CHAPTER

27

Mechanism of Action—Part II (Cancer)

I. INTRODUCTION

Drugs against cancer include small-molecule drugs, such as methotrexate and cisplatin, as well as biologicals, such as cytokines, antibodies, and vaccines.

Small-molecule anticancer drugs include drugs that cause damage to the genome, such as methotrexate, 5-fluorouracil, and cisplatin. Fluorouracil, for example, is widely used for the treatment of colorectal, pancreatic, breast, head and neck, gastric, and ovarian cancers (1). DNA damage arises in different ways, depending on the drug. Damage can be caused by incorporation of the drug as part of the polynucleotide chain, by covalent damage directly to the double-stranded helix (other than by incorporation into the chain), or by provoking imbalances in the normal pools of deoxynucleotides, resulting in abnormal incorporation of a naturally occurring deoxynucleotide, for example, dUTP, into the chromosome.

For the above drugs, it is possible to provide a generic mechanism of action (MOA). As shown in the following diagram, drugs that act on the genome often have the following mechanism. First, the drug is incorporated, resulting in DNA damage, second apoptosis is activated, and third, apoptosis kills the cancer cell. This mechanism is responsible, at least in part, for the cytotoxic effects of methotrexate (2), 5-fluorouracil (3), cladribine (4),

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