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Characteristics and Long-term Outcomes of Pulmonary Venocclusive Disease Induced by Mitomycin C

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BACKGROUND: Pulmonary venocclusive disease (PVOD) is an uncommon form of pulmonary hypertension (PH) predominantly characterized by pulmonary vein and capillary involvement. An association between chemotherapy, in particular mitomycin C (MMC), and PVOD has been reported.

RESEARCH QUESTION: What are the characteristics of MMC-induced PVOD, and what is the prognosis for patients with MMC-induced PVOD?

STUDY DESIGN AND METHODS: We report the clinical, functional, radiologic, and hemodynamic characteristics at diagnosis and outcomes of patients with PVOD from the French PH Registry after exposure to MMC. The results are expressed as the median (minimum-maximum).

RESULTS: From June 2011 to December 2018, 17 incident cases of MMC-induced PVOD were identified. At diagnosis, these patients had severe clinical and functional impairment, with 12 patients having a New York Heart Association (NYHA) functional class of III or IV and a 6-min walk distance of 220 (0-465) m. Right heart catheterization confirmed severe precapillary PH with a mean pulmonary artery pressure of 38 (30-52) mm Hg, a cardiac index of 2.2 (1.5-4) L/(min × m²), and pulmonary vascular resistance of 8.3 (5.1-14.5) Wood units. The diffusing capacity of the lungs for carbon monoxide was markedly decreased at 31% (20%-51%) of the theoretical values associated with severe hypoxemia. MMC was withdrawn for all patients, and 14 patients received specific pulmonary arterial hypertension (PAH) therapies. Among these patients, mild but statistically insignificant improvements were observed in NYHA functional class ($P = .10$), 6-min walk distance ($P = .09$), and pulmonary vascular resistance (-4.7 Wood units; $P = .052$) at reassessment (median delay of 4.8 months). Three patients experienced pulmonary edema requiring the cessation or reduction of PAH treatment. The median overall survival was 20 months, and the 6-, 12-, and 24-month survival rates were 76%, 58%, and 18%, respectively.

INTERPRETATION: PVOD after MMC treatment is a rare but life-threatening complication associated with a poor prognosis despite MMC withdrawal and PAH-specific therapy.

KEY WORDS: mitomycin C; pharmacovigilance; pulmonary hypertension; pulmonary venocclusive disease

ABBREVIATIONS: 5-FU = 5-fluorouracil; 6MWD = 6 min-walk test; *BMP2* = gene encoding bone morphogenetic protein receptor type 2; BNP = brain natriuretic peptide; CI = cardiac index; CO = cardiac output; DLCO = diffusing capacity of the lungs for carbon monoxide; *EIF2AK4* = gene encoding eukaryotic translation initiation factor 2 α kinase 4; ERA = endothelin receptor antagonist; HRCT = high-resolution CT; MMC = mitomycin C; mPAP = mean pulmonary arterial

pressure; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; NYHA FC = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PAWP = pulmonary arterial wedge pressure; PDE5i = phosphodiesterase type 5 inhibitor; PH = pulmonary hypertension; PVOD = pulmonary venocclusive disease; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right heart catheterization; TLC = total lung capacity; WU = Wood units

Pulmonary venoocclusive disease (PVOD) is a rare subgroup of precapillary pulmonary hypertension (PH). According to the 2015 European Society of Cardiology/European Respiratory Society guidelines,¹ its diagnosis is characterized by an elevated mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg and normal pulmonary arterial wedge pressure (PAWP) ≤ 15 mm Hg. The World Symposium on Pulmonary Hypertension offered a comprehensive and simplified version of the clinical classification of PH in 2018 and included PVOD in the pulmonary arterial hypertension (PAH) group.² The clinical presentation of PVOD is similar to that of PAH, and the two conditions are difficult to discriminate from one another.³ The pathologic description of PVOD includes the involvement of pulmonary septal veins and preseptal venules with loose, fibrous remodeling of the intima

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and medial hypertrophy associated with capillary proliferation.^{4,5} Although a definite diagnosis requires a pathologic assessment, lung biopsy is a high-risk procedure in these patients and is not recommended.^{1,6} The diagnosis of PVOD relies on a noninvasive approach with a body of evidence, such as severe hypoxemia, reduced diffusing capacity of the lungs for carbon monoxide, and high-resolution CT (HRCT) findings including septal lines, centrilobular ground-glass opacities, and mediastinal lymph node enlargement.⁶ The prognosis for patients with PVOD is poor, and there is no established medical therapy for PVOD. Specific PAH therapies must be used with caution because of the high risk of pulmonary edema.^{6,7} The only curative therapy is lung transplantation.⁶ PVOD may be sporadic or heritable due to biallelic mutations in the gene encoding eukaryotic translation initiation factor 2 α kinase 4 (*EIF2AK4*)⁸ or a complication from exposure to organic solvents or chemotherapy.^{6,9} A previous report underlined the role of alkylating agents as a predominant chemotherapy class of drugs associated with PVOD,¹⁰ in particular with mitomycin C (MMC).¹¹⁻¹³

The aim of this study is to describe the clinical, functional, and hemodynamic characteristics; the response to specific PAH therapies; and long-term outcomes of a large series of patients with MMC-induced PVOD.

