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CARDIOVASCULAR, PULMONARY, AND RENAL PATHOLOGY

Chemotherapy-Induced Pulmonary Hypertension

Role of Alkylating Agents

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Pulmonary veno-occlusive disease (PVOD) is an uncommon form of pulmonary hypertension (PH) characterized by progressive obstruction of small pulmonary veins and a dismal prognosis. Limited case series have reported a possible association between different chemotherapeutic agents and PVOD. We evaluated the relationship between chemotherapeutic agents and PVOD. Cases of chemotherapy-induced PVOD from the French PH network and literature were reviewed. Consequences of chemotherapy exposure on the pulmonary vasculature and hemodynamics were investigated in three different animal models (mouse, rat, and rabbit). Thirty-seven cases of chemotherapy-associated PVOD were identified in the French PH network and systematic literature analysis. Exposure to alkylating agents was observed in 83.8% of cases, mostly represented by cyclophosphamide (43.2%). In three different animal models, cyclophosphamide was able to induce PH on the basis of hemodynamic, morphological, and biological parameters. In these models, histopathological assessment confirmed significant pulmonary venous involvement highly suggestive of PVOD. Together, clinical data and animal models demonstrated a plausible cause-effect relationship between alkylating agents and PVOD. Clinicians should be aware of this uncommon, but severe, pulmonary vascular complication of alkylating agents. *(Am J Pathol 2015, 185: 356—371; http://dx.doi.org/10.1016/j.ajpath.2014.10.021)*

Pulmonary veno-occlusive disease (PVOD) is a rare subgroup of pulmonary hypertension (PH) characterized by predominant pulmonary venous involvement.[1] Although a definite diagnosis of PVOD requires histological confirmation,[2] lung biopsy is often considered to be a high-risk procedure in these critically ill patients. More recently, a noninvasive approach on the basis of compatible clinical and radiological assessment can be sufficient to support a confident diagnosis of PVOD.[3]

The pathophysiological mechanisms of PVOD remain poorly understood.[4] Several drugs have been suggested to induce PVOD and, in particular, chemotherapeutic agents,

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such as bleomycin, carmustine, and mitomycin,[5–7] have been reported to be associated with PVOD. Moreover, bone marrow transplantation (BMT) is also considered to be a risk factor for the development of PVOD.[8–10] Despite the recognition that chemotherapy can potentially provoke PVOD, no specific drug or therapeutic class has been clearly identified as a risk factor for PVOD.

The first objective of the present study was to determine the chemotherapeutic agents that could be involved in the development of PVOD. Thus, we reviewed cases of chemotherapy-induced PVOD from the French PH network and performed a systematic literature review to identify potential chemotherapeutic agents implicated in the development of PVOD. Furthermore, additional treatment, including radiotherapy and the role of BMT, was investigated. Herein, we demonstrate that alkylating agents are the predominant chemotherapeutic class associated with PVOD, with cyclophosphamide (CP) being detected in nearly half of all chemotherapy-induced PVOD cases. On the basis of this finding, we investigated the consequences of CP exposure on the pulmonary vasculature and hemodynamics in three different animal models (mouse, rat, and rabbit). The influences of sex, time course, and dose-response to CP were also evaluated. We analyzed right heart and pulmonary artery (PA) hemodynamics, morphological parameters (in heart and lungs), and biological parameters (in lungs and serum/blood cells) relevant to pulmonary vascular dysfunction and inflammation. Finally, we performed *in vivo* experiments on whether cytoprotective agents (mesna and amifostine) used during treatment with CP could prevent the development of PH.

Materials and Methods

Identified Cases of Chemotherapy-Related PVOD in the French PH Network and in the Literature

We reviewed all cases from the French PH Registry of confirmed precapillary PH among patients in whom PVOD was suspected after commencement of chemotherapy, radiotherapy, and/or BMT.

The French PH Registry was established in accordance with French bioethics laws (National Commission on Informatics and Liberty) in 2004, and all included patients gave their informed consent.

Routine evaluation at baseline included demographics, medical history, physical examination, echocardiography, chest high-resolution computed tomography, ventilation/perfusion lung scan, abdominal ultrasound, autoimmunity screening, and HIV serological test. Precapillary PH was confirmed in all cases by right heart catheterization (RHC). At diagnosis, New York Heart Association functional class and 6-minute walk distance were recorded.

Data were centrally collected and analyzed at the French referral center for severe PH (Hôpital Bicêtre, University Paris-Sud, Le Kremlin-Bicêtre, Paris, France).

The systematic literature review in PubMed and Medline was performed on December 1, 2013. Key words entered in the medical subject headings (MESH) database were as follows: *cancer* [MESH] and *pulmonary veno-occlusive disease*, *radiotherapy* [MESH] and *pulmonary veno-occlusive disease* and *chemotherapy* [MESH], and *pulmonary veno-occlusive disease*. The chosen key words *cancer*, *chemotherapy*, and *radiotherapy* [MESH] were also crossed to *pulmonary capillary hemangiomatosis*, an entity considered to be similar to PVOD. In addition, we crossed specific chemotherapeutic agents implicated in the development of PVOD, including *cisplatin*, *cyclophosphamide*, and *mitomycin* [MESH] with *pulmonary veno-occlusive disease*. With respect to different search terms, the following number of articles were retrieved: *cancer* [MESH] and *pulmonary veno-occlusive disease* ($n = 115$), *radiotherapy* [MESH] and *pulmonary veno-occlusive disease* ($n = 14$), *chemotherapy* [MESH] and *pulmonary veno-occlusive disease* ($n = 48$), *cancer* [MESH] and *pulmonary capillary hemangiomatosis* ($n = 62$), *chemotherapy* [MESH] and *pulmonary capillary hemangiomatosis* ($n = 2$), and *radiotherapy* [MESH] and *pulmonary capillary hemangiomatosis* ($n = 0$). Search terms containing specific chemotherapeutic agents yielded the following: *cisplatin* [MESH] and *pulmonary veno-occlusive disease* ($n = 3$), *cyclophosphamide* [MESH] and *pulmonary veno-occlusive disease* ($n = 21$), and *mitomycin* [MESH] and *pulmonary veno-occlusive disease* ($n = 3$).

Analysis of Case Reports

All identified case reports were adjudicated to determine whether a diagnosis of PVOD was compatible. This was on the basis of functional, radiological, hemodynamic, and histological data (if available) presented in each case report. Functional evaluation was on the basis of reported worsening dyspnea, as determined by the New York Heart Association functional class; radiological assessment included chest radiography and/or chest high-resolution computed tomography; and hemodynamic evaluation included echocardiographic examination and/or RHC. Two pneumologists (S.G. and D.M.) reviewed all case reports independently, and one pathologist specializing in pulmonary vascular diseases (P.D.) reviewed all histological data. Final decision on the classification of PVOD was reached by consensus, and patients were classified into the following three groups: i) confirmed PVOD, ii) highly probable PVOD, and iii) probable PVOD. Criteria for confirmed PVOD required histological proof of PVOD by either lung biopsy or post-mortem examination. Patients were considered to have highly probable PVOD if RHC confirmed precapillary PH in association with consistent radiological findings. Diagnosis of probable PVOD was given even in the absence of a histological proof or the presence of PH on RHC, on the basis of clinical presentation and functional evaluation, including echocardiography.

Detailed information was recorded concerning administrated chemotherapeutic agents, including frequency and duration of exposure. Each chemotherapeutic agent was recorded once, even if administrated several times during the