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Combination Tissue Plasminogen Activator and DNase for Loculated Malignant Pleural Effusions

A Single-center Retrospective Review

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Background: **Indwelling pleural catheters (IPCs) are frequently used for the management of malignant pleural effusions (MPEs), but drainage can be impaired by pleural loculations. We aimed to evaluate the safety and effectiveness of intrapleural tissue plasminogen activator (tPA) versus combination tPA-deoxyribonuclease (DNase) in the treatment of loculated MPE.**

Methods: **We performed a retrospective review of patients with confirmed or presumed MPEs requiring IPC insertion. We compared the efficacy of intrapleural tPA, tPA-DNase, and procedural intervention on pleural fluid drainage. Secondary endpoints included the need for future pleural procedures (eg, thoracentesis, IPC reinsertion, chest tube insertion, or surgical intervention), IPC removal due to spontaneous pleurodesis, and IPC-related complications.**

Results: **Among 437 patients with MPEs, loculations developed in 81 (19%) patients. Twenty-four (30%) received intrapleural tPA, 46 (57%) received intrapleural tPA-DNase, 4 (5%) underwent a procedural intervention, and 7 (9%) received ongoing medical management. tPA improved pleural drainage in 83% of patients, and tPA-DNase improved pleural drainage in 80% of patients. tPA alone may be associated with increased rates of spontaneous pleurodesis compared with tPA-DNase. There was no difference in complications when comparing tPA, combination tPA-DNase, procedural intervention, and no therapy.**

Conclusion: **Both intrapleural tPA and combination tPA-DNase appear to be safe and effective in improving pleural fluid drainage in selected patients with loculated MPE, although further studies are needed.**

Key Words: pleural effusion, chest tube, indwelling pleural catheter, lung cancer

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Malignant pleural effusions (MPEs) are a common cause of morbidity, with an annual incidence of over 150,000 cases in the United States alone.[1] Indwelling pleural catheters (IPCs) have emerged as a first-line intervention option for symptomatic MPE.[2] Increased procoagulant and decreased fibrinolytic activity in malignant pleural diseases lead to excessive fibrin deposition and formation of pleural septations, a mechanism similar to that seen in parapneumonic effusions and tuberculous pleurisy.[3,4] This can complicate drainage of the pleural space, leaving the patient with disabling dyspnea.

Three randomized trials with moderate sample sizes (ranging from 40 to 71 patients) have demonstrated that intrapleural instillation of fibrinolytics in patients with MPEs results in improved radiographic appearance following instillation.[5–7] The use of combination tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) in the treatment of loculated MPE, however, has not been well studied due to theoretical concerns of pleural hemorrhage. Pleural malignancy stimulates the formation of new blood vessels, which can be friable and increase the risk of bleeding.[8] Combination tPA-DNase has been used successfully for the treatment of loculated pleural infections. A landmark trial in 2011 showed that combination therapy

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improved the radiographic appearance of effusions, decreased surgical referrals, and decreased hospital length of stay compared with placebo, with no difference in adverse events.[9] One retrospective review of 21 patients with symptomatic loculated MPE and nondraining IPC or chest tube demonstrated that combination tPA-DNase resulted in improved radiographic appearance of MPEs, increased pleural fluid drainage, and improved dyspnea scores with no noted pleural bleeding.[10] However, this study did not provide a control arm. The role of combination intrapleural tPA-DNase for loculated MPE is the subject of an upcoming small clinical trial.[11]

Given the lack of definitive data surrounding the treatment of loculated MPE, patients in our clinic have been variably treated with tPA or combination tPA-DNase (off-label) or in some cases, procedural intervention. We aimed to review patients with loculated MPEs to evaluate the safety and effectiveness of intrapleural tPA versus combination tPA-DNase in the treatment of loculated MPEs.

METHODS

Patient Population

Our tertiary care center has established a specialized pleural effusion clinic that includes interventional respirologists, thoracic surgeons, and specialized nurse practitioners. We performed a retrospective single-center review of patients with confirmed or presumed MPEs requiring IPC insertion by a physician associated with our pleural effusion clinic. Patients who had their IPCs inserted between November 1, 2012, to December 31, 2018, were considered for enrollment, and data were extracted up to December 31, 2019. Patients were included if they developed significant pleural loculations, defined as a nondraining IPC with loculations that were verified on bedside ultrasound associated with significant respiratory symptoms. This study was approved by the University of Alberta Research Ethics Board (Pro00108928).

