

is serious or clinically significant. The expected adverse drug reaction can be based on what is known about the pharmacology, chemistry, or class of the drug.

## V. MOA AND DRUG COMBINATIONS

Once the mechanism of action of various drugs is known, this knowledge can guide the design of therapies, for example therapeutic approaches that include combinations of drugs. One particular approach is to administer two drugs, where the two drugs have different mechanisms of action, and where these two mechanisms are related in a way that would be expected to result in synergy between the two drugs.

### a. Drug combinations that are complementary or synergic

Ifosfamide in combination with etoposide is used in anti-cancer therapy. As reviewed by Grier et al. (13) ifosfamide has the effect of alkylating chromosomal DNA, while etoposide has the effect of uncoiling chromosomal DNA. When ifosfamide is administered, the result is increased alkylation of the DNA, where this is followed by the action of DNA repair enzymes, where the DNA repair enzymes cleave the tumor cell's chromosome, thereby killing the tumor cell. When etoposide is administered, the result is increased uncoiling of the DNA of the tumor's chromosome, which is expected to enhance the enzyme-mediated cleavage, and enhance killing of the tumor cell. The end-result of administering both drugs together is a synergic increase of tumor killing. Miles et al. (14) describe the combination of capecitabine plus docetaxel. These two drugs have distinctly separate mechanisms of action, and their effects are synergic. Moreover, they are both toxic, but their toxicities do not overlap. The mechanism of action of any drug encompasses its toxicity. Piccart et al. (15) describe another example of drugs with complementary mechanisms, namely, cisplatin plus gemcitabine.

### b. Drug combinations that avoid inducing cross-resistance

Drug resistance is a common problem in oncology, bacterial infections, and viral infections. In oncology, drug resistance can arise where a tumor increases the activity of a pump that forces drugs out of the tumor cell, or where the target of the drug acquires a mutation that enables the target to avoid the inhibiting action of the drug. Cross-resistance is the phenomenon where a patient is being treated with one drug, and where the tumor acquires a type of drug resistance that enables it to

<sup>13</sup> Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *New Engl J Med.* 2003;348:694–701.

<sup>14</sup> Miles D, von Minckwitz G, Seidman AD. Combination versus sequential single-agent therapy in metastatic breast cancer. *Oncologist.* 2002;7(suppl 6):13–19.

<sup>15</sup> Piccart MJ, Lamb H, Vermorken JB. Current and future potential roles of the platinum drugs in the treatment of ovarian cancer. *Ann Oncol.* 2001;12:1195–1203.