and pigtail installation at the Cardiovascular Invasive Diagnostic Unit. We evacuated 500 ml of pericardial fluid (serohemorrhagic).

The patient was diagnosed with stage IV right lung adenocarcinoma, post pericardiocentesis massive pericardial effusion, and bilateral pleural effusion. The therapy given was O_2 nasal cannula 3 l/min, KCl infusion 50 meq

Fig. 3. *Transthoracic echocardiography before pericardiocentesis: there was massive pericardial effusion (PE) at [A] anterior (2.1 cm), [A] posterior (2.7 cm), [B] apical (2.5 cm), [B] left lateral (2.9 cm), [B] right lateral (2.1 cm); moderate PE at [A] inferior (1.4 cm); and mild PE at [B] basal (0.8 cm). There were signs of RA/RV collapse ([C] RA index 33.19 %, [D] tricuspid respirophasic variation 60.31 %)*



500 ml/24 hours, followed by NaCl infusion of 500 ml/24 hours, ranitidine 50 mg/12 hours, furosemide 20 mg/24 hours, spironolactone 50 mg/24 hours, KSR 600 mg/8 hours, paracetamol 500 mg/8 hours, and pericardial fluid tapping every 8 hours, with a maximum amount of 250 ml for each tapping.

On day 6, his complaints of shortness of breath were reduced. The average daily amount of fluid tapped was still around 150 ml of serohemorrhagic fluid per day, with a total tapping for six days around 1,263 ml. On day 7, we performed pericardial sclerosis using bleomycin preparations. Bleomycin (10 mg) dissolved in 20 ml normal saline was injected through a catheter into the pericardial cavity as a bolus within 5 minutes, followed by 10 ml of saline solution. The catheter was clamped for 2 hours, then opened again and allowed to drain. The catheter was flushed with normal saline every 12 hours. The pigtail was removed when the drain was < 25ml/24 hours and echocardiography showed minimal or no effusion.

Two days after bleomycin injection, we conducted a TTE examination. A septated pericardial effusion was found (Fig. 4):

- moderate at inferior (1.1 cm); posterior (1.4 cm); left lateral (1.5 cm); apical (1.7 cm),
- mild at anterior (0.7 cm); right lateral (0.8 cm),
- no signs of RA or RV collapse (tricuspid respirophasic variation 23.29 %).

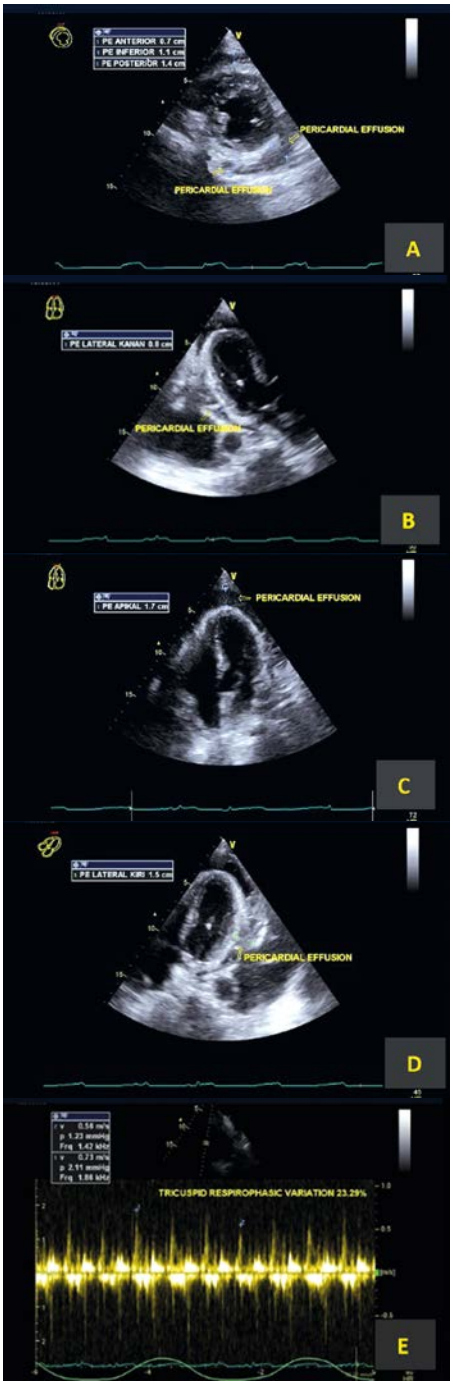
After about nine days of treatment, the patient was hemodynamically stable and could be discharged and switched to outpatient treatment. On follow-up at two weeks, one month, and three months, there was no recurrence of MPE. The patient died five months after receiving bleomycin talcage because of his lung cancer worsening.

