

Cancer Chemotherapy Update

Hyper-Fractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone Alternating with Methotrexate and Cytarabine (Hyper-CVAD) Regimen

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The increasing complexity of cancer chemotherapy heightens the requirement that pharmacists be familiar with these highly toxic agents. This column will review various issues related to preparation, dispensing, and administration of cancer chemotherapy. It will also serve as a review of various 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 Boulevard #110-545, Arlington, VA 22203, E-mail: OncRxSvc@aol.com; or J. Aubrey Waddell, Associate Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 East Lamar Alexander Parkway, Maryville, TN 37804; E-mail: waddfour@charter.net.

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Regimen name: Hyper-CVAD

Origin of Name: Hyper-CVAD is an acronym of the hyper-fractionated delivery of the four drugs in the initial treatment cycle. **Hyper**-fractionated Cyclophosphamide, **Vincristine**, doxorubicin (**Adriamycin**), and **Dexamethasone**.

INDICATION(S)

The Hyper-CVAD regimen is used to treat adult hematologic malignancies, such as acute lymphocytic leukemia, Burkitt lymphoma, lymphoblastic lymphoma, and mantle cell lymphoma.¹⁻¹⁰

DRUG PREPARATION

A. Cyclophosphamide

1. Follow institutional policies for preparation of hazardous medications when preparing cyclophosphamide.
2. Use cyclophosphamide powder for injection.
3. Reconstitute cyclophosphamide to a concentration of 20 mg/mL with sterile water for injection or 0.9% sodium chloride.
4. Dilute with 250 mL of 0.9% sodium chloride injection, 5% dextrose injection, or a saline/dextrose solution.

B. Doxorubicin

1. Follow institutional policies for preparation of hazardous medications when preparing doxorubicin.
2. Use doxorubicin injection, 2 mg/mL, or doxorubicin powder for injection.
3. If the powder for injection is used, it should be reconstituted to a concentration of 2 mg/mL with 0.9% sodium chloride.
4. Dispense in a syringe, or in 50 to 100 mL of 0.9% sodium chloride or 5% dextrose in water for infusion.

C. Dexamethasone

1. Dexamethasone is available in 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets, 0.5 mg/5 mL and 1 mg/mL oral solutions, 0.5 mg/5 mL elixir, and 4, 10, and 24 mg/mL solution for injection.
2. For intravenous (IV) infusion: Dilute with 50 or 100 mL 0.9% sodium chloride or 5% dextrose injection.

D. Vincristine

1. Follow institutional policies for preparation of hazardous medications when preparing vincristine.

Table 1. Hyper-CVAD^{4,7-10}

Courses 1,3,5,6*				
Drug	Dose	Day(s)	Route	Total Dose/Cycle
Cyclophosphamide	300 mg/m ² every 12 h	1,2,3	IV	1,800 mg/m ²
Mesna	600 mg/m ² /day	1,2,3	CIVI	1,800 mg/m ²
Vincristine	2 mg	4,11	IV	4 mg
Doxorubicin	50 mg/m ²	4	IV	50 mg/m ²
Dexamethasone	40 mg/day	1-4,11-14	Oral/IV	320 mg
Methotrexate	12 mg	2***	IT***	12 mg
Cytarabine	100 mg	8***	IT***	100 mg
Courses 2,4,6,8*				
Drug	Dose	Day(s)	Route	Total Dose/Cycle
Methotrexate	200 mg/m ²	1	IV	
Methotrexate	800 mg/m ²	1	IV	1,000 mg/m ²
Leucovorin	15 mg every 6 h, starting at the end of the methotrexate infusion**	2,3**	Oral/IV	120 mg
Cytarabine	3 g/m ² every 12 h	2,3	IV	12 g/m ²
Methylprednisolone	50 mg	1-3	IV	150 mg
Methotrexate	12 mg	2***	IT***	12 mg
Cytarabine	100 mg	8***	IT***	100 mg

*During cycles 1 through 8, a new cycle begins after hematologic recovery from the previous cycle.

**If methotrexate level is greater than 20 micromolar at the end of the infusion, greater than 1 micromolar 24 hours after the end of the infusion, or greater than 0.1 micromolar 48 hours after the end of the infusion, then the leucovorin dose is changed to 50 mg every 6 hours until the methotrexate level is less than 0.1 micromolar.

