Hematologic Malignancies: An Opportunity for Targeted Drug Therapy

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Molecular and cellular analyses over the last two decades have demonstrated unregulated growth, maturation, and cell survival as basic characteristics of many types of cancers [1]. Hematologic malignancies are among the most studied and well understood of all cancers. Common influences driving cell proliferation and survival in many of these diseases are growth factors. The aberrant production or overproduction of growth factors and chronic activation of their receptors are characteristic of many malignancies. Autocrine stimulation of malignant cells involves secretion of growth factors by the malignant cell itself, whereas paracrine stimulation occurs when the malignant cell depends on externally derived growth factors [2]. Regardless of their sources, these growth factors activate signal transduction pathways within the cell by binding to specific cell surface receptors and activating enzymatic functions. Many of the receptors are tyrosine kinases or are associated with kinase activity. Other enzymatic functions associated with signal transduction pathways include serine/threonine kinase activity, phosphatase, and GTPase activity [3]. The specific functions that are altered by growth factors in malignant cells ultimately lead to changes in gene expression and cell survival.

Hypomethylating Agents

Targeted chemotherapies for hematologic malignancies that will be discussed in this supplement include the differentiating agent 5-azacytidine, which causes nonselective demethylation of genomic DNA, resulting in changes in the gene expression profile of the malignant cell [6-8]. Progress in the understanding of myeloproliferative disorders and myelodysplasia has lead to the initiation of clinical trials for this agent in these disorders, as discussed in the article by Dr. Lewis Silverman [9]. Although not immediately obvious candidates for use in hematologic malignancies, the highly publicized and anticipated angiogenesis inhibitors also have considerable promise [10]. Preclinical and clinical studies with these agents will be discussed by Drs. Alan List and Francis Giles [11, 12]. The potential utility of angiogenesis inhibitors in this arena can be illustrated using the biologic effects of autocrine and paracrine cytokine signaling in chronic lymphocytic leukemia.

Anti-Angiogenic Agents

Angiogenic growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF), are generally induced in response to limited oxygen and nutrients [10]. For solid tumors, the necessity for sprouting new blood vessels and remodeling the tumor’s microenvironment is clear.
However, it is becoming increasingly apparent that many types of hematologic cancer cells also produce growth factors with angiogenic activity. These factors are integrally involved in the establishment and progression of all types of malignancies.

Chronic lymphocytic leukemia B cells are influenced by numerous cytokines or growth factors derived from bone marrow stromal cells. In addition, growth factors derived from bone marrow stromal cells also appear to inhibit apoptosis and promote malignant cell survival [13, 14]. Such factors have been shown to increase as disease progresses [14]. These results suggest that strategies to block the response to stromal cell-derived cytokines may be effective in the treatment of other hematologic malignancies.

Agents that interfere with VEGF-R and c-kit responses are now in clinical trials for acute myelogenous leukemia and are discussed in the articles by Drs. List and Giles [11, 12]. These angiogenesis inhibitors are examples of targeted therapies and may demonstrate an enhanced therapeutic index in selectively retarding the growth of malignant cells and increasing their susceptibility to apoptotic signals from the microenvironment [15, 16]. At the same time, these targeted agents may offer decreased toxicities, because their cytotoxic action on normal dividing cells is expected to be minimal. Additionally, they may enhance the clinical activity of current therapeutics without significantly increasing their toxicities. Finally, angiogenesis inhibitors are directed mainly at the function of endothelial cells and other normal cells surrounding a tumor and not specifically at the tumor cells. Therefore, hypoxia and inefficient kinetics of drug delivery to the tumor are not significant theoretical barriers to therapy. Drug resistance that may arise in response to standard chemotherapeutic agents may not affect the response to angiogenesis inhibitors.

THROMBOPOIETIC AGENTS

Targeted therapies used in cancer therapy also include growth factors that bind to specific receptors on normal hematopoietic progenitor cells to promote hematopoietic reconstitution. While not targeted directly at the cancer cells or aimed at eliminating or reducing tumor load, these therapeutics are extremely important in minimizing the side effects and toxicities of standard chemotherapies and allowing patients to maintain a reasonable quality of life during treatment [5]. Recombinant G-CSF and recombinant erythropoietin have shown dramatic success in ameliorating the neutropenia and anemia, respectively, associated with chemotherapy as well as in enabling the appropriate intensity and schedule to be used for delivery of planned doses of cytotoxic agents. However, one frequent complication for which there is still a considerable unmet need for effective growth factor support is thrombocytopenia [17]. Thrombocytopenia is associated with inadequate or abnormal platelet production and occurs in patients receiving chemotherapy, and in aplastic anemia, premalignant conditions such as myelodysplastic syndromes, and liver transplantation. It can also be the result of increased platelet destruction in idiopathic thrombocytopenia purpura, HIV-associated thrombocytopenia, sepsis with disseminated intravascular coagulation, and vasculitis. Another article in this supplement, by Dr. George Demetri [18], discusses the development of recombinant human thrombopoietin for the treatment and prevention of thrombocytopenia.

In summary, this supplement presents new information on a variety of targeted therapeutic interventions, highlighting angiogenesis inhibitors, DNA hypomethylating agents, and specific hematopoietic growth factors. Clinical development of many targeted drug therapies is expected to improve the efficacy, safety, and tolerability of treatment for a large number of patients with cancer.

REFERENCES


