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Thrombotic microangiopathies and antineoplastic agents

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ABSTRACT

Thrombotic microangiopathy is a well-described complication of cancer treatment. Its incidence has increased these last decades, as a result of a better awareness of this complication in cancer patients in one hand, but also of a larger array of therapeutic compounds including anti-vascular endothelium growth factor (VEGF) drugs. It is therefore mandatory to recognize these conditions since they have a significant impact in thrombotic microangiopathies management and prognosis. Practitioners should be aware of the more classical antineoplastic agents associated with thrombotic microangiopathies, the mechanisms by which they induce them, and the resulting management and prognosis. Since malignancy itself can induce thrombotic microangiopathies, it is also mandatory to know how to distinguish rapidly those caused by antineoplastic agents from those associated with cancer, for an adapted management. Thrombotic microangiopathies associated with chemotherapy remain of dismal prognosis. A better understanding of pathophysiology in these forms of thrombotic microangiopathies, in association with a more empirical approach through the use of new therapeutic agents that can also help in the understanding on new mechanisms a posteriori, should improve their prognosis. The preliminary encouraging results reported with complement blockers in this field could represent a convincing example.

1. Introduction

The diseases collectively termed the thrombotic microangiopathies are various life-threatening disorders characterized by microangiopathic hemolytic anemia, peripheral thrombocytopenia, and organ failure of variable severity caused by microvascular occlusion. In thrombotic thrombocytopenic purpura, the systemic microvascular aggregation of platelets causes ischemia in the brain, kidneys, heart, and other organs. In hemolytic-uremic syndrome, fibrin-rich thrombi predominantly occlude the renal circulation. A thrombotic microangiopathy can also be typically observed in patients with the hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, disseminated cancer, or a human immunodeficiency virus infection and within the context of chemotherapy or transplantation.

Thrombotic microangiopathy is a well-described complication of cancer treatment. Its incidence has increased these last decades, as a result of a better awareness of this complication in cancer patients in one hand, but also of a larger array of therapeutic compounds including anti-vascular endothelial growth factor (VEGF) drugs. It can sometimes be difficult to establish a causal relationship between a specific chemotherapeutic agent and thrombotic microangiopathy given that malignancy itself can induce thrombotic microangiopathy. Moreover, many patients are treated with multiple chemotherapeutic agents, which can lead to difficulty indicting a particular drug. Practitioners should be aware of the more classical antineoplastic agents associated with thrombotic microangiopathy, the mechanisms by which they induce it, and the resulting management and prognosis. It is also mandatory to know how to distinguish rapidly thrombotic microangiopathies caused by antineoplastic agents from those associated with cancer for an adapted management. Recognition of

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an antineoplastic drug-etiology in a patient with thrombotic microangiopathy is also critical to avoid re-exposure and recurrent illness. This review addresses these goals.

2. Mitomycin C and gemcitabine-associated thrombotic microangiopathy

The most classical antineoplastic agents associated with thrombotic microangiopathies include mitomycin C and gemcitabine (Table 1). Pathophysiology still remains unclear, and may involve a direct damage of renal endothelial cells resulting in the formation of platelet aggregates. Mitomycin C also causes decreased prostacyclin production in human endothelial cell cultures, which may participate to platelet aggregation. Plasma levels of thrombomodulin, tissue plasminogen activator and plasminogen activator inhibitor-1 are elevated in patients with mitomycin C-induced thrombotic microangiopathy that are similar to those observed in patients with idiopathic thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome [1]. The onset of outcome is delayed, and ranges from 6 to 12 months after treatment initiation. Thrombotic microangiopathy results from a dose-dependent toxicity and is cumulative. Hematologic manifestations are usually present. Hypertension, acute renal failure, pulmonary edema and acute respiratory distress syndrome are common. Microthrombi involve both glomerular capillaries and arterioles. Clinical features are typically permanent and irreversible, and respond poorly to therapeutic plasma exchange.