***High-risk patients for central nervous system disease receive 16 IT injections. Low-risk patients receive four IT injections. Unknown-risk patients receive eight IT injections.

Maintenance Therapy: 2 yr*

Drug	Dose	Day(s)	Route	Total Dose/Cycle
Mercaptopurine	50 mg three times a day	Each day	oral	4,200 to 4,650 mg
Methotrexate	20 mg/m ²	Once each wk	oral	80 mg/m ²
Vincristine	2 mg	Once each mo	IV	2 mg
Prednisone	200 mg	5 days each mo	Oral	1,000 mg

*Whether or not a patient receives maintenance therapy and the duration of this therapy are determined by the karyotype and immunophenotype of the leukemia.

Variations

1. Rituximab 375 mg/m² IV has been given on day 1 of each cycle of Hyper-CVAD.¹¹⁻¹³
2. Imatinib mesylate 400 mg orally has been given on days 1-14 of each cycle of Hyper-CVAD.¹⁴

CIVI = continuous (24 h) IV infusion; IV = intravenous; IT = intrathecal

2. Use vincristine sulfate solution 1 mg/mL.
3. Withdraw the volume required; dispense in a syringe.
4. The syringe must have the following warning attached to it: "Fatal if given intrathecally. For IV use only."
5. Additionally, the syringe must be enclosed in an overwrap bearing the following warning: "Do not remove covering until moment of injection. Fatal if given intrathecally. For IV use only."
6. Vincristine can be diluted in 25 or 50 mL of 0.9% sodium chloride injection in polyvinyl chloride bags; or in 20 mL of 0.9% sodium chloride injection in 30 mL polypropylene syringes.¹⁶
7. Dispensing diluted vincristine in minibags, rather than undiluted in syringes, has been recommended to prevent inadvertent intrathecal injection.¹⁶

E. Methotrexate

1. Follow institutional policies for preparation of hazardous medications when preparing methotrexate.
2. Methotrexate is available as 2.5, 5, 7.5, 10, and 15 mg tablets, 20 mg (preservative-free) and 1 g powder for injection, and 25 mg/mL injection (preservative-free or containing benzyl alcohol as preservative).
3. For intrathecal doses:
 - a. Reconstitute preservative-free methotrexate powder to a concentration less than or equal to 2.5 mg/mL with

preservative-free sterile water for injection, 0.9% sodium chloride or Ringer's lactate injection.

- b. Or, dilute preservative-free methotrexate injection to a concentration less than or equal to 2.5 mg/mL.
4. For IV infusion:
 - a. Use methotrexate injection 25 mg/mL; or powder for injection.
 - b. If the powder for injection is used, it should be reconstituted to a concentration of 25 to 100 mg/mL with sterile water for injection, 0.9% sodium chloride, or 5% dextrose in water. (Preserved diluents may be used.)
 - c. Dispense in 50 to 100 mL of 0.9% sodium chloride or 5% dextrose solution for 2-hour infusion; dispense in 500 to 1,000 mL 0.9% sodium chloride or 5% dextrose solution for 24-hour infusion.

F. Cytarabine

1. Follow institutional policies for preparation of hazardous medications when preparing cytarabine.
2. Cytarabine is available as 100 mg, 500 mg, 1 g, and 2 g powder for injection and 20 and 100 mg/mL injection.
3. For IV infusion:
 - a. Reconstitute cytarabine to a concentration of 50 mg/mL to 100 mg/mL with sterile water for injection, 0.9% sodium chloride or 5% dextrose in water.

b. Dilute with 250 to 1,000 mL of 0.9% sodium chloride, 5% dextrose solution or a saline/dextrose solution.

4. For intrathecal doses:
 - a. Reconstitute cytarabine powder to a concentration less than or equal to 20 mg/mL with preservative-free sterile water for injection, 0.9% sodium chloride, or Ringer's lactated injection.
 - b. Or, dilute preservative-free cytarabine injection to a concentration less than or equal to 20 mg/mL.

G. Mesna

1. Use 100 mg/mL injection.
2. Dispense in 250 to 1,000 mL of 0.9% sodium chloride, 5% dextrose in water or a saline/dextrose solution for infusion.

