Fluoropyrimidine Cardiotoxicity: Management Strategies at ESC Cardio Oncology 2026

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Fluoropyrimidine chemotherapy agents, including 5-fluorouracil (5-FU) and capecitabine, are cornerstones in the treatment of various solid tumours. However, their use is frequently complicated by cardiovascular toxicity, ranging from angina to myocardial infarction and sudden cardiac death. The ESC Cardio Oncology 2026 congress highlighted the ongoing clinical dilemma of balancing oncologic efficacy with the imperative to mitigate cardiotoxic risk, presenting current understanding and emerging strategies for detection and management.

KEY TAKEAWAYS

- The Pivot: The congress emphasized a shift towards proactive risk stratification and personalized management for fluoropyrimidine-induced cardiotoxicity.
- The Data: Cardiotoxicity affects 1% to 18% of patients receiving fluoropyrimidine therapy, with severe events occurring in 0.5% to 5%.
- The Action: Clinicians should implement pre-treatment cardiac risk assessment and consider dose modifications or alternative agents for high-risk patients.

Fluoropyrimidines are antimetabolite agents widely used in the treatment of colorectal, breast, gastric, and head and neck cancers. Their mechanism of action involves interfering with DNA and RNA synthesis, leading to cell death. While effective, these agents are associated with a spectrum of adverse effects, with cardiovascular toxicity being a significant concern. The incidence of fluoropyrimidine-induced cardiotoxicity (FIC) varies, affecting approximately 1% to 18% of treated patients, with severe events such as myocardial infarction or cardiogenic shock occurring in 0.5% to 5% of cases.1 The pathogenesis of FIC is multifactorial, involving coronary vasospasm, direct myocardial injury, and endothelial dysfunction.2 Symptoms often manifest within the first few days of treatment and can include angina, dyspnoea, arrhythmias, and elevated cardiac biomarkers.3

The clinical presentation of FIC can range from asymptomatic electrocardiographic changes to life-threatening events. Angina pectoris is the most common symptom, often occurring without evidence of obstructive coronary artery disease. Other manifestations include acute coronary syndromes, heart failure, myocarditis, pericarditis, and sudden cardiac death. The timing of onset is crucial, as most events occur during or shortly after the first cycle of treatment, typically within the first 72 hours of infusion. However, delayed presentations have also been reported, underscoring the need for sustained vigilance throughout the treatment course. The broad spectrum of symptoms and the potential for rapid

progression necessitate a comprehensive understanding of FIC for all clinicians involved in the care of cancer patients receiving fluoropyrimidines.

Clinical Challenges and Emerging Strategies

The ESC Cardio Oncology 2026 congress addressed the diagnostic and therapeutic challenges associated with FIC. A primary challenge lies in the unpredictable nature of FIC, as it can occur in patients with no pre-existing cardiac disease.4 Furthermore, symptoms can be non-specific, making early diagnosis difficult. The congress underscored the importance of pre-treatment risk stratification. Factors associated with an increased risk of FIC include pre-existing coronary artery disease, hypertension, diabetes mellitus, and prior cardiotoxic chemotherapy.5 Genetic polymorphisms, particularly in dihydropyrimidine dehydrogenase (DPD) enzyme activity, have also been implicated, as DPD deficiency leads to increased systemic exposure to 5-FU.6

The patient populations most frequently exposed to fluoropyrimidines, such as those with advanced colorectal or breast cancer, often have multiple comorbidities that can independently increase cardiovascular risk. This overlap complicates the attribution of cardiac events solely to fluoropyrimidine therapy. The congress emphasized the need for a thorough baseline cardiovascular assessment, including a detailed medical history, physical examination, and baseline ECG, for all patients prior to initiating fluoropyrimidine treatment. This initial evaluation helps establish a reference point for subsequent monitoring and aids in distinguishing pre-existing cardiac conditions from treatment-induced toxicity.

Emerging management strategies discussed at the congress focused on both prevention and early intervention. Pre-treatment DPD phenotyping or genotyping was highlighted as a potential tool to identify patients at high risk of severe toxicity, including cardiotoxicity.7 For patients identified with partial DPD deficiency, dose reduction or the use of alternative chemotherapy regimens may be considered.8

During treatment, close cardiac monitoring is essential. The utility of serial electrocardiograms (ECGs) and cardiac troponin measurements was reviewed. Elevated troponin levels, even in the absence of overt symptoms, may indicate subclinical myocardial injury and warrant treatment interruption or dose modification.9 The role of echocardiography in detecting changes in left ventricular ejection fraction (LVEF) was also discussed, though LVEF changes are often a late manifestation of FIC.10

For the acute management of FIC, treatment typically involves immediate cessation of the fluoropyrimidine infusion. Symptomatic management includes nitrates for angina, calcium channel blockers to alleviate vasospasm, and beta-blockers for rate control.11 Uridine triacetate (Vistogard) was presented as an effective antidote for severe or life-threatening 5-FU overdose or toxicity, including cardiotoxicity, when administered within 96 hours of 5-FU completion.12 Its mechanism involves competitive inhibition of 5-FU phosphorylation, reducing the formation of toxic metabolites.13

The congress also explored the potential of novel cardioprotective agents. While no definitive prophylactic strategies were endorsed, ongoing research into agents like statins, angiotensin-converting enzyme (ACE) inhibitors, and

antioxidants was noted.14 The consensus emphasized a multidisciplinary approach involving oncologists and cardiologists to optimize patient outcomes and minimize treatment-related morbidity.15

CLINICAL IMPLICATIONS

The discussions at ESC Cardio Oncology 2026 reinforce that fluoropyrimidine cardiotoxicity remains a persistent and challenging issue in oncology. The continued reliance on these agents, despite their known cardiac risks, underscores the need for more rigorous pre-treatment assessment. It is no longer sufficient to simply monitor for symptoms; proactive identification of at-risk patients, perhaps through routine DPD testing, should become standard practice. The cost-effectiveness of widespread DPD screening versus the cost of managing severe cardiotoxicity events warrants further investigation by health systems.

For clinicians, the message is clear: a higher index of suspicion for cardiotoxicity is required, particularly in the early phases of treatment. The availability of uridine triacetate for severe 5-FU toxicity provides a critical rescue option, but its efficacy is time-dependent. This necessitates rapid recognition and intervention, which may require enhanced training for oncology nurses and junior doctors on the early signs of FIC. Furthermore, the lack of robust, evidence-based cardioprophylactic strategies means that prevention largely hinges on careful patient selection and dose adjustment, rather than pharmacological pre-emption.

The pharmaceutical industry has a role to play in developing less cardiotoxic alternatives or adjunct therapies that can mitigate this risk without compromising oncologic efficacy. While uridine triacetate addresses acute toxicity, a preventative solution would be more impactful. Guideline bodies like the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) should consider incorporating DPD testing and more explicit cardiac monitoring protocols into their recommendations for fluoropyrimidine use, moving beyond general advice to specific, actionable steps for clinicians.

EDITORIAL & AI STANDARDS

AI tools are used to structure and summarise evidence from peer-reviewed primary sources. Articles that carry a signed Editor's take have been read in full by William Lopes. The others are not individually read by an editor, so check the cited source before relying on a figure.

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