

Biologically Risk Directed Therapy for Improved Trial Development and Outcomes in Patients with AML

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Abstract

The outcome for patients with acute myelogenous leukemia has substantially improved over the past several decades. A significant part of this improvement has resulted from the dose intensification of treatment strategies. However, while dose intensification increased the cure rate for patients with AML, there has also been increased treatment related morbidity and mortality. Further, despite such toxicity, the primary cause of death is still leukemia.

These outcomes underscore the problem that most currently used therapies may be effective at killing the majority of leukemic cells, but not capable of eradicating the leukemic stem cell. Recent data would suggest that in most types of AML, the transformation process occurs in a very early hematopoietic progenitor and that specific subtypes of AML are dependent on the nature of the transforming, genetic events. Observations such as these have profound implications for how we should be developing more effective therapies that not only cytoreduce, but eradicate or control the expansion of leukemic stem cells.

Potential targets for future treatments include 1) targeting unique myeloid differentiation or proliferation associated antigens 2) cytokine receptor mutations and downstream signal transduction pathways, 3) differentiation based targets involving chromatin remodeling and altered gene expression, and 4) immunologic approaches to stimulating both autologous and allogeneic anti-leukemic immune responses. The impact of host genotype and its influence on drug metabolism and elimination will also play an increasingly important role. Detailed examples of such approaches will be discussed along with the advantages and disadvantages in order to build the foundation for future biologically risk directed therapies for patients with AML.
