Cancer Chemotherapy Update

Clofarabine and Cytarabine Regimen for Acute Myeloid Leukemia

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The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net.

Regimen name: Clo+Ara-C
Origin of name: The regimen is named for the 2 medications in the regimen: clofarabine and cytarabine.

COMMENTS

Clofarabine is a second-generation deoxyadenosine analog that was rationally synthesized to combine the cytotoxic properties of fludarabine and cladribine while avoiding the dose-limiting neurotoxicity of other deoxyadenosine analogs.¹ The regimen, clofarabine and cytarabine, was developed in an effort to improve the outcomes of older, poor prognosis, acute myeloid leukemia patients with comorbidities such as a cardiovascular disease (Table 1).²⁻⁵

INDICATIONS

Clofarabine and cytarabine is an alternative treatment for patients with de novo, relapsed, or refractory acute myeloid leukemia.²⁻¹² The regimen has also been used as a conditioning regimen for allogeneic bone marrow transplantation.¹³ Current guidelines recommend clofarabine and granulocyte colony stimulating factor with or without cytarabine, and/or idarubicin for aggressive therapy in appropriate patients with relapsed or refractory disease.¹⁴

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing and dispensing clofarabine and cytarabine.

A. Clofarabine

1. Use clofarabine injection 1 mg/mL.
2. Filter through a 0.2 micron filter into the final container.
3. Dilute in 250 to 1000 mL of 0.9% sodium chloride (NS) or 5% dextrose in water (D5W) to a final concentration of 0.15 to 0.4 mg/mL.

B. Cytarabine

1. Use cytarabine injection 20 mg/mL, 100 mg/mL, or cytarabine powder for injection.
2. Reconstitute the powder with NS, D5W or sterile water for injection to a concentration of 20 mg/mL, 50 mg/mL, or 100 mg/mL.
3. Dilute in 250 to 1000 mL NS or D5W.
4. To avoid potential toxicity, benzyl alcohol preserved diluents should be avoided for the reconstitution of cytarabine.

DRUG ADMINISTRATION

- A. Clofarabine** is administered by intravenous (IV) infusion over 60 minutes.^{2,3}

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Table 1. Clofarabine and cytarabine regimen^{2,3,11,13}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Clofarabine	40 mg/m ²	IV	1,2,3,4,5	200 mg/m ²
Cytarabine	1000 mg/m ²	IV	1,2,3,4,5	5000 mg/m ²

Cycle repeats: every 4 weeks^{2,3}

Variations

1. Faderl et al used the above regimen but clofarabine was administered on days 2 through 6 for induction; clofarabine 40 mg/m² IV on days 1 through 3 and cytarabine 1000 mg/m² IV on days 1 through 3 for consolidation.⁴
2. Faderl et al used clofarabine 30 mg/m² IV on days 1 through 5 and cytarabine 20 mg/m² SQ on days 1 through 14 for induction; clofarabine 30 mg/m² IV on days 1 through 3 and cytarabine 20 mg/m² SQ on days 1 through 7 for consolidation.⁵
3. Faderl et al used clofarabine 20 mg/m² IV on days 1 through 5 and cytarabine 20 mg/m² SQ twice daily on days 1 through 10 for induction, then alternated with decitabine 20 mg/m² IV on days 1 through 5 in patients not in complete remission; clofarabine 20 mg/m² IV on days 1 through 3 and cytarabine 20 mg/m² SQ twice daily, then alternating with decitabine 20 mg/m² IV days 1 through 5 for consolidation.⁶
4. Faderl et al used clofarabine 40 mg/m² IV on days 2 through 6 and cytarabine 1000 mg/m² IV on days 1 through 5 for induction; clofarabine 30 mg/m² IV on days 2 through 6 and cytarabine 750 mg/m² IV on days 1 through 5 for consolidation.⁷
5. Martinez-Cuadron et al used clofarabine 20 mg/m² IV on days 1 through 5 and cytarabine 20 mg/m² SQ on days 1 through 14 for induction; clofarabine 15 mg/m² IV on days 1 through 5 and cytarabine 20 mg/m² SQ on days 1 through 7 for consolidation.⁸
6. Becker et al used filgrastim 5 mcg/kg SQ on day 0 and continuing until ANC ≥1000 cells/mcL for 2 consecutive days, clofarabine 25 mg/m² IV on days 1 through 5, and cytarabine 2000 mg/m² IV on days 1 through 5 for induction; filgrastim 5 mcg/kg SQ on day 0 and continuing until ANC ≥1000 cells/mcL for 2 consecutive days, clofarabine 20 mg/m² IV on days 1 through 5, and cytarabine 1000 mg/m² IV on days 1 through 5 for consolidation.⁹
7. Scappini et al used clofarabine 22.5 mg/m² IV on days 1 through 5 and cytarabine 1000 mg/m² SQ on days 1 through 5 for induction; clofarabine 22.5 mg/m² IV on days 1 through 4 and cytarabine 1000 mg/m² SQ on days 1 through 4 for consolidation.¹⁰
8. Cooper et al used clofarabine 52 mg/m² IV on days 1 through 5 and cytarabine 1000 mg/m² IV on days 1 through 5.¹¹
9. Inaba et al used sorafenib 200 mg/m² PO twice daily on days 1 through 12, clofarabine 40 mg/m² IV on days 8 through 12 and cytarabine 1000 mg/m² IV on days 8 through 12.¹²
10. Martin et al used clofarabine 40 mg/m² IV on days -6 through -2, cytarabine 1000 mg/m² IV on days -6 through -2, and rabbit anti-thymocyte globulin 1 mg/kg IV over 6 hours on day -4 and 2.5 mg/kg IV on days -3 and -2 for allogeneic stem cell transplant conditioning for myelodysplastic syndrome or acute myeloid leukemia.¹³

