should select capecitabine versus 5-fluorouracil rationally based on analysis of tumor *thymidine phosphorylase* levels using a simple test for enzyme expression, for example, by measuring RNA levels by a PCR-based method, or protein levels, by an antibody-based method (42).

XIII. DRUG COMBINATIONS THAT INCLUDE CAPECITABINE

The Meropol et al. (43) study administered a combination of irinotecan and cepecitabine in a clinical study of colorectal cancer. In a different clinical trial on colorectal cancer, using a different drug combination (capecitabine plus oxiplatin), Petrioli et al. (44) also found that higher expression of *thymidine phosphorylase* is associated with a more favorable clinical response. The common use of drug combinations in oncology, and the frequent decision to change one of the drugs used in a two-drug combination therapy, raises the issue of synergy. In this context, synergy refers to an effect that is more than additive, as it applies to efficacy, and an effect that is more than additive, as it applies to toxicity. Aprile et al. (45) report that taxane drugs stimulate the expression of *thymidine phosphorylase*, and that this effect accounts for the increased antitumor activity of the combination of capecitabine and taxane. Kikuno et al. (46) report the induction of this enzyme, with use of the taxane, paclitaxel. Paclitaxel is distinguished in that it is a natural product isolated from the Western yew tree.

XIV. METHODOLOGY TIP—DO CHANGES IN mRNA EXPRESSION RESULT IN CORRESPONDING CHANGES IN EXPRESSION OF POLYPEPTIDE?

Meropol et al. (47) measured the expression of thymidine phosphorylase with immunological assays sensitive to the polypeptide, and with PCR-based assays sensitive to the expressed mRNA. As a general proposition, it is hoped that changes in mRNA expression correlate with changes in the polypeptide. But it must not be assumed that an increase in mRNA results in a corresponding increase in protein. Pennica et al.

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