Induction Protocols for Newly Diagnosed AML

Standard and Poor Risk Cytogenetics, Age <60

The back-bone of our induction regimen in patients younger than 60 is a combination of high dose cytarabine and idarubicin as several studies have suggested that idarubicin is superior to daunorubicin even in equivalent doses. We have recently investigated the role of the addition of the Raf/ FLT3 inhibitor, sorafenib, or the histone deacetylase inhibitor, vorinostat, to the above regimen (Ravandi F, JCO, 2010, 28, 1856)(Jabbour E, ASCO, 2009). The latter protocol has shown impressive responses in patients with mutated FLT3 and continues to accrue that specific population of patients. More recently, we are investigating the regimen of clofarabine, Idarubicin, and cytarabine (CIA) in this population with promising early results.

Patients who are 60-65 and have a low risk of early death and a higher potential for achieving a CR and remaining in remission at 1 year (Kantarjian H, Cancer, 2006, 106, 1090) are also eligible to receive these two regimens. The preliminary data for both regimens is promising and we have been able to compare these cohorts with a similar group of patients receiving the same regimen but without either sorafenib or vorinostat and demonstrate a benefit.

Protocols:

- 2009-0431, Phase II clofarabine + Idarubicin + cytarabine
- 2006-0813, Phase II cytarabine + idarubicin (15-75)
- 2007-0835, Phase II cytarabine + idarubicin + SAHA (15-65 with FLT3 ITD)
- 2009-0503, Phase I Plerixafor + cytarabine + idarubicin (18-70)
- 2007-0685, Phase II Azacitidine + SAHA (>18 not eligible for standard induction)

Favorable Risk Cytogenetics (CBF Leukemias)

High dose cytarabine is essential in induction and/ or consolidation in patients with inv (16) or t(8;21). A recent report by the MRC suggested that the addition of a low dose of GO (3 mg/m^2) to the standard AML induction/consolidation regimens is beneficial for improving disease-free and overall survival in patients with favorable/intermediate risk cytogenetics (Burnett AK, JCO, 2010, In press). We have examined the role of low dose GO (more recently replaced by a dose of idarubicin) in addition to the standard fludarabine + cytarabine + GCSF (FLAG) regimen in this subset of patients with AML. This regimen has been well tolerated and early results suggest a benefit. Furthermore, identification of Kit mutations as an indicator of poor prognosis in patients with CBF leukemias has led to testing for this mutation in all patients with potential future strategies with Kit tyrosine kinase inhibitors such as dasatinib.

Protocol:

- 2007-0147, Phase II Fludarabine + cytarabine + GCSF + idarubicin

Acute Promyelocytic Leukemia

The tremendous improvement in the outcome of patients with APL has been due to the introduction of all-trans retinoic acid (ATRA) as well as arsenic trioxide (ATO) in the regimens used to treat APL, both in the frontline setting and at the time of relapse. We have been conducting a study of the use of ATRA and ATO with GO (in high risk patients with presenting WBC $\geq 10 \times 10^9$/L) but without chemotherapy (Ravandi F, JCO, 2009, 27, 504). This is an effective and very well tolerated regimen with at least equivalent outcome to the standard chemotherapy + ATRA regimens. The few failures on this study have been patients early in the course of diagnosis and therapy succumbing to the complications of the coagulopathy associated with the disease, underscoring the need for rapid diagnosis and initiation of ATRA. With the decision by the FDA to withdraw GO, we have amended the study to substitute one dose of idarubicin for GO for patients with high-risk disease and those with a rising WBC.

Protocol:

- 2006-0706, Phase II ATRA + ATO ± Idarubicin

Older Adults with AML, Age ≥ 60

The outcome of older patients with AML treated with traditional cytarabine and anthracycline based regimens has been poor and although about 40-60% of these patients achieve a complete remission with such regimens, there are few long term survivors. This has led to questioning the benefit of therapy in the elderly AML by some. However, a study using the SEER-Medicare linked data demonstrated that patients who receive therapy are about 3 times as likely to be alive at 1-year and there was little difference in hospitalization rates between those who do or do not receive treatment (Menzin J, Arch Intern Med, 2002, 162, 1597; Menzin J, ASH 2006). Furthermore, a study by the MRC demonstrated the benefit of low dose subcutaneous cytarabine over supportive care (with hydrea to control counts) in older patients deemed unfit to receive chemotherapy (Burnett AK, Cancer, 2007,109, 1114). Recent reports have tried to distinguish subgroups of elderly patients who may benefit from the more intensive traditional regimens from those less likely to achieve long term responses (Kantarjian H, Cancer, 2006, 106, 1090). Most patients 60 years and older are in the latter group and as such, more effective and less toxic strategies are needed for them.

We are conducting several clinical trials examining the benefit of treatment with a number of agents in older AML patients who are less likely to benefit from more intensive strategies.

Protocols:

- 2007-0039, Phase II Clofarabine + low dose SC cytarabine alternating with decitabine
- 2009-0536, Phase I Plerixafor + clofarabine (> 60)
- 2009-1002, Phase II Decitabine alternating with sapacitabine (> 70)
- 2009-1001, Phase II Azacitidine vs conventional care (> 65)
- 2007-0727, Phase II Oral sapacitabine (≥ 70 with t-AML)