Note: ANC = absolute neutrophil count; IV = intravenous; SQ = subcutaneous.

- B. Cytarabine** is administered by IV infusion over 120 minutes, 3 to 4 hours after completion of the clofarabine infusion.^{2,3}

SUPPORTIVE CARE

- A. Acute and Delayed Emesis Prophylaxis:** The clofarabine and cytarabine regimen is predicted to cause acute emesis in 30% to 90% of patients.¹⁵⁻¹⁸ However, nausea was reported in only one of the trials reviewed, with 3% of patients reporting grade 3 or 4 nausea.³ Prophylactic antiemetic therapy with a serotonin antagonist is recommended,¹⁶⁻¹⁸ but may not be required in all patients. One group suggests addition of a neurokinin (NK₁) antagonist

may be appropriate in some patients.¹⁶ One of the following regimens given 30 minutes prior to therapy is recommended:

1. Ondansetron 8 mg to 16 mg orally (PO), ±dexamethasone 12 mg PO, given 30 minutes before clofarabine each day.
2. Granisetron 1 mg to 2 mg PO, ±dexamethasone 12 mg PO, given 30 minutes before clofarabine each day.
3. Dolasetron 100 mg PO, ±dexamethasone 12 mg PO, given 30 minutes before clofarabine each day.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO, given 30 minutes before clofarabine on day 1 only.

If a neurokinin antagonist is used, one of the following regimens is recommended:

1. Ondansetron 8 mg to 16 mg and dexamethasone 12 mg, 30 minutes before clofarabine each day, and aprepitant 125 mg given PO 30 minutes before clofarabine on day 1.
2. Granisetron 1 mg to 2 mg, dexamethasone 12 mg, 30 minutes before clofarabine each day, and aprepitant 125 mg given PO 30 minutes before clofarabine on day 1.
3. Dolasetron 100 mg, dexamethasone 12 mg PO, 30 minutes before clofarabine each day, and aprepitant 125 mg given PO 30 minutes before clofarabine on day 1.
4. Palonosetron 0.25 mg IV, dexamethasone 12 mg, and aprepitant 125 mg given PO 30 minutes before clofarabine on day 1 only.
5. Aprepitant 80 mg PO should be given on the morning of days 2 and 3. Although not well supported by clinical trials, some clinicians prefer to give aprepitant 80 mg daily on days 2 through 5.

The antiemetic therapy should continue for at least 3 days after the last dose of clofarabine and cytarabine. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (greater than 24 hours) use of these agents, making a steroid, or steroid and dopamine antagonist combination, most appropriate for follow-up therapy.¹⁹ One of the following regimens is recommended, beginning on day 6:

1. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ prochlorperazine 10 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ promethazine 25 to 50 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹⁵⁻¹⁸ There is no evidence that substituting granisetron for ondansetron in subsequent treatment cycles or increasing the dose, even to very high doses, is effective. This approach is not recommended.²⁰⁻²⁴

B. Breakthrough Nausea and Vomiting¹⁵⁻¹⁸: Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is recommended:

1. Metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Prochlorperazine 10 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Prochlorperazine 25 mg rectally every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.
4. Promethazine 25 to 50 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

Patients who do experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹⁵⁻¹⁸ There is no evidence that substituting granisetron for ondansetron in subsequent treatment cycles or increasing the dose, even to very high doses, is effective. This approach is not recommended.²⁰⁻²⁴

C. Hematopoietic Growth Factors: Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen have a 20% or higher incidence of febrile neutropenia before prophylactic use of colony stimulating factors (CSFs) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSFs should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of CSFs is not recommended.^{25,26}

Severe (grade 3 or 4) neutropenia was reported in 11% of patients in the clofarabine and cytarabine trials reviewed; febrile neutropenia was reported in 47% of patients.² Usually prophylactic use of CSFs is recommended in regimens that cause febrile neutropenia in greater than 20% of patients; however current guidelines for using prophylactic growth factors in patients with acute myeloid leukemia warn that use of CSFs following induction therapy may interfere with interpretation of the post-remission bone marrow biopsy results.¹⁴