H. Methylprednisolone

1. Use 40, 125, or 500 mg, or 1 or 2 g methylprednisolone sodium succinate sterile powder.
2. Reconstitute to a concentration of 40 to 125 mg/mL with the provided diluent or bacteriostatic water for injection.
3. Dilute with 50 or 100 mL 0.9% sodium chloride or 5% dextrose injection.

I. Mercaptopurine

1. Follow institutional policies for preparation of hazardous medications when preparing mercaptopurine.
2. Mercaptopurine is available in 50 mg tablets.

J. Leucovorin

1. Leucovorin is available as 5, 10, 15, or 25 mg tablets, 50, 100, 200, 350, and 500 mg powder for injection,

and 10 mg/mL injection.

2. For IV infusion:
 - a. Reconstitute with bacteriostatic water for injection, bacteriostatic 0.9% sodium chloride injection, sterile water for injection, or 5% dextrose in water to a concentration of 5, 10, or 20 mg/mL.
 - b. Dispense in a syringe, or dilute in 50 or 100 mL of 0.9% sodium chloride injection or 5% dextrose injection.

K. Prednisone

Prednisone is available as 1, 2.5, 5, 10, 20, and 50 mg tablets.

DRUG ADMINISTRATION

A. Cyclophosphamide: is given as a 3-hour IV infusion.

B. Doxorubicin: is given as a slow IV push (1 to 10 min), or as a short (10 to 30 min) infusion. Other administration methods in the studies reviewed were 2, 24, 48, and 72-hour IV infusions.^{1-3,6}

C. Dexamethasone:

1. Oral: Dexamethasone is given once daily. Administration with or immediately after a meal, or with milk or a small snack, is recommended to minimize gastric irritation.
2. IV infusion: Infuse over 5 to 15 minutes.

D. Vincristine: is given as a slow (1 to 2 min) IV push, or as a short (5 to 15 min) IV infusion.

E. Methotrexate:

1. Loading dose – given as a 2-hour IV infusion. Some studies omitted the loading dose and gave the full 1,000 mg/m² methotrexate dose as a 24-hour infu-

sion.^{1,3}

2. Infusion – infuse over 22 to 24 hours.

F. Cytarabine: is given as a 2-hour infusion (3 g/m² dose) and by intrathecal injection.

G. Mesna: is given by continuous infusion starting with the first cyclophosphamide dose and ending 6 hours after the last cyclophosphamide dose.

H. Methylprednisolone: is given by infusion over approximately 15 to 30 minutes.

I. Mercaptopurine: usually given orally as a single daily dose on an empty stomach (1 h before or 2 h after a meal).

J. Leucovorin:

1. Oral: Leucovorin is given orally every 6 hours.
2. IV: Leucovorin is given as a slow (2 to 4 min) IV push or as a 5 to 15 min IV infusion.

K. Prednisone:

1. Prednisone is given orally, usually once daily.
2. Administration with or immediately after a meal, or with milk or a small snack, is recommended to minimize gastric irritation.

SUPPORTIVE CARE

A. Acute Emesis Prophylaxis: The Hyper-CVAD regimen is predicted to cause emesis in 60% to 90% of patients on days 1 through 4 of cycles 1, 3, 5, and 7, and on days 1 through 3 of cycles 2, 4, 6, and 8.¹⁷ However, one study reported nausea/vomiting in 15% (grade 1 or 2) and 3% (grade 3 or 4)⁴ of patients, respectively. Another study reported nausea in 34% (grade 1 or 2) and 3% (grade 3 or 4) of patients, respectively, and vomiting in 13% (grade 1 or 2) and 1% (grade 3 or 4) of patients, respectively.⁶ Approp-

riate acute emesis prophylaxis includes a serotonin receptor antagonist and a corticosteroid.^{18,19} Since cycles 1 through 8 include high doses of corticosteroids, no additional corticosteroids are required in the acute emesis prophylaxis regimen. One of the following regimens is suggested:

1. Ondansetron 8 mg orally, given 30 minutes before each cyclophosphamide, doxorubicin, methotrexate, or cytarabine infusion.
2. Granisetron 1 mg orally, given 30 minutes before each cyclophosphamide, doxorubicin, methotrexate, or cytarabine infusion.
3. Dolasetron 100 mg orally, given 30 minutes before each cyclophosphamide, doxorubicin, methotrexate, or cytarabine infusion.
4. Palonosetron 0.25 mg IV, given 30 minutes before chemotherapy on day 1 only of each cycle.