Discussion

Malignant pericardial effusion is a local metastatic process. The administration of antineoplastic agents is not only curative, but also prevents effusion as a secondary effect. Local chemotherapy can control not only the neoplastic process, but also re-accumulation of pericardial fluid. Injection of chemotherapy agents into the pericardium, with the help of cardiac motion, allows diffusion of the agent across the surface and slow absorption back through the lymphatic vessels. Thus, this will lead to high intrapericardial chemotherapy concentrations over several days, low blood concentrations, and reduced systemic side effects (3).

Malignant pericardial effusions have many complications and are associated with a poor prognosis. Early management of effusion is usually combined with efforts to prevent recurrence by a prolonged fluid drainage and pericardial window either with or without pericardial sclerosis (5). Talcage, by administering a sclerosing agent intrapericardially, aims to produce inflammation and form scar tissue from the pericardium to the epicardium, thereby eliminating the potential space for fluid re-accumulation and preventing recurrent effusions. The many agents studied for this procedure include tetracycline and doxycycline (6), minocycline (7), thiotepa (8), platinum

Fig. 4. *Transthoracic echocardiography post-bleomycin evaluation: septated pericardial effusion (PE) was found with moderate PE at [A] apical (1.7 cm), [A] inferior (1.1 cm), posterior (1.4 cm), [D] left lateral (1.5 cm); mild PE at [B] right lateral (0.8 cm) and [A] anterior (0.7 cm). There were no signs of RA/RV collapse ([E] tricuspid respirophasic variation 23.29 %)*



derivatives (9), mitoxantrone (10), mitomycin C (11), and bleomycin (3, 12). The success rates of these various sclerosing agents range from 70 % to 90 %, with no recurring effusion within 30 days. A study by Kunitoh et al. reported a successful prevention of recurrent effusion for up to 60 days, although it was not statistically significant (p = 0.086) (12).

Bleomycin is usually used for chemotherapy in several types of malignancies, especially in squamous cell carcinoma and malignant lymphoma. Rapid fluid drainage and pericardial bleomycin administration effectively control symptoms and prevent the recurrence of effusions in the majority of patients. A previous study by Maher et al., found that 5 % of bleomycin failure bleomycin, and 19 % required a second procedure (6). Adequate therapy in cases of MPE can almost always prevent death. In chemosensitive patients, the administration of bleomycin had a fairly good survival rate.

Bleomycin is an ideal agent in the combined regimen because of its lack of significant myelosuppression. However, bleomycin has pulmonary toxicity and severe mucocutaneous side effects. Pulmonary toxicity can be progressive, irreversible, and cause respiratory failure in some cases. In 15–30 % of patients, nausea, fatigue, and anorexia occur (13). The most common manifestations of bleomycin toxicity are mucocutaneous reactions which are partially due to low levels of an enzyme that deactivates bleomycin in the skin. The onset of these skin reactions is related to the total dose and, depending on the dose and schedule of treatment, typically presents within 2–4 weeks after the start of therapy (13).

