ACUTE MYELOID LEUKEMIA

INDUCTION

**CYTARABINE (LOW DOSE)**
**ELDERLY NOT CONSIDERED FOR FOR INTENSIVE CHEMOTHERAPY**
Cytarabine 20 mg BID SQ Days 1 – 10

Repeat cycle every 4 – 6 weeks.


**7+3 (CYTARABINE – ANTHRACYCLINE/ANTHRACENEDIONE)**
Cytarabine 100 mg/m²/day CIVI* Days 1 – 7

*Administer as a continuous infusion over 24 hours.

With either

Daunorubicin 45 mg/m²/day IV Days 1 – 3

OR

Idarubicin 12 mg/m²/day IV Days 1 – 3

OR

Mitoxantrone 12 mg/m²/day IV Days 1 – 3

NOTE: Reference supporting cytarabine doses of 100 mg/m²/day over 200 mg/m²/day is Dillman RO, et al. Blood 1991;78:2520 – 6.

References:

**7 + 3 + 7 (CYTARABINE – DAUNORUBICIN – ETOPOSIDE)**
Cytarabine 100 mg/m²/day CIVI* Days 1 – 7
Daunorubicin 50 mg/m²/day IV Days 1 – 3
Etoposide 75 mg/m²/day IV** Days 1 – 7

*Administer as a continuous infusion over 24 hours; **Administer over 1 hour.

FLAG (FLUDARABINE – CYTARABINE – FILGRASTIM)

Fludarabine 30 mg/m²/day IV* Days 1 – 5

Followed 3.5 hours later by

Cytarabine 2000 mg/m²/day IV** Days 1 – 5
G–CSF 400 mcg/m²/day IV# Day 0 until ANC recovery

*Administer over 30 minutes at the same time daily for 5 days; **Administer over 4 hours; #Subsequent trials have shown that G–CSF before, during, and after fludarabine and cytarabine had no effect on CR or infection rates in an elderly leukemia population.

DOSE MODIFICATIONS: If the pretreatment SCr was 2 mg/dL or greater, the fludarabine dose was reduced to 15 mg/m²; while if the pretreatment creatinine level was 1.6 – 1.9 mg/dL and the patient older than 60 years, the daily fludarabine dose was 20 mg/m².

NOTE: The United Kingdom Medical research Council (UK–MRC) recently published a comparative study of FLA (fludarabine and high dose cytarabine) vs. standard chemotherapy (cytarabine, daunorubicin and etoposide) in patients with high–risk AML (de novo or secondary AML and (a) had relapsed from 1st CR; (b) had received one course of chemotherapy and were found to have poor risk cytogenetics at initial diagnosis (–5, –7, del 5q, abnormal 3q, or complex karyotype defined as more than 4 abnormalities) whether they had achieved CR with course 1; (c) had resistant disease defined as greater than 15% marrow blasts after recovery from course 1; (d) had refractory disease defined as failure to achieve CR after 2 induction courses). There were no significant differences in the CR rate, deaths in CR, relapse rate or disease–free survival between conventional chemotherapy and FLA. However survival at 4 years was worse with FLA (16% vs. 27%, p = 0.05). These findings indicate that FLA may be inferior to standard chemotherapy in high–risk AML. The outcome is not improved with the addition of either G–CSF or ATRA [Reference: Milligan DW, et al. Blood 2006;107:4614 – 22].


IA (IDARUBICIN – CYTARABINE)

Idarubicin 12 mg/m²/day IV Days 1 – 3
Cytarabine 1500 mg/m²/day CIVI* Days 1 – 4
G–CSF 200 – 400 mcg/m²/day SQ Day 0 until ANC recovery**

*Administer over 24 hours as a continuous infusion; **Start G–CSF 1 day prior to chemotherapy and continue until ANC recovery. If the presenting WBC is greater than 10 x 10⁹/L, then delay the start of G–CSF until 1 – 2 days after initiation of chemotherapy.

**AMR REINDUCTION**

**ALSO SEE INDUCTION SECTION** – can consider re-dosing with any of these regimens.

**5+2**

- **Cytarabine**
  - 100 mg/m²/day
  - CIVI
  - Days 1 – 5

  *With*

- **Daunorubicin**
  - 45 mg/m²/day
  - IV
  - Days 1 and 2

  **OR**

- **Mitoxantrone**
  - 12 mg/m²/day
  - IV
  - Days 1 and 2

*For reinduction only; **Administer as a continuous infusion over 24 hours.*


**5+3**

- **Cytarabine**
  - 25 mg/m²
  - IVB
  - Day 1 only

  *Followed by*

- **Cytarabine**
  - 200 mg/m²/day
  - CIVI
  - Days 1 – 5

  *With*

- **Idarubicin**
  - 12 mg/m²/day
  - IV
  - Days 1 – 3

*Administer as a continuous infusion over 24 hours.*

**NOTE:** If using mitoxantrone the dose is 12mg/m²/day on Day 1 and 2 (unpublished).


**7+3**

- **Cytarabine**
  - 25 mg/m²
  - IVB
  - Day 1 only

  *Followed by*

- **Cytarabine**
  - 100 mg/m²/day
  - CIVI
  - Days 1 – 7

  *With*

- **Idarubicin**
  - 12 mg/m²/day
  - IV
  - Days 1 – 3

*Administer as a continuous infusion over 24 hours.*


Last Updated on September 24, 2007
HDAC (HIGH DOSE CYTARABINE)
Cytarabine 3000 mg/m² Q12H IV\* Days 1 – 6