Methods

Study Design and Patients

We conducted a multicentric retrospective study collecting data from the registry of the French PH network (French PH Referral Center, Hôpital Bicêtre, Université Paris Sud, Le Kremlin-Bicêtre and its 25 associated centers across France), and from the pharmacovigilance program VIGIAPATH dedicated to drug-associated PH.¹⁴ The French PH Registry was established in accordance with French bioethics laws (National Commission on Informatics and Liberty, No. 842063). We selected patients exposed to MMC and receiving a diagnosis of precapillary PH subsequent to right heart catheterization (RHC), defined as mPAP ≥ 25 mm Hg with normal PAWP ≤ 15 mm Hg and pulmonary vascular resistance (PVR) > 3 Wood units (WU). After receiving a diagnosis of precapillary PH, patients were treated as recommended by European Society of Cardiology/European Respiratory Society guidelines.¹ CT angiography and lung V/Q scans were acquired to exclude chronic thromboembolic PH. Patients with a history of liver disorders underwent abdominal ultrasound examinations to detect portal hypertension. A multidisciplinary team discussed all cases, and the diagnosis of PVOD was confirmed on the basis of previously described criteria. Concerning PVOD risk factors, antibody tests for connective tissue diseases and HIV serology were assessed. Any history of organic solvent and tobacco exposure was also determined. Genetic counseling and screening for the bone morphogenetic protein

receptor type 2 gene (*BMPR2*) and *EIF2AK4* were offered to gene patients. The patients signed genetic consent forms before genetic testing.

Clinical, Functional, and Radiologic Characteristics

We reviewed the chemotherapy regimen, number of cycles of MMC therapy, indications, cancer status at the time of diagnosis of PVOD, and delay between the first and the last injection of MMC and diagnosis. The symptoms were reported, and clinical status was assessed on the basis of New York Heart Association functional class (NYHA FC). The nonencouraged 6-min walk distance (6MWD) was recorded. For subjects with NYHA FC IV and unable to perform the 6-min walk test, the distance was judged as 0 m. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels were separated into three groups according to multiparameter risk assessments: low risk (BNP < 50 ng/L or NT-pro-BNP < 300 ng/L), intermediate risk (BNP 50-300 ng/L or NT-pro-BNP 300-1,400 ng/L), and high risk (BNP > 300 ng/L or NT-pro-BNP > 1,400 ng/L).¹ Arterial blood gases were determined, and pulmonary function tests, including PaO₂, Paco₂, FEV₁, FVC, total lung capacity (TLC), and diffusing capacity of the lungs for carbon monoxide corrected for hemoglobin concentration (Dlco), were done. HRCT images were recorded for all subjects at diagnosis. The presence of septal lines, centrilobular ground-glass opacities, mediastinal lymph node enlargement, pleural effusion, and pericardial effusion was reported.

Results

Patient Population

From June 2011 to December 2018, 17 incident cases of patients with precapillary PH with MMC exposure were identified in the French PH network, all with a diagnosis of PVOD (Table 1). Thirteen of the patients (76%) were female, and the median age at PH diagnosis was 55 (33-71) years. Smoking status was available for 14 patients, including five current smokers (36%) and nine former smokers (64%) (> 5 pack-years). Nine patients benefited from genetic counseling and screening, and no *BMPR2* or *EIF2AK4* mutations were identified. However, a variation of unknown significance in the *BMPR2* gene was identified in one patient (c.746C>T; p.Val249Gly). None of the patients were exposed to organic solvents. Two patients had HIV infection. Three patients (18%) had a history of liver disease without portal hypertension. COPD or emphysema was reported in six patients (35%). Three patients (18%) had a history of thromboembolic events, and one patient had polycythemia vera; none of them had chronic thromboembolic PH.

Hemodynamic Measurements

The hemodynamic parameters recorded included mPAP, PAWP, and right atrial pressure (RAP). Cardiac output (CO) was measured by the standard thermodilution technique. The cardiac index (CI) was calculated as CO divided by body surface area. PVR was calculated as (mPAP – PAWP)/CO, expressed in Wood units. A positive acute vasodilator test result was defined by a reduction in mPAP \geq 10 mm Hg to reach an absolute mPAP value \leq 40 mm Hg with an increase or no change in CO.²

Outcomes

Management of PAH therapies after diagnosis and during follow-up was assessed. The clinical, functional, and hemodynamic data at diagnosis were compared with those at the first evaluation performed between 2 and 6 months after diagnosis. The date of PH diagnosis was defined as the date of the first RHC. Overall survival was evaluated according to the date of death or was censored at the date of the last update or at the date of lung transplantation.

