Acute Myeloid Leukemia

Selection of therapy for patients with acute myeloid leukemia is dependent on a number of patient- and disease-related predictors of response to therapy and outcome. Age and cytogenetics remain important prognostic indicators used by our group to assign therapy as indicated below. However, about half of patients with AML have a normal karyotype with an intermediate probability of survival at 5 years of about 45%. This group is molecularly heterogeneous and has a high likelihood of achieving CR with standard induction regimens.

The need to define risk factors within cytogenetic subgroups (particularly with diploid AML) has led to the identification of several prognostic molecular abnormalities including mutations of FLT3, NPM1, CEBPα, MLL, and WT1 genes, as well as BAALC expression (Schlenk R, NEJM, 2008, 358, 1909).

Some of these abnormalities such as mutant FLT3 gene/kinase have been identified to be targets for therapy (Gilliland DG, Blood, 2002, 100, 1532). At MD Anderson, all patients with AML have a molecular panel including FLT3, NPM1, CEBPα, RAS, as well as the newly defined IDH1/2 performed at diagnosis which better enables us to assign therapy with regimens including FLT3 inhibitors as well as to predict outcome and monitor minimal residual leukemia.

Several trials as well as a meta-analysis have demonstrated a benefit for the use of high dose cytarabine in induction to improve disease-free and overall survival of patients younger than 60 (Kern W, Cancer, 2006, 107, 116). A recent report by the French group suggested that Idarubicin was superior to daunorubicin in producing complete responses in patients with AML, aged 50 to 70 (Pautas C, JCO, 2010, 28, 808). Therefore all of our induction regimens for patients younger than 60 contain high dose cytarabine as well as idarubicin.

The effectiveness of high dose cytarabine based therapy in patients with favorable prognosis, corebinding factor (CBF) leukemias [(inv(16) and t(8;21)] is well-established. A recent report by the Medical Research Council (MRC) group suggested that the addition of a very low dose of gemtuzumab ozogamicin (GO) to standard chemotherapy was beneficial in improving disease-free survival in patients with favorable and intermediate risk cytogenetics (Burnett AK, JCO, In press) . We have been investigating this in our frontline regimen of fludarabine, cytarabine, and GCSF (Borthakur G, Cancer 2008;113:3181) by the addition of GO (more recently substituted by a dose of idarubicin).

For older patients with AML (60 and older), it is clear that although a proportion are able to tolerate intensive traditional cytarabine plus anthracycline based regimens, a significant proportion will need less intensive, and more effective therapeutic strategies (Kantarjian H, Cancer, 2006, 106, 1090 and Kantarjian H, Blood, 2010, In press). We are conducting several studies to establish the role of various candidate agents for induction therapy in older patients with AML.