Vasospasm in Fluoropyrimidine-Induced Ischemic Heart Disease

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Cardiovascular diseases and cancer are the leading cause of morbidity and mortality globally. Cardiotoxicity from chemotherapeutic agents results in substantial morbidity and mortality in cancer survivors and patients with active cancer. Cardiotoxicity induced by 5-fluorouracil (5-FU) has been well established, yet its incidence, mechanisms, and manifestation remain poorly defined. Ischemia secondary to coronary artery vasospasm is thought to be the most frequent cardiotoxic effect of 5-FU. The available evidence of 5-FU-induced epicardial coronary artery spasm and coronary microvascular dysfunction suggests that endothelial dysfunction or primary vascular smooth muscle dysfunction (an endothelial-independent mechanism) are the possible contributing factors to this form of cardiotoxicity. In patients with 5-FU-related coronary artery vasospasm, termination of chemotherapy and administration of nitrates or calcium channel blockers may improve ischemic symptoms. However, there are variable results after administration of nitrates or calcium channel blockers in patients treated with 5-FU presumed to have myocardial ischemia, suggesting mechanisms other than impaired vasodilatory response.

cardiotoxicity cancer fluoropyrimidines

1. Risk Factors for Chest Pain Due to Fluoropyrimidines

Several potential risk factors for 5-FU chest pain have been suggested, including underlying CAD, older age, and concomitant use of other treatments with cardiac side effects. Patients with pre-existing cardiac disease were at elevated risk of cardiotoxicity (risk ratio = 6.83, *p*-value = 0.0023) in a small cohort in which cardiotoxicity occurred in 7 of the 209 patients receiving their first course of 5-FU [1]. Nevertheless, there have been some inconsistencies with such hypotheses, as documented by further studies including patients who underwent coronary angiography for persisting angina. Coronary angiography did not show obstructive CAD in any of these patients [2]. Older age was supposed to be a risk factor for 5-FU chest pain. However, data did not support this belief [3][4]. Concomitant administration of other chemotherapeutic agents with cardiac side effects has been suggested as a reason for an increased risk of 5-FU cardiotoxicity. Still, this is a further assumption as there was only some evidence for increased cardiotoxicity with concomitant cisplatin treatment. The effects of previous or current chest radiotherapy were also ambiguous [5].

In summary, to date, there are insufficient data to ascertain risk well enough to justify withholding therapy in patients undergoing 5-FU treatment.

2. Uncertainties in Vasospasm Characterization and Its Impact on Management

Despite the clear clinical and pathophysiologic importance of vasospasm as a putative mechanism of fluoropyrimidine-related cardiotoxicity, this side effect is yet to be fully characterized. Indeed, most studies investigating this issue included small, heterogeneous samples that did not undergo routine coronary angiography during the onset of symptoms [6][7]. Chest pain and ECG findings cannot establish a firm diagnosis of coronary vasospasm. In cancer patients, the perception of chest pain is altered [8], either by a direct effect exerted by the tumor itself or by the administration of analgesics and narcotics prescribed to treat cancer pain, such as opioids in combination with non-steroidal anti-inflammatory drugs [9] or acetaminophen [10]. The lack of a clear symptomatology suggestive of coronary vasospasm in oncological patients has been confirmed by Rezkall and colleagues [11]. These authors conducted a prospective study on 25 patients undergoing 5-FU infusion. Following continuous ECG monitoring, 17 patients had asymptomatic ECG changes during infusion. It follows that the real epidemiology of coronary vasospasm following fluoropyrimidines administration is complex and needs to be fully understood.