Acute emesis prophylaxis is usually not needed for the vincristine doses in cycles 1, 3, 5, and 7, or for any of the maintenance phase medications.

B. Delayed Nausea and Vomiting: Delayed nausea and vomiting usually does not occur with the Hyper-CVAD regimen. No special precautions are necessary.

C. Breakthrough Nausea and Vomiting: Patients should receive an antiemetic to treat breakthrough nausea and vomiting. One of the following regimens is suggested:

1. Metoclopramide 20 to 40 mg orally every 4 to 6 hours as needed, ± diphenhydramine 25 to 50 mg orally every 4 to 6 hours.
2. Prochlorperazine 10 mg

- orally every 4 to 6 hours as needed, or
3. Prochlorperazine 25 mg rectally every 6 hours as needed.
 4. Promethazine 25 to 50 mg orally every 6 hours as needed.

D. Hemorrhagic Cystitis Prophylaxis: Patients receiving cyclophosphamide must be adequately hydrated to reduce the risk of hemorrhagic cystitis secondary to acrolein, the urotoxic metabolite of cyclophosphamide. Patients should be encouraged to void their bladder frequently. This can be accomplished by encouraging liberal fluid consumption (3 to 4 L/day) during each day of treatment with cyclophosphamide, and for at least 24 hours after the last cyclophosphamide dose. No hemorrhagic cystitis was reported in the studies reviewed; however, Stillwell reports it may occur following a single IV dose.²⁰ The risk of hemorrhagic cystitis increases with higher total doses of cyclophosphamide, and may be further amplified by radiation therapy. In Hyper-CVAD studies^{1,6-8} and in clinical practice, hemorrhagic cystitis prophylaxis is enhanced by concurrent administration of mesna, which binds to and inactivates acrolein.

E. Hypersensitivity Precautions:^{21,22} Doxorubicin can induce acute hypersensitivity reactions. However, such reactions are very rare and require no specific precautions. Doxorubicin may also cause a "flare reaction," manifested by erythema, pruritis, and urticaria surrounding the injection site, or extending along the vein being infused. Although sometimes confused with an extravasation or allergic reaction, generally it is self-limiting and resolves at the end of the infusion. Additional doses of the drug can be administered without concern.²¹

F. Hematopoietic Growth Factors: Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen has a greater than 18% to 40% (depending on institutional cost differences) incidence of febrile neutropenia before prophylactic use of colony stimulating factors is warranted.²³⁻²⁵

Since severe (grade 3 or 4) neutropenia was reported in up to 100% of patients in the trials reviewed; and febrile neutropenia was reported in 8% to 37% of patients, prophy-

lactic use of colony stimulating factors is recommended with the Hyper-CVAD regimen. The largest trial evaluating Hyper-CVAD use employed G-CSF, 10 mcg/kg daily given in two divided doses beginning 24 hours after the end of chemotherapy.^{1,7,8}

A comparison of delaying filgrastim to begin on day 10 of Hyper-CVAD vs day 5 showed no adverse outcomes.⁹

G. Extravasation: Doxorubicin is a potent vesicant, and extravasation should be avoided. If extravasation occurs, stop the infusion immediately, and aspirate as much of the extravasated solution as possible before withdrawing the needle. The limb should be elevated and cooled intermittently (ice packs for 15 to 20 min four times a day for 3 days).²⁶⁻²⁸

Vincristine is a moderate vesicant, and extravasation should be avoided. If extravasation occurs, stop the infusion immediately, and aspirate as much of the extravasated solution as possible before withdrawing the needle. The limb should be elevated and cooled intermittently (ice packs for 15 to 20 min four times a day for 3 days).

