Published in final edited form as:

Curr Opin Pulm Med. 2018 July ; 24(4): 384–391. doi:10.1097/MCP.0000000000000490.

Pleural effusions in hematologic malignancies and their management with indwelling pleural catheters

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Abstract

Purpose of the review—Pleural effusions in patients with hematologic malignancy may represent malignant pleural effusion (MPE) or occur secondary to infection, treatment effects, and other common etiologies. The impact of MPE on prognosis in this cohort remains unclear. Indwelling pleural catheters (IPCs) are routinely placed for palliation of recurrent symptomatic MPEs, but perceived concerns over infection and bleeding may limit their use in patients with hematologic malignancies. However, recent evidence suggests IPCs are both safe and effective in this cohort. In this review, the evaluation of pleural effusions in hematologic malignancies and their management with an IPC are outlined.

Recent findings—Two retrospective studies have been published regarding the use of IPCs in hematologic malignancies. Lymphomatous effusions are the most common etiology of MPE in this cohort. The rates of complications and pleurodesis with IPC in hematologic malignancies are similar to those with solid organ tumors.

Summary—Pleural effusions in patients with hematologic malignancies may be managed safely with an IPC. Sterile technique, barrier protection, standardized algorithms for placement and removal, and quality assurance initiatives are crucial to centers that place IPCs for all patients. The safety of IPC in hematologic malignancies warrants a paradigm shift in the management of pleural disease for this cohort.

Keywords

malignant pleural effusion; indwelling pleural catheter; hematologic malignancies; pleurodesis; empyema

Introduction

Malignant pleural effusions (MPEs) typically herald limited survival and advanced disease in patients with solid organ tumors, but their significance on the extent of disease and prognosis in hematologic malignancies remains unclear(1**). Unlike solid organ tumors, hematologic malignancies are often accompanied by aberrant hematologic parameters

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Conflicts of interest: No financial disclosures from any of the authors

related to myelosuppression from chemotherapy or the underlying disease with an increased risk of bleeding due to thrombocytopenia, dysfibrinogenemia or hemolysis. Management of recurrent MPEs typically includes indwelling pleural catheters (IPCs), pleurodesis with a sclerosing agent or a combination of both (2*). Data from randomized trials suggest first line therapy of recurrent MPE with an IPC is equivalent to talc pleurodesis across a variety of clinical domains, and cohort data suggests use of an IPC may be superior in terms of cost, length of hospital stay and quality of life (3–10). However, MPEs secondary to hematologic malignancy are underrepresented in these studies. Fortunately, two large retrospective studies have emerged regarding the use of IPCs in hematologic malignancies (11**, 12**). The first study is multi-centered (8 centers) reviewing 91 patients over 4 years (2009 to 2013), and the second study is single centered evaluating 172 patients over 14 years (1997 to 2011). These investigations are distinct in their methodology and follow up, but they both provide valuable information for this cohort. Our objective is to review data regarding pleural effusions in hematologic malignancies and to describe the current evidence for use of IPCs in this population.

Pleural effusions in hematologic malignancies

Etiology

Pleural effusion may occur at any time during the course of hematologic malignancies and may signal the presence of disease or indicate relapse (1**, 13). Other etiologies including infection, therapy-induced, and other systemic causes (thrombosis, liver dysfunction, cardiomyopathy, renal insufficiency, autoimmune conditions) should be carefully excluded (Figure 1). Tyrosine kinase inhibitors are now standard treatment of chronic myelogenous leukemia (CML) and other leukemias, but frequently cause pleural effusions (dasatinib in particular) (14). Treatment may require dose interruption or cessation, initiation of steroid or diuretic therapy, and pleural interventions. Radiation may be used in treatment of lymphoma and acute lymphocytic leukemia (ALL), and evaluation of the radiation field and/or pleural biopsy may help confirm the diagnosis (15).

Lymphomas are the most common hematologic malignancies associated with pleural effusions, and these effusions may occur in 30% of Hodgkin lymphoma and in up to 20% of non-Hodgkin lymphoma, but they are rarely the sole manifestation in either (16). Concurrent mediastinal lymphadenopathy often exists with both, but non-Hodgkin lymphoma may present with parenchymal infiltrates or extra-thoracic disease and without mediastinal disease. Lymphomatous effusions are typically serous or serosanguinous and exudates by Light's criteria, but they may also be chylous or transudative due to venous compression or lymphatic blockage (17). In both studies, lymphoma comprises the largest group of IPCs in hematologic malignancies (11**, 12**).

