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Adverse cardiac events to monoclonal antibodies used for cancer therapy

The risk of Kounis syndrome

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Monoclonal antibodies are currently used in the treatment of neoplastic, hematological, or inflammatory diseases, a practice that is occasionally associated with a variety of systemic and cutaneous adverse events. Cardiac adverse events include cardiomyopathy, ventricular dysfunction, arrhythmias, arrests, and acute coronary syndromes, such as acute myocardial infarction and vasospastic angina pectoris. These events generally follow hypersensitivity reactions including cutaneous erythema, pruritus chills, and precordial pain. Recently, IgE specific for therapeutic monoclonal antibodies have been detected, pointing to the existence of hypersensitivity and Kounis hypersensitivity-associated syndrome. Therefore, the careful monitoring of cardiovascular events is of paramount importance in the course of monoclonal antibody-based therapies. Moreover, further studies are needed to elucidate the pathophysiology of cardiovascular adverse events elicited by monoclonal antibodies and to identify preventive, protective, and therapeutic measures.

Keywords: cancer therapy; cardiac hypersensitivity; cardiac toxicity; Kounis syndrome; monoclonal antibodies

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Introduction

When allergic, hypersensitivity, anaphylactic, or anaphylactoid episodes are complicated with cardiovascular events, we are in front of a Kounis hypersensitivity-associated acute coronary syndrome, hereafter referred to as Kounis syndrome.[1] Three variants of this syndrome have been described so far: vasospastic angina (type I), acute coronary thrombosis (type II) and stent thrombosis (type III). Kounis syndrome is mainly caused by inflammatory mediators released locally or systemically upon mast cell degranulation. Mast cells degranulate when 2000 antibodies attached to mast cell surface in close proximity to each other are cross-linked by the corresponding antigens and make the critical number of 1000 bridges.[2] Platelets, which express various Fc receptors including FcγRI, FcγRII, FcεRI, and FcεRII, are also activated in the course of Kounis syndrome and participate in the allergic thrombosis process.[3]

In a recent review published in *Oncoimmunology*,[4] dealing with the adverse events caused by monoclonal antibodies currently employed in cancer therapy, the author focused on cardiac adverse events such as cetuximab-induced arrest, rituximab-induced arrhythmias, trastuzumab-induced myocardial dysfunctions and cardiomyopathies, and pertuzumab-induced left ventricular dysfunctions. It seems likely that many of the above cardiac toxicities share the same pathophysiology with the Kounis syndrome (**Table 1**).

Monoclonal Antibodies Inducing Adverse Cardiac Events and the Kounis Syndrome

The Kounis syndrome has been reported in association with rituximab infusion in a patient suffering from hairy cell leukemia.[5] This patient developed an allergic reaction manifesting with chills, erythema, dyspnea, precordial pain, and associated

Table 1. Monoclonal antibodies used for cancer therapy able to induce, so far, hypersensitivity-associated acute coronary syndromes (ACS) of Kounis type (KS)

Generic name	Trade name	Coronary syndrome-induced
-ximabs		
Rituximab	Rituxan®, MabThera®	type II of KS[6,7]
Cetuximab	Erbitux®	type I of KS[10]
Brentuximab	Adcetris®	none, so far
-zumabs		
Alemtuzumab	Campath-1H®	type I of KS[11]
Bevacizumab	Avastin®	ACS[12–14]
Trastuzumab	Herceptin®	ACS[15,16]
Ranibizumab	Lucentis®	ACS[14]
Pertuzumab	Perjeta®	none, so far
Trastuzumab	Kadcyla™	none, so far
-umabs		
Denosumab	Prolia® Xgeva®	none, so far
Ipilimumab	Yervoy®	none, so far
Ofatumumab	Arzerra®	none, so far
Panitumumab	Vectibix®	none, so far
-omabs		
Catumaxomab	Removab®	none, so far
Ibritumomab	Zevalin®	none, so far
Tositumomab-131I	Bexxar®	none, so far

