Sequential Flavopiridol, Cytosine Arabinoside, and Mitoxantrone: A Phase II Trial in Adults with Poor-Risk Acute Myelogenous Leukemia

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Abstract

Purpose: Flavopiridol is a cyclin-dependent kinase inhibitor that is cytotoxic to leukemic blasts. In a phase I study of flavopiridol followed by 1-β-D-arabinofuranosylcytosine (ara-C) and mitoxantrone, overall response rate for adults with relapsed and refractory acute myelogenous leukemias (AML) was 31%. We have now completed a phase II study of sequential flavopiridol, ara-C, and mitoxantrone in 62 adults with poor-risk AML.

Experimental Design: Flavopiridol (50 mg/m²) was given by 1-h infusion daily × 3 beginning day 1 followed by 2 gm/m²/72 h ara-C beginning day 6 and 40 mg/m² mitoxantrone on day 9.

Results: Flavopiridol caused a ≥50% decrease in peripheral blood blasts in 44% by median day 2 and ≥80% decrease in 26% by day 3. Self-limited tumor lysis occurred in 53%. Three (5%) died during therapy (2 multiorgan failure and 1 fungal pneumonia). Complete remissions (CR) were achieved in 12 of 15 (75%) newly diagnosed secondary AML, 18 of 24 (75%) first relapse after short CR (median CR, 9 months, including prior allograft), and 2 of 13 (15%) primary refractory but 0 of 10 multiply refractory AML. Disease-free survival for all CR patients is 40% at 2 years, with newly diagnosed patients having a 2-year disease-free survival of 50%.

Conclusions: Flavopiridol has anti-AML activity directly and in combination with ara-C and mitoxantrone. This timed sequential regimen induces durable CRs in a significant proportion of adults with newly diagnosed secondary AML (including complex cytogenetics) and adults with AML in first relapse after short first CR.

Flavopiridol (L86-8275), a synthetic flavone derivative that was initially isolated from the stem bark of the Indian tree Dysoxylum binectariferum (1, 2), is a potent growth inhibitor of diverse human tumor cell lines and induces apoptosis in hematopoietic cell lines derived from acute myelogenous leukemia (AML), B- and T-cell lymphomas, and multiple myelomas (3–5). Flavopiridol-induced apoptosis results at least in part from inhibition of multiple serine-threonine cyclin-dependent kinases (2). Whereas inhibition of cyclin-dependent kinase 2 and cyclin-dependent kinase 4 contributes to cell cycle arrest in G1 and G2 (6–8), flavopiridol-triggered inactivation of the cyclin-dependent kinase 9/cyclin T complex (also known as PTEF-b) inhibits the activating phosphorylation of RNA polymerase II and diminishes mRNA synthesis (9, 10).

Consequently, flavopiridol-treated cells are unable to synthesize transcripts encoding polypeptides, such as cyclin D1 (11), which is expressed in a cell cycle-dependent manner. Cytosine arabinoside [1-β-D-arabinofuranosylcytosine (ara-C)] and mitoxantrone exhibit significant clinical activity against acute leukemias (12, 13). Both drugs induce double-strand breaks in DNA, ara-C by inhibiting DNA replication and repair and mitoxantrone by poisoning topoisomerase II. These insults not only lead to cell cycle arrest in S phase during ara-C exposure (14) and late S–G2 after mitoxantrone (15) but also subsequently trigger apoptosis in susceptible leukemic cells (14–16).

These drugs have been combined in adults with acute leukemias (12, 13) to induce complete remissions (CR) in both older patients and patients with relapsed and refractory disease. Previous studies from our laboratories have examined the effect of combining flavopiridol with a variety of antineoplastic agents (17, 18). Because flavopiridol induces cell cycle arrest, it antagonizes the effects of S-phase–dependent agents, such as ara-C and topotecan, when administered concomitantly (17). In contrast, when flavopiridol is administered first and then withdrawn in vitro, the surviving cells reenter the cell cycle and are sensitized to S-phase poisons (17). These observations, coupled with the ability of flavopiridol to kill noncycling cells (3), suggested that flavopiridol might be particularly effective when administered first and then followed several days later by

