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# Salvage Treatment Options in AML

## INTRODUCTION

The standard therapy for AML is a combination of cytarabine and an anthracycline. With standard therapy the complete remission (CR) rates are 60% to 70% and the cure rates are 15% to 25%. Prognosis is related to 1) karyotype, 2) patient age, and 3) performance status and organ functions (Avivi I, Curren Opin Hematol, 2005, 12, 62-67). Patients with t(8;21), inversion 16 or t(15;17) have CR rates of 90% and cure rates of 50% to 80% (Byrd J, Blood, 2002, 100, 4325-4336) and (Slovak ML, Blood, 2000, 96, 4075-4083). Younger patients (age < 65 years) without these favorable chromosomal markers have CR rates of 70% to 80%, but the cure rates are only 30% to 35% (Bloomfield C, Cancer Res., 1998, 58, 4173-4179). Older patients and those with adverse karyotypes have CR rates of 35% to 50% and cure rates of 10% or less (Estey E, Lancet, 2006, 368, 1894-1907) and (Godwin J, Crit Review Oncol Hematol, 2003, 48, S17-26). Although a "3+7" combination is very widely used, several studies have shown that higher doses of ara-C are associated with a better outcome, and this is best represented in the meta-analysis published recently by Kern (Kern W, Cancer, 2006, 107, 116-124). Still, despite the use of higher doses of cytarabine or addition of other chemotherapy agents (e.g., etoposide, fludarabine) to the standard combination, the median progression-free survival is only approximately 7 months and most patients with AML will still relapse and require salvage therapy (Appelbaum F, Blood, 2006, 107, 3481-3485).

Salvage therapy options in AML are usually categorized based on cytogenetic and molecular markers at relapse. Foremost amongst these molecular markers are FLT3 (FMS-like tyrosine kinase) status. FLT3 is a Receptor tyrosine kinase (RTK) that activates intracellular pathways. Other well defined molecular markers that are used to stratify salvage therapeutic options are being identified. Further stratification is based on duration of initial remission and whether therapy is for first or subsequent relapses. Acute promyelocytic leukemia is treated as a separate entity due to its varied clinical course and treatment regimens.

In this issue, Drs. Elias Jabbour and Naval Daver discuss salvage options currently available at MD Anderson Cancer Center. If you have any questions about these or any other study, do not hesitate to contact them or any Leukemia physician.

*(continued on page 2)*

### *In This Issue*



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## FLT3 POSITIVE AT RELAPSE

FLT3 plays a role in the regulation of survival and proliferation of hematopoietic progenitor cells, in particular by synergy with other RTKs and cytokine receptors. Two major types of FLT3 mutations have been identified in up to 30% of AML patients. The most common class of mutations found in approximately 15% to 25% of AML patients, with a higher frequency in the elderly, is internal tandem duplications (ITD) in the juxtamembrane (JM) domain. The second-class of mutation, present in approximately 7% of patients, are point mutations of residue 835 in the activation loop of FLT3 that also result in ligand-independent, constitutive kinase activation. The prognosis of patients with FLT3-ITD mutations is significantly worse than that for patients with wild type FLT3 when treated with standard therapy.

The following studies are currently open for salvage treatment in patients with AML who are FLT3 positive at relapse:

1. Ph II AC220 (1st salvage Age ≥ 60)
2. Ph I/II Sorafenib and 5-Azacitidine
3. Ph I/II PKC412 and AZA
4. Ph I G-CSF & Plerixafor + Sorafenib
5. Ida + Ara-C with Vorinostat (SAHA) (Ages 15-65)
6. Ph I/II Vidaza + Revlimid

AC220 (Cortes J, Blood, 2009, 114, Abstract 636), Sorafenib (Borthakur G, Haematologica, 2011, 96, 62-68) and PKC412 (Fischer T, J Clin Oncol., 2010, 28, 4339-45) are inhibitors of FLT3 internal tandem duplication (ITD) signaling and have single agent activity in AML with FLT3-ITD mutation.

AC220 is a novel second-generation Class III RTK inhibitor with potent and highly efficacious FLT3 activity in vitro and in vivo. Interim results from the phase I dose-escalation study CP0001 showed that AC220 was well tolerated in the 76 treated patients. The overall response (complete remission [CR] + partial remission [PR]) observed in all AC220-treated patients was 30%. Consistent with the proposed mechanism of action of AC220, the response in the FLT3-ITD positive population was the highest, with an overall response rate of 56%; however, evidence of clinical activity was also observed in FLT3-ITD negative patients, with 20% of patients responding (Cortes J, Blood, 2009, 114, Abstract 636).