Chylous effusions may be found in 19% of non-Hodgkin lymphoma and 3% of Hodgkin lymphoma and are suspected to develop by either lymphomatous pleural infiltration, blockage of pleural lymphatic drainage, or adenopathy with obstruction of thoracic duct by tumor (1**). In the single center study, chylothorax was reported in 20% of the patients (primarily lymphoma, chronic leukemia and one multiple myeloma) (12**).

ALL and chronic lymphocytic leukemia (CLL) are both leukemic variants of lymphoid neoplasms. ALL may present with a mediastinal mass and pleural or pericardial effusion. The pleura, central nervous system and testes are common sites of relapse (15). Pleural effusions in CLL typically occur in advanced disease or indicate a synchronous cancer, of which melanoma, sarcoma and lung cancer are the most frequent (18, 19).

Pleural effusions in acute myelogenous leukemia (AML), ALL, myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN) are rare. In a 10 year series of 111 patients with pleural effusion and acute leukemia at our institution, the most frequent cause was infection (47%) followed by malignancy (36%) (20). Similarly, earlier autopsy series for acute leukemia also describe parapneumonic effusions as the most common etiology (21). MPEs in this series were typically large in volume (greater than 1.5 L), exudates, and serosanguinous or sanguineous (15). IPCs were placed in 6% of the cohort. Evidently, MPE in multiple myeloma is rare and may be related to extramedullary disease and amyloidosis, but in general, pleural effusions in this populations are often due to cardiac dysfunction, renal insufficiency and thrombosis (13, 22).

Diagnostic workup

The diagnosis of MPE in hematologic malignancies may be challenging. Analysis of pleural fluid should include standard biochemical analysis, cell count with differential, cultures, and cytology. Especially in hematologic malignancies, flow cytometry and special immunohistochemical studies may aid in diagnosis (15). In the multi-center study, MPE was confirmed through a combination of pleural fluid cytology (46%) and pleural biopsy (9%). An additional 26% of patients were suspected of having MPEs but were not confirmed (11**). Some (7%) IPCs were placed in transudates. In the single-center study, IPCs were placed for recurrent and/or symptomatic effusions with mainly exudative (87.8%) etiology (12**). MPE was confirmed in 85.5% via a combination of cytology, flow cytometry, and pleural biopsy. Malignant pleural effusion was most common among patients undergoing IPC placement, particularly those with lymphoma and chronic leukemia. Infection and volume overload were the second most frequent etiologies in acute leukemia and multiple myeloma, respectively.

In cases where an etiology remains unclear, meticulous review to exclude infection, volume overload, thrombosis and therapy-related causes should be performed. A bone marrow biopsy may help elucidate relapsed or transformation of disease (15). Finally, image-guided or thorascopic pleural biopsies may be considered to help guide further management (Figure 2). In the single center study, pleural biopsies were performed in 8% patients and confirmed the following etiologies: malignancy (3.5%), infection (1.2%), therapy related (1.7%), volume overload (1.2%) (12**).

Prognosis

The impact of MPE in hematologic malignancies on prognosis remains unclear and may vary based on the underlying malignancy. The LENT score was developed to assist with prognostication of patients with MPE using pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group performance score, neutrophil-to-lymphocyte ratio and tumor

type. Hematologic malignancies were classified as having a favorable prognosis (23). However, of the 789 patients studied, only 35 (4%) had a hematologic malignancy (all lymphoma), and their median survival after first diagnosis of MPE was 218 days (95% CI 160–484). Therefore, the applicability of the LENT to this population is limited, although the median survival noted in this study was similar to the one reported for lymphoma in the single center study (12**).

The single center study has the largest population of both hematologic malignancies and non-lymphomatous hematologic malignancies with IPCs to date, with at least 6 months of follow up over a 14 year period (12**). Overall survival in the single center study, stratified by malignancy type following IPC insertion, was longer in the lymphoma and chronic leukemia groups, compared with acute leukemia and multiple myeloma (Figure 3A) (12**). Interestingly, overall survival stratified by malignancy type from time of diagnosis, revealed that once pleural effusion develops in chronic leukemia, it follows a course similar to lymphoma, likely due to similar lymphoid origin (Figure 3B). Limited survival after pleural effusion has been reported previously for both acute leukemia and multiple myeloma (20, 22). In the 10 year series of acute leukemia and MDS/MPN, multivariate analysis revealed that older age, AML, MDS/MPN and active disease status were associated with a shorter median overall survival (20). Although there may be some trends present with pleural effusions and hematologic malignancies, further prospective study is needed.

