Warfarin–5-FU interactions

We read with great interest the two reports regarding the warfarin–FOLFOX interaction [1, 2]. We agree with the comments made by Kuter [3] regarding the increased likelihood of an increased International Normalized Ratio (INR) and possible bleeding when warfarin is used concomitantly with 5-fluorouracil (5-FU). Differences in drug response among patients are common, often leading to challenges in optimizing a dosage regimen for an individual patient. Such variability in drug response among patients is multifactorial, including environmental, genetic and disease determinants that affect the disposition (absorption, distribution, metabolism and excretion) of a given drug. Cytochrome P-450 enzymes (CYPs) are important in the biosynthesis and degradation of endogenous compounds such as steroids, lipids and vitamins. They metabolize many chemicals present in the diet and environment. CYPs are involved in the metabolism of many drugs, reducing or altering the pharmacologic activity of them and facilitating their elimination. CYPs are classified by their amino acid similarities and are designated by a family number, a subfamily letter, a number for an individual enzyme within the subfamily, and an asterisk followed by a number and a letter for each genetic (allelic) variant. The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine, and to a lesser extent into the bile. The cytochrome P-450 isoenzymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2 and 3A4. 2C9 is likely to be the principal form of human liver P-450 that modulates the in vivo anticoagulant activity of warfarin. A review of several retrospective studies among outpatients receiving long-term warfarin therapy indicates that the mean maintenance dose of warfarin depends on the CYP2C9 genotype [4]. 5-FU seems to inhibit hepatic metabolism of warfarin by inhibiting the synthesis of cytochrome P-450 2C9. Similar effects have been reported with capecitabine, the prodrug of 5-FU [5]. This interaction may occur with either low and full doses of warfarin with or without other drugs. Most patients with cancer are treated with multiagent regimens concomitantly with warfarin administration, but an INR elevation has only been observed in connection with 5-FU application. Patients receiving concomitant 5-FU and oral warfarin anticoagulant therapy should have their anticoagulant response (INR) monitored frequently in order to adjust the anticoagulant dose accordingly.

G. Giunta*
Servizio di Oncologia Medica Ospedale di S. Donà di Piave, Venice, Italy
(*E-mail: giovanni.giunta@libero.it)

references

doi:10.1093/annonc/mdj001
Published online 26 August 2005