*Administer over 2 hours for a total of 12 doses. Steroid or methylcellulose eye drops should be administered four times a day beginning prior to/with cytarabine and continuing 48 hours after last cytarabine dose. Patient to sign name prior to each dose of cytarabine to test for cerebellar neurotoxicity.

A second course of reinduction therapy was given if the Day 14 bone marrow biopsy was hypocellular or normocellular with blasts and promyelocytes between 10 and 25%.

DOSE MODIFICATION: The dose of cytarabine was reduced to 2000 mg/m²/dose in patients over the age of 50 years.

**AML POST–REMISSION/CONSOLIDATION**

**5+2**  
Cytarabine 25 mg/m² IVB* Day 1 only  

*Followed by*  
Cytarabine 100 mg/m²/day CIVI** Days 1 – 5  

*With*  
Idarubicin¹ 12¹ – 13² mg/m²/day IV Days 1 and 2  

OR  
Daunorubicin² 45 mg/m²/day IV Days 1 and 2  

OR  
Mitoxantrone³ 12 mg/m²/day IV Days 1 and 2  

*IV bolus cytarabine not administered in the Wiernik reference; **Administer as a continuous infusion over 24 hours.*


**STANDARD DOSE CYTARABINE**  
Cytarabine 100 mg/m²/day CIVI* Days 1 – 5  

*Administer as a continuous infusion over 24 hours.*

Repeat cycle every 28 days for 4 cycles.

HDAC – CALGB VERSION (HIGH DOSE CYTARABINE)
Cytarabine 3000 mg/m² Q12H IV* Days 1, 3 and 5

*Administer over 3 hours for a total of 6 doses. Doses to be administered every other day. Steroid or methylcellulose eye drops should be administered four times a day beginning prior to/with cytarabine and continuing 48 hours after last cytarabine dose. Patient to sign name prior to each dose of cytarabine to test for cerebellar neurotoxicity.

DOSE MODIFICATION: Renal insufficiency has been shown to increase the risk of neurotoxicity associated with high-dose cytarabine. Consider reducing the dose of cytarabine to 2000 mg/m²/dose in patients with renal insufficiency. Renal insufficiency was defined as a serum creatinine of 1.5 – 1.9 mg/dL, or an increase in serum creatinine between 0.5 and 1.2 mg/dL during treatment [Reference: Smith GA, et al. J Clin Oncol 1997;15:833 – 9].

NOTE: This regimen only for patients 60 years of age or less.

Repeat cycle every 28 days for 4 cycles.

AML SALVAGE THERAPY

CECA (CYCLOPHOSHAMIDE – ETOPOSIDE – CARBOPLATIN – CYTARABINE)

Cyclophosphamide 1000 mg/m²/day IV* Days 1 – 3
Etoposide 200 mg/m²/day IV** Days 1 – 3
Carboplatin 150 mg/m²/day CIVI *** Days 1 – 3
Cytarabine 1000 mg/m²/day IV# Days 1 – 3

*Administer over 2 hours; **Administer over 3 hours; ***Administer as a continuous infusion over 24 hours; #Administer over 2 hours.

NOTE: Administer agents sequentially with cyclophosphamide first, followed by etoposide, and then cytarabine.

DOSE MODIFICATIONS: Carboplatin dose was reduced by 50% for a serum creatinine greater than 1.5 mg/dL, or for a serum bilirubin greater than 2 mg/dL. The etoposide dose was reduced by 25% for a serum bilirubin of 2 mg/dL or greater, and by 50% if the bilirubin was greater than 3 mg/dL. Patients with Grade 3 or 4 toxicity were eligible to receive a second course with a 25% dose reduction.


CLOFARABINE

Clofarabine 40 mg/m²/day IV* Days 1 – 5

*Administer over 1 hour.

Repeat cycle every 3 – 6 weeks.


FLANG (FLUDARABINE – CYTARABINE – MITOXANTRONE – G-CSF)

G-CSF 300 mcg/day SQ* Days 1 – 3
Fludarabine 30 mg/m²/day IV** Days 1 – 3

Followed 4 hours later by

Cytarabine 1000 mg/m²/day IV*** Days 1 – 3
Mitoxantrone 10 mg/m²/day IV# Days 1 – 3
G-CSF 300 mcg/day SQ* Day 10 until ANC recovery

*Start G-CSF 12 hours prior to the first fludarabine dose and administer daily for 3 days. Then discontinue, and resume 7 days following completion of chemotherapy until ANC recovery; **Administer over 30 minutes; ***Administer over 2 hours; #Administer over 30 minutes.