Procedural aspects and complications

A clinical algorithm for IPC placement and management are detailed in Table 1 (12**, 24). A standardized location and sterile drapes and gowns are strongly recommended for IPC placement. Use of established guidelines for placement and removal of IPC, implementation of algorithms to manage complications and quality assurance initiatives are important for institutions that place IPCs as interventions have been shown to decrease complications (25–27).

Typical complications related to IPCs include catheter malfunction, catheter dislodgement, infection, pain, tract metastases and bleeding. Previously published reports of IPC in all MPEs report a complication rate ranging from 1 to 12% (28–31). Among patients with hematologic malignancies receiving an IPC, the cumulative incidence of all significant catheter-related complications was comparable at 9.5% (12**).

The risk of infection is the most commonly perceived concern for IPC placement in hematologic malignancies, primarily in the context of immunosuppression. However, there have been several studies corroborating the safety of IPCs in patients undergoing chemotherapy (31–33). In a recent study, 72% of the patients were undergoing active chemotherapy, and multivariate analysis revealed that the absolute neutrophil count was not independently associated with an increased risk of complications (12**). The rate of empyema in a meta-analysis of all patients with MPE who received an IPC was 2.8% (33). Among patients with hematologic malignancies, empyema occurred in 7% of patients in the multi-center study and in 2.9% of patients in the single center study (11**, 12**, 34). Differences in empyema rates may be partially attributed to differences in institutional

practice and follow up. The rate of empyema in the single center study is similar to solid organ tumors.

Risk of bleeding at the time of insertion or removal is another major concern in this population. The single center study reported a 1.7% risk of bleeding compared with 0.4% in the IPC meta-analysis (12**, 34). The tunneling involved for IPC placement may result in greater vascular disruption with continuous oozing or hematoma formation if hematologic parameters are abnormal. Adherence to guidelines for placement and removal may decrease the risk of bleeding (Table 1).

Finally, there have been concerns about immunosuppression, electrolyte imbalance and nutritional deficiencies with drainage of chylous effusions. A small retrospective study from our institution of patients with chylous MPE demonstrated that an IPC provided palliation without a rapid decline in albumin levels and decreased the risk of a second pleural intervention (35–37). In the more recent study, chylothorax had no effect on the cumulative incidence of pleurodesis or significant complications (12**).

Outcomes

Symptoms

The primary function of an IPC for MPE is palliative symptom relief, and large studies and a meta-analysis have demonstrated symptom relief in 94.2% of subjects (2, 33, 34, 38). The IPC also enables patients and their caregivers to manage recurrent MPE at home and often avoid or reduce hospitalizations (2, 3, 7).

Pleurodesis

Pleurodesis is a secondary outcome, and in a systematic review, pleurodesis rates are lower with IPC compared to other palliative measures (45.6% with median time to pleurodesis of 52 days) (34). However, only a fraction these studies included hematologic malignancies, and pleurodesis rates stratified by tumor type are not available. The recent multi-center study reported a pleurodesis rate of 21% (21 of 97 patients) with a median time to catheter removal of 63 days (11**). The cumulative incidence of pleurodesis in the recent single center study was 49% (85 of 172 patients) by 180 days with a median time to catheter removal of 81 days (12**). In the medical literature to date, data on pleurodesis is confounded by high mortality rates, the definition of pleurodesis used, follow-up duration, and study design, so the rates of pleurodesis between studies are rarely directly comparable. However, the information available suggests that a reasonable proportion of patients with hematologic malignancies and MPE managed with an IPC will achieve pleurodesis at rates similar to those with solid organ tumors.

Quality of Life

Studies evaluating quality of life using validated tools show significant benefit with IPCs (8–10). A study from our institution followed 266 patients with MPE prospectively after placement of an IPC and demonstrated a median quality-adjusted survival of 95.1 quality-adjusted life days; 12.8% of these patients had hematologic malignancies (8).

Cost

The true cost of MPE on health care systems is unknown, however, given that in solid organ tumors it signals advanced disease and high mortality, the financial impact is likely significant. A recent large retrospective study evaluating MPE-related hospitalizations in the United States in 2012 reviewed more than 125,000 hospitalizations per year and estimated annual charges greater than 5 billion (39*). The primary tumors in order of frequency were lung (37.8%), breast (15.2%), unknown primary (11.2%), hematologic (11.2%) and gastrointestinal (11.0%). The median length of stay in patients with MPE was 5.5 days and factors independently associated with a prolonged length of stay included a primary cancer diagnosis of the gastrointestinal tract or a hematologic malignancy (39*). In both the recent single center and multi-center studies on hematologic malignancies, the majority of IPCs were placed in hospitalized patients.