A study by Liu et al. comparing doxycycline and bleomycin found fewer side effects and a shorter length of hospital stay in the bleomycin group (14). Thus, when talcage is performed, bleomycin can be considered an active and safe agent (3). A recent study by Defruyt et al. evaluated 31 cancer patients (22 women and 9 men) presenting with cardiac tamponade who received intrapericardial bleomycin instillation (15). There was a recurrence in one patient and three cases of non-fatal complications. At the end of the study, the overall survival was less than 10 %, with a median survival of 104 days (15).

In recurrence cases, further talcage may be considered although alternative procedures to pleuro-pericardial surgery are also considered. Complete improvement was defined as the absence of fluid accumulation at first evaluation (14 days). The presence of fluid effusion which did not require pericardiocentesis was defined as partial improvement. Treatment failures were defined as patients needing repeated drainage within 14 days. The frequency of free pericardial effusion was estimated from bleomycin administration to the date of MPE recurrence, death, or final follow-up (3). Pericardial sclerosis with bleomycin seemed to be effective in preventing the recurrence of MPE, but failed to show statistical significance when compared to prolonged catheter drainage alone in one prospective randomized trial of lung cancer (12).

A randomized trial comparing prolonged drainage with the addition of intrapericardial bleomycin in lung cancer-associated MPE patients showed that two-month survival rates were better when bleomycin was administered (29 % and 46 %, respectively) (14). In a review by Jama et al. presenting the results of various procedures, extended pericardial drainage led to complete effusion resolution in only 55 % of cases (16). A recently published study by Lambert et al. evaluated 46 patients with MPE who were given bleomycin (60 mg) instillation (17). Of the 46 patients, 36 % were breast cancer patients and 26 % were lung cancer patients. The overall median survival rate was 2.6 months (95 % CI 1.7–4.7). The lung cancer subgroup had a survival rate of 18 % at three months while the breast cancer subgroup had 73 % and 46 % at three and six months, respectively (17). In this study, a rise in the overall survival with intrapericardial chemotherapy injections was not found, but an advantage in itself is the avoidance of recurrence of MPE, thus avoiding lethal doses of chemotherapy.

Poor prognosis in patients can be influenced by the patient's general condition, cancer status, previous therapy, and limitations in systemic treatment. Lung cancer is the most common malignancy with a poor prognosis. In one study, patients had a median survival of 1.5 months, suggesting that MPE recurrence was a problem for systemic care patients (3). In primary lung cancer, MPE is associated with lymphatic blockage due to involvement of mediastinal lymph nodes (N2 or N3 disease) or direct pericardial invasion. Malignancy shows a response from bleomycin injection by controlled local pericardial effusions. However, it has been noted in non-malignant diseases that the insertion of a catheter into the pericardium is necessary to avoid further effusion. To compare the intrapericardial administration of bleomycin versus pericardial drainage alone, more research is required (18). Simple pericardiocentesis is recommended in patients with a poor prognosis. Patients suitable for systemic treatment will likely benefit most from sclerosis or surgical decompression; no clear evidence currently suggests that one strategy is superior to another (3).

Conclusion

We report a patient with a history of lung cancer and recurrent MPE. We performed immediate pericardiocentesis with fixed drainage. Pericardial sclerosis with bleomycin is a safe and effective method of preventing recurrent MPE and repeated invasive procedures. This palliative procedure can improve the quality of life in patients with malignancy.

The authors declare that there is no conflict of interest.

Not applicable.

This article was presented in the poster section of the 2020 Annual Scientific Meeting of the Indonesian Heart Association (ASMIHA).

