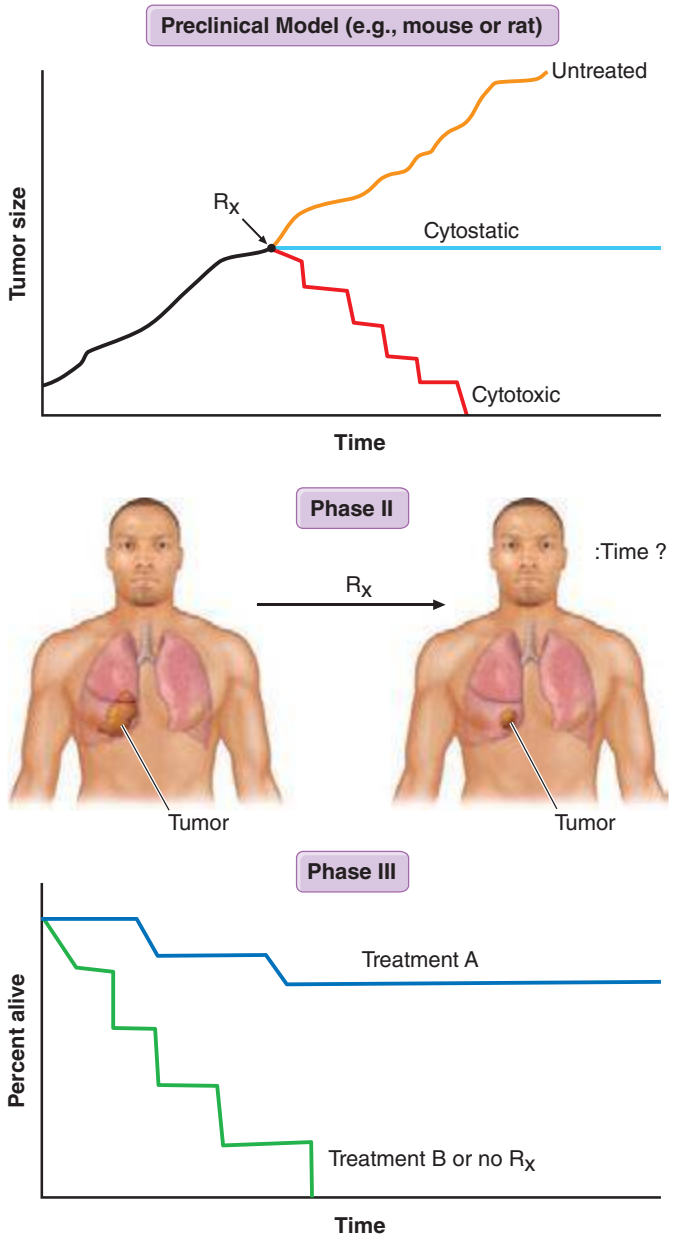

FIGURE 103e-2 Steps in cancer drug discovery and development. Preclinical activity (*top*) in animal models of cancers may be used as evidence to support the entry of the drug candidate into phase 1 trials in humans to define a correct dose and observe any clinical antitumor effect that may occur. The drug may then be advanced to phase 2 trials directed against specific cancer types, with rigorous quantitation of antitumor effects (*middle*). Phase 3 trials then may reveal activity superior to standard or no treatment (*bottom*).

agents on quality of life. Cancer drug clinical trials conventionally use a toxicity grading scale where grade 1 toxicities do not require treatment, grade 2 toxicities may require symptomatic treatment but are not life-threatening, grade 3 toxicities are potentially life-threatening if untreated, grade 4 toxicities are actually life-threatening, and grade 5 toxicities are those that result in the patient's death.