Incidence of coronary vasospasm in 2021, a large cohort study by Zafar and colleagues [12], aimed to better define the real incidence of fluoropyrimidine-induced vasospasm. The study comprised 4019 patients who received either bolus or infusion therapy with 5-FU. Of these patients, 87 (2.6%) developed coronary vasospasm, mostly after the first cycle of therapy. These patients were younger (age 58 ± 13 years vs. 64 ± 13 years; $p = 0.001$) and had fewer cardiovascular risk factors (70.1% vs. 84.5%; $p = 0.007$) when compared to those not developing coronary vasospasm. No sex- or race-dependent differences were observed between the two groups. Although in the analysis by Zafar and colleagues, no differences in prognosis were observed between patients with and those without coronary vasospasm, other investigations have observed patients with severe outcomes, ranging from the development of myocardial infarction to sudden cardiac death [4].

The risk of coronary vasospasm depends on the cumulative dose [13], the schedule [14], and the route of administration [15] and it is increased in the presence of a concomitant administration of cisplatin-based chemotherapy which leads to hypomagnesemia [16]. Re-challenge is not advised since there is a higher risk of death, myocardial infarction, and cardiogenic shock [17]. If a re-challenge is needed, the American College of Cardiology recommends switching to a bolus regimen rather than continuous infusion. Further, it recommends administering nifedipine and isosorbide mononitrate before treatment, short-acting diltiazem, and sublingual nitroglycerin during the treatment, and the association of nifedipine with isosorbide 12 h after the treatment. Finally, it recommends administering only nifedipine 24 h after the treatment [18].

3. Focal Coronary Spasm

Focal epicardial coronary artery spasm may be identified in some patients with angiographically normal or near-normal coronary arteries. Focal epicardial coronary artery spasm is often considered a synonymous of variant angina, also called Prinzmetal's angina. However, it should be recognized that coronary artery spasm is not

specific to Prinzmetal angina. On selective coronary angiography, 0.5–0.8% of patients could show evidence of coronary artery spasm stimulated either by the tip of the catheter or the contrast medium [19]. Focal epicardial coronary vasospasm can be effectively detected through intravenous administration of ergonovine or acetylcholine [20][21]. It is characterized by local segmental coronary hyperreactivity of the smooth muscle to a variety of stimuli that produce only mild constriction in non-spastic segments of the coronary arteries [22]. Focal coronary vasospasm is usually found in correspondence of mild atherosclerotic plaques. Atherosclerotic disease affecting large coronary arteries altered their vasomotor tone and reactivity. There is an intimate association of spasm with sites of organic stenosis. Atherosclerotic segments may be deficient in the production of prostacyclin, which has marked endothelial-dependent vasodilation and platelet aggregation inhibiting properties. This could result in unopposed effects of thromboxane A2 released by platelets and subsequent vasoconstriction and activation of platelet glycoprotein IIb/IIIa receptor [23].

4. Diffuse Coronary Spasm: Vasotonic Angina

Diffuse spasm is a manifestation of endothelial dysfunction that alters and enhances vessel reactivity to normal sympathetic stimulation, partly due to reduced shear-mediated nitric oxide (NO) release and excess of reactive oxygen species [24][25]. A heightened direct constrictor response of vascular smooth muscle can also be implied [26]. This disorder may affect the epicardial coronaries as well as the microcirculation. Coronary microcirculation includes different anatomically and functionally vascular compartments (<500 μm diameter) and has a critical role in the physiological regulation of myocardial perfusion [27]. Since it cannot be seen in invasive procedures such as angiography, its role is often just an assumption.

A study conducted by a research group of the University of Bologna is crucial to demonstrate that vasotonic angina actually is a disorder of the entire coronary arterial tree [21][28]. Patients with vasotonic angina showed epicardial vasoconstriction which was usually severe and confined to the distal segments of the coronary arteries. Despite the administration of intracoronary nitroglycerin and the resolution of spasm in the epicardial arteries, the researchers found that the resistance to blood flow was persisting, which suggests that the microcirculation is still the major culprit. It has been estimated that coronary microvascular spasm accounts for approximately 27% of patients with myocardial infarction with non-obstructive coronary artery disease (MINOCA) [27][29].