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The tolerated dose was 50 mg/m²/d. The CR rate achieved with profound neutropenia >40 days duration, and maximal ara-C and mitoxantrone (19). Flavopiridol was given as sequential therapy (TST) approach in which flavopiridol was enhancing the cell cycle progression of the remaining leukemic cell and was followed by the cycle-dependent agents ara-C and mitoxantrone (19). Flavopiridol was given as 1-h infusion daily × 3 followed by 2 gm/m²/72 h ara-C beginning day 6 and 40 mg/m² mitoxantrone bolus on day 9 in adults with relapsed and refractory acute leukemias. Of 34 adults receiving induction therapy, 16 (47%) evinced direct leukemia cytotoxicity in response to flavopiridol with ≥50% drop in peripheral blast counts and tumor lysis in 9 (26%). Four (12%) died during therapy (2 fungal infections and 2 sudden death). Dose-limiting toxicity occurred at 60 mg/m²/d with profound neutropenia >40 days duration, and maximal tolerated dose was 50 mg/m²/d. The CR rate achieved with flavopiridol, ara-C, and mitoxantrone in 26 AML was 23% and 12.5% in acute lymphoblastic leukemia. Flavopiridol pharmacokinetics showed that a linear two-compartment model with first-order elimination provided the best fit of the observed concentration versus time data. Flavopiridol down-regulated one or more target proteins in marrow blasts in vivo in some patients, including MCL-1 and phospho-RNA polymerase 2. Flavopiridol inhibited expression and secretion of vascular endothelial growth factor in the vascular endothelial growth factor–expressing monoblastic leukemia cell line U937 and inhibited endothelial cell proliferation at clinically achievable concentrations in vitro. Patient sera were obtained at the end of the day 3 flavopiridol infusion and contained concentrations of flavopiridol that inhibited bovine aortic endothelial cell proliferation in vitro in a dose-dependent fashion (19).

We have extended these observations by conducting a phase II trial at the determined flavopiridol maximal tolerated dose of 50 mg/m²/d in 62 adults with relapsed and refractory AML. In this phase II setting, we confirm our previous findings that flavopiridol exerts direct antileukemic cytotoxicity and that the TST regimen of flavopiridol followed by ara-C and mitoxantrone is associated with acceptable and reversible toxicity and a low death rate. Importantly, this therapy has an encouraging CR rate for adults with newly diagnosed, poor-risk AML and for AML in first relapse following relatively short CR. Finally, this regimen may be useful for inducing CR before allogeneic stem cell transplantation (SCT) for adults with poor-risk acute leukemias for whom alternative curative options do not yet exist.

**Patients, Materials, and Methods**

**Patient eligibility and selection.** Adults age 18 years or older with pathologically confirmed AML who were unlikely to be cured by existing therapies, including primary refractory (induction failure), multi-refractory, or newly diagnosed secondary AML [myelodysplasia/AML, myeloproliferative disorder (MPD)/AML, or treatment-related AML] and/or known adverse cytogenetics were eligible provided that they had Eastern Cooperative Oncology Group performance status of 0 to 2, normal bilirubin, hepatic enzymes ≤2× normal, serum creatinine ≤1.5× normal, and left ventricular ejection fraction ≥45%. All patients with myelodysplasia/AML or MPD/AML had previously documentation of the original hematologic disorder. Patients who had undergone allogeneic or autologous SCT and had relapsed or were refractory thereafter were eligible for this study. Complete history, physical examination, laboratory, imaging, and cardiac evaluations (electrocardiogram and left ventricular ejection fraction) were done within 3 days of study entry. Recovery from toxicities of previous treatment and intervals of ≥3 weeks from prior chemotherapy and ≥1 week from any growth factor therapy were required before beginning ara-C and mitoxantrone. Patients were ineligible if they had a peripheral blast count ≥50,000/mm³; disseminated intravascular coagulation; active uncontrolled infection; active central nervous system leukemia; history of ara-C–related neurotoxicity; prior radiation of ≥25% of bone marrow; comitant radiotherapy, chemotherapy, or immunotherapy; or coexisting medical or psychiatric conditions that could interfere with study procedures. Pregnant or lactating women were ineligible. All patients provided written informed consent according to The Johns Hopkins Medical Institutional Review Boards and guidelines.

