Targeted therapy in Adult Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is a disease of young children that carries good prognosis, but in adults the results of therapy are inferior to those of the childhood ALL.

The adult ALL is heterogeneous regarding immunophenotyping and molecular abnormalities with different clinical courses and response to treatment. There is a wide range of survival results ranging from 70% in some-ALL subtypes to 20% for some cases with complex cytogenetic aberrations, as a whole the 5 year survival rates range is 30-40%. Adverse prognostic factors include a WBC count > $30x10^9$ /l, age > 35 years ,late Complete Remission(CR), pro-B and mature T phenotypes, t(9:22) t(4:11),t(1:19),and complex Aberrations and positive minimal residual disease after induction.

The classical chemotherapy protocols for ALL include induction phase followed by consolidation along with CNS prophylaxis followed by maintenance that includes some sort of pulse therapy. Autologous and allogeneic stem cell transplantation had been adopted as a part of treatment schedules for relapsing patients and sometimes for patients in first CR with one or more adverse prognostic factors.

A great interest is growing regarding the potential beneficial effects of incorporating targeted therapies in the treatment protocols of selected cases of adult ALL. These strategies include using therapies that target signal transduction cascade, **Antibody Therapy:** ALL blast cells express a variety of CD molecules like CD20, CD19, CD22, CD33 and CD52 which may be targeted by monoclonal antibodies.

The antigen should be present on at least 20% of blast cells to be suitable for targeting.

CD20 (>20%)is present in around one third of cases of precursor B-ALL specially in the elderly and more than 80% of cases of mature B-ALL. Rituximab (anti CD20 antibody) is being explored in several pilot studies in B- (CD20+) ALL in the elderly and in standard risk patients. In a GMALL protocol for elderly ALL rituximab was added prior to induction phase and along with it for patients 55-79 year old and the CR was 63%. Rituximab was added for Hyper-CVAD and showed promising results. Long term results are still pending.

CD52 is expressed by blast cells of some cases of T-ALL. Campath-H1 (anti CD52 antibody) had showed some effect in some cases of T-ALL.

CD33 is expressed in some cases of pro B-ALL and early T-ALL and is under investigation as a potential target for therapy.

Molecular Targeting Treatment:

Adult ALL with Philadelphia chromosome (t9:22/BCR-ABL positive) carries a bad prognosis with the majority of the patients relapsing after chemotherapy .The disease comprises 20-25% case of adult ALL increasing with age to >40% in patients above 50 years with a survival of <20%. antibody therapy and tyrosine kinase inhibitors Imatinib mesylate (Abl tyrosine kinase inhibitor) had been explored as a part of induction therapy for Ph+ adult ALL in the young and the elderly and the results showed a CR of > 90% even when imatinib

was used as a monotherapy for induction over 4 weeks in the elderly, but long term results without performing bone marrow transplantation are still not much changed .Imatinib also has been used following allogeneic stem cell transplantation for patients with positive minimal residual disease. Newer tyrosine kinase inhibitors like AMN107 (nilotinib) are under study for cases which are resistant to Imatinib.

The above mentioned targeted therapy strategies are examples of a rapidly expanding concept of treatment lines that may change the treatment options and results, once the mature data of controlled trials are ready and it is expected that risk stratification and assignment to treatment protocols according to immunophenotyping, molecular and microarray analysis criteria will revolutionize disease management.

References:

1-Gokbuget N, Hoezler D. Therapy of adult acute lymphoblastic leukemia according to prognostic factors and minimal residual disease. Hematology (EHA Education Program) 2006; 2(1):140-145.

2-Hoezler D, Gokbuget N, Beck J. Subtype adjusted therapy improves outcome of elderly patients with acute lymphoblastic leukemia. Blood 2004; 104: 2732.

3-Ottman OG, Wassmann B. Treatment of Philadelphia chromosome–positive acute lymphoblastic leukemia. Hematology (AM Soc Hematol Educ program) 2005; 118:22.

4- Ottman OG, Wassmann B. Pfeifer H. Aristotele G. Matthias S. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome–positive acute lymphoblastic leukemia. Cancer 2007; 109:2068-76.

5- Gokbuget N, Hoezler D. Rituximab in the treatment of Adult ALL. Ann Hematol 2006; 85:117-9.

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