Procedures

Patients at our pleural effusion clinic are followed by physicians and nurse practitioners until IPC removal or death. A follow-up chest x-ray and clinical assessment occurs 2 weeks after IPC insertion and every 3 months thereafter. Procedures are performed in an outpatient setting. Nondraining IPCs with significant pleural effusion and loculations are initially flushed with saline. If unsuccessful, patients are presented with the options of intrapleural fibrinolytic therapy (tPA or combination tPA-DNase), procedural intervention (thoracentesis, replacement of the IPC, or surgical intervention), or conservative medical management. The choice between tPA and tPA-DNase (usually 10 and 5 mg, respectively) is left to the discretion of the treating physician. In some cases, the physician may suggest procedural intervention, for example, if the complexity of the pleural space may render fibrinolytic therapy futile or if the current IPC does not access the dominant fluid pocket. The final therapeutic decision is ultimately determined by the treating physician in consultation with the patient, following a discussion of the benefits and risks of each option, considering comorbidities, the success of prior therapies, and patient preference.

Outcomes

The primary outcome was an improvement in respiratory symptoms, or if this was not documented, an increase in IPC drainage volume or decrease in pleural effusion on subsequent chest x-ray was used as a surrogate. Secondary endpoints included repeat pleural procedures (eg, thoracentesis, IPC reinsertion, chest tube insertion, or surgical intervention), IPC removal due to spontaneous pleurodesis, and IPC-related complications including pleural infection, skin infection, hemorrhage requiring transfusion, catheter tract metastasis, IPC-related hospitalization, and IPC-related death. As a tertiary objective, we also aimed to characterize the natural history, prognosis, and complications of IPCs and pleural fluid loculations.

Statistical Analysis

We summarized the demographic and clinical characteristics of patients with symptomatic loculated MPEs using descriptive statistics. For the primary outcome, we constructed frequency tables based on each intervention and used bivariate logistic regression to estimate the odds ratio with associated 95% confidence intervals of each intervention compared with tPA as the reference. For the secondary outcomes of pleurodesis, repeat procedure, and complications, we conducted survival analysis using cumulative incidence functions with death as a competing risk. Patients were censored if they did not meet the outcome of interest or death by the end of the study period. We then used the Fine-Gray subdistribution hazard model to estimate the hazard

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TABLE 1. Characteristics of Patients With Loculated Nondraining IPCs

	n (%)				
Characteristics	**Total**	**No Intervention**	**tPA**	**tPA-DNase**	**Procedural Intervention**
N	81	7	24	46	4
Age at first IPC insertion (mean ± SD) (y)	65 ± 13	71 ± 9	61 ± 12	66 ± 14	57 ± 8
Female	50 (62)	3 (43)	14 (58)	30 (65)	3 (75)
30+ pack-year smoking history	29 (36)	1 (14)	9 (38)	17 (37)	2 (50)
Malignancy diagnosis					
Lung malignancy	41 (51)	3 (43)	14 (58)	23 (50)	1 (25)
Breast malignancy	22 (27)	2 (29)	7 (29)	11 (24)	2 (50)
Gastrointestinal malignancies	4 (5)	2 (29)	0 (0)	2 (4)	0 (0)
Gynecologic/peritoneal malignancies	4 (5)	0 (0)	1 (4)	3 (7)	0 (0)
Renal/urothelial malignancies	4 (5)	0 (0)	1 (4)	2 (4)	1 (25)
Other*	6 (7)	0 (0)	1 (4)	5 (11)	0 (0)
Right-sided effusion	35 (43)	5 (71)	12 (50)	17 (37)	1 (25)
Positive pleural cytology/biopsy†	55 (77)	4 (57)	15 (83)	32 (76)	4 (100)
IPC placed percutaneously‡	77 (95)	6 (86)	22 (92)	46 (100)	3 (75)
Treatment received during IPC					
Chemotherapy	24 (30)	2 (29)	10 (42)	11 (24)	1 (25)
Immunotherapy	10 (12)	1 (14)	5 (21)	3 (7)	1 (25)
Targeted therapy	17 (21)	2 (29)	5 (21)	9 (20)	1 (25)
Hormonal therapy	6 (7)	2 (29)	0 (0)	4 (9)	0 (0)
Chest radiation	10 (12)	0 (0)	3 (13)	6 (13)	1 (25)
Complications					
Any complication	14 (17)	0 (0)	4 (17)	10 (22)	0 (0)
Hemorrhage requiring transfusion	1 (1)	0 (0)	0 (0)	1 (2))	0 (0)
Pleural infection	7 (9)	0 (0)	1 (4)	5 (11)	1 (25)
Skin/soft tissue infection	10 (12)	0 (0)	2 (8)	7 (15)	1 (25)
Catheter tract metastasis	3 (4)	0 (0)	0 (0)	3 (7)	0 (0)
IPC-related ER visit/hospitalization	6 (7)	0 (0)	2 (8)	4 (9)	0 (0)
IPC-related death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IPC final outcome					
Removed for autopleurodesis	19 (23)	0 (0)	10 (42)	8 (17)	1 (25)
Removed for nondraining loculations	25 (31)	5 (71)	3 (13)	15 (33)	2 (50)
Removed for other reasons§	10 (12)	1 (14)	5 (21)	4 (9)	0 (0)
Dead with IPC in situ	27 (33)	1 (14)	6 (25)	19 (41)	1 (25)
Mortality	68 (84)	6 (86)	19 (79)	40 (87)	3 (75)