**Treatment schema.** Flavopiridol was administered at a dose of 50 mg/m² over 1 h daily × 3 beginning on day 1 (19–21). Administration of 2 gm/m² ara-C as a 72-h continuous infusion [667 mg/m²/24 h; refs. 19, 22–25] began on day 6. Mitoxantrone (40 mg/m²) was administered as a single i.v. bolus over 30 to 60 min on day 9, 12 h after completion of the ara-C infusion (19, 24). Patients who achieved CR or partial remission after cycle 1 were eligible to receive a secondary cycle of flavopiridol, ara-C, and mitoxantrone beginning 30 ± 7 days following hospital discharge from the first cycle.

**Supportive care.** To decrease the severity of the expected flavopiridol-induced secretory diarrhea (21, 26, 27) without inducing changes in gastrointestinal motility, all patients received 100 µg octreotide (somatostatin analogue) every 8 h, beginning 2 to 4 h before the first dose of flavopiridol and continuing through day 4. All patients received daily oral 300 mg allopurinol and 30 cc aluminum hydroxide every 6 h until 24 h after the completion of ara-C and mitoxantrone (days 1–9). Corticosteroid eyedrops were used on days 6 to 12 to prevent ara-C–related conjunctivitis. Antiemetics were used according to standard practices. Premenopausal women were placed on hormonal therapy to suppress menstrual bleeding. Norfloxacin (400 mg twice daily) for gastrointestinal decontamination and acyclovir prophylaxis against Herpes Simplex virus activation began day 1 and continued until absolute neutrophil count >100,000/mm³ was reached.

**Response and toxicity evaluations.** To assess response to therapy, bone marrow aspiration and biopsy were done before treatment, on day 14, and at the time of hematologic recovery or when leukemia regrowth was suspected. Hematologic recovery was defined as absolute neutrophil count ≥500/mm³ and a transfusion-independent platelet count of 50,000/mm³. CR required a normal bone marrow aspirate with absence of identifiable leukemia, absolute neutrophil count ≥1,000/mm³, platelet count ≥100,000/mm³, and absence of blasts in peripheral blood (28). Clearance of cytogenetic abnormalities was not required for CR but was noted and described separately. Partial remission was defined as the presence of trilineage hematopoiesis in the marrow with normalization of peripheral counts but with 5% to 25% blasts in the marrow. No response was defined as persistent leukemia in marrow and/or blood without significant decrease from pretreatment levels. The National Cancer Institute Common Toxicity Criteria, version 2.0, was the basis on which all adverse events were described and graded, based on the treating physician’s assessment.

**Results**

**Patient characteristics.** Between January 2004 and March 2006, 62 adults with poor-risk newly diagnosed, relapsed, or refractory AML were entered on this phase II study of
Flavopiridol in AML

flavopiridol, ara-C, and mitoxantrone. Detailed clinical demographics are delineated in Table 1. Fifteen (24%) had newly diagnosed secondary AML. 24 (39%) were in first relapse, and 23 (37%) had refractory leukemia (13 patients primary refractory and 10 patients refractory to multiple therapies). The 15 patients with newly diagnosed AML (Table 2) had a median age of 61 years (range, 51-69), with 10 myelodysplasia/AML, 2 treatment-related AML, and 3 previous MPD. Six (40%) had adverse cytogenetics (2 monosomy 7, 1 20q- and 11p-, 3 complex) and two had FLT3 aberrations (1 D835 point mutation and 1 internal tandem duplication). All newly diagnosed patients had at least 2 poor-risk factors (age, ≥60; secondary AML; adverse genetic features; and/or Eastern Cooperative Oncology Group performance status 2) and six had 3 poor-risk features.

For the 24 patients with relapsed AML, the median duration of CR 1 was 9 months (range, 4-22 months). Of the 13 patients with primary refractory AML, 5 had received standard ara-C plus anthracyclines ("7+3") with 3 of the 5 receiving ara-C, daunorubicin, and etoposide. A large majority of the 62 patients had received ara-C and/or anthracyclines for acute leukemia or a prior malignancy. Twenty-three (37%) had received at least one cycle previously of TST with ara-C and anthracycline with/without etoposide, including 6 patients with primary refractory AML and 7 patients in first relapse with CR 1 duration of ≤9 months.