Last Updated on September 24, 2007
### MITOXANTRONE – CYTARABINE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
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<tbody>
<tr>
<td>Cytarabine</td>
<td>2000 mg/m²</td>
<td>IV</td>
<td>Day 1**</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>30 mg/m²</td>
<td>IV***</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

*Followed 96 hours later by*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine</td>
<td>2000 mg/m²</td>
<td>IV</td>
<td>Day 5**</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>30 mg/m²</td>
<td>IV***</td>
<td>Day 5</td>
</tr>
</tbody>
</table>

*Administer over 3 hours; **Two doses are to be administered on Day 1 and again on Day 5 (96 hours later); ***Administer the mitoxantrone after the second dose of Cytarabine on Day 1 and again on Day 5 (total of 2 doses of mitoxantrone administered). Administer over 1 hour.*


### GEMTUZUMAB OZOGAMICIN (MYLOTARG®)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemtuzumab‡</td>
<td>9 mg/m²</td>
<td>IV*</td>
<td>1 and 15</td>
</tr>
</tbody>
</table>

‡Routine premedications administered; *Administer over 2 hours.

NOTE: Only administer if leukemia is CD33 positive.

AML – CLINICAL TRIALS

ECOG 1900
INDUCTION
ARM A
Daunorubicin  45 mg/m²/day  IV*  Days 1 – 3
Cytarabine    100 mg/m²/day  CIVI**  Days 1 – 7

ARM B
Daunorubicin  90 mg/m²/day  IV*  Days 1 – 3
Cytarabine    100 mg/m²/day  CIVI**  Days 1 – 7

*Administer over 10 – 15 minutes through a free-flowing line; **Administer over 24 hours as a continuous infusion.

NOTE: Up to 2 cycles of induction therapy are permitted to gain a CR. Regardless of which arm the patient was initially randomized to, they will receive the following reinduction regimen:
Daunorubicin  45 mg/m²/day  IV*  Days 1 – 3
Cytarabine    100 mg/m²/day  CIVI**  Days 1 – 7

DOSE MODIFICATIONS FOR INDUCTION CYCLE 2: Dosage adjustment for hepatotoxicity is required. Reduced the dose of daunorubicin by 50% if the bilirubin (total) is 1.5 – 3 mg/dL or the SGPT is 150 – 300 U/L. Reduce the dose of daunorubicin by 75% if the bilirubin is greater than 3 mg/dL and the SGPT is greater than 300 U/L. Dosage adjustment for cardiotoxicity: A repeat MUGA/echo must be performed if the patient requires a second cycle of daunorubicin. The anthracycline will be stopped if a significant absolute drop (> 15%) in LVEF occurs.

Within 2 – 3 weeks of documentation of a complete remission, patients will be randomized to post-remission therapy. If the patient is eligible there will be a genetic randomization to an allogeneic transplant. For patients in whom an allogeneic transplant is not an option, they will be randomized to consolidation therapy or an autologous HSCT. Prior to the initiation of consolidation chemotherapy patients will be randomized to receive an additional gemtuzumab consolidation (Arm D), followed by an autologous transplant or proceed directly to transplant (Arm C). Both groups (C and D) will receive consolidation therapy with high-dose cytarabine.

CONSOLIDATION (ARM C AND D ONLY – SEE SCHEMA ON NEXT PAGE)
Cytarabine    3000 mg/m² Q12H IV*  Days 1, 3 and 5

*Administer each dose over 3 hours. Administer each dose 12 hours apart on Day 1, 3 and 5. Patient to receive corticosteroid (prednisone or dexamethasone) 2 drops OU QID, starting 12 hours prior to cytarabine and continued for 10 days. Patient to sign name prior to each dose to assess for neurotoxicity.

Repeat cycle once 3 weeks following hematopoietic recovery.

GEMTUZUMAB CONSOLIDATION (ARM D ONLY – SEE SCHEMA ON NEXT PAGE)
Gemtuzumab†  6 mg/m²  IV*  Day 1

†Routine premedication required; *Administer over 2 hours. Dose on actual body weight (per protocol).
Reference: ECOG 1900 Protocol; IRB# 191–03.
ECOG 1900 PROTOCOL

Schema

1. On ARM B, if needed for the second course, patients will receive Daunorubicin 45 mg/m²/day IV, days 1,2,3 and Cytarabine (Ara-C) 100 mg/m²/day continuous IV, days 1-7.

2. For patients at high risk or intermediate risk for relapse and with HLA-compatible family member (identical or haploidentical with one locus mismatch).

3. GM-CSF Support

4. Mobilization with G-CSF

5. BM biopsy and aspirates prior to proceeding to next step, to assess CR.

6. Current status, risk, and prognosis must be discussed with all patients. Patients must be willing to continue participation with the study.

7. Cytogenetic Risk status must be determined by central review by the Cytogenetics Review Committee. See Section 11.1.