Pediatric Acute Lymphoblastic Leukemia

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Abstract

The outcome for children with acute lymphoblastic leukemia (ALL) has improved dramatically with current therapy resulting in an event free survival exceeding 75% for most patients. However significant challenges remain including developing better methods to predict which patients can be cured with less toxic treatment and which ones will benefit from augmented therapy. In addition, 25% of patients fail therapy and novel treatments that are focused on undermining specifically the leukemic process are needed urgently.

In Section I, Dr. Carroll reviews current approaches to risk classification and proposes a system that incorporates well-established clinical parameters, genetic lesions of the blast as well as early response parameters. He then provides an overview of emerging technologies in genomics and proteomics and how they might lead to more rational, biologically based classification systems.

In Section II, Drs. Mary Relling and Stella Davies describe emerging findings that relate to host features that influence outcome, the role of inherited germline variation. They highlight technical breakthroughs in assessing germline differences among patients. Polymorphisms of drug

metabolizing genes have been shown to influence toxicity and the best example is the gene thiopurine methyltransferase (TPMT) a key enzyme in the metabolism of 6-mercaptopurine. Polymorphisms are associated with decreased activity that is also associated with increased toxicity. The role of polymorphisms in other genes whose products play an important role in drug metabolism as well as cytokine genes are discussed.

In Sections III and IV, Drs. James Downing and Cheryl Willman review their findings using gene expression profiling to classify ALL. Both authors outline challenges in applying this methodology to analysis of clinical samples. Dr. Willman describes her laboratory's examination of infant leukemia and precursor B-ALL where unsupervised approaches have led to the identification of inherent biologic groups not predicted by conventional morphologic, immunophenotypic and cytogenetic variables. Dr. Downing describes his results from a pediatric ALL expression database using over 327 diagnostic samples, with 80% of the dataset consisting of samples from patients treated on a single institutional protocol. Seven distinct leukemia subtypes were identified representing known leukemia subtypes including: *BCR-ABL*, *E2A-PBX1*, *TEL-AML1*, rearrangements in the *MLL* gene, hyperdiploid karyotype (i.e., > 50 chromosomes), and T-ALL as well as a new leukemia subtype. A subset of genes have been identified whose expression appears to be predictive of outcome but independent verification is needed before this type of analysis can be integrated into treatment assignment.

Chemotherapeutic agents kill cancer cells by activating apoptosis, or programmed cell death. In Section V, Dr. John Reed describes major apoptotic pathways and the specific role of key proteins in this response. The expression level of some of these proteins, such as BCL2, BAX, and caspase 3, has been shown to be predictive of ultimate outcome in hematopoietic tumors. New therapeutic approaches that modulate the apoptotic pathway are now available and Dr. Reed highlights those that may be applicable to the treatment of childhood ALL.

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