Conquering Blood Diseases – From Research to Patient Care

Acute Lymphoblastic Leukemia: An Historical Perspective

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Astute observations, dedicated researchers, cooperative groups, and clinical trials as well as guinea pig serum, hypoglycemic cows, and periwinkle plant extracts—all contributed to the evolution of the term "cure" used with acute lymphoblastic leukemia (ALL), a disease that was invariably fatal until the 1960s. Over 50 years ago methotrexate, asparaginase (discovered when guinea pig serum inhibited experimental lymphomas by degrading the essential amino acid asparagine to aspartic acid), 6 mercaptopurine (the first designer drug) and steroids were being used to treat children with ALL. Remissions were short lived and children died, generally within a year. Since many patients were needed to study these agents, ALL was the stimulus for the formation of modern cancer cooperative study groups. In the mid 1950s, three children's cooperative groups—Acute Leukemia Group A (eventually Children's Cancer Group [CCG]), Acute Leukemia Group B (which became Cancer and Leukemia Group B [CALGB]), and the Southwest Cancer Chemotherapy Study Group (which evolved into the Southwest Oncology Group [SWOG])—formed in rapid succession. Internists also soon joined and began to enter patients into clinical trials. The 1960s were characterized by the discovery of vincristine, an extract from the periwinkle plant, which was being studied as a possible antiglycemic agent for hypoglycemic cows. It was noted to have a myelosuppressive effect; when given to children with ALL, 60% of them went into remission, a rate that increased to 90% when combined with prednisone. The incidence of remission was not increased significantly when vincristine, prednisone, and L-asparaginase were combined, but it was noted that when all three agents were used remissions lasted longer.

A major milestone occurred in the late 1960s when physicians began to treat occult central nervous system leukemia. Realizing that central nervous system was present but not measurable, clinicians at St. Jude Children's Research Hospital began to use cranial radiation and later intrathecal therapy prophylactically to prevent the spread of hidden disease. The 1970s witnessed the dramatic results of this therapy, as the first "cures" were recognized and survival rates improved dramatically to over 50%. The 1980s witnessed the development of risk-based therapy and the beginnings of bone marrow transplantation as therapy for children with refractory or relapsed leukemia. The 1990s saw the application of the knowledge and tools of molecular biology, and a uniform system of risk classification was developed. European investigators from Berlin, Frankfurt, and Munich (BFM) intensified postinduction therapy (consolidation) by using higher doses and cycling multiple agents (the BFM regimen). This type of approach has resulted in a significant improvement in survival, especially for patients at high risk of failure.

The first decade of the twenty-first century saw the merger of the CCG and Pediatric Oncology Group into the Children's Oncology Group, the incorporation of the molecularly targeted tyrosine kinase inhibitor, imatinib mesylate, in treatment for patients with Philadelphia chromosome–positive ALL, use of a long-acting form of PEG L-asparaginase in newly diagnosed patients, and approval of nelarabine for patients with recurring T-cell ALL and clofarabine for patients with recurring ALL. Retrospective studies have shown that young adults with ALL treated with pediatric protocols have a better outcome. Optimal treatment for older patients still remains a challenge. Selecting therapy based on patient- and disease-specific prognostic factors has led to a significant improvement in outcomes for childhood ALL, and the more recent adoption of this approach for adults has had a similar favorable impact.

See the related ASH 50th Anniversary Review articles under the ACUTE AND CHRONIC LEUKEMIAS section of the publication ASH 50th Anniversary Reviews: A Salute to the American Society of Hematology.