Sorafenib (Nexavar) is an oral, small molecule multikinase inhibitor of several other targets including vascular endothelial growth factor receptor-2 (VEGFR-2), VEGFR-3, and platelet-derived growth factor receptor-beta (PDGFR-β). In vitro studies conducted at MD Anderson Cancer Center demonstrated that sorafenib is a potent inhibitor of FLT3 kinase (Zhang W, J Natl Cancer Institute, 2008, 100, 184-98). In a phase I dose-escalation study conducted at M D Anderson 50 patients were enrolled. Complete remissions or complete remissions with incomplete recovery of platelets (CRp) were achieved in 10% of the patients (all with fms-like tyrosine kinase 3-internal tandem duplication) (Borthakur G, Haematologica, 2011, 96, 62-8).

Azacitidine (AZA), an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism. Results of clinical investigations demonstrated activity of azacitidine in the treatment of AML. A randomized open label, phase III trial compared the efficacy of Azacitidine to Conventional Care Regimens (CCR). Azacitidine demonstrated statistically superior overall survival compared to CCR, with a median overall survival of 24.4 months vs. 15 months for CCR (p=0.0001). Two-year survival approximately doubled in the azacitidine arm compared to CCR: 51% vs. 26% (Fenaux P, Lancet Oncol, 2009, 10, 223-232).

Plerixafor disrupts the interaction between SDF/CXCR4, a homing mechanism for leukemia cells to survive in the bone marrow microenvironment, and thus expected to sensitize AML cells to the effects of chemotherapy (Burger J, Leukemia, 2009, 23, 43-52). This was the rationale for combining Plerixafor with Sorafenib in patients with relapsed AML. It is thought that G-CSF will further potentiate the activity of Plerixafor by promoting differentiation of latent Leukemic stem cells (LSC's) to progenitor cells which are more susceptible to chemotherapy.

Analysis of our experience with the combination of Ida + Ara-C with Vorinostat, a histone deacetylase

inhibitor, showed that the subgroup of patients with AML and FLT3-ITD mutation appears to benefit from this combination. We have reported results from a phase II trial of Vorinostat, Idarubicin and Cytarabine in Previously Untreated Acute Myelogenous Leukemia (AML) or High Risk Myelodysplastic Syndrome (MDS). A total of 75 patients were enrolled with response rate as follows: CR 57 (76%), CRp 7 (10%) for an overall response (ORR) of 86%. Of note, patients with FLT3 ITD had a CR of 91% and CRp of 9% for an ORR of 100%. This was in contrast to an ORR of 85% for the wt FLT3 group (p=0.2) (Garcia-Manero G, Blood (ASH Annual Meeting Abstracts), 2010, 116, 604) and (Garcia-Manero G, Blood, 2008, 111, 1060-6).

A recent study of Azacitidine in MDS has shown a better outcome for those patients treated with Azacitidine compared with those receiving supportive care. Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to low- or Intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Patients age >60 years with AML that refuse standard therapy but willing to receive lower intensity programs will be considered for the study combining Vidaza and Revlimid (Garcia-Manero G, Am. J. Hematol., 2011, 86, 490-8).

## FLT3 NEGATIVE AT RELAPSE

Therapeutic options for FLT3 negative patients are separated based on duration of initial CR and whether treatment is for first salvage or subsequent salvage.

A. 1st salvage & 1st CR duration > 12 months
   1. Ph III Vosaroxin + cytarabine vs. Placebo + Ara-C
   2. Ph I/II Sorafenib and 5-Azacitidine
   3. Ph I/II PKC412 and AZA
   4. Ph II MK-2206 (Age ≥ 60)
   5. Ph II AC220
   6. Ph I/II CIA vs. FAI
   7. Ph I MDX-1338/BMS936564

B. 1st salvage & 1st CR duration < 12 months
   1. Ph III Vosaroxin + Ara-C vs. Placebo + Ara-C
   2. Ph I/II Sorafenib and 5-Azacitidine
   3. Ph I/II PKC412 and AZA
   4. Ph II AC220
   5. Ph I MDX-1338/BMS936564

C. 2nd salvage
   1. Ph II MK-2206 (Age ≥ 60)
   2. Ph I/II Sorafenib and 5-Azacitidine
   3. Ph I/II PKC412 and AZA
   4. Ph I MDX-1338/BMS936564

Vosaroxin is mechanistically similar to the anthracyclines such as idarubicin and daunorubicin, and the anthracenedione, mitoxantrone. Vosaroxin in combination with cytarabine is being compared in this phase III trial to cytarabine alone as first salvage therapy for relapsed AML, an area of significant unmet need for therapeutic options (Lancet J, Leukemia 2011;Jul 15, 10.1038).