Statistical Analysis

Variables are presented as the median (minimum-maximum) for quantitative variables and as the number (percentage) for categorical variables. Comparisons before and after treatment were performed using the Wilcoxon signed-rank test for quantitative data and the Friedman test for NYHA FC. Overall survival was estimated by the Kaplan-Meier method. The statistical analysis was performed with bilateral hypotheses, and a *P* value < .05 was considered statistically significant.

Cancer and Chemotherapy

The median age at cancer diagnosis was 54 (33-71) years. The indication for MMC was mostly squamous anal canal cancer (16 patients), and one patient received MMC for uterine cancer. The chemotherapy regimen was a combination of MMC and 5-fluorouracil (5-FU) for 15 patients (88%), one patient received a combination of MMC and vinorelbine, and one received MMC as monotherapy. The median number of cycles of MMC was three (two to seven). Cancer control status was available for 14 patients and was considered satisfactory for seven patients (50%) at the time of PH diagnosis; two patients (14%) experienced tumor progression, and five patients (36%) relapsed (Table 1). None of the patients had clinical evidence of PH before the initiation of MMC therapy. The median delays between the diagnosis of PVOD and the first injection and last injection of MMC were 8.5 (4-20) months and 5.5 (2-12) months, respectively (Table 1).

Clinical and Functional Characteristics

At diagnosis, 16 patients (94%) presented with progressive dyspnea. The median delay between

symptom onset and diagnosis was 3.5 (0-7) months. One patient was asymptomatic, and PH was suspected on Doppler echocardiography performed as a preoperative assessment. Five patients (30%) were NYHA FC I or II, six (35%) were class III, and six (35%) were class IV. Baseline 6MWD was available for 16 of 17 patients (94%). The median 6MWD (n = 16) was 220 (0-465) m, including four patients unable to perform the test. The median FEV₁ (n = 16), FVC (n = 16), and TLC (n = 15) were 80% (48%-127%), 90% (50%-128%), and 100% (63%-125%) of the theoretical values, respectively. DLCO was available for 15 patients (88%) and was reduced for all of them, with a median DLCO of 31% (20%-51%) of the theoretical value. Severe hypoxemia was observed with a median PaO₂ of 55 (39-

71) mm Hg. All patients had an increase in plasma BNP or NT-pro-BNP level at diagnosis, and 16 patients (94%) were part of the high-risk population based on multiparameter risk assessments (Table 2).

Analysis of High-Resolution CT Imaging of the Chest

HRCT imaging of the chest found septal lines, centrilobular ground-glass opacities, and mediastinal lymph node enlargement in 15 patients (88%), 14 patients (82%) and 13 patients (76%), respectively (Table 2). Eight patients (47%) presented pleural effusions, and pericardial effusion was observed in five patients (29%) (Fig 1). HRCT imaging of the chest as

TABLE 1] Characteristics at Diagnosis of Mitomycin C-Induced Pulmonary Venoocclusive Disease

Characteristic	MMC-Induced PVOD
	(n = 17)
Age, y	55 (33-71)
Sex, female/male	13/4
Tobacco exposure (n = 14)	
Current smokers	5 (36%)
Former smokers (> 5 pack-years)	9 (64%)
Organic solvent exposure	0
<i>EIF2AK4</i> mutation carriers (n = 9)	0
MMC	
No. of MMC injections	3 (2-7)
Delay between the first injection of MMC and PVOD, mo	8.5 (4-20)
Delay between the last injection of MMC and PVOD, mo	5.5 (2-12)
Indication for MMC	
Anal cancer	16 (94%)
Uterine cancer	1 (6%)
Chemotherapy regimen	
MMC + 5-FU	15 (88%)
MMC + vinorelbine	1 (6%)
MMC	1 (6%)
Cancer status at time of diagnosis (n = 14)	
Remission	7 (50%)
In progress	2 (14%)
Relapse	5 (36%)
Other risk factors for PH	
HIV	2 (13%)
Respiratory disease (COPD or emphysema)	6 (35%)
Hematologic disorders (polycythemia vera)	1 (6%)

Data are presented as median (minimum-maximum) or No. (%). 5-FU = 5-fluorouracil; *EIF2AK4* = gene encoding eukaryotic translation initiation factor 2 α kinase 4; MMC = mitomycin C; PH = pulmonary hypertension; PVOD = pulmonary venoocclusive disease.

