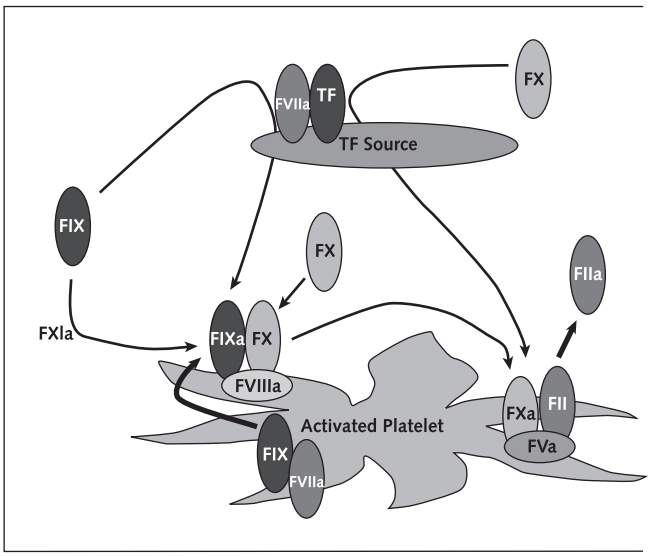
Figure. **Formation of the tenase complex and the prothrombinase complex.**



Infused recombinant-activated human factor VII (rFVIIa) may initiate hemostasis by a tissue factor (*TF*)–dependent mechanism or by a TF-independent mechanism. Classically, TF expressed at an injury site activates factor VIIa (*FVIIa*). Then, FVIIa/TF activates both factor IX (*FIX*) and factor X (*FX*). Factor IXa (*FIXa*) and factor Xa (*FXa*) lead to stable thrombin formation by the assembly of the tenase complex (factor VIIIa [*FVIIIa*]/FIXa/FX) and the prothrombinase complex (factor Va [*FVa*]/FXa/factor II [*FII*]) on the surface of activated platelets. Infused rFVIIa may also initiate hemostasis by directly interacting with FIX on activated platelet surfaces. FIIa = factor IIa; FXIa = factor XIa.

hemorrhage. Therapy with rFVIIa, 90 μg/kg, improved oxygenation in minutes. This dose was repeated for the next 2 days. Diffuse alveolar hemorrhage and bloody effusion did not recur after the first dose. The patient was discharged on room air and was receiving immunosuppressive therapy.

In case 3, diffuse alveolar hemorrhage requiring intubation occurred after unrelated matched allogeneic bone marrow transplantation in a 28-year-old man with acute leukemia. The hemorrhage was refractory to treatment with methylprednisolone sodium succinate, 500 mg/m^2, and platelet transfusions. Diffuse alveolar hemorrhage occurred twice on day 49 after bone marrow transplantation. The patient received rFVIIa, 120 μg/kg, and then 180 μg/kg 6 hours later when diffuse alveolar hemorrhage recurred. Diffuse alveolar hemorrhage occurred again on day 54 and was treated with rFVIIa, 90 μg/kg. Oxygenation improved within minutes of each use of rFVIIa. The patient was extubated but later died of leukemia.

Discussion: Diffuse alveolar hemorrhage is associated with high morbidity and mortality. In bone marrow transplantation, high-dose steroids reduce mortality from approximately 90% to 70% (1). In small-vessel vasculitis, diffuse alveolar hemorrhage is the single best predictor of death (2). Diffuse alveolar hemorrhage develops in 12% to 30% of patients with microscopic polyangiitis, with an "early" mortality rate of approximately 30% (1). Pulmonary hemorrhage carries the greatest risk for death early in the course of antineutrophil cytoplasmic autoantibody–positive small-vessel vasculitis (2).

Diffuse alveolar hemorrhage in systemic lupus erythematosus is associated with nephritis and the antiphospholipid antibody syndrome, conditions seen in case 2. Despite the increased risk for thrombosis in the antiphospholipid antibody syndrome, no pathologic clotting was observed with rFVIIa therapy (3).

Factor VIIa initiates coagulation by interacting with factor X and factor IX (**Figure**) (4). Zymogen factor X and factor IX activation classically occur by interaction with an FVIIa–tissue factor complex at injury sites (5). However, zymogen factor IX activation by rFVIIa also occurs in a concentration-dependent fashion on activated platelet surfaces, that is, independently of tissue factor (Gabriel DA, Monroe MD, Li X, Roberts HR. The effect of a high concentration of recombinant factor VIIa (rhFVIIa) on the activation of platelet-bound zymogen factor IX. 2002. Unpublished data). Tissue factor–independent hemostasis by FVIIa probably results from direct activation of platelet-bound zymogen factor IX, which combines with factor VIIIa to form a tenase complex (that is, factor VIIIa/factor IXa/factor X). This complex in turn activates zymogen factor X to generate thrombin and clot. Therefore, pharmacologic concentrations of rFVIIa may also directly activate zymogen factor IX on platelets at bleeding sites in diseases that generally have little apparent tissue damage, for example, the Goodpasture syndrome. Thrombin modulators, such as antithrombin III and protein C, may limit deleterious clot propagation at rFVIIa's site of action. Concentrations of thrombin modulators should be considered before using rFVIIa, especially in patients with liver disease.

Conclusion: The rapid effect of rFVIIa prolonged life in 3 patients with diffuse alveolar hemorrhage of different causes. No adverse events were observed.

David Henke, MD, MPH
Ronald J. Falk, MD
Don A. Gabriel, MD, PhD
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599

Acknowledgments: The authors thank Dr. Harold Roberts for help with the Discussion section and Jean Brown and Melissa Lawrence for editorial and secretarial assistance. They also thank the clinical teams who cared for the patients.