REFERENCES

1. Yonemori K, Kunitoh H, Tsuta K, et al. Prognostic factors for malignant pericardial effusion treated by pericardial drainage in solid-malignancy patients. Med Oncol. 2007; 24(4): 425–30.
2. Thurber D, Edwards J, Achor R. Secondary Malignant Tumors of the Pericardium. Circulation. 1962; 26(2): 228–41.
3. Numico G, Cristofano A, Occelli M, et al. Prolonged Drainage and Intrapericardial Bleomycin Administration for Cardiac Tamponade Secondary to Cancer-Related Pericardial Effusion. Medicine (Baltimore). 2016; 95(15): e3273.
4. Virk SA, Chandrakumar D, Villanueva C, Wolfenden H, Liou K, Cao C. Systematic review of percutaneous interventions for malignant pericardial effusion. Heart. 2015; 101(20): 1619–26.
5. Çelik S, Lestuzzi C, Cervesato E, et al. Systemic chemotherapy in combination with pericardial window has better out-

comes in malignant pericardial effusions. J Thorac Cardiovasc Surg. 2014; 148(5): 2288–93.
6. Maher EA, Shepherd FA, Todd TJR. Pericardial sclerosis as the primary management of malignant pericardial effusion and cardiac tamponade. J Thorac Cardiovasc Surg. 1996; 112(3): 637–43.
7. Lashevsky I, Yosef RB, Rinkevich D, Reisner S, Markiewicz W. Intrapericardial Minocycline Sclerosis for Malignant Pericardial Effusion. Chest. 1996; 109(6): 1452–4.
8. Martinoni A, Cipolla CM, Cardinale D, et al. Long-term Results of Intrapericardial Chemotherapeutic Treatment of Malignant Pericardial Effusions With Thiotepa. Chest. 2004; 126(5): 1412–6.
9. Maisch B. Neoplastic pericardial effusion. Efficacy and safety of intrapericardial treatment with cisplatin. Eur Heart J. 2002; 23(20): 1625–31.
10. Musch E, Gremmler B, Nitsch J, Rieger J, Malek M, Chrissafidou A. Intrapericardial Instillation of Mitoxantrone in Palliative Therapy of Malignant Pericardial Effusion. Oncol Res Treat. 2003; 26(2): 135–9.
11. Kaira K. Management of Malignant Pericardial Effusion with Instillation of Mitomycin C in Non-small Cell Lung Cancer. Jpn J Clin Oncol. 2005; 35(2): 57–60.
12. Kunitoh H, Tamura T, Shibata T, et al. A randomised trial of intrapericardial bleomycin for malignant pericardial effusion with lung cancer (JCOG9811). Br J Cancer. 2009; 100(3): 464–9.
13. Evans WE, Yee GC, Crom WR, Pratt CB, Green AA. Clinical pharmacology of bleomycin and cisplatin. Head Neck Surg. 1981; 4(2): 98–110.
14. Liu G, Crump M, Goss PE, Dancey J, Shepherd FA. Prospective comparison of the sclerosing agents doxycycline and bleomycin for the primary management of malignant pericardial effusion and cardiac tamponade. J Clin Oncol. 1996; 14(12): 3141–7.
15. Defruyt L, Özpak E, Gevaert S, et al. Malignant cardiac tamponade: safety and efficacy of intrapericardial bleomycin instillation. Acta Clinica Belgica. 2020; 1–8.
16. Jama GM, Scarci M, Bowden J, Marciniak SJ. Palliative treatment for symptomatic malignant pericardial effusion. Interact Cardiovasc Thorac Surg. 2014; 19(6): 1019–26.
17. Lambert A, Salleron J, Kieffer A, Raymond P, Geoffrois L, Gavoille C. Intrapericardial instillation of bleomycin prevents recurrence of malignant pericardial effusions: Series of 46 cases and comprehensive literature review. Bull Cancer. 2020; 107: 756–762.
18. Yano T, Yokoyama H, Inoue T, Takanashi N, Asoh H, Ichinose Y. A Simple Technique to Manage Malignant Pericardial Effusion with a Local Instillation of Bleomycin in Non-Small Cell Carcinoma of the Lung. Oncology. 1994; 51(6): 507–9.