TABLE 2] Clinical, Biological, Functional, Hemodynamic, and Radiologic Data at Diagnosis of Pulmonary Venooclusive Disease

Data Collected	No. of Patients	At Diagnosis of MMC-Induced PVOD
NYHA functional class	17	
I or II		5 (30)
III		6 (35)
IV		6 (35)
6MWD, m	16	220 (0-465)
BNP or NT-pro-BNP ^a	17	
Low risk		0
Intermediate risk		1 (6)
High risk		16 (94)
Arterial blood gas parameters at ambient room air	17	
PaO ₂ , mm Hg		55 (39-71)
Paco ₂ , mm Hg		30 (23-40)
Pulmonary function tests		
FEV ₁ , % pred	16	80 (48-127)
FVC, % pred	16	90 (50-128)
TLC, % pred	15	100 (63-125)
Dlco, % pred	15	31 (20-51)
Hemodynamic parameters		
mPAP, mm Hg	17	38 (30-52)
PAWP, mm Hg	17	6 (2-15)
RAP, mm Hg	17	6 (0-13)
CO, L/min	17	3.5 (2.6-6.5)
CI, L/(min × m ²)	17	2.2 (1.5-4)
PVR, Wood units	17	8.3 (5.1-14.5)
Acute vasodilator response	11	1 (9)
High-resolution CT imaging	17	
Interlobular septal lines		15 (88)
Centrilobular ground-glass opacities		14 (82)
Mediastinal lymph node enlargement		13 (76)
Pleural effusion		8 (47)
Pericardial effusion		5 (29)

Data are presented as median (minimum-maximum) or No. (%). (n = x): number of patients for whom data were available. 6MWD = 6-min walk distance; BNP = brain natriuretic peptide; CI = cardiac index; CO = cardiac output; Dlco = diffusing capacity for carbon monoxide corrected for hemoglobin concentration; MMC = mitomycin C; mPAP = mean pulmonary artery pressure; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PAWP = pulmonary artery wedge pressure; % pred = percentage of predicted value; PVOD = pulmonary venooclusive disease; PVR = pulmonary vascular resistance; RAP = right atrial pressure; TLC = total lung capacity.

^aMultiparameter risk assessments: low risk (BNP < 50 ng/L or NT-pro-BNP < 300 ng/L), intermediate risk (BNP 50-300 ng/L or NT-pro-BNP 300-1,400 ng/L), and high risk (BNP > 300 ng/L or NT-pro-BNP > 1,400 ng/L).

well as \dot{V}/\dot{Q} scans of the lungs excluded chronic thromboembolic disease or pulmonary tumor emboli.

Hemodynamic Assessment at Diagnosis

RHC showed a median mPAP of 38 (30-52) mm Hg, CO of 3.5 (2.6-6.5) L/min, CI of 2.2 (1.5-4) L/(min × m²), and PVR of 8.3 (5.1-14.5) WU (Table 2). Acute vasodilator testing was performed in 11 patients, and

one patient responded with a decrease in mPAP from 40 to 30 mm Hg with a normal CO.

Pathologic Assessment

In our cohort, one patient was listed for urgent lung transplantation because of refractory right heart failure and was successfully transplanted.¹⁵ The pathologic assessment of the explanted lungs is described in

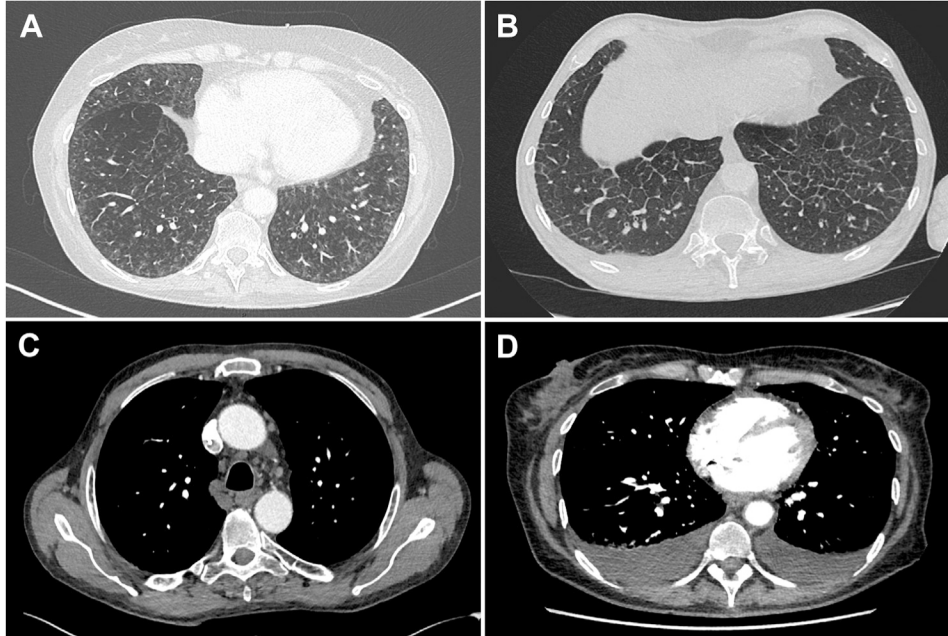


Figure 1 – High-resolution CT (HRCT) imaging of the chest in patients with pulmonary venoocclusive disease (PVOD) exposed to mitomycin C. A-C, HRCT imaging at diagnosis showed centrilobular ground-glass opacities (A), septal lines (B), and mediastinal lymph nodes (C) highly suggestive of PVOD. D, Pleural effusions may be seen.