A large retrospective cohort study using SEER-Medicare data from 2007 to 2011 identified thoracentesis for MPE in 23,431 patients, of which a second pleural procedure was required in 55%, and more than half of the recurrent effusions occurred within 2 weeks (40). The majority of patients had solid organ tumors, but in the group with rapidly reaccumulating pleural effusions, 8.3% had lymphoma. The authors identified a quality gap in the appropriate use of definitive pleural intervention, with the majority only receiving a repeat thoracentesis for rapidly recurrent MPE. They found that definitive pleural procedures compared with repeat thoracenteses resulted in fewer subsequent pleural procedures, pneumothoraces and emergency room procedures (40). In hematologic malignancies, definitive procedures may also be delayed due to aberrant hematologic parameters or perceived risk of infection, so these patients may also fall into this quality gap but for different reasons. However, there are no studies specifically addressing healthcare cost in this population.

The main expenses associated with IPCs are contingent on the length of time the catheter remains in place (drainage supplies, clinic visits), the occurrence and extent of complications, and the possible need for professional domiciliary assistance. Evaluation of clinical data from the Second Therapeutic Intervention in Malignant Effusion (TIME2) trial concluded no significant difference in the mean cost of IPC versus talc pleurodesis, and for patients with limited survival, IPC is less costly (6). A cost analysis specific to hematologic malignancies is not available, and since survival of hematologic malignancies may vary significantly, further study is needed regarding cost-effectiveness. Further analysis including morbidity and mortality with each procedure as well as cost and sequelae of blood product transfusions would also need to be incorporated.

Conclusion

Pleural effusions in hematologic malignancies may represent MPE once infection and other common etiologies are excluded. The poor prognosis associated with pleural effusions in solid organ tumors does not necessarily occur with all hematologic malignancies. Sterile technique, barrier protection, standardized algorithms for placement and removal, and quality improvement initiatives are crucial to centers that place IPCs for all patients. Pleural effusions in hematologic malignancies may be managed safely with an IPC. The rates of

complications and pleurodesis with IPC in hematologic malignancies are similar to those with solid organ tumors. The safety of IPC in hematologic malignancies warrants a paradigm shift for management of pleural disease in this cohort.

Acknowledgments

Funding: This research is supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant (CA016672).

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Key points

1. Pleural effusions in hematologic malignancies are most commonly related to infection, malignant disease, therapy (radiation or chemotherapy), or volume overload, but lymphatic blockage or thromboembolic disease may also occur.
2. Indwelling pleural catheters may be performed safely in both hematologic and solid organ malignancies with similar complication profiles.
3. With image guidance and optimization of hematologic parameters, indwelling pleural catheters can be safely placed in patients with hematologic malignancies.
4. If the etiology of a pleural effusion is not evident after close review of pleural fluid studies and clinical findings, then pleural and/or bone marrow biopsies should be considered.
5. Pleural effusions in hematologic malignancies do not necessarily portend poor prognosis as they do in solid organ tumors.

Figure 1. Pleural effusion related to treatment effect

84 year old woman with history of lymphoma recently treated for squamous cell carcinoma of the right lung treated with radiotherapy. She presented 3 months later with recurrent right pleural effusion. Pleural biopsy revealed exuberant mesothelial cell hyperplasia, reactive atypia, acute and chronic inflammation, and giant cell reaction. Hematoxylin and eosin (H&E) stain (A, magnification 100x) shows chronic inflammatory lymphoid aggregates on the left and atypical mesothelial cells on the right, and keratin staining (B, magnification 40x) highlights the mesothelial cells. Radiation simulation (C) of the right lung mass and hemithorax is shown. (Pleural biopsy images courtesy of George A. Eapen, MD and pathologic images courtesy of John Stewart, MD)

