

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, CEBP α , 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 M D Anderson, all patients with AML have a molecular panel including FLT3, NPM1, and CEBP α 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). 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, core-binding 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. We are investigating this in our frontline regimen of fludarabine, cytarabine, and GCSF (Borthakur G, Cancer 2008;113:3181) by the addition of GO. 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. We are conducting several studies to establish the role of various candidate agents for induction therapy in older patients with AML.

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 are currently

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investigating the role of the addition of the Raf/FLT3 inhibitor, sorafenib, or the histone deacetylase inhibitor, vorinostat, to the above regimen (Ravandi F, ASH, 2008)(Jabbour E, ASCO, 2009). 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: 2006-0977, Phase II Idarubicin + cytarabine + sorafenib
2007-0835, Phase II Idarubicin +cytarabine + vorinostat*

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/m²) to the standard AML induction/consolidation regimens is beneficial for improving disease-free survival in patients with favorable/intermediate risk cytogenetics. We are examining the role of low dose GO 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 + GO

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.

Protocol: 2006-0706, Phase II ATRA + ATO \pm GO

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 40-50% 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 hydra to control counts) in older patients deemed unfit to receive chemotherapy (Burnett AK, Cancer, 2007,109, 1114). Recent reports have tried to distinguish sub-groups 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
2006-0686, Randomized Phase II Decitabine \pm valproic acid
2007-0727, Phase II Oral sapacitabine
2008-0288, Phase II Decitabine + GO*

2007-0965, Phase II Voreloxin
2008-0603, Randomized Phase IIB CPX-351 vs. 3+7

Protocol: 2007-0512, Phase II oral Tamibarotene in relapsed APL

Maintenance therapy in remission

Maintenance therapy is a well-established strategy in acute lymphoblastic leukemia (ALL) but has not become part of routine treatment of AML. Prior studies using cytotoxic agents similar to induction have demonstrated a benefit for prolonging disease-free survival (DFS). Immunomodulating strategies such as interleukin-2 with or without histamine have been evaluated and have shown benefits in prolonging DFS. Hypermethylation of a number of genes in CR have been associated with an increased likelihood of relapse. Hypomethylating agents such as 5-azacytidine and decitabine are being evaluated in this setting. We are conducting a randomized phase II study looking at the feasibility and efficacy of decitabine in this setting.

Protocol: 2006-0358, Randomized Phase II decitabine vs. Conventional care

Salvage Regimens

Acute promyelocytic leukemia

Tamibarotene is a synthetic retinoid that has been shown to be well-tolerated and effective in both the newly diagnosed and relapsed/refractory APL populations in studies in Japan. In April 2005, tamibarotene received regulatory approval in Japan for use in relapsed/refractory APL following the successful completion of two Phase II studies. We are conducting a study looking at the benefits of this agent in patients with APL relapsing from prior ATRA and ATO. Early results are very encouraging with patients achieving a second complete remission.

Other salvage regimens

The outcome of patients with relapsed AML is guarded; current strategies are based on achieving a second CR and proceeding to an allogeneic stem cell transplant, if available.

For patients with primary refractory disease or those who relapse a short time (generally less than a year) after achieving a CR, the prognosis is especially poor. A number of investigational approaches such as epigenetic modification with hypomethylating agents and histone deacetylase inhibitors, use of FLT3 tyrosine kinase inhibitors, inhibitors of other signaling pathways (such as JAK-STAT and RAF/ERK/MEK/MAPK), use of aurora kinase inhibitors, as well as new cytotoxic agents and new formulations of traditional cytotoxic agents are under investigation.

The prognosis for patients who relapse after a long first CR is better as they are generally more likely to respond to regimens similar to their original treatment. Combinations of cytarabine with clofarabine, with clofarabine and idarubicin, or with new topoisomerase inhibitors are under investigation. New formulations of cytarabine with better intracellular delivery are also being examined as is a liposomal combination of cytarabine and daunorubicin.

Additionally, improvements in supportive care measures such as infection prophylaxis and treatment, also under study at MDACC, may contribute to a better outcome in relapsed patients.

For information about these or any Leukemia protocol, please call Dr. Farhad Ravandi or any Leukemia physician.

Leukemia Insights and other valuable information are now available via the World Wide Web.