Figure 2. The lung parenchyma displayed architectural changes characterized by emphysema and vascular remodeling. The septal veins appeared heavily narrowed, with pronounced intimal fibrosis (Figs 2A, 2C). The foci of capillary dilation and congestion were scattered along the lung parenchyma and were easily identified close to the remodeled septal veins (Fig 2B). Small pulmonary arteries were excessively muscularized and exhibited intimal fibrosis and mild medial thickening (Figs 2D, 2E). Eventually, isolated lesions of constrictive bronchiolitis were found (Fig 2F).

Response to PAH-Specific Therapies

After a median delay of 4.8 (2.5-6) months, 14 patients (82%) were reassessed after initiation of specific PAH therapy, including eight patients (57%) receiving monotherapy with endothelin receptor antagonist (ERA) or phosphodiesterase type 5 inhibitor (PDE5i), five patients (36%) receiving a combination of ERA and PDE5i, and one patient receiving a combination of ERA, PDE5i, and a prostacyclin derivative (Table 3). Initiation and dose were managed according to the clinical judgment and discretion of the physician. As European Society of Cardiology/European Respiratory Society guidelines¹ recommend a great caution with vasodilators because of the risk of severe drug-induced pulmonary edema, monotherapy was privileged and when an association was decided, sequential combination therapy

was the most widely used strategy dosages. Only two patients received a half-dose of PDE5i (one in monotherapy and one receiving a combination of ERA and PDE5i) because of the risk of pulmonary edema. PAH therapy induced pulmonary edema in three patients (20%). Three patients were treated with a combination of corticosteroids and PAH therapy at diagnosis. There was no significant clinical improvement in NYHA FC ($n = 14$, $P = .10$) (Fig 3). Among the nine of 14 patients (65%) with 6MWD data available, five of the nine patients (56%) had a mild but not statistically significant increase in 6MWD (+314 m, $n = 9$; $P = .09$). Among the 12 of 14 patients (86%) with RHC data available, we also observed a mild but not statistically significant improvement in hemodynamic parameters in CI [$+1.3 \text{ L}/(\text{min} \times \text{m}^2)$, $n = 12$; $P = .10$] and PVR (-4.7 WU , $n = 12$; $P = .052$) (Table 3). Of note, one patient treated with ERA and PDE5i achieved normal hemodynamic status with an mPAP of 19 mm Hg, RAP of 4 mm Hg, CI of $2.4 \text{ L}/(\text{min} \times \text{m}^2)$, and PVR of 2.6 WU. Two patients did not receive PAH therapy and were treated with corticosteroids only. These two patients died after 4 and 5 months, respectively, before reassessment.

Outcomes

After a median follow-up of 12.6 (3.7-29) months, 13 patients (76%) had died. Death occurred following acute right cardiac failure in five patients (38%), tumor

