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Is the focus moving toward a combination of targeted drugs?

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The concept of combining targeted agents for the treatment of acute myeloid leukemia (AML) is a relatively new but potentially promising area of investigation. A number of targeted agents may have limited single-agent activity but could show significant promise when used in conjunction with other types of similar compounds. Combinations of targeted agents may effectively interrupt multiple pathways in either a linear or parallel fashion. There are currently numerous combination regimens under investigation at either the preclinical or clinical levels, including histone deacetylase (HDAC) and CDK inhibitors; HDAC and proteasome inhibitors; HDAC and NF-κB (IKKβ) inhibitors; CHK1 and MEK1/2 inhibitors; and BCL-2 antagonists and CDK inhibitors. Although combinations of targeted agents will not displace conventional cytotoxic regimens in AML or related disorders in the foreseeable future, these combinations clearly warrant further attention.

Key words: targeted agents; histone deacetylase inhibitors; HDAC; NF-κB inhibitors; CDK inhibitors; proteasome inhibitors; MEK inhibitors; BCL-2 inhibitors.

INTRODUCTION

The introduction of the prototypical targeted agent imatinib mesylate (Gleevec) for the treatment of chronic myelogenous leukemia (CML) has given hope that similar approaches may be effective in the case of acute myelogenous leukemia (AML). One novel approach to the treatment of AML involves the concept of combining targeted agents, although it is only one of a number of options currently being explored. For example, the concept of combining targeted agents with more standard chemotherapy for AML is currently the focus of intense interest. Nevertheless, the introduction of

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targeted agents provides many new therapeutic options in this disease and has ushered in an exciting era in leukemia therapy.

The term "targeted agent" could be considered a misnomer because such agents often have multiple targets, some of which may be as or more important than the one originally intended. In fact, such agents rarely, if ever, affect only the primary target for which they were designed. There are several categories of targeted agents, and the use of each of these has distinct but interrelated goals, including induction of differentiation, dysregulation of the cell cycle, modulation of apoptosis, and inhibition of signal transduction pathways (Figure 1). This multiplicity of categories results in a large number of possible combinations, many of which have a rational molecular basis.

DUAL INHIBITION

The two-hit theory of leukemogenesis, as described by Gilliland[1], provides a theoretical basis for combining targeted agents for AML therapy. According to this concept, leukemogenesis represents a cooperative process involving mutations of two types of proteins ie, Class I proteins (eg, core-binding proteins), disruption of which leads to interference with the normal differentiation process, and Class II proteins (eg, FLT3), disruption of which results in enhanced cell survival. In a limited number of cases, inhibiting a single pathway may occasionally be sufficient, as in the case of CML, in which cells that are addicted to the BCR-ABL pathway are exquisitely sensitive to imatinib mesylate, which

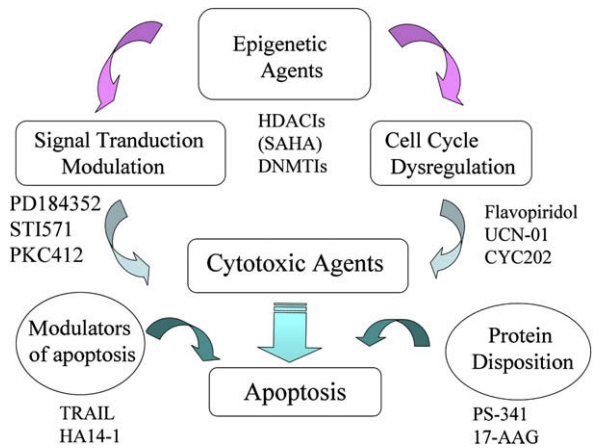

Figure 1. Categories of targeted agents used in AML. A general classification of targeted agents with possible utility in AML and their potential for combination therapy in this disease. Epigenetically acting agents include HDAC inhibitors and inhibitors of DNA methyltransferases. Cell cycle inhibitors include CDK inhibitors, such as flavopiridol, and more recently, inhibitors of CHK1 (eg, UCN-01) and aurora kinases. Small molecule inhibitors of survival signaling pathways include tyrosine kinase inhibitors, such as the FLT3 inhibitor PKC412, and serine threonine kinase inhibitors, such as the MEK1/2/ERK1/2 inhibitor AZD6244. Modulators of apoptosis include small molecule BCL-2 antagonists (ABT-737), TRAIL, and XIAP antagonists. Finally, agents which interfere with protein disposition include Hsp90 antagonists and proteasome inhibitors, such as bortezomib. In addition to combination of these agents with established chemotherapeutic drugs, numerous combinations of targeted agents are under investigation at both the preclinical and clinical levels in AML, including HDAC inhibitors and DNA methyltransferase inhibitors, HDAC inhibitors and CDK inhibitors (flavopiridol), proteasome inhibitors and HDAC inhibitors, HSP90 antagonists and tyrosine kinase inhibitors, and MEK1/2 and CHK1 inhibitors, among numerous others.