with left anterior hemiblock, right bundle branch block, mid-ventricular ballooning pattern, and intracoronary thrombus. The patient finally needed angioplasty with stenting. Several other cases of rituximab-induced acute myocardial infarction have been reported.[6,7] Of note, anti-rituximab antibodies have been found in some rituximab-treated patients. A recent study demonstrated for the first time the presence of rituximab-specific IgE antibodies and T_H2 cells, suggesting that Type I hypersensitivity is responsible for rituximab-induced infusion reactions, in particular cardiovascular events.[8] In the CARRE study, which included patients with rheumatoid arthritis receiving rituximab, 3,4% of the subjects developed an acute myocardial infarction over a 3-y period.[9] Thus, the risk of myocardial infarction in patients treated with rituximab appears to be increased by up to 5-fold as compared with individuals who do not received this drug. A patient with recurrent colon cancer perceived chest tightness during the first course of cetuximab therapy. He was diagnosed with vasospastic angina that responded to vasodilatating agents, resembling a Type I Kounis syndrome.[10] Alemtuzumab is a monoclonal antibody specific for CD52 that has activity against T-cell leukemia and lymphoma. The infusion of alemtuzumab to a 52-y-old male patient, without any previous history of cardiac disease, affected by Lennert T-cell lymphoma provoked chills, sweats, and fever within 1 h.[11] This was followed by severe chest pain associated with nausea, vomiting, and hypotension. Electrocardiogram, troponin, and cardiac enzymes confirmed acute antero-septal myocardial infarction reminiscent of a Type II Kounis syndrome. Of note, the patient had received the same treatment 3 y earlier without manifesting cardiac symptoms.

Known adverse events associated with the use of bevacizumab are hemorrhage, impaired wound healing, and arterial thromboembolism. This said, 2 colorectal cancer patients with liver and/or pulmonary metastases who had previously received repeated courses of bevacizumab developed angina pectoris during the last course of this drug.[12] Both were found to have coronary artery disease by coronary angiography and underwent percutaneous coronary intervention with stenting. In a study comparing patients treated with the intravitreal injection of bevacizumab or phototherapy, in a non-treated community sample[13], the adjusted acute myocardial infaction rate was found to be 2.3-fold higher among bevacizumab-receiving patients than in the community group (95% confidence interval, 1.2–4.5) and among subjects treated with photodynamic therapy (95% confidence interval, 0.7–7.7). Another study compared retrospectively the incidence of arterial thromboembolic events in 378 patients treated with bevacizumab or ranibizumab for exudative age-related macular degeneration.[14] Stroke, myocardial infarction, angina pectoris, peripheral thromboembolic disease, transient ischemic attack, and sudden death were some of the adverse events manifesting with higher incidence in bevacizumab-treated, as compared with ranibizumab-treated patients. Additional reports have pointed to trastuzumab as a possible cause of acute myocardial infarction.[15,16] In a 45-y-old woman suffering from metastatic breast carcinoma, the administration of trastuzumab plus vinorelbine and capecitabine induced chest and arm pain that was responsive to nitroglycerine. The electrocardiogram was compatible with a diagnosis of acute myocardial ischemia.

Cardiac Hypersensitivity or Cardiac Toxicity?

Confusion exists, in medical literature, concerning the terms "cardiac hypersensitivity" and "cardiac toxicity," especially when these terms are used to characterize the acute adverse effects of therapeutic monoclonal antibodies. Cardiac toxicity generally refers to a dose-dependent cardiovascular adverse reaction that persists despite the discontinuation of the causative treatment. The final outcome of cardiac toxicity is a fibrotic response that should be confirmed histologically, a procedure that has never undertaken

until now. Cardiac hypersensitivity is more appropriate than cardiac toxicity to describe the adverse events elicited by therapeutic antibodies and should be used instead. Hypersensitivity refers to an inflammatory response that (1) is not dose-dependent, (2) may arise at any time during treatment, even with minimal drug concentrations and (3) is accompanied by of anti-drug antibodies. Anti-drug antibodies are most often of the IgG isotype, but a proportion of hypersensitivity reactions involve IgE antibodies. Indeed, IgE reactions specific for therapeutic antibodies have already been detected in patients, especially treated with rituximab.[8]

Conclusions

Based on these observations, one should be always bear in mind that the production of anti-drug antibodies is a reality in a variety of clinical setting, including the treatment of neoplastic, hematological or inflammatory diseases with monoclonal antibodies. Anti-drug antibodies can cause hypersensitivity reactions, worsen overt or incipient heart failure and induce myocardial infarction, manifesting as Kounis syndrome. Thus, the careful monitoring of cardiovascular events during the administration of therapeutic monoclonal antibodies is of paramount importance. Further studies are necessary in order to elucidate the pathophysiology of cardiovascular adverse events elicited by monoclonal antibodies and identify preventive, protective, and therapeutic measures.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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