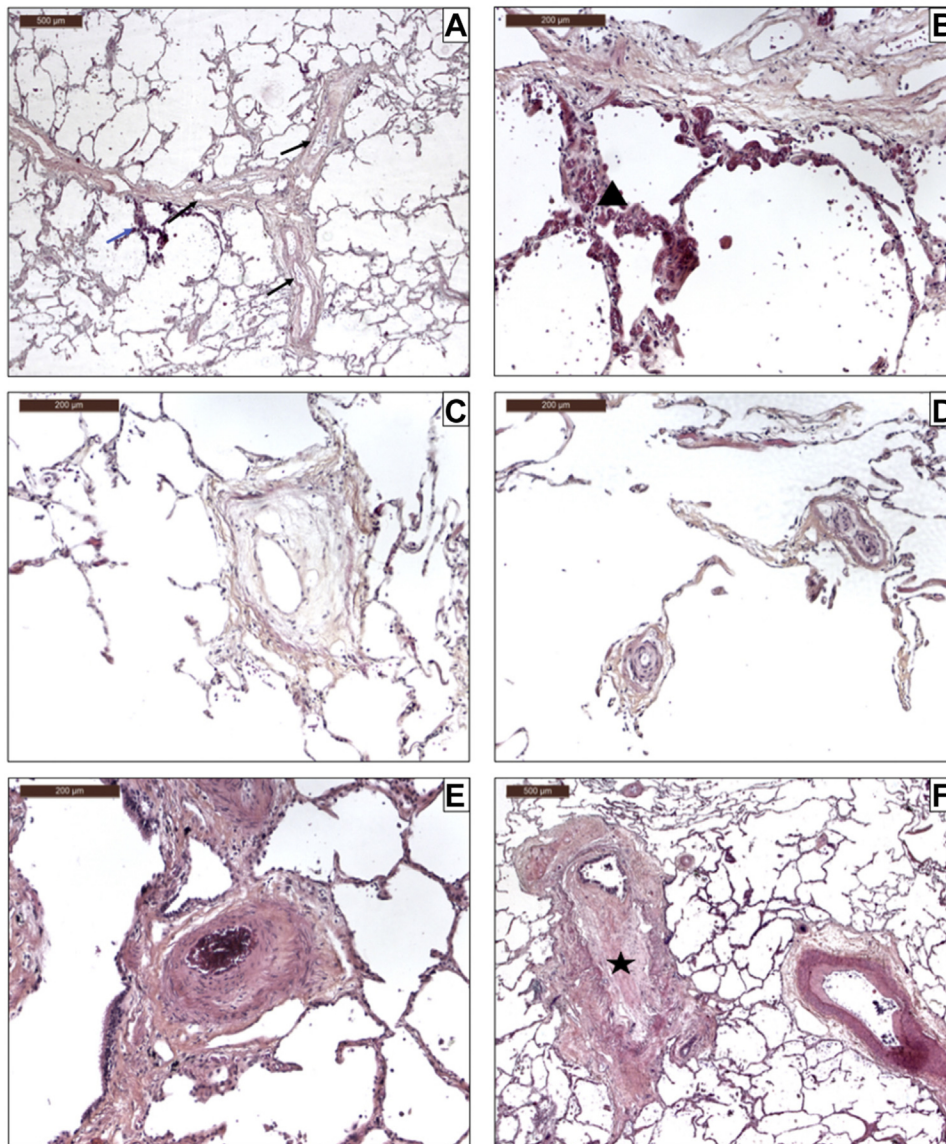


Figure 2 – Histology of explanted lungs from patient with mitomycin C-induced pulmonary venoocclusive disease. A, Septal veins with a significant increase in wall thickness and lumen narrowing (black arrows). Blue arrow, foci of capillary dilation and congestion close to the septal veins. B, Capillary dilation and congestion are easily identified close to the septal veins (black triangle). C, Small veins are severely altered with an increase in wall thickness by loose connective tissue and lumen narrowing. D, Arteries smaller than 70 μm are also altered, with an increase in the smooth muscle layer and lumen narrowing. E, Lung vasculopathy is characterized by small artery remodeling and intimal fibrous thickening without plexiform lesions. F, Bronchiolar obliteration by dense collagen (black star). Bronchiolar lesions were scattered in the lung parenchyma.

progression in six patients (46%), mesenteric ischemia with septic shock in one patient, and severe bilateral pneumonia in one patient. One patient underwent transplantation 21 months after diagnosis and 2 years after satisfactory neoplasia disease control. Three subjects were still alive and treated with specific PAH therapy with a follow-up of 9, 14, and 27 months. The overall survival of patients with MMC-induced PVOD is presented in Figure 4. The median overall survival was 20 months, and the 6-, 12-, and 24-month survival rates were 76%, 58%, and 18%, respectively.

Discussion

MMC is an alkylating agent with antibiotic and antitumor characteristics derived from *Streptomyces caesitosus*. This treatment is commonly used in GI cancer, adenocarcinoma of the breast, urothelial carcinoma, and cervical cancer. The most common toxicity associated with MMC is myelosuppression. Several pulmonary adverse effects have been identified, including acute interstitial pneumonitis, interstitial fibrosis, ARDS, and diffuse alveolar damage.¹⁶ A few cases of MMC-induced PVOD have been published.¹¹⁻¹³

TABLE 3] Clinical, Functional, and Hemodynamic Data at Diagnosis and Second Assessment After Initiation of Pulmonary Arterial Hypertension Therapy (n = 14)

Data Collected	No. of Patients	At Diagnosis	At Second Assessment	P Value
NYHA functional class	14			
I or II		3 (21)	6 (43)	.10
III		6 (43)	5 (36)	...
IV		5 (36)	3 (21)	...
6MWD, m	9	60 (0-423)	374 (0-511)	.09
Pao ₂ at ambient room air, mm Hg	8	58 (39-71)	58 (37-95)	.95
Hemodynamic parameters	12			
mPAP, mm Hg		39 (33-46)	34 (19-44)	.07
PAWP, mm Hg		6 (2-10)	8 (2-17)	.29
RAP, mm Hg		7 (0-13)	5 (2-23)	.79
CO, L/min		3.4 (2.7-6.5)	5.3 (1.8-9.9)	.13
CI, L/(min × m ²)		2.1 (1.5-4)	3.4 (1.2-4.9)	.10
PVR, Wood units		10.2 (5.5-12.1)	5.5 (2.4-15.6)	.052
Time between diagnosis and second assessment, mo		4.8 (2.5-6)		
PAH therapies (n = 14)				
ERA monotherapy		6 (43)		
PDE5i monotherapy		2 (14)		
ERA + PDE5i		5 (36)		
ERA + PDE5i + prostacyclin derivative		1 (7)		