References

1. Fraser RS, Muller NL, Colman N, Pare ED, Bralow L, eds. Fraser and Pare's Diagnosis of Diseases of the Chest. 4th ed. Philadelphia: WB Saunders; 1999.
2. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol. 1996;7:23-32. [PMID: 8808106]
3. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995;74:1185-90. [PMID: 8560433]
4. Roberts HR, Monroe DM, Oliver JA, Chang JY, Hoffman M. Newer concepts of blood coagulation. Haemophilia. 1998;4:331-4. [PMID: 9873750]
5. Lawson JH, Mann KG. Cooperative activation of human factor IX by the human extrinsic pathway of blood coagulation. J Biol Chem. 1991;266:11317-27. [PMID: 2040636]

Capecitabine Induces Severe Angina-Like Chest Pain

TO THE EDITOR: *Background:* The cardiovascular side effects of fluoropyrimidines have been extensively reported (1). However, cardiotoxicity associated with capecitabine, a novel oral fluoropyrimi-

dine prodrug increasingly used in advanced breast, colorectal, and gastric cancer, has been infrequently described.

Objective: To describe 3 cases of severe angina-like chest pain possibly or probably related to capecitabine treatment. These cases were reported to the Netherlands Pharmacovigilance Centre.

Case Reports: Patient 1, a 44-year-old woman in good clinical condition, was receiving chemotherapy for advanced ovarian cancer. When her disease progressed, she was treated with 1500 mg of capecitabine twice daily. On the third day of treatment, she developed severe, reversible angina-like chest pain. Treatment with capecitabine was discontinued, and symptoms of chest pain fully disappeared within 2 days.

Patient 2, a 60-year-old man with metastatic colon cancer, received chemotherapy consisting of intravenous irinotecan, 250 mg/m^2 once every 3 weeks, plus capecitabine, 1000 mg/m^2 twice per day for 14 days. Two days after capecitabine therapy was started, he developed continuous, severe chest pain that lasted for 1 hour and radiated to the left arm. He was also nauseated. Treatment with capecitabine was stopped, and the patient was rechallenged 4 days later. Two days after the rechallenge, he again developed severe chest pain. Electrocardiographic monitoring showed significant but reversible ST-segment abnormalities indicative of myocardial ischemia. Treatment with nitrates was initiated, and capecitabine was withdrawn. Chemotherapy was continued 3 days later with irinotecan, 125 mg/m^2, plus a 1-hour bolus infusion of fluorouracil–leucovorin (500 mg/m^2 of fluorouracil and 20 mg/m^2 of leucovorin). Chest pain did not recur.

Patient 3, a 68-year-old man with colon cancer, was prescribed 1000 mg/m^2 of capecitabine twice daily. He was supposed to receive the drug for 14 days every 3 weeks but developed severe chest pain and severe nausea on day 3. The patient was pale but hemodynamically stable. Electrocardiography and cardiac ultrasonography showed a large myocardial infarction and hypokinesia, and troponin I and creatine kinase–MB levels were substantially elevated. Several hours later, the patient developed major complex tachycardia and hypotension; he died within 3 days of onset of angina pectoris.

In summary, all 3 patients developed chest pain 48 to 72 hours after initiation of capecitabine therapy. In the second patient, identical chest pain recurred after rechallenge with capecitabine, but symptoms were not observed during a subsequent bolus infusion of fluorouracil during co-treatment with isosorbide–mononitrate and nifedipine.

Discussion: Several factors can predispose patients to angina-like chest pain induced by fluoropyrimidines, especially previous chest radiation, history of cardiovascular disease, and concurrent treatment with other cardiotoxic agents (for example, anthracyclines) (2). However, we could not identify predisposing factors in any of our patients. In the database of the World Health Organization Monitoring Centre in Uppsala, Sweden, angina pectoris is reported statistically significantly more frequently in association with capecitabine (reporting odds ratio, 8.35 [95% CI, 4.82 to 14.44]) and fluorouracil (reporting odds ratio, 9.40 [CI, 7.76 to 11.38]) than with other drugs in the database. For fluorouracil, cardiotoxicity is more common after 96-hour continuous infusion than after bolus administration (7.6% vs. 2%). Oral capecitabine given for 14 days is thought to have toxic effects similar to those associated with continuous infusion of fluorouracil (3).

Conclusion: In view of the increasing use of capecitabine and the severity of the possible associated symptoms, it is important to inform patients about the risk for angina-like chest pain. Symptoms will most likely occur within 2 to 3 days after capecitabine therapy is started. If chest pain is reported, capecitabine treatment must be stopped immediately and the patient should be monitored closely until the pain resolves. Patients who develop angina-like chest pain should not be retreated with capecitabine.

Isa E.L.M. Kuppens, PharmD
Henk Boot, MD, PhD
Jos H. Beijnen, PharmD, PhD
Jan H.M. Schellens, MD, PhD
The Netherlands Cancer Institute
1066 CX Amsterdam, the Netherlands

Jerry Labadie, MD
LAREB
5237 MH 'sHertogenbosch, the Netherlands

References

1. Becker K, Erckenbrecht JF, Haussinger D, Frieling T. Cardiotoxicity of the antiproliferative compound fluorouracil. Drugs. 1999;57:475-84. [PMID: 10235688]
2. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug Saf. 2000;22:263-302. [PMID: 10789823]
3. Bertolini A, Flumano M, Fusco O, Muffatti A, Scarinci A, Pontiggia G, et al. Acute cardiotoxicity during capecitabine treatment: a case report. Tumori. 2001;87:200-6. [PMID: 11504378]