*Other malignancies included mesothelioma (n = 3), sarcoma (n = 2), and hematologic malignancy (n = 1).
†Available for n = 71.
‡IPCs were placed either percutaneously (noninvasively at bedside) or via video-assisted thoracoscopic surgery.
§Other reasons included no symptom benefit, malfunction or migration, complications, other.
ER indicates emergency room; IPC, indwelling pleural catheter.

ratio and associated 95% confidence intervals of each intervention compared with tPA as the reference. For patients who had multiple IPCs during the study period, only the first IPC with loculations was included. All analyses were performed using SAS 9.4 software. Statistical significance was defined as P-value <0.05 for all analyses.

RESULTS

A total of 437 patients with MPEs were identified, and 515 IPCs were inserted. The rate of spontaneous pleurodesis in our cohort was 30%. The rate of any complication was 7%, including skin/soft tissue infection in 4%, pleural infection in 3%, and IPC-related emergency room (ER) visit or hospitalization in 2%. Mortality at the end of the study period was 86%.

Eighty-one (19%) patients developed symptomatic loculated effusions with nondraining IPCs. Among these patients, 24 (30%) received intrapleural tPA, 46 (57%) received tPA-DNase, 4 (5%) had a repeat pleural procedure, and 7 (9%) had no pleural intervention. A summary of clinical and demographic data for patients with loculated MPE is provided in Table 1. Of the patients that received tPA monotherapy, only 3 were on anticoagulant therapy. The median number of doses was 1, the mean number of doses was 1.53, and up to 6 doses were administered. Among the patients who received a procedural intervention, 2 underwent thoracentesis, 1 received a chest tube, and 1 underwent thoracic

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TABLE 2. Outcomes of Patients With Loculated Nondraining Indwelling Pleural Catheters

	tPA	tPA+DNase	Procedural Intervention	No Therapy
Total	24	46	4	7
Improved drainage*				
n (%)	20 (83)	35 (80)	3 (75)	0 (0)
OR (95% CI)	Reference	0.82 (0.23-2.92)	0.51 (0.05-5.53)	0.02 (<0.001-0.37)
Repeat procedure†				
n (%)	4 (17)	12 (26)	2 (50)	3 (43)
HR (95% CI)	Reference	1.54 (0.48-4.89)	3.90 (0.65-23.58)	2.80 (0.63-12.35)
Autopleurodesis				
n (%)	11 (46)	9 (20)	1 (25)	0 (0)
HR (95% CI)	Reference	0.36 (0.15-0.84)	0.48 (0.06-3.79)	0
Any complication				
n (%)	4 (17)	10 (22)	0 (0)	0 (0)
HR (95% CI)	Reference	1.30 (0.41-4.16)	0	0

*Unavailable outcome data for 2 patients.
†Procedures included thoracentesis, chest tube/indwelling pleural catheter insertion, or thoracic surgery.
CI indicates confidence interval; DNase, deoxyribonuclease; HR, hazard ratio; OR, odds ratio; tPA, tissue plasminogen activator.

surgery. Table 2 outlines the safety and efficacy of tPA-DNase, procedural intervention, and no therapy compared with tPA as the standard.

Efficacy of Intrapleural Therapy

Intrapleural tPA, tPA-DNase, procedural intervention, and no therapy was effective in 83%, 80%, 75%, and 0% of patients, respectively (Table 2). Two patients who received intrapleural tPA-DNase were excluded from analysis due to unavailable outcome data. Of patients in whom intervention was effective, 41% had documented improvement in breathlessness and/or other respiratory symptoms, whereas in 59% improved drainage volume or chest x-ray appearance was used as a surrogate marker of efficacy. Intrapleural tPA, tPA-DNase, or procedural intervention all resulted in improvements compared with no therapy, however, neither tPA-DNase nor procedural intervention was associated with improved drainage compared with tPA.