**Toxicities.** Similar to our phase I study (19), flavopiridol induced direct antileukemic cytotoxicity with a ≥50% decrease in peripheral blood blast counts in 27 (44%) patients by median day 2 (range, ≤12 h after first dose, day 3) and a ≥80% decrease in 16 (26%) by day 3 of flavopiridol (Table 3). Overall, there was no clear relationship between either the magnitude or the rate of blast cell decrease and clinical outcome. Nonetheless, of the six newly diagnosed patients whose blast counts did not decrease by at least 50%, three were nonresponders. No such pattern was evident for either relapsed or refractory patient cohorts. No patient had sustained increases in peripheral counts during flavopiridol. Tumor lysis occurred in 33 (53%) and was manifested by transient hyperphosphatemia (range, 4.9-11.1 mg/dL) with or without hyperuricemia in 27 (44%) and elevations in D-dimer (range, 4.5-55.7 mg/L) without clinical coagulopathy in 19 (31%). Nine of 15 (60%) patients with newly diagnosed secondary AML had evidence of tumor lysis, in contrast to 15 of the 47 (32%) patients with relapsed or refractory AML, although this difference did not reach statistical significance (chi^2 = 3.84; P > 0.05 and P ≤ 0.10). Hyperkalemia was not observed in any patient and only one patient with refractory AML required hemodialysis.

The toxicity profile detailed in Table 4 was similar to that detected in our phase I trial (22–24), with ≤grade 2 mucositis (oral and gastrointestinal) occurring in 15% following flavopiridol and in 29% following ara-C and mitoxantrone. Time to hematologic recovery was similar to other TST regimens (22–24), with the median time to absolute neutrophil count >500/mm^3 being day 31 (range, 24-46) and median time to platelets ≥50,000/mm^3 being day 35 (range, 24-55). Cardiovascular events occurred in two (3%) post-flavopiridol, both transient atrial arrhythmias, and in six (10%) post-ara-C and mitoxantrone, including grade 3 decreases in left ventricular ejection fraction in three patients. Adult respiratory distress syndrome occurred in one patient following flavopiridol and one patient following ara-C and mitoxantrone, in both instances related to underlying fungal pneumonia. Toxicities ≥grade 3 occurred in seven (11%) and death occurred in three (5%) from multiorgan failure and fungal pneumonia, all of whom had multirefractory AML.

**Clinical outcome.** Responses to flavopiridol, ara-C, and mitoxantrone were related to stage of disease. Assessment of bone marrow aspirates and biopsies on day 14 of therapy revealed complete leukemia clearance in 41 (66%) of the entire patient population. Within the cohort of 15 newly diagnosed patients, 13 (87%) had complete clearance, 1 had marked marrow hypoplasia with small numbers of residual blasts, and 1 had significant residual leukemia. Eleven of the 13 with complete clearance and the patient with marked marrow hypoplasia achieved CR. For the 24 patients with relapsed AML, 19 (79%) had complete clearance, 2 had marked hypoplasia with small numbers of blasts, and 3 had significant residual leukemia. CR was achieved in 16 who had complete clearance and the 2 who had marked marrow hypoplasia. In contrast, only two patients with primary refractory AML and no patients with multirefractory AML achieved deep leukemia clearance (1 complete and 1 marked hypoplasia) and CR.

As depicted in Table 5, patients with newly diagnosed secondary AML and AML in first relapse had CR rates of 75%, whereas only 2 of 13 (15%) patients with primary refractory AML and no patients with multirefractory AML achieved CR. For the cohort of patients with newly diagnosed, poor-risk AML, we compared the CR rate achieved with flavopiridol, ara-C, and mitoxantrone with the CR rates achieved for similar newly diagnosed, poor-risk patients treated with other TST regimens (22, 24). Table 6 shows that, for this small group of poor-risk patients, the CR rate achieved with current flavopiridol-based regimen seems to be higher than the CR...
rate with either of the other regimens for patients with comparable poor-risk features.