The PI3K/AKT signaling pathway is essential for different physiological processes of cell growth, survival and suppression of apoptosis, and its constitutive activation has been implicated in the pathogenesis as well as the progression of a wide variety of neoplasias, including AML (Pal S, Expert Opin Investig Drugs, 2010, 19, 1355-66). MK-2206 is the first oral allosteric inhibitor of AKT to enter clinical development.

In a recent update of a phase II study of 63 patients treated with clofarabine, cytarabine and idarubicin (CIA), the overall response rate was 38% including 21% with complete remission (Faderl S, Blood, 2005, 105, 940). In view of this experience and in light of the possible usefulness of higher doses of anthracyclines (Fernandez H, N Engl J Med, 2009, 361, 1249-1259), and the synergistic activity of the combination of anthracyclines with nucleoside analogues, we are evaluating a randomized phase II Bayesian design the CIA combination at higher doses than established versus fludarabine, cytarabine and idarubicin (FAI) in patients with relapsed/refractory AML.

Based on preclinical studies, MDX-1338 (BMS-936564) a monoclonal antibody, is expected to achieve efficacy by potentiating the chemotherapeutic

*(continued on page 6)*

## CLL Treatment Priorities

### 1. Untreated

- Fludarabine + Cytoxan + Rituximab (FCR) (2008-0431)
- Ofatumumab (2010-0241)
- CAL-101 + Rituximab (2010-0388)

### 2. Prior Therapy

- Fludarabine + Cytoxan + Rituximab (ID99-338)
- FBR (2009-0546)
- ABT-263 + FCR or BR (2009-0077)
- Revlimid (2007-0213)
- Bafetinib (2010-0175)
- Sapacitabine + Cytoxan + Rituximab (2010-0516)
- PCI-32765 (2011-0142)

### 3. Other

- 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 +/- Idarubicin (2006-0706)

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

C. **Younger Patients:**

- Ida + Ara -C (2006-0813)
- Clofarabine + IA (2009-0431)
- Oral Panobinostat + IA (2010-0591)

**Older Patients:**

- Clofarabine + Ara-C + DAC (2007-0039)
- DAC +/- Clofarabine (2008-0092)
- Vorinostat + Aza (2007-0685)
- AZD1152 vs low-dose Ara-C (2009-0217)
- Plerixafor + Clofarabine (2009-0536)
- Alternating DAC + Sapacitabine (2009-1002)
- Azacitidine vs Conventional Care (2009-1001)
- Sorafenib + Azacitidine (2010-0511)
- Omacetaxine + LD Ara-C (2010-0736)

### 2. Salvage Programs

- Tamibarotene (2007-0512) in APL
- Sapacitabine (2007-0727)
- IA + SAHA (2007-0835)
- Plerixafor + Sorafenib (2008-0501)
- SAR103168 (2009-0196)
- GSK1120212 (2009-0239)
- Vidaza + Revlimid (2009-0467)
- AC220 (2009-0560)
- Oral Panobinostat + Vidaza (2009-0619)
- MK-2206 (2010-0243)
- PKC 412 + Aza (2010-0374)
- SGI-110 (2010-0615)
- Ara-C +/- Vosaroxin (2010-0692)
- CIA vs FAI (2010-0788)
- MDX-1338 (2010-0825)

### 3. Low Risk MDS and CMML with <10% Blasts

- Oral Clofarabine (2005-0536/2007-0410)
- Lenalidomide (2006-0293/2009-0737)
- Azacitidine (2007-0405)
- ARRY-614 (2009-0129)
- Alemtuzumab (2010-0187)
- ON 01910 (2010-0209)
- TXA 127 (2010-0805)

## ALL Treatment Priorities

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

A. Modified Hyper CVAD (ID02-230)
B. Age <40:Augmented BFM (2006-0375)
C. Hyper CVAD + Ofatumumab (2010-0708)
D. Burkitt's: Hyper CVAD + Rituximab (ID02-229)
E. Ph+: Hyper CVAD + Dasatinib (2006-0478)
F. T cell: Hyper CVAD + Nelarabine (2006-0328)

**2. Salvage Programs**

- MOAD (2008-0267)
- DT2219ARL (2008-0519)
- RAD001 + Hyper CVAD (2009-0100)
- CMC-544 (2009-0872)

## Phase I/II Agents for Hematologic Malignancies

- L-Grb2 Antisense (2003-0578)
- SB939 (2007-0848)
- RO5045337 (2007-0408)
- DT388IL3 (2008-0313)
- DCC-2036 (2008-0732)
- AS703026 (2009-0195)
- Nelarabine (2009-0717)
- Belinostat + Bortezomib (2009-0752)
- PR104 (2009-0772)
- LY2523355 (2009-0785)
- ABT348 (2009-0788)
- Thiarabine (2009-1000)
- PF-04449913 (2010-0078)
- TG02 (2010-0244)
- TH-302 (2010-0268)
- INCB018424 (2010-0450)
- KB004 (2010-0509)
- CA-18C3 (2010-0933)
- PM01183 (2010-0965)

