Intergroup Trial C10403: A Pediatric Treatment Approach to Improve Outcomes in Adolescents and Young Adults with Acute Lymphoblastic Leukemia

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Official trial name: An Intergroup Phase II Clinical Trial for Adolescents and Young Adults with Untreated Acute Lymphoblastic Leukemia (ALL)

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Overall survival among children with acute lymphoblastic leukemia (ALL) has dramatically increased since the 1970s, with cure rates approaching 85%. In comparison, poorer outcomes are found in adolescents and young adults (AYAs, those older than 15 years of age). The rate of ALL-related mortality in 15–24 year olds is greater than any other 10-year age group. ALL is relatively rare among the AYA population, whereas it is the most commonly diagnosed leukemia in childhood, accounting for 75% of leukemias diagnosed in pediatric patients.

The biology of this disease also changes with respect to age. Favorable cytogenetics such as hyperploidy and the TEL-AML1 translocation at t(12;21) are expressed in approximately a quarter of ALL cases diagnosed in childhood, but decrease dramatically in incidence among the AYA population. T-cell immunophenotype occurs in greater frequency among AYAs than in either younger children or older adults with ALL, and is associated with increased white blood cell count at presentation, higher levels of hemoglobin, and lymphomatous features. Incidence of the Philadelphia chromosome, associated with worse outcomes, increases with age: while it is detected in 25–30% of adult cases, Ph+ ALL is present in only a small percentage of AYAs (5–7%), and is extremely rare among children with ALL. Cytogenetics, immunophenotype, leukocyte count at presentation, and time to achieve complete remission are all prognostically significant factors in ALL. However, age may be the most significant factor pertaining to survival in ALL.

Until recently, minimal outcome data have been available specific to the AYA population. This population is difficult to evaluate and characterize because patients are seen and treated by both pediatric and adult hematologists. Incidence of ALL and enrollment to clinical trials is comparable in children up to the age of 15 years. In contrast, AYAs enroll to and participate on clinical trials in much smaller numbers. Because this population represents a small percentage of individuals on clinical trials, they are often included in analyses of either children or older adults.

Adult treatment regimens have historically evolved out of pediatric approaches. However, stark differences exist: pediatric treatment protocols give more frequent doses of non-myelosuppressive therapy (vincristine, peg-asparaginase, glucocorticoids), central nervous system prophylaxis is given up front and at more frequent intervals, and maintenance therapy is prolonged. In comparison, adult protocols use chemotherapy that is more myelosuppressive with an effort to deliver dose intensity that is tolerated by a broad age range, and overall therapy duration is shorter. The type of therapy AYAs with ALL receive with respect to practitioner (pediatric vs. adult) varies significantly. A retrospective comparison of AYAs who received treatment on Children’s Cancer Group (CCG) trials and adult Cancer and Leukemia Group B (CALGB) studies demonstrated that overall survival of patients was superior in AYAs treated on CCG protocols. Although the overall complete response (CR) rate was 90% in both groups, AYAs treated on adult CALGB trials had only a 34% event-free survival (EFS) at 7 years, compared to 63% EFS in demographically similar patients treated on CCG trials. Similar results are reported in the French FRALLE-93 and LALA-94 trial, as well as reports from Dutch, Italian, and British groups (for review, see Stock, 2010).
In response to the retrospective analyses, a number of studies have been initiated that are pioneering a “pediatric-inspired” approach to the treatment of young adults with ALL. One of these studies is the U.S. intergroup trial C10403, developed to examine and describe outcomes among AYAs with newly diagnosed ALL treated using a successful Children’s Oncology Group regimen (COG ALL0232) that resulted in a 78% survival rate for older adolescents aged 16–21 years. This trial opened to accrual in October 2007, with enrollment currently ongoing at 163 sites nationwide. At present, two-thirds of the estimated 300-participant enrollment have been accrued. Individuals aged 16–39 with newly diagnosed ALL are eligible for participation. This trial will test the feasibility of treating young adults up to the age of 40 with a pediatric regimen, evaluate adherence by patients and adult oncologists, and describe observed toxicities. A component of this trial will analyze outcomes based on demographics, psychosocial characteristics, and pretreatment features of disease that are unique to the AYA population. The results of this trial will be compared with patients up to the age of 29 years who were enrolled and treated by pediatric oncologists on the COG AALL0232 study (now closed to accrual). The goal of this trial is to demonstrate that the adult cancer cooperative groups can deliver a “pediatric” regimen to AYA patients and achieve comparable outcomes. Achievement of this goal would result in a significant improvement in overall survival for young adults with ALL.

References


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