Data are presented as median (minimum-maximum) or No. (%). (n = x): number of patients for whom data were available. Comparisons between groups were analyzed by the Wilcoxon signed-rank test. 6MWD = 6-min walk distance; CI = cardiac index; CO = cardiac output; ERA = endothelin receptor antagonist; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PDE5i = phosphodiesterase type 5 inhibitor; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

Since 2011, the French PH Registry has identified 17 incident cases, which represents the largest systematic cohort of patients with MMC-induced PVOD. The incidence of MMC-induced PVOD in patients with anal cancer is currently unknown for two reasons: first, many cases of PVOD are misclassified as PAH, and second, the total number of patients exposed to MMC is difficult

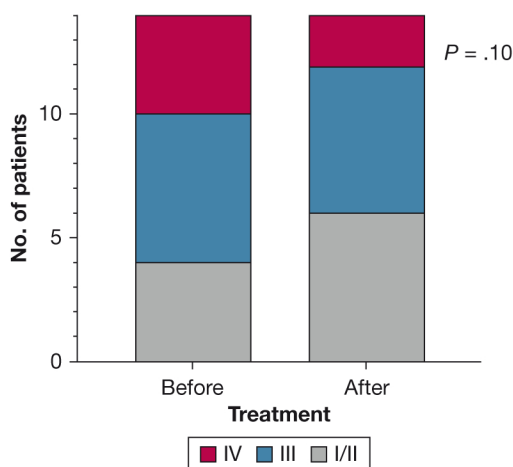


Figure 3 – New York Heart Association functional class evaluation before and after pulmonary arterial hypertension-specific therapies.

to determine. However, taking into account the estimated incidence of PVOD at 0.5/million people per year and the number of new cases of anal cancer per year in France, the incidence of MMC-induced PVOD in patients with anal cancer was estimated to be 3.9 per 1,000 patients per year.¹⁷

In this cohort, we observed a female predominance (76%), whereas there is a male predominance in sporadic PVOD among mutation noncarriers and no sex differences in PVOD among *EIF2AK4* mutation carriers.¹⁸ This female predominance may be explained at least in part by the female-to-male ratio (2.5:1) reported in France for anal cancer (which was the indication for MMC in almost all of our subjects).^{19,20} In an animal model, after an injection of MMC, male and female rats developed PH. Even if there is no significant difference, female rats developed a more severe response to MMC than did male rats.¹⁷ The link between sex and MMC-induced PVOD is unknown, but we may suggest that a hormonal factor or pharmacokinetic/ pharmacodynamic susceptibility may have a role. Several risk factors for PVOD have been identified, including a genetic predisposition to *EIF2AK4*

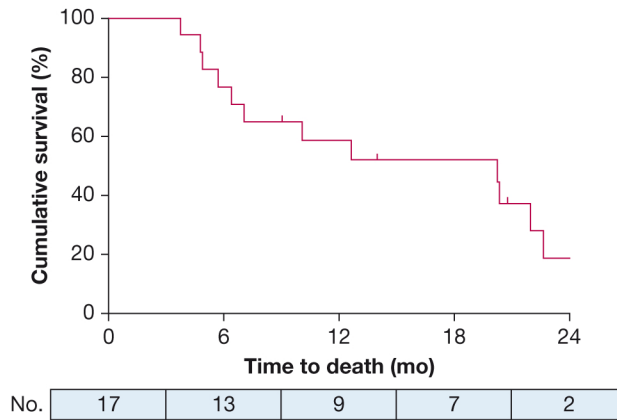


Figure 4 – Overall survival of patients with mitomycin C-induced pulmonary venoocclusive disease. For the overall survival analysis, patients who were alive or receiving transplantation were censored and are represented by a line. At 24 months, one patient was alive after 27 months of follow-up and one died after 29 months of follow-up.

mutations, smoking, exposure to organic solvents such as trichloroethylene, bone marrow transplantation, chemotherapeutic agents, and connective tissue diseases.^{2,6} In our cohort, none of the screened patients had *EIF2AK4* mutation, organic solvent exposure, or antibodies specific for connective tissue diseases.