## CML Treatment Priorities

**1. CML Chronic Phase**

- Dasatinib (2005-0422)
- Nilotinib (2005-0048)

**2. TKI Failures, T315I Mutations or Advanced Phases**

- Ponatinib (2010-0570)
- DCC-2036 (2008-0732)
- Nilotinib (2009-0683)

## Myeloproliferative Disorders

**1. Myelofibrosis**

- Pomalidomide (2007-0199)
- INCB018424 (2007-0169)
- AZD1480 (2009-0067)
- LY2784544 (2010-0167)
- SB939 (2010-0319)
- BMS-911543 (2010-0782)
- INC (2010-0964)
- AB0024 (2011-0016)
- NS-018 (2011-0090)
- INCB 018424 (2011-0213)
- Ruxolitinib (2011-0359)

**2. Polycythemia Vera**

- INC 424 (2010-0808)

**3. Essential Thrombocythemia**

- Imetelstat (2010-0672)

**4. Systemic Mastocytosis**

- Masatinib (2008-0275)

effect due to its ability to release malignant cells from a protective environment and by direct apoptosis (Fuchs E, Cell, 2004, 116, 769-778). The chemotherapy regimen consisting of mitoxantrone, etoposide, and cytarabine, was chosen to combine with MDX 1338 (BMS-936564), since this regimen is considered standard of care for relapsed, refractory AML.

## RAS MUTATED

- Ph II GSK1120212
- Ph I/II Mek Inhibitor MSC1936369B

Both GSK1120212 (Gilmartin A, Clin Cancer Res, 2011, 17, 989-1000) and AS703026 (Yoon J, Cancer Res, 2011, 71, 445-53) are inhibitors of MEK 1/2 and are expected to be active in hematological malignancies associated with activation of RAS/RAF/MAP kinase pathway, a pro-survival pathway activated through mutations or otherwise in myeloid malignancies. All patients with AML, MDS or CMML are routinely tested for RAS at MD Anderson Cancer Center.

Data from a phase I study of GSK1120212 presented at the 2010 ASH annual meeting showed that GSK1120212 administered at 2mg/day orally was tolerable in subjects with relapsed or refractory AML and other leukemias. This dose regimen achieved plasma concentrations sufficient for target inhibition and showed preliminary anti-leukemic clinical activity. Based on these results, a phase II study in AML, MDS and CMML has been initiated (Borthakur G, Blood, ASH Annual Meeting Abstracts, 2010, 116, 3281).

Eleven patients were treated with MSC1936369B at our institution. Stable disease lasting 12 weeks or more has been reported in 3 patients with relapsed/refractory AML, 1 of 3 patients had transient clearance of blasts from peripheral blood (Ravandi F, Blood, ASH Annual Meeting Abstracts, 2010, 116, 3296). This study continues to accrue.

## APL

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 (Takeuchi M, Leuk Lymphoma, 1998, 31, 441-51). Compared to ATRA, Tamibarotene is 10 times more potent as it shows lower affinity for the cellular retinoic acid binding protein allowing for greater drug availability in the nucleus (Ohnishi K, International Journal of Clinical Oncology, 2007, 12, 313-317). Tamibarotene is currently approved in Japan for treatment of recurrent APL. There is a Special Protocol Assessment (SPA) in place with the FDA for a phase II clinical trial, known as STAR-1, which is evaluating the efficacy and safety of Tamibarotene as a third-line treatment for APL. The STAR-1 trial is ongoing and currently includes six clinical sites in the U.S. Of the 11 patients enrolled in the STAR-1 trial to date, three (27%) achieved a hematologic complete response, and four (36%) a morphologic leukemia-free state (Cortes-Franco J, Blood, ASH Annual Meeting Abstracts, 2009, 114, 2050).

## CONCLUSION

Recent discoveries confirm the complexity involved in understanding and treating acute leukemia. Targets for therapeutic intervention have been identified in both AML and ALL and further investigation of novel therapies will hopefully improve outcomes in patients with leukemia. Although considered less toxic than traditional chemotherapy, targeted therapy will produce new adverse effects necessitating updated management strategies. Identifying disease characteristics and determining prognosis will continue to be important for directing treatment. With advancements in personalized therapy aimed at molecular or cytogenetic features of disease, long-term survival of patients with leukemia appears promising.

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