Secondary Outcomes

Repeat pleural procedures were required in 17%, 26%, 50%, and 43% of patients in the tPA, tPA-DNase, procedural intervention, and no therapy groups, respectively (Table 2). These included thoracenteses, chest tube insertion, reinsertion of an IPC, or surgical intervention.

Spontaneous pleurodesis resulting in catheter removal occurred in 46% of patients treated with tPA versus 20% of patients treated with tPA-DNase (hazard ratio = 0.36, 95% confidence interval: 0.15-0.84; Table 2). Among patients who achieved pleurodesis, median time to pleurodesis was 30 days following first fibrinolytic instillation in the tPA group versus 34 days in the tPA-DNase group. Pleurodesis did not occur in any patients in the no therapy group and in only 1 patient in the procedural intervention group following thoracic surgery with placement of a new IPC.

There was no difference in total complications when comparing tPA versus tPA-DNase (Table 2). In particular, only 1 patient, who was on rivaroxaban for atrial fibrillation, received tPA-DNase and subsequently developed a hemothorax requiring transfusion. There were no IPC-related deaths. Skin/soft tissue infections and pleural infections developed in 12% and 9% of patients who had loculated MPEs, compared with 4% and 3% in our total cohort. Overall, 7% of patients with loculated MPE had an IPC-related ER visit or hospitalization, compared with 2% in our total cohort.

DISCUSSION

Patient demographic and clinical data, including age, sex, and underlying cancer diagnosis, were grossly similar in our cohort compared with those reported in contemporary studies.[7,12,13] Loculations developed in 19% of patients in our cohort, which is similar to recent cohorts as well.[7,13–15]

Our data demonstrate that IPCs and intrapleural fibrinolytic therapy are safe with low complications rates and no IPC-related deaths in our highly selected patient population.[7,12,13] The somewhat higher complication rate among patients with loculated MPE appears to be driven by infections and ER visits/hospitalizations. The former is likely related to the predilection of pleural infection to form loculations, and the

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latter seems unsurprising given loculations impair IPC drainage, which may increase symptom burden and result in a hospital visit. Importantly, the rate of significant hemorrhage (defined as those requiring transfusions) following intrapleural tPA or tPA-DNase administration was low and not increased compared with those who did not receive any therapy.

Overall, 9% of patients with IPCs complicated by significant loculations did not receive any intrapleural therapy, despite benefit noted in prior studies. Most of these instances occurred earlier on in our cohort when tPA use had not yet become widespread practice. Given that both tPA or tPA-DNase appeared to be associated with a decreased need for future pleural procedures compared with no therapy, it may be reasonable to trial tPA or tPA-DNase before proceeding to further procedural interventions, particularly given both have an acceptable safety profile. In our cohort, up to 6 doses of fibrinolytics were administered with ongoing benefit.

In our center, the use of tPA was associated with higher rates of spontaneous pleurodesis compared with tPA-DNase. The reason for this discrepancy is unclear. Given this was a retrospective study and the choice of intrapleural therapy was left to the discretion of the treating physician, there may be an inherent selection bias to the cohort of patients that received a particular treatment, though it did not appear to be solely related to anticoagulation. Alternatively, this could be a spurious result due to small sample size. In the MIST2 trial of intrapleural tPA-DNase for the treatment of empyema, authors postulated that DNase was required to cleave free extracellular DNA and other bacterial components, reducing fluid viscosity and thus permitting pleural clearance by fibrinolytic drugs.[9] MPEs have a far lower burden of extracellular DNA, reducing the need for DNase.[16]

There are several limitations to this study, most notably its retrospective nature and small sample size, in particular for patients treated with repeat procedures. There was no formal protocolized manner in which a particular intervention was selected outside of standard risk-benefit discussion between physicians and patients, which increases the potential for selection bias. Our combined primary outcome of increased drainage, decreased dyspnea, or improved chest x-ray was broadly defined given the retrospective nature of our study. We did not correct for multiple comparisons, and could not control for confounders that may potentially affect outcome (eg, malignancy subtype, pleural fluid parameters) given the small sample size and retrospective design. However, this study has several strengths. It is the largest review of patients who received tPA-DNase for loculated MPE and the first to compare intrapleural tPA-DNase to tPA monotherapy or no therapy.

In conclusion, there was no difference between tPA versus combination tPA-DNase on pleural drainage in patients with nondraining IPCs due to pleural loculations, though both improved drainage compared with no therapy. Both intrapleural tPA and combination tPA-DNase were safe in a selected population, with low risk for complications including pleural hemorrhage. Overall, our data supports a trial of either tPA or combination tPA-DNase for loculated MPE, although tPA alone may be sufficient. Given this was a retrospective single-center study with limited sample size, further prospective studies are needed to characterize the optimal management of nondraining IPCs.

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