Of the 32 patients achieving CR, 12 patients (6 of 12 newly diagnosed, 5 of 18 relapsed, and 1 of 2 primary refractory) underwent matched sibling allogeneic SCT and an additional 2 patients who had relapsed after prior SCT received donor lymphocyte infusions in CR induced by flavopiridol, ara-C, and mitoxantrone. An additional 11 CR patients received a second

Table 2. Clinical features of 15 adults with newly diagnosed AML

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Poor-risk feature</th>
<th>Cytogenetics</th>
<th>Response</th>
<th>Prescription in CR/type</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
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<tr>
<td>51/F</td>
<td>T*</td>
<td>46XX, +11p, -20q</td>
<td>CR</td>
<td>FLAM2/AlloSCT</td>
<td>27.5+</td>
<td>29+</td>
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<td>51/F</td>
<td>MDS †</td>
<td>46XX</td>
<td>CR</td>
<td>AlloSCT</td>
<td>7.5</td>
<td>8.5</td>
</tr>
<tr>
<td>52/M</td>
<td>MDS</td>
<td>46XY</td>
<td>CR</td>
<td>AlloSCT</td>
<td>13+</td>
<td>14+</td>
</tr>
<tr>
<td>52/M</td>
<td>MDS</td>
<td>Complex</td>
<td>CR</td>
<td>FLAM2/AlloSCT</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
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<td>46XX</td>
<td>CR</td>
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<td>9.5</td>
<td>12</td>
</tr>
<tr>
<td>57/F</td>
<td>T</td>
<td>Complex</td>
<td>CR</td>
<td>FLAM2</td>
<td>6</td>
<td>8.5</td>
</tr>
<tr>
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<td>46XY, -7q</td>
<td>PR</td>
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</tr>
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<td>46XX</td>
<td>CR</td>
<td>AlloSCT</td>
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<td>28</td>
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<td>46XY, -7q</td>
<td>CR</td>
<td>FLAM2</td>
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<td>9+</td>
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<tr>
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<td>MDS</td>
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<td>CR</td>
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<td>15+</td>
<td>16+</td>
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<tr>
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<td>MDS</td>
<td>46XX, -7</td>
<td>NR</td>
<td>—</td>
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</tr>
<tr>
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<td>CR</td>
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<td>4.5</td>
<td>6</td>
</tr>
<tr>
<td>69/M</td>
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<td>46XY</td>
<td>CR</td>
<td>AlloSCT</td>
<td>11.5+</td>
<td>13+</td>
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<tr>
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<td>MDS</td>
<td>46XY</td>
<td>CR</td>
<td>FLAM2</td>
<td>6.5</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviations: M, male; F, female; PR, partial remission; NR, no remission; AlloSCT, allogeneic SCT; FLAM2, flavopiridol, ara-C, and mitoxantrone consolidation in early CR.
* Treatment-related AML.
† Myelodysplasia-related AML.
‡ AML arising from prior MPD.

Table 3. Clearance of peripheral blood blasts by flavopiridol

<table>
<thead>
<tr>
<th>Disease status</th>
<th>Day 1 (pre-flavopiridol)</th>
<th>After 12 h (1st dose)</th>
<th>Day 2</th>
<th>Day 3/4 (nadir)</th>
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<tbody>
<tr>
<td>New diagnosis (9/15 patients)</td>
<td>2.5*</td>
<td>0.9</td>
<td>0.8</td>
<td>0.3 †</td>
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<tr>
<td>3.3</td>
<td>1.2</td>
<td>1.5</td>
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<td>4.5</td>
<td>2.3</td>
<td>1.7</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>4.6</td>
<td>2.4</td>
<td>1.7</td>
<td>1.7</td>
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</tr>
<tr>
<td>6.4</td>
<td>1.1</td>
<td>0.7</td>
<td>0.2 †</td>
<td></td>
</tr>
<tr>
<td>13.5</td>
<td>6.0</td>
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<td>22.9</td>
<td>4.8</td>
<td>2.7</td>
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</tr>
<tr>
<td>29.1</td>
<td>5.4</td>
<td>2.8</td>
<td>1.2 †</td>
<td></td>
</tr>
<tr>
<td>48.6</td>
<td>20.4</td>
<td>18.6</td>
<td>4.2 †</td>
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</tr>
<tr>
<td>Relapse (10/24 patients)</td>
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<td>0.4</td>
<td>0.5</td>
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<td>2.8</td>
<td>ND</td>
<td>0.5</td>
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<td>3.8</td>
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<td>10.6</td>
<td>6.3</td>
<td>2.1</td>
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<td>12.4</td>
<td>1.9</td>
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<td>15.4</td>
<td>7.9</td>
<td>4.3</td>
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<td>19.1</td>
<td>11.8</td>
<td>8.5</td>
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<td>63.3</td>
<td>ND</td>
<td>39.5</td>
<td>10.3 †</td>
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<tr>
<td>Refractory (8/23 patients)</td>
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<td>0.2</td>
<td>0.4</td>
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<td>1.6</td>
<td>0.9</td>
<td>0.8</td>
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<td>56.7</td>
<td>ND</td>
<td>8.5</td>
<td>2.4 †</td>
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</table>

