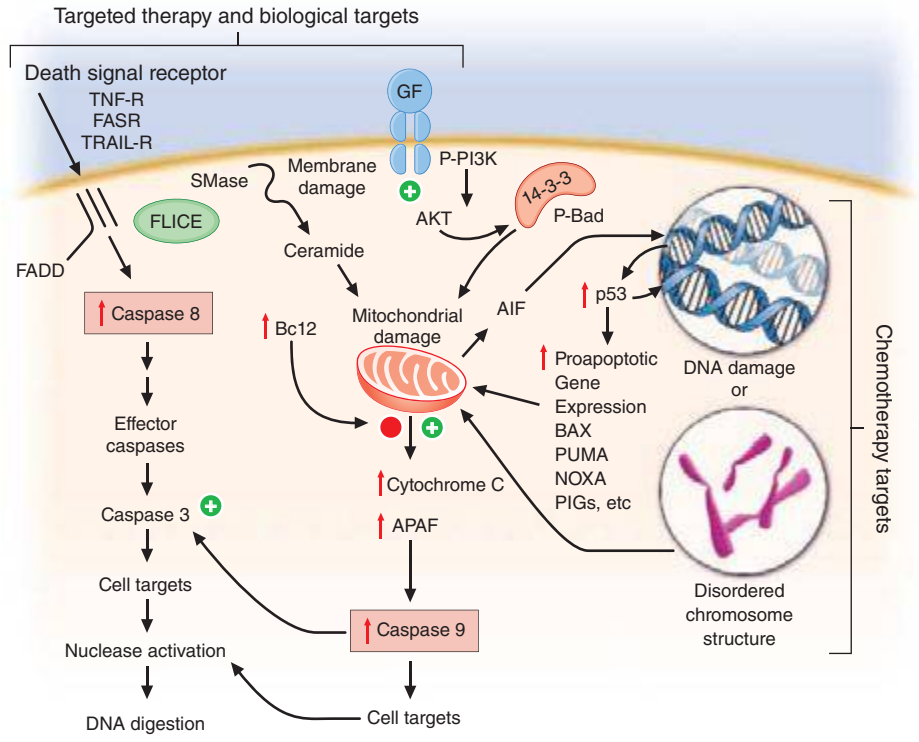

FIGURE 103e-3 Integration of cell death responses. Cell death through an apoptotic mechanism requires active participation of the cell. In response to interruption of growth factor (GF) or propagation of certain cytokine death signals (e.g., tumor necrosis factor receptor [TNF-R]), there is activation of "upstream" cysteine aspartyl proteases (caspases), which then directly digest cytoplasmic and nuclear proteins, resulting in activation of "downstream" caspases; these cause activation of nucleases, resulting in the characteristic DNA fragmentation that is a hallmark of apoptosis. Chemotherapy agents that create lesions in DNA or alter mitotic spindle function seem to activate aspects of this process by damage ultimately conveyed to the mitochondria, perhaps by activating the transcription of genes whose products can produce or modulate the toxicity of free radicals. In addition, membrane damage with activation of sphingomyelinases results in the production of ceramides that can have a direct action at mitochondria. The antiapoptotic protein bcl2 attenuates mitochondrial toxicity, while proapoptotic gene products such as bax antagonize the action of bcl2. Damaged mitochondria release cytochrome C and apoptosis-activating factor (APAF), which can directly activate caspase 9, resulting in propagation of a direct signal to other downstream caspases through protease activation. Apoptosis-inducing factor (AIF) is also released from the mitochondrion and then can translocate to the nucleus, bind to DNA, and generate free radicals to further damage DNA. An additional proapoptotic stimulus is the bad protein, which can heterodimerize with *bcl2* gene family members to antagonize apoptosis. Importantly, though, bad protein function can be retarded by its sequestration as phospho-bad through the 14-3-3 adapter proteins. The phosphorylation of bad is mediated by the action of the AKT kinase in a way that defines how growth factors that activate this kinase can retard apoptosis and promote cell survival.

when used to address disseminated or metastatic cancers. If a tumor is localized to a single site, serious consideration of surgery or primary radiation therapy should be given, because these treatment modalities may be curative as local treatments. Chemotherapy may then be used after the failure of these modalities to eradicate a local tumor or as part of multimodality approaches to offer primary treatment to a clinically localized tumor. In this event, it can allow organ preservation when given with radiation, as in the larynx or other upper airway sites, or sensitize tumors to radiation when given, e.g., to patients concurrently receiving radiation for lung or cervix cancer (Table 103e-3, *B*). Chemotherapy can be administered as an *adjuvant*, i.e., in addition to surgery or radiation (Table 103e-3, *C*), even after all clinically apparent disease has been removed. This use of chemotherapy has curative potential in breast and colorectal neoplasms, as it attempts to eliminate clinically unapparent tumor that may have already disseminated. As noted above, small tumors frequently have high growth fractions and therefore may be intrinsically more susceptible to the action of antiproliferative agents. *Neoadjuvant* chemotherapy refers to administration of chemotherapy prior to any surgery or radiation to a local tumor in an effort to enhance the effect of the local treatment.

Chemotherapy is routinely used in "conventional" dose regimens. In general, these doses produce reversible acute side effects, primarily consisting of transient myelosuppression with or without gastrointestinal toxicity (usually nausea), which are readily managed. "High-dose" chemotherapy regimens are predicated on the observation that the dose-response curve for many anticancer agents is rather steep, and increased dose can produce markedly increased therapeutic effect, although at the cost of potentially life-threatening complications that require intensive support, usually in the form of hematopoietic stem cell support from the patient (*autologous*) or from donors matched for histocompatibility loci (*allogeneic*), or pharmacologic "rescue" strategies to repair the effect of the high-dose chemotherapy on normal tissues. High-dose regimens have definite curative potential in defined clinical settings (Table 103e-3, *D*).

If cure is not possible, chemotherapy may be undertaken with the goal of palliating some aspect of the tumor's effect on the host. In this usage, value is perceived by the demonstration of improved symptom relief, progression-free survival, or overall survival at a certain time from the inception of treatment in the treated population, compared to a relevant control population established as the result of clinical research protocol or other organized comparative study. Such clinical research protocols are the basis for U.S. Food and Drug Administration (FDA) approval of a particular cancer treatment as safe and effective and are the benchmark for an evidence-based approach to the use of chemotherapeutic agents. Common tumors that may be meaningfully addressed by chemotherapy with palliative intent are listed in Table 103e-3, *E*.

Usually, tumor-related symptoms manifest as pain, weight loss, or some local symptom related to the tumor's effect on normal structures. Patients treated with palliative intent should be aware of their diagnosis and the limitations of the proposed treatments, have access to supportive care, and have suitable "performance status," according to assessment algorithms such as the one developed by Karnofsky (see Table 99-4) or by the Eastern Cooperative Oncology Group (ECOG) (see Table 99-5). ECOG performance status 0 (PS0) patients are without symptoms; PS1 patients are ambulatory but restricted in strenuous physical activity; PS2 patients are ambulatory but unable to work and are up and about 50% or more of the time; PS3 patients are capable of limited self-care and are up <50% of the time; and PS4 patients are totally confined to bed or chair and incapable of self-care. Only PS0, PS1, and PS2 patients are generally considered suitable for palliative (noncurative) treatment. If there is curative potential, even poor–performance status patients may be treated, but their prognosis is usually inferior to that of good–performance status patients treated with similar regimens.

An important perspective the primary care provider may bring to patients and their families facing incurable cancer is that, given the limited value of chemotherapeutic approaches at some point in the