MAJOR TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades

represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (<http://ctep.info.nih.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities, but make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Arrhythmia (grade 3 or 4) 3% to 10%;³ edema (grade 3 or 4) 7%;³ hypertension (grade 3) 8%,² (grade 4) 1%;² hypotension (grade 3) 4%, (grade 4) 2%;² myocardial infarction (grade 3 or 4) 3%.³
- B. Constitutional:** Fatigue (grade 3) 6%.²
- C. Gastrointestinal:** Anorexia (grade 3 or 4) 14%;¹¹ diarrhea 100%,¹³ (grade 3) 8%,² (grade 3 or 4) 12% to 29%;^{11,13} increased lipase (grade 3) 4%,² (grade 4) 1%;² mucositis 100%,¹³ (grade 3 or 4) 13%;¹³ nausea (grade 3 or 4) 3% to 12%.^{3,11}
- D. Hematologic:** Anemia (grade 3) 11%,² (grade 3 or 4) 43%,¹³ (grade 4) 2%;² febrile neutropenia (grade 3) 45%,² (grade 3 or 4) 41%,¹¹ (grade 3 or 4) 100%,¹³ (grade 4) 2%;² leukopenia (grade 4) 6%;² neutropenia (grade 3) 1%,² (grade 3 or 4) 71%,¹³ (grade 4) 10%;² pancytopenia (grade 3 or 4) 100%;³ thrombocytopenia (grade 3) 1%,² (grade 3 or 4) 57%,¹³ (grade 4) 15%.²
- E. Hepatic:** Increased alanine aminotransferase (ALT) 100%,¹³ (grade 3) 10%,² (grade 3 or 4) 12% to 57%;^{11,13} increased aspartate aminotransferase (AST) 100%,¹³ (grade 3) 10%, (grade 3 or 4) 8% to 86%,^{11,13} (grade 4) 1%;² increased bilirubin 86%,¹³ (grade 3) 4%,² (grade 3 or 4) 29%,¹³ (grade 4) 1%.²
- F. Infection:** Bacteremia (grade 3) 7%,² (grade 3 or 4) 57%,¹³ (grade 4) 2%;² cytomegalovirus (CMV) (grade 3 or 4) 14%;¹³ *Clostridium difficile* colitis (grade 3 or 4) 14%;¹³ enterococcal bacteremia (grade 3) 7%,² (grade 4) 1%;² staphylococcal bacteremia (grade 3) 6%;² pneumonia (grade 3) 12%,² (grade 4) 2%;² sepsis (grade 3) 2%,² (grade 4) 2%;² unspecified infections and infestations (grade 3 or 4) 47%.¹¹
- G. Metabolic:** Hyperglycemia (grade 3) 6%,² (grade 3 or 4) 12%;¹¹ hypocalcemia (grade 3) 4%,² (grade 4) 1%;² hypokalemia (grade 3) 15%,²

(grade 3 or 4) 20%,¹¹ (grade 4) 3%;² hyponatremia (grade 2) 6%.²

- H. Neurologic:** Palmar-plantar erythrodysesthesia 10% to 57%.^{3,13}
- I. Pulmonary:** Dyspnea 86%,¹³ (grade 3 or 4) 71%.¹³
- J. Renal:** Acute renal failure (grade 3) 4%,² (grade 4) 1%.²

PRETREATMENT LABORATORY STUDIES NEEDED

- A. Baseline**
 1. AST/ALT
 2. Total bilirubin
 3. Serum creatinine
 4. Complete blood count (CBC) with differential
 5. Electrocardiogram (EKG)
- B. Prior to Each Treatment**
 1. CBC with differential
 2. AST/ALT
 3. Total bilirubin
 4. Serum creatinine
- C. Recommended Pretreatment Values:** The minimally acceptable pretreatment CBC values required to begin a cycle with full dose therapy in the protocols reviewed were:
 1. Serum creatinine less than 2 mg/dL or creatinine clearance (CrCl) greater than or equal to 60 mL/min.^{2,3}
 2. Serum bilirubin less than 2 mg/dL or less than or equal to 1.5 times the upper limit of normal (ULN).^{2,3}
 3. ALT and AST less than or equal to 2.5 times the ULN.^{2,3}

In clinical practice, a pretreatment absolute neutrophil count (ANC) of 1000 cells/mcL and platelets of 75,000 cells/mcL are usually considered acceptable.

DOSAGE MODIFICATIONS

- A. Renal Function**
 1. Clofarabine:
 - a. CrCl greater than or equal to 30 mL/min and less than 60 mL/min, give 50% of dose.²⁷
 - b. CrCl less than 30 mL/min, no information is available.²⁷
 - c. CrCl less than 60 mL/min/m², adjustment may be required but no guideline is available.²⁸
 2. Cytarabine:
 - a. CrCl 46 to 60 mL/min, give 60% of dose.²⁹
 - b. CrCl 31 to 45 mL/min, give 50% of dose.²⁹

- c. Serum creatinine less than 30 mL/min, do not give drug.²⁹
- d. Adjustment may be required, but no guideline is available.³⁰
- e. No adjustment is required.³¹

B. Liver Function

1. Clofarabine: Bilirubin greater than 3 times the ULN, give 50% of dose.²⁷
2. Cytarabine:
 - a. Bilirubin greater than 2 mg/dL, give 50% of dose.³²
 - b. Any elevation in transaminases, give 50% of dose.^{33,34}
 - c. No information is available.³⁰

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