2.1. Mitomycin C-associated thrombotic microangiopathy

Mitomycin C is an antitumor alkylating agent isolated from *Streptomyces caespitosus* that has been in use since 1958. It is an active agent in salvage combination chemotherapy regimens for adenocarcinoma of the breast, lung, stomach, pancreas, rectum, and head and neck. It is one of the primary agents for anal carcinoma. Thrombotic microangiopathy usually occurs 4 to 8 weeks after the last dose of mitomycin C, with most cases occurring after 6 to 12 months of chemotherapy. The threshold total cumulative dose of 40 to 60 mg is associated with the development of thrombotic microangiopathy. In the largest registry of mitomycin C-associated thrombotic microangiopathy, 83 (99%) of 84 patients received a cumulative dose of 40 mg or more, and all but nine received a cumulative dose greater than 60 mg. Pulmonary edema, generally noncardiogenic, developed in 65% of patients, often after blood product transfusion. In a series of 142 patients with gastrointestinal cancer treated with combination chemotherapy including mitomycin C, ten patients developed renal failure, and five of the ten also developed microangiopathic hemolytic anemia. The ten patients received a total cumulative dose of 75 to 180 mg of mitomycin C, with a correlation between the prevalence of renal toxicity and the total cumulative dose. Dyspnea, caused typically by pulmonary edema, is the most common presenting symptom of mitomycin C-associated thrombotic microangiopathy; it can progress to the adult respiratory distress syndrome. Progressive renal failure is present in almost all patients. Neurologic abnormalities are less common. Treatment consists mainly in the interruption of mitomycin C immediately with diagnosis of thrombotic microangiopathy. As opposed to thrombotic thrombocytopenic purpura, response to therapeutic plasma exchange is typically poor, although some reports suggested a role for staphylococcal protein A immunopheresis. Acute mortality is elevated, approaching 75% at 4 months [2].

Table 1
Antineoplastic agents associated with thrombotic microangiopathies.

Chemotherapy	Anti-VEGF therapy	Other targeted therapies
Mitomycin C	Ligands	Other tyrosine kinase inhibitors
Gemcitabine	Bevacizumab	Imatinib mesylate
Platinum salts	Afilbercept	Dasatinib
Pegylated liposomal doxorubicin	Tyrosine kinase inhibitors	Immunotoxins
	Sunitinib	Targeting typically CD22 or IL-2
	Sorafenib	Other immunotherapies
	Cediranib	Apolizumab
	Brivanib	
	Pazopranib	
	Lucitanib	

VEGF: vascular endothelial growth factor; IL-2: interleukin-2.

2.2. Gemcitabine-associated thrombotic microangiopathy

As for mitomycin C, gemcitabine-associated thrombotic microangiopathy is typically chronic with cumulative dose dependence. Gemcitabine was approved by the US Food and Drug Administration (FDA) in 1996 for the treatment of metastatic pancreatic cancers and is currently used for the treatment of malignancies such as lymphomas, lung, bladder and breast cancers. The incidence of gemcitabine-associated thrombotic microangiopathy was initially estimated to be of 0.015%. However, more recent works reported incidences as high as 0.4% [3,4], which could result from an increasing recognition of milder forms due to a better awareness of practitioners about this complication. Given the possible clinically silent presentation of gemcitabine-associated thrombotic microangiopathy, its clinical features should be sought before each new cycle of treatment.

From a series of 56 cases, the mean duration between the initiation of gemcitabine and thrombotic microangiopathy occurrence was reported to be 7.5 months, although the range was wide (0.5 to 19 months). The median cumulative dose of gemcitabine was 22.5 g ± 14 g (range 2–70 g). A mild proteinuria and a microscopic hematuria could be observed in two-third of cases. A de novo arterial hypertension or the worsening of a preexisting arterial hypertension was observed in 75% of patients [3]. Patients were managed with a plasma-based therapy and/or steroids although this approach has never proved its efficacy. Although patients may improve hematological findings, renal prognosis is usually poor and patients maintain chronic renal failure in 70% of cases. Median survival was 16.5 months [3].

Physiopathology of gemcitabine-induced thrombotic microangiopathy is still poorly understood. Gemcitabine was suggested to have direct endothelial toxicity with a concomitant activation of the coagulation cascade. Histological data obtained from renal biopsies suggest a possible role of complement activation: a thickening of capillary walls, fibrin thrombi, necrotic endothelial cells, and granular deposits of immunoglobulins and C3 in the wall of small arteries and arterioles, and in glomeruli [5]. The hypothesis that complement could be involved in gemcitabine-induced thrombotic microangiopathy physiopathology and the unmet need with current treatments led to propose eculizumab to patients with such condition. Eculizumab is a monoclonal antibody targeting the C5 fraction of the terminal complement pathway and provided remarkable benefit in atypical hemolytic-uremic syndrome. To date six patients were treated with eculizumab for gemcitabine-induced-thrombotic microangiopathy that did not improve despite chemotherapy discontinuation [5–7]. Eculizumab was started 3 to 5 weeks after thrombotic microangiopathy diagnosis, with a median total dose of 6 g (range 3.6–9.6 g). Eculizumab was associated with hematological improvement and afforded a partial renal response. Four patients still had chronic renal failure with an estimated glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 at last follow-up (median of 4 months