PVOD is a severe and life-threatening complication with a poor prognosis. According to previous reports, the 1-, 2-, and 3-year event-free survival probabilities are 63%, 52%, and 32% among those with *EIF2AK4* mutations and 75%, 44%, and 34% among noncarriers.¹⁸ In our cohort, patients with MMC-induced PVOD had a worse prognosis because of the presence of cancer and the resulting contraindications to transplantation. Indeed, the use of PAH therapy in patients with PVOD is controversial, and the benefits are unclear with a risk of pulmonary edema in a significant proportion of patients with PVOD (23% among mutation carriers and 21% among noncarriers).¹⁸ Among the patients treated by PAH therapy, we observed mild but not statistically significant improvements in clinical, functional, and hemodynamic parameters. Only one patient reached the criteria of low risk defined as NYHA FC I or II, 6MWD > 440 m, and CI > 2.5 L/(min × m²).¹ Pulmonary edema occurred in three patients, who required a withdrawal from or reduction in PAH therapy. Experimental animal models have shown evidence of a significant eosinophilic inflammatory component in rats with PVOD¹⁷ that is not seen in explanted lungs. In the current study, three patients received both corticosteroids and PAH therapy on diagnosis of PVOD. At reassessment, two patients had temporary clinical and functional improvements (6MWD, +462 and +151

m) associated with a decrease in RVP (-7.9 and -5.6 WU) and an increase in CI [+2.2 and +1.3 L/(min × m²)]. In contrast, the third patient died before reassessment. We can hypothesize a time-dependent evolution of histologic abnormalities: at the beginning, an initial inflammatory phase that could explain a response to corticosteroids in some patients; then, irreversible vascular remodeling insensitive to corticosteroids. At present, lung transplantation is the only cure for PVOD.⁶ Nevertheless, the delay between the first injection and diagnosis of MMC-induced PVOD occurs early since this duration was 8.5 (4-20) months; therefore, patients do not have a satisfactory level of control on their cancer and cannot be on the lung transplantation list when they develop severe right heart failure. Only two patients could be on the urgent lung transplantation list: one patient died before the procedure, and one patient successfully underwent transplantation and was still alive 42 months after the procedure.

The pathologic assessment of explanted lungs showed specific remodeling of the pulmonary venous and capillary compartments.¹⁵ These abnormalities are consistent with the pathologic analysis of MMC-induced PVOD in animal models.¹⁷ Indeed, in rats, MMC induced the following: obstructive lesions with adventitial and intimal thickening and smooth muscle cell hypertrophy in the pulmonary artery, neomuscularization of small distal vessels, and foci of pulmonary edema and foci of alveolar wall thickening suggesting pulmonary capillary hemangiomatosis lesions. In addition, as observed in other previous reports,²¹ there was a decrease in the expression of the

general control nonderepressible 2 (GCN2) protein, encoded by *EIF2AK4*, which may be involved in oxidative and inflammatory pulmonary injuries. Interestingly, the depletion of pulmonary GCN2 was dose-dependent. Finally, in a cultured pulmonary artery endothelium model, MMC induced the inhibition of prostacyclin biosynthesis.²² The structural and functional alterations in endothelial cells are similar to those of monocrotaline-induced PH in rat models.²³ Interestingly, amifostine was tested in MMC-induced PVOD as a preventive therapy and led to improvements in survival, right ventricular hypertrophy, and pulmonary hemodynamics.¹⁷

Our study had several limitations. The retrospective data may be a source of information bias and were limited to a small sample because of the rarity of this complication. Nevertheless, the current study represents the largest systematic cohort of patients with MMC-induced PVOD. In addition, it was difficult to interpret the delay between the last injection of MMC and diagnosis because of possible delays of in diagnosing PVOD. Indeed, a diagnosis of PVOD is usually difficult to obtain because of the absence of specific symptoms, and radiologic abnormalities may be confounded by lymphangitic carcinomatosis or interstitial pneumonitis. Finally, most of these patients received various

chemotherapeutic agents, especially in combination with 5-FU. This chemotherapy regimen was published as the current recommendation for locoregional anal cancer.²⁴ To the best of our knowledge, no role of 5-FU in PVOD development has been described; however, it is not possible to exclude the potential additive effects of this combined chemotherapy regimen.

Conclusions

We have reported the characteristics and outcomes of the largest series of patients with MMC-induced PVOD. The prognosis for patients with this condition is poor, and there is no recommendation for specific PAH therapies or immunosuppressive treatment. Physicians must pay attention to unexplained dyspnea during or after treatment with MMC and explore the possibility of pulmonary vascular toxicity. We recommend a noninvasive approach with echocardiography, pulmonary function tests to determine DLCO, and arterial blood gas determination and HRCT imaging. On the basis of these results, RHC should be performed to confirm the diagnosis of PVOD. There should be increased awareness and dissemination of information to physicians of the potential side effects that these drugs can cause.

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