Figure 2. Malignant pleural effusion in hematologic malignancy

41 year old woman with history of CLL and secondary AML presented with recurrent right pleural effusion with negative cytology. Pleural biopsy confirmed extramedullary myeloid proliferation consistent with disseminated acute myeloid leukemia. Hematoxylin and eosin (H&E) stain (A, magnification 200x) shows myeloid blasts infiltrating pleura, and CD43 immunostains (B, magnification 100x) highlights blast cells. 74 year old woman with history of breast cancer and synchronous pancreatic adenocarcinoma and marginal zone lymphoma. She developed recurrent left pleural effusion after 3 cycles of gemcitabine. Pleural biopsy revealed low grade B-cell Lymphoma plasmacytoid differentiation consistent with marginal zone lymphoma. H&E stain (C, magnification 40x) shows diffuse infiltration and thickening of the pleural by lymphoid proliferation, and bcl2 immunostain (D, magnification 100x) demonstrates diffuse strong expression in neoplastic B-cell infiltrating pleura. (Pleural biopsy images (A, B) courtesy of Carlos A. Jimenez, MD and images (C,D) courtesy of Horiana B. Grosu, MD; pathologic images courtesy of John Stewart, MD)

Figure 3.

Overall survival by (A) hematologic group (since malignancy diagnosis) and by (B) hematologic group (since indwelling pleural catheter insertion) (12**)

Log-rank p-value<0.0001.

The median overall survival (OS) time from cancer diagnosis was 45.6 months (95% CI, 27.6-63.8) for the entire cohort. Median OS times from cancer diagnosis were 51.1 months (26.3-74.8) for lymphoma, 12.5 months (9.4-27.3) for acute leukemia, 106.8 months (65.3-134.7) for chronic leukemia, and 23.7 months (9.8-44.9) for multiple myeloma.

Log-rank p-value=0.0009.

The median overall survival (OS) time from indwelling pleural catheter (IPC) insertion was 5.5 (95% CI, 3.5-8.0) months for entire group. Median OS times (95% CI) from IPC insertion were 9.1 months (3.7-16.3) for lymphoma, 1.9 months (1.1-6.1) for acute leukemia, 5.2 months (1.9-11.0) for chronic leukemia, and 3.0 months (0.7-7.2) for multiple myeloma.

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Table 1

Clinical algorithm for indwelling pleural catheter placement and management (12**, 24)

Clinical Scenario	Recommendation
Prior to placement and removal	<ul style="list-style-type: none"> ■ Platelet count ≥ 30 K/uL ⁺ ■ INR ≤ 1.5 ■ For patients receiving the following medications if not contraindicated(24) [^]: <ul style="list-style-type: none"> ◆ Stop enoxaparin (bid dosing) for ≥ 12 hours prior ◆ Stop unfractionated heparin drip for ≥ 4 hours prior ◆ Clopidogrel will be stopped ≥ 5 days ◆ Aspirin does not need to be stopped and should be continued for patients with vascular stents ◆ For other anticoagulants and anti-platelet agents [*]
During placement	<ul style="list-style-type: none"> ■ Sterile gown, mask, gloves and surgical hat for proceduralist(s) ■ Surgical hat and mask for any provider in the procedure room ■ Sterile drape over procedure field and full body draping ■ Placement of IPC using sterile technique
After placement	<ul style="list-style-type: none"> ■ For those receiving platelet transfusions for platelet count, maintain platelet count ≥ 30 K/uL for 48 to 72 hours ■ Educate patient and family member on the care and drainage of IPC ■ Resume anticoagulation or anti-platelet therapy within 12 to 48 hours if no procedural issue and/or clinically feasible
Follow up	<ul style="list-style-type: none"> ■ Initial follow up 10 to 14 days for suture removal ■ Monthly follow up in clinic with chest radiograph ■ Continued patient and family member education on the care and drainage of IPC
Drainage	<ul style="list-style-type: none"> ■ Drain daily until output < 150 cc or less for 3 days in a row, then continue with alternate day drainage. ■ If drainage ≥ 150 cc, then to return to daily drainage. ■ If drainage remains < 150 cc then schedule follow up in clinic for imaging and removal of IPC

INR, international normalized ratio; bid, twice daily dosing; IPC, indwelling pleural catheter

⁺In those with a platelet count correctable to 30 K/uL, consider platelet transfusion prior to placement or removal[^]These are general recommendations intended to provide a reference to the clinical team regarding the risks of bleeding associated with these interventions. These recommendations are not meant to be inclusive of all risks for bleeding and are not intended to be used during urgent situations or to prevent a clinician from performing an intervention when these parameters are not met but the perceived benefits of the procedure outweigh potential risks. Appropriate documentation in the medical record pertinent to risks and benefits of the intervention is indicated.^{*}Anticoagulants and anti-platelets agents should be held depending on dosing and half-life for 12 to 48 hours depending on their pharmacodynamicsReprinted with permission of the American Thoracic Society. Copyright ©2018 American Thoracic Society (12**). *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society