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CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytosine + Rituximab (FCR) (2008-0431)
- Lenalidomide (2006-0715)

2. Prior Therapy

- Fludarabine + Cytosine + Rituximab (ID99-338)
- FCR + Bevacizumab (2005-0992)
- HuMax-CD20 (2006-0314)
- Dasatinib (2005-0497)
- OFAR2 (2006-1026)
- FCR ± Lumiliximab (2006-0789)
- 5-aza (2006-0428)
- Lenalidomide + Rituximab (2007-0208)
- Alemtuzumab (2007-0626)
- ABT-263 (2007-0096)
- GS-9219 (2007-0087)
- 8-Chloro-adenosine (2004-0144)

3. Minimal Residual Disease

- Alemtuzumab vs Rituximab vs Both (2006-0767)

4. Other

- T-cell LPD: Alemtuzumab + Pentostatin (2004-0408)
- Hairy Cell: 2CDA + Rituximab (2004-0223)

AML/MDS Treatment Priorities

1. Newly Diagnosed

A. Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17): ATRA + Arsenic Trioxide +/- Gemtuzumab (2006-0706)

B. Cytogenetic feature: Inv16 or t(8;21): Fludarabine + Ara-C + Gemtuzumab (2007-0147)

C. Younger Patients:

- IA + Sorafenib (2006-0977)
- IA + SAHA (2007-0835)

Older Patients:

- Clofarabine + Ara-C + DAC (2007-0039)
- Ida + Ara -C (2006-0813)
- IV Clofarabine (2005-0535)
- Low Dose Decitabine +/- Valproic Acid (2006-0686)

- DAC vs low-dose Ara-C (2005-0647)
- SNS-595 (2007-0965)
- CPX-351 vs. 3+7 (2008-0603)

2. Salvage Programs

- Tamibarotene (2007-0512) in APL
- Clofarabine ± Ara-C ± Ida (ID03-0181)
- Lenalidomide (2006-0293)
- HuM195/rGel (DM98-342)
- Ara-C ± Clofarabine (2006-0069)
- Oral Clofarabine (2005-0536)
- IA + Sorafenib (2006-0977)
- FAO (2006-1089)
- Azacitidine (2007-0405)
- DAC + Mylotarg (2008-0288)
- Sapacitabine (2007-0727)
- IA + SAHA (2007-0835)
- LY2181308 (2007-0707)

3. Maintenance Therapy

- DAC vs Observation (2006-0358)

4. Low Risk MDS and CMML with <10% Blasts

- Decitabine (2007-0883)
- Azacitidine (2007-0405)
- Thymoglobulin + Cyclosporin (2005-0115)
- AMG531 (2006-0772)
- Gimatecan (2006-0943)
- Romiplostim (2008-0249)
- Revlimid + Darbepoetin alfa (2006-0657)
- JNJ-26481585 (2008-0245)
- Telintra (2008-0081)

ALL Treatment Priorities

1. Newly Diagnosed or Primary Refractory (one non-hyper-CVAD induction)

- A. Modified Hyper CVAD (ID02-230)
- B. Burkitt's: Hyper CVAD + Rituximab (ID02-229)
- C. Ph+: Hyper CVAD + Dasatinib (2006-0478)
- D. Age <31: Augmented BFM (2006-0375)
- E. T cell: Hyper CVAD + Nelarabine (2006-0328)

2. Salvage Programs

- Clofarabine + Cytosine (2005-0552)
- 5-aza + Hyper CVAD (2005-0895)
- Marquibo (2006-1109)
- Augmented Hyper CVAD (ID03-0166)
- MOAD (2008-0267)

CML Treatment Priorities

1. CML Chronic Phase

- Dasatinib (2005-0422)
- Bosutinib vs. Imatinib (2007-0709)
- Nilotinib (2005-0048)
- Bosutinib (2005-0813)
- Dasatinib (2007-0606)
- HHT (2006-0926/2006-0192)

2. CML Accelerated Phase

- HHT (2006-0926/2006-0192)
- Bosutinib (2005-0813)

3. CML Blastic Phase

- HHT (2006-0926/2006-0192)
- Bosutinib (2005-0813)

4. Minimal Residual Disease

- Dasatinib + Ipilimumab (2008-0157)

5. T315I Mutations

- XL228 (2007-0502)
- PHA-739358 (2007-0939)
- AP24534 (2008-0046)
- HHT (2006-0192)
- DCC-2036 (2008-0732)

Myeloproliferative Disorders

- Bevacizumab (2008-0025)(MF)
- Pegasys (DM03-0109)
- INCB018424 (2007-0169)
- 2CDA + Ara-C (DM97-232) (HES only)
- TG101348 (2007-0837)(MF)

Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- AT9283 (2006-0177)
- SAHA + DAC (2006-1096)
- AZD4877 (2007-0287)
- XL228 (2007-0502)
- Bendamustine (2007-0634)
- SB939 (2007-0848)
- INCB018424 (2007-0925)
- PHA-739358 (2007-0939)
- RO5045337 (2007-0408)
- OPB-31121 (2007-0488)
- ARRY-520 (2007-0879)
- SB1518 (2008-0032)
- AP24534 (2008-0046)
- DCC-2036 (2008-0732)

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