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## **Therapy of Acute Myeloid Leukemia: Past Achievements and Future Directions of the Eastern Cooperative Oncology Group (ECOG)**

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Four major hypotheses have guided the development and conduct of Eastern Cooperative Oncology Group (ECOG) leukemia studies. First, the outcome of patients with leukemia can be improved and toxicities reduced with targeted therapies based on the specific biology of the disease. Second, resistance can be overcome by multiple mechanisms including dose intensification and specific inhibitors of multidrug resistance. Third, simulation of a graft-vs-leukemia effect, particularly with alternative donor transplantation, can improve the cure rate of patients with acute myeloid leukemia (AML). Fourth, better understanding of leukemia cell biology and the perturbed cellular signaling pathways involved, will guide therapy with an emphasis on the detection of minimal residual disease. Although there has been improvement in the outcome of younger patients with AML, the prognosis for older adults remains quite poor. The overall survival for patients under the age of 55 years with newly diagnosed AML entered on front line studies is approximately 45%. However, the overall survival for patients ages 55 years and older is only approximately 10-15%. A number of studies have confirmed that the karyotype at diagnosis is one of the most important prognostic factors and specific biologic subtypes can be defined based on karyotype. Furthermore, molecular studies including the identification of internal tandem duplications (ITDs) of the FLT-3 gene can further serve to identify specific subsets of patients, including those with a normal karyotype. A variety of new agents have been identified which may target specific perturbed genes or molecular pathways.

Perhaps the best example is the treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA). The results of North American Intergroup protocol 0129 have recently been updated. In this study, all patients with newly diagnosed APL were randomized to either standard chemotherapy with daunorubicin and cytarabine, or ATRA until the achievement of complete remission (CR). Subsequently, all patients were given two courses of intensive consolidation chemotherapy, and then randomized again to one year of daily maintenance ATRA or observation. For those patients who randomized to ATRA for induction, and one year of ATRA maintenance, the five-year disease-free survival is approximately 75%. This, as well as other studies, now confirm that APL is highly curable, and, in fact, represents the most curable subtype of AML in adults. A United States multicenter trial has shown that arsenic trioxide (ATO) is a very effective agent for patients with relapsed and refractory APL. After two courses of therapy (25 days each), approximately 80% of patients achieved a complete molecular remission. The current North American Intergroup study (C9710) in APL randomizes patients to receive or not receive two courses of arsenic trioxide as a first consolidation after induction with daunorubicin, cytarabine, and ATRA. Subsequent to this randomization, all patients received two courses of consolidation with daunorubicin, and one week of ATRA followed by a second randomization of one year of ATRA on a one week on, one week off schedule, or the combination of ATRA plus low-dose chemotherapy with

6-mercaptopurine and methotrexate. This trial has accrued 444 patients, and will meet its accrual goal in approximately 6 months. The recent observation that approximately 30% of patients with APL have ITDs of the FLT-3 gene, suggests a role for FLT-3 inhibitors in this subset of patients with AML. Another agent which represents a targeted delivery system is gemtuzumab ozogamicin (Mylotarg) which is currently being tested in protocol in E1900 for younger adults with newly diagnosed AML. Patients are randomized to one of two doses of daunorubicin, followed by two courses of consolidation with high-dose cytarabine, and then randomized to receive or not receive one dose of gemtuzumab ozogamicin prior to autologous hematopoietic stem cell transplantation (HSCT) for patients with favorable and intermediate risk disease. This study is evaluating the role of gemtuzumab ozogamicin as an in vivo purging agent in the setting of minimal residual disease. Patients who have high-risk disease, based on presenting white blood cell count and cytogenetics, proceed to matched allogeneic HSCT or alternative donor transplantation. One of the more promising new agents is farnesyltransferase inhibitor R115777 (Zarnestra). The farnesylation of proteins (the addition of a 15 carbon unsaturated polymer derived from the lipid pathway) appears to be important in posttranslation modification of several proteins, important in cell signaling, proliferation, and differentiation. The Ras protooncogene is one protein which appears to rely on farnesylation for its efficacy. Therefore, ECOG will embark on a phase III study designed to explore the role of R115777 as maintenance therapy in patients with achievement of complete remission and have completed any planned consolidation. The ECOG Leukemia Committee is exploring several mechanisms to overcome drug resistance in AML. On protocol E1900, patients are randomized to either 45 mg/m<sup>2</sup> of daunorubicin for 3 days, or 90 mg/m<sup>2</sup> for 3 days, each combined with cytarabine in the standard dose. In addition, the Committee has carried out a series of studies exploring multidrug resistance inhibitors in AML. An initial study in the relapsed and refractory

setting was carried out with cyclosporine, and then subsequently, PSC833. The randomized trial, protocol E2995, tested the addition of a more potent multidrug resistance inhibitor, LY335979 (Zosuquidar) given with the standard induction regimen for newly diagnosed older adults with AML. Both of these clinical trials are currently ongoing. LY335979 has the potential benefit of being a more potent inhibitor, and have pharmacokinetics such that the dose of concomitant chemotherapy does not need to be reduced. Approximately 70% of older adults express moderate to high levels of P-glycoprotein, and such expression is indeed associated with lower complete remission rates. The Committee tested growth factor priming as another mechanism to overcome drug resistance. The concept that administering hematopoietic growth factors to render leukemic cells more sensitive to chemotherapy was tested in protocol E3993 in older adults with newly diagnosed AML. Two days of priming did not affect the percentage of cells in S-phase, and no benefit in the complete remission rate was observed. This trial also tested, for the first time, three anthracyclines or anthracenedione (daunorubicin, idarubicin, or mitoxantrone) each given with cytarabine in induction and showed no advantage to any one.

ECOG has tested the ability of the immune system to eradicate leukemia. Protocol E3489 suggested that allogeneic HSCT may confer an advantage in patients with high-risk cytogenetics. Therefore, we plan to extend these observations in a clinical trial exploring the role of haploidentical transplantation in patients with high-risk (poor cytogenetics) disease. In addition, we intend to test both matched sibling, as well as matched unrelated donor transplantation, in patients with high risk myelodysplastic syndromes, where patients will receive pentostatin and photopheresis, plus fractionated total body radiation as the conditioning regimen. It is increasingly clear that AML is a heterogeneous group of diseases with different abnormal cellular signaling pathways. Therefore, the ECOG Leukemia Committee has carried out

a variety of correlative laboratory studies to understand such pathways. These include the identification of ITDs of the FLT-3 gene which now have been described in approximately 20-30% of patients with AML, and are the most common gene mutation in AML; the correlation of multidrug resistance (MDR) – 1 expression and response to LY335979; the determination of specific antigen profiles; and the detection of minimal residual disease. Such studies will facilitate the identification and development of other targeted agents which should provide increased effectiveness with less toxicity and, therefore, improve the outcome for patients with AML.