Abbreviation: ND, not done.
* Peripheral blood blasts × 10⁹/mm³.
† Decrease (≥80%) from day 1 pre-flavopiridol peripheral blood blast counts.
cycle of flavopiridol, ara-C, and mitoxantrone, 1 patient underwent autologous SCT in CR after the first cycle of flavopiridol, ara-C, and Mitoxantrone, and 6 CR patients did not receive additional therapy after cycle 1.

Median overall survival (OS) for all 62 patients was 8 months (range, 0.5-30+), and median OS for the 15 newly diagnosed patients was 18 months (range, 4-29+). Figure 1 shows that, for the entire group of 32 CR patients, median disease-free survival (DFS) was 11 months (range, 2.5-26.5+), with 11 patients currently remaining in CR from 9+ to 26.5+ months. Median OS for all CR patients was 18 months (3.5-30+), with 13 of the 31 still alive at 10+ to 30+ months. For the 16 patients who received chemotherapy only (either one or two cycles of flavopiridol, ara-C, and mitoxantrone), median DFS was 9 months (4-22), whereas the median DFS for the 15 patients undergoing SCT or donor lymphocyte infusions in CR was 13 months (range, 3.5-26.5+). For the 11 newly diagnosed patients who achieved CR, median DFS and OS have not yet been reached (Fig. 2; Table 2) at 26.5 and 28 months, respectively.

**Discussion**

This phase II trial of TST with flavopiridol, ara-C, and mitoxantrone confirms and extends our initial observations that this regimen has significant clinical activity in adults with poor-risk AML. The timed sequential combination induced morphologic and cytogenetic CRs in 75% of patients with newly diagnosed, secondary AML, including those with adverse and complex cytogenetics, and in patients with AML in relapse after short CR (median, 9 months), including those who have relapsed after previous allogeneic SCT. Whereas the entire group of AML patients treated with flavopiridol, ara-C, and mitoxantrone spanned diverse stages of disease and poor-risk features, the 15 patients in the newly diagnosed subgroup shared several characteristics, including older age (100%, >50 years), secondary AML in 100%, and adverse genetic features in 53% (8 of 15: 6 adverse cytogenetics and 2 mutated FLT3). The 75% CR rate achieved for newly diagnosed patients with flavopiridol, ara-C, and mitoxantrone compares favorably with historical TST regimens using sequential ara-C, anthracycline, and either amsacrine (24) or etoposide (22), in which CR rates are 40% to 50% for patients ≥55 years of age and 30% to 40% for adverse cytogenetics. Likewise, the use of flavopiridol with ara-C and mitoxantrone compares favorably with TST consisting of ara-C, mitoxantrone, and bevacizumab, where two of three newly diagnosed patients with poor-risk AML and 50% of first relapse patients achieved CR (25).

Both CR duration and OS for those patients achieving CR are encouraging, with 40% of the entire group and ≥50% of newly diagnosed patients being alive and in CR at ≥2 years. Again, these data compare favorably with historical TST regimens (22, 24, 25), where OS for newly diagnosed patients with secondary AML was 7 months (24) and 10.7 months (22). The data in these patient subgroups compare favorably with historical results from multiple trials of combination chemotherapy with or without allogeneic SCT, where 2-year DFS and OS are commonly in the range of 25% to 35% for both approaches (12, 13, 29–32). Nonetheless, 6 of the 31 (19%)...
CR patients relapsed within 6 months of achieving CR, 3 with newly diagnosed treatment-related AML, 2 with short first CRs (6 and 9 months), and 1 primary refractory patient who achieved CR. Moreover, the results in patients with primary refractory and multirefractory AML remain poor with this regimen.