Development of targeted agents may proceed quite differently. While phase 1–3 trials are still conducted, molecular analysis of human tumors may allow the precise definition of target expression in a patient's tumor that is necessary for or relevant to the drug's action. This information might then allow selection of patients expressing the drug target for participation in all trial phases. These patients may then have a greater chance of developing a useful response to the drug by virtue of expressing the target in the tumor. Clinical trials may be designed to incorporate an assessment of the behavior of the target in relation to the drug (pharmacodynamic studies). Ideally, the plasma concentration that affects the drug target is known, so escalation to MTD may not be necessary. Rather, the correlation of host toxicity while achieving an "optimal biologic dose" becomes a more relevant endpoint for phase 1 and early phase 2 trials with targeted agents.

Useful cancer drug treatment strategies using conventional chemotherapy agents, targeted agents, hormonal treatments, or biologics have one of two valuable outcomes. They can induce cancer cell death, resulting in tumor shrinkage with corresponding improvement in patient survival, or increase the time until the disease progresses. Another potential outcome is to induce cancer cell *differentiation* or *dormancy* with loss of tumor cell replicative potential and reacquisition of phenotypic properties resembling normal cells. A blocking in normal cellular differentiation may be a key feature in the pathogenesis of certain leukemias.

Cell death is a closely regulated process. *Necrosis* refers to cell death induced, for example, by physical damage with the hallmarks of cell swelling and membrane disruption. *Apoptosis*, or programmed cell death, refers to a highly ordered process whereby cells respond to defined stimuli by dying, and it recapitulates the necessary cell death observed during the ontogeny of the organism. Cancer chemotherapeutic agents can cause both necrosis and apoptosis. Apoptosis is characterized by chromatin condensation (giving rise to "apoptotic bodies"), cell shrinkage, and, in living animals, phagocytosis by surrounding stromal cells without evidence of inflammation. This process is regulated either by signal transduction systems that promote a cell's demise after a certain level of insult is achieved or in response to specific cell-surface receptors that mediate physiologic cell death responses, such as occurs in the developing organism or in the normal function of immune cells. Influencing apoptosis by manipulation of signal transduction pathways has emerged as a basis for understanding the actions of drugs and designing new strategies to improve their use. *Autophagy* is a cellular response to injury where the cell does not initially die but catabolizes itself in a way that can lead to loss of replicative potential. A general view of how cancer treatments work is that the interaction of a chemotherapeutic drug with its target induces a "cascade" of further signaling steps. These signals ultimately lead to cell death by triggering an "execution phase" where proteases, nucleases, and endogenous regulators of the cell death pathway are activated (Fig. 103e-3).

Targeted agents differ from chemotherapy agents in that they do not indiscriminately cause macromolecular lesions but regulate the action of particular pathways. For example, the $p210^{bcr\text{-}abl}$ fusion protein tyrosine kinase drives chronic myeloid leukemia (CML), and HER2/neu stimulates the proliferation of certain breast cancers. The tumor has been described as "addicted" to the function of these molecules in the sense that without the pathway's continued action, the tumor cell cannot survive. In this way, targeted agents directed at $p210^{bcr\text{-}abl}$ or HER2/neu may alter the "threshold" tumors driven by these molecules may have for undergoing apoptosis without actually creating any molecular lesions such as direct DNA strand breakage or altered membrane function.

While apoptotic mechanisms are important in regulating cellular proliferation and the behavior of tumor cells in vitro, in vivo it is unclear whether all of the actions of chemotherapeutic agents to cause cell death can be attributed to apoptotic mechanisms. However, changes in molecules that regulate apoptosis are correlated with clinical outcomes (e.g., *bcl2* overexpression in certain lymphomas conveys poor prognosis; proapoptotic *bax* expression is associated with a better outcome after chemotherapy for ovarian carcinoma). A better understanding of the relationship of cell death and cell survival mechanisms is needed.

Chemotherapy agents may be used for the treatment of active, clinically apparent cancer. The goal of such treatment in some cases is cure of the cancer, that is, elimination of all clinical and pathologic evidence of cancer and return of the patient to an expected survival no different than the general population. Table 103e-3, *A* lists those tumors considered curable by conventionally available chemotherapeutic agents