Although Larson reported applying ice to all extravasations, most other groups suggest dry heat for 30 minutes four times a day for 3 days. Hyaluronidase 150 units/1 mL injected intradermally at the extravasation site has also been recommended for treatment of vinca alkaloid extravasations.²⁶

H. Nephrotoxicity Prophylaxis:³ The methotrexate dose used in Hyper-CVAD may cause renal

damage. This can result in delayed clearance of methotrexate with accompanying toxicities such as mucositis and bone marrow suppression. In the studies reviewed, prophylaxis of methotrexate-induced renal damage was accomplished as follows:

1. Creatinine clearance at least 60 mL/min.
2. Serum creatinine less than or equal to 1.5 mg/dL.
3. Hydration to maintain a urine output greater than 100 mL/h.
4. Urine alkalinization to a pH greater than 7.

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 Toxicity Criteria (<http://ctep.info.nih.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities; but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities.

A. Cardiovascular: Arrhythmias 8%;³ cardiac complications, unspecified (grade 3 or 4) 1% to 2%;^{1,4,5,7,8} pericarditis (grade 3 or 4) 3%.⁶

B. Dermatologic: Alopecia 32%;⁴ desquamation of palms and feet 2% to 3% (during methotrexate/cytarabine courses);^{1,4,7,8} perirectal abscess 2%;^{2,5} rash 4% to 8%.^{1,4,7,8}

C. Endocrine/Metabolic: Diabetes insipidus 4%;³ fatigue (grade 1 or 2) 10%, (grade 3

or 4) 3%.⁴

D. Gastrointestinal: Diarrhea (grade 3 or 4) 3%;^{1,5,7,8} ileus 1%;^{1,5,7,8} mucositis 1% to 36%;^{1-5,7,8} nausea/vomiting (grade 1 or 2) 15% to 34%, (grade 3 or 4) 3%;^{4,6} stomatitis (grade 1 or 2) 9%, (grade 3 or 4) 33%.⁶

E. Hematologic: Disseminated intravascular coagulopathy 3%;¹ hemorrhage related to thrombocytopenia 8%;³ myelosuppression (grade 3 or 4) 100%.^{1,2,5,7,8}

F. Hepatic: Hepatic failure 2%;¹ increased serum bilirubin 9%;⁶ increased transaminases 18%.⁶

G. Infection: Bacterial meningitis 4%;³ fever of unknown origin 23 to 45%;^{2,7,8,10} HSV infection 8%;³ other infections 14% to 28%;^{1,2,7,8} pneumonia 5% to 30%;^{2,7,8,10} sepsis 5% to 24%.^{7,8,10}

H. Neurologic: Cytarabine-related cerebellar toxicity 4% to 31%;^{3-5,9,11-15} neurologic toxicity, unspecified 4% to 5%;¹ peripheral neuropathy 15% to 17%;^{3,6} psychiatric changes 4%;³ vocal cord paresis 1%.²

I. Other: Colony stimulating factor-related bone pain 5%;^{1,7,8} tumor lysis syndrome 15%.³

J. Pancreatic: Pancreatitis 3%.⁶

K. Pulmonary: Dyspnea (grade 3 or 4) 1%.⁴

L. Renal: Renal failure 2%;¹ renal toxicity, unspecified 20%.³

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. AST/ALT
2. Total bilirubin
3. Serum creatinine
4. CBC with differential

B. Prior to each treatment cycle

1. AST/ALT
2. Total bilirubin

3. Serum creatinine
4. CBC with differential

C. Recommended pretreatment values: In the treatment of acute leukemia, it is normal for white and red blood cells, hemoglobin, neutrophil, and platelet counts to be markedly low when treatment is due. The usual practice is to adhere to the treatment schedule, and support the patient with red blood cell and platelet transfusions, and appropriate colony stimulating factors.

DOSAGE MODIFICATIONS

A. Renal Function^{1,7}

1. Methotrexate doses were reduced by 25% when serum creatinine levels were 1.5 to 2 mg/dL and by 50% when serum creatinine was greater than 2 mg/dL.
2. Cytarabine dose was reduced to 1 g/m² in patients greater than 60 years old, if the serum creatinine was greater than 2 mg/dL or if the methotrexate level at the end of the methotrexate infusion was greater than or equal to 20 micromole/L after repeat assays.

B. Liver Function

1. Vincristine was reduced to 1 mg if the total bilirubin level was greater than 2 mg/dL.¹
2. Doxorubicin was reduced by 25% if the bilirubin level was 2 to 3 mg/dL, by 50% if it was 3 to 4 mg/dL, and by 75% if it was greater than 4 mg/dL.¹

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