5. Type of Coronary Spasm Associated with Fluoropyrimidine Administration

In the case of fluoropyrimidine-induced cardiotoxicity, several case reports and case series reported clinical pictures compatible with variant angina in patients who had a history of angiographically documented coronary artery lesions [30]. However, invasive assessment of the coronary tree was often not repeated after fluoropyrimidine administration, so a definite causal association between coronary atherosclerotic plaques and coronary vasospasm could not be ascertained. In 1989, Kleinman and colleagues [6] described the case of a 63-year-old man treated with 5-FU who presented with recurrent episodes of angina followed by transient ST-segment elevation that was

promptly relieved by nitrates administration and effectively controlled by the use of CCBs. These elements induced the authors to hypothesize that the patient may have developed Prinzmetal's angina. Still, no angiographic testing was conducted to document the occurrence of coronary spasm. In a study by Luwaert and colleagues [31], the type of coronary spasm detected at angiography appeared to be focal, with a 70% narrowing of the left circumflex artery, a degree of vasoconstriction that may induce chest pain even in the absence of significant ST elevation. Other investigators, however, were unable to uncover focal spasm during ergonovine testing [32]. Moreover, recent reports described cases of capecitabine-induced diffuse spasm accompanied by clinical and echocardiographic signs of Takotsubo Syndrome [33].

The evidence of fluoropyrimidine-induced diffuse spasm of the coronary arterial tree is compliant with the hypothesis that endothelial dysfunction or primary vascular smooth muscle dysfunction (an endothelial-independent mechanism) is a possible contributing factor to this form of cardiotoxicity. Fluoropyrimidines exert their toxic effect on the endothelium through a plethora of different mechanisms. Cwikiel and colleagues [34] observed that these antitumor agents caused a direct cytotoxic effect on endothelial cells, as demonstrated by the high level of the vessel wall and endothelial cell contraction, cell edema, cytolysis, occurrence of denuded areas, platelet adhesion/aggregation and fibrin formation. These factors certainly act through endothelial nitric oxide synthase (eNOS) [35], as NO produced by eNOS and its interaction with serine/threonine-protein kinase Akt/PKB [36], is a key determinant of cardiovascular tone [37][38][39]. These factors have also been demonstrated to increase the levels of free radicals and endothelin-1, which has a potent vasoconstricting effect [40].

6. The Role of Microcirculation

Microvascular dysfunction appears to be involved in fluoropyrimidine-induced coronary vasospasm. This hypothesis is supported by the evidence of global akinesia or dyskinesia at echocardiography in myocardial regions not supplied by stenotic coronary arteries [41]. However, this finding must be interpreted cautiously in light of a recent report [42]. The combination of endothelial dysfunction (defined as a decrease in luminal diameter of >20% after intracoronary acetylcholine) and microvascular dysfunction (defined as an index of microcirculatory resistance of ≥25) is present in only 10% of the overall population of patients with normal or near-normal coronary arteries. Indeed, the majority of these patients were found to have myocardial bridging (55%), and a substantial number of patients had some evidence of atherosclerosis based on intravascular ultrasound examination. It follows that microvascular dysfunction and atherosclerosis, although causally related in many patients, are distinct problems and may exist separately. Thus, many patients may show myocardial ischemia subsequent to hidden atherosclerosis, normal coronary arteries at angiography, and normal microvascular function. Coronary thromboemboli, without causing significant obstruction, could induce coronary artery spasm and cause acute myocardial infarction [43]. Such thromboemboli could occur mainly in patients with prosthetic valves or cancer [44][45].

7. Type of Spasm and Impact on Therapy

Focal coronary artery spasm can be effectively treated by CCBs and nitrates [30][46][47][48][45]. The renin-angiotensin system inhibitors may prove to be useful in long-term management as well. Treatment of diffuse coronary spasm is less defined, with a possible role for angiotensin-converting enzyme inhibitor therapy and supplementation with folic acid, which may alleviate the impaired endothelium-dependent arterial vasodilation. Of note, some studies were at variance and showed that in a few patients with variant angina the administration of L-type CCBs (nifedipine, verapamil, and diltiazem) or nitrates were not successful in relieving symptoms [49][50][51][52]. This finding may support the possible role of microcirculation at least in some patients, as the microvessels have a greater prevalence of T-type calcium channels, and L/T-type CCBs (e.g., mibefradil and efonidipine) have higher efficacy compared with L-type CCBs [53]. The positive role of L/T-type CCBs on the microcirculation has been shown by studies that described clinical and angiographic improvements in the coronary slow flow phenomenon following the administration of mibefradil [54] or nicardipine [55].