Flavopiridol has direct anti-AML cytotoxicity, as manifested by ≥50% decrease in peripheral blood blasts in 44% and induction of one or more manifestations of tumor lysis in 53%. The tumor lysis sequelae were short lived, generally resolved within 72 h, and in only 1 instance did the magnitude of lysis result in the need for temporary hemodialysis. The pattern of tumor lysis that we detected using a 1-h flavopiridol infusion is strikingly different from the pattern noted with the new pharmacologically modeled, “hybrid” bolus infusion schedule of flavopiridol administration developed by Byrd et al. (33) and Blum et al. (34). The hybrid schedule is designed to overcome the effects of avid flavopiridol binding by human plasma proteins. In this construct, ~50% of the total flavopiridol dose is administered by 30-min bolus followed by a 4-h infusion of the remaining half of the flavopiridol dose. Data in high-risk chronic lymphocytic leukemia show acute tumor lysis syndrome characterized by striking hyperkalemia along with hyperphosphatemia and increase in LDH, with dramatic clinical responses in >50% of refractory chronic lymphocytic leukemia patients (33). Studies in refractory acute leukemia show a similar but less striking pattern of metabolic derangements (34).

TST with flavopiridol, ara-C, and mitoxantrone was associated with a relatively low incidence and severity of nonhematologic toxicities, and the duration of profound marrow aplasia was commensurate with other TST regimens (22–25). Indeed, no patient with newly diagnosed AML and only 3 (5%) of the entire patient cohort died. The very low death rate compares very favorably with any type of intensive multiagent anti-AML therapy (TST or non-TST) for all stages of disease. This low death rate may relate at least in part to the extremely low incidence of grade 3/4 oral or lower gastrointestinal mucositis with this regimen, which stands in contrast to other regimens including TST (22, 24). Patients with newly diagnosed, relapsed, or primary refractory AML who achieved CR were able to undergo allogeneic SCT. Patients who achieved CR after relapse post-allogeneic SCT were able to receive donor lymphocyte infusions without difficulty and with CR duration that surpassed that achieved with the previous SCT (8 versus 11 months; 14 versus 22.5+ months).

In summary, flavopiridol has significant anti-AML activity, both directly and in sequential combination with ara-C and mitoxantrone. This TST regimen induces durable CRs in a significant proportion of adults with newly diagnosed secondary AML (including those with adverse and complex cytogenetics) and adults with AML in first relapse, including those with short CRs and those with previous allogeneic SCT.

Table 6. CR rates for adults with newly diagnosed, poor-risk AML: comparison of flavopiridol, ara-C, and mitoxantrone with other TST regimens

<table>
<thead>
<tr>
<th></th>
<th>FAM*</th>
<th>AcDamsa †</th>
<th>ATRA-AcIda-etoposide †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>CR%</td>
<td>95% CI</td>
</tr>
<tr>
<td>CR</td>
<td>12/15</td>
<td>75</td>
<td>59-96</td>
</tr>
<tr>
<td>P value vs FAM (Fisher’s exact two-tailed test)</td>
<td>0.03</td>
<td>0.05</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Abbreviation: 95% CI, 95% confidence interval.

*Flavopiridol, ara-C, and mitoxantrone (current regimen).
†Timed sequential therapy with ara-C, daunorubicin, and m-AMSA (24).
‡Timed sequential therapy with all-trans-retinoic acid, ara-C, idarubicin, and etoposide (22).
¶Patients with both secondary AML and adverse cytogenetics.
next steps in the development of flavopiridol-based regimens for AML include an expansion of experience in the newly diagnosed secondary AML population. Additionally, the new “hybrid” bolus infusion schedule of flavopiridol administra-
tion, which has shown dramatic cytotoxicity in chronic lymphocytic leukemia (33), should be tested in combination regimens in the acute leukemias, including refractory AML and relapsed and refractory acute lymphoblastic leukemia.

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