A further caveat should be noted. Shimokawa et al. [56] demonstrated that as the vessel size of the coronary microcirculation decreases, there is a progressive major role of endothelium-derived hyperpolarizing factor (EDHF) rather than nitric oxide, the latter being more important in the vasodilatation of epicardial large vessels.

In summary, the heterogeneity in the response to CCBs and to nitrates could explain why there are variable results after administration of CCBs or nitrates in some patients with 5-FU presumed to have myocardial ischemia. Induced chest pain persisted after the administration of some types of CCBs or nitrates. One point is critical. Testing that separates those patients whose symptoms are due to myocardial ischemia from those whose pain is non-ischemic is strictly necessary. Even minimal atherosclerotic disease on angiography (or intravascular ultrasound imaging) warrants risk-factor modification and prevention therapies.

8. Management of Cardiotoxicity

Cardiotoxicity related to 5-FU administration is a poorly understood but relatively common clinical entity that deserves special consideration given the frequent use of this agent and the cardiac complications associated with its use. The mechanism of 5-FU-related cardiotoxicity may occur from a combination of ischemia related to epicardial coronary vasospasm and microvascular dysfunction. Further clinical studies in humans are required to clarify these mechanisms. Patients with 5-FU-based chemotherapy who develop vasospasm are difficult to manage. Patients who present with chest-pain symptoms should be routinely referred to cardio-oncology for optimization of their medications. Patients should receive a baseline ECG. Patients should also be instructed to stop therapy and to call the emergency department if experiencing any chest discomfort at home. Clinicians should determine if further 5-FU is required or whether acceptable alternative treatments can be safely used. When further doses of 5-FU are necessary, clinicians should proceed cautiously. Management of the affected patients should focus on separating patients whose symptoms are due to myocardial ischemia from those whose pain is non-ischemic. Coronary angiography or computed tomography angiography is required as it would seem prudent to perform a sensitive screen for significant fixed coronary disease prior to performing any provocative testing for a diagnosis of coronary spasm. Patients with normal or near-normal coronary arteries may undergo ergonovine or acetylcholine tests, which would result in a better characterization of the vasospastic disease [57]. The possible

coexistence of coronary spasm in patients with severe coronary disease is clinically irrelevant. Patients that have severe “fixed” coronary disease at angiography need revascularization. Old, but still current guidelines support the usefulness of provocative testing for coronary spasm in patients with “recurrent episodes of apparently ischemic cardiac pain at rest” and “normal or mildly abnormal coronary angiogram” but no clinical observations, such as ST-segment shifts during rest ECG or 24 h ECG monitoring to substantiate the diagnosis of variant angina [58]. It should not go unnoticed, however, that physicians have abandoned the use of intracoronary provocative testing in the last two decades. Some cardiologists believe that ex-juvantibus criteria such as the use of CCBs, possibly combined with nitrates, may be helpful as provocative testing in the diagnostic evaluation of spasm. Researchers may argue that chest pain with or without ECG shifts is not synonymous of variant angina. Coronary spasm in variant angina is a distinct entity and should be managed with CCBs and nitrates. Symptom-relieving drugs, such as beta-blockers, have been found to be effective in patients with vasotonic angina and/or microvascular dysfunction [59]. Even minimal atherosclerotic disease warrants risk-factor modification and prevention therapies. Avoiding unnecessary medicines and optimizing therapy when linked to the correct diagnosis will benefit patients, health care providers, and the health care system.

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