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Cancer Chemotherapy Update

Dinutuximab and Panobinostat

Ashley Chasick, PharmD[*]*; Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP; and J. Aubrey Waddell, PharmD, FAPhA, BCOP*

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.

Name: Dinutuximab

Synonyms: Unituxin, Ch14.18, MOAB Ch14.18

MECHANISM OF ACTION

Dinutuximab is a GD2-binding human/mouse chimeric monoclonal antibody.[1,2] GD2 is a glycolipid expressed on neuroblastoma cells and on normal neurons, peripheral nerve fibers, and melanocytes.[3,4] Dinutuximab binds to cell surface GD2 and induces cell lysis of cells expressing GD2 through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[1,5,6] Additionally, dinutuximab may prevent attachment of circulating malignant cells to the extracellular matrix.[1,7] To generate a stronger cytotoxic effect, granulocyte-macrophage colony-stimulating factor and interleukin-2 are often given with dinutuximab to stimulate native antitumor immune effects.[5,8]

PHARMACOKINETICS

Following a dose of 17.5 mg/m^2/day for 4 days, the maximum plasma concentration (C_{max}) is 11.5 mcg/mL.[1] The mean volume of distribution at steady state (V_{dss}) is 5.4 L.[1] The clearance is 0.21 L/day; clearance increases with body size.[1] Mean $AUC_{0-\infty}$ is 1,380 µg•h/mL.[9] Terminal half life ($T_{1/2}$) is 7 to 10 days[1,9]

Selected therapeutic regimens of dinutuximab are shown in **Table 1**.

PREPARATION

A. Follow institutional policies for preparing of hazardous medications when preparing dinutuximab.
B. Withdraw the required volume of dinutuximab from the vial and dilute with 100 mL 0.9% sodium chloride injection (NS).
C. Mix by gentle inversion. Do not shake vigorously.

STABILITY

A. Store vials in refrigerator at 2°C to 8°C (36°F to 46°F).
B. Dinutuximab solutions diluted for administration should be kept under refrigeration [2°C to 8°C (36°F to 46°F)].
C. Initiate infusion within 4 hours of preparation.
D. Discard diluted solution 24 hours after preparation.

ADMINISTRATION

A. Dinutuximab is given as an intravenous (IV) infusion over several hours; do not administer as an IV push or bolus.

[*]Dr. Chasick is a Clinical Pharmacy Specialist for Oncology and Bone Marrow Transplant at Ochsner Medical Center in New Orleans, Louisiana.

Table 1. Selected therapeutic regimens of dinutuximab

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/ cycle	References
2-10 mg/m^2	IV	1, 2, 3, 4, 5	28-35 days	10-50 mg/m^2	13
10-200 mg/m^2	IV	Dose given over 1 to 4 days	2-3 weeks	10-200 mg/m^2	15
12 mg/m^2	IV	1, 2, 3	28 days	36 mg/m^2	11
17.5 mg/m^2 Cycles 1, 3, 5	IV	4, 5, 6, 7	24 days	70 mg/m^2	1
17.5 mg/m^2 Cycles 2, 4	IV	1, 3, 5	32 days	52.5 mg/m^2	1
20-40 mg/m^2	IV	1,2, 3, 4	28 days	80-160 mg/m^2	12
25 mg/m^2	IV	1, 2, 3, 4	28 days	100 mg/m^2	10
30-50 mg/m^2	IV	1, 2, 3, 4, 5	8-12 weeks	150-250 mg/m^2	14

Note: IV = intravenous.
[a]Conforms to dosing information listed in the manufacturer's labeling.

B. Initiate at an infusion rate of 0.875 mg/m^2/h for 30 minutes. The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m^2/h.
C. Hydration with NS and premedication with an antihistamine, antipyretic, and opioid analgesic is recommended.
D. For mild to moderate adverse reactions, the infusion rate should be reduced by 50%, and the patient monitored closely. If symptoms resolve, the infusion rate can be gradually increased to a maximum rate of 1.75 mg/m^2/h.
E. For prolonged or severe adverse reactions, the infusion should be stopped. If symptoms resolve, the infusion may be resumed at 50% of the previous rate and the patient monitored closely.
F. If a prolonged or severe adverse reaction recurs, the dinutuximab infusion should be discontinued until the following day.
G. If symptoms resolve and continued treatment is warranted, hydrocortisone 1 mg/kg (maximum dose 50 mg) IV should be added to the premedication regimen, and the drug should be administered at 0.875 mg/m^2/h in an intensive care unit.
H. If a prolonged or severe adverse reaction continues or recurs, permanently discontinue dinutuximab.

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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). 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%.

(All toxicities reported below are grade 3 or 4.)

A. Cardiovascular: Hypotension (3% to 18%)[10,11]; low diastolic blood pressure (3% to 15%)[12]; low systolic blood pressure (16%).[12]

B. Central Nervous System: CNS cortical symptoms (3% to 10%),[10,12] seizure (1%).[12]

C. Constitutional: Acute capillary leak syndrome (1% to 23%),[10-12] decreased performance status (5%),[12] fever without infection (13% to 20%),[12] fever without neutropenia (39%).[10]

D. Dermatologic: Urticaria (13%).[10]

E. Endocrine/Metabolic: Hypercalcemia (5%),[10] hypokalelmia (3% to 35%),[10,12] hyponatremia (23%).[10]

F. **Gastrointestinal:** Diarrhea (2% to 13),[10,12] nausea (3% to 21%),[10,12] vomiting (6%).[10]
G. **Hematologic:** Anemia (13% to 25),[12] leukopenia (2% to 25%),[12] lymphopenia (5% to 25%),[12] neutropenia (14% to 30%),[12] prolonged partial thromboplastin time (PTT) (5% to 6%),[12] thrombocytopenia (19% to 35%).[12]
H. **Hepatic:** Elevated alanine transaminase (ALT) (2% to 23%),[10,12] elevated aspartate aminotransferase (AST) (2% to 10),[10,12] elevated alkaline phosphatase (5%),[12] elevated bilirubin (10%).[12]
I. **Hypersensitivity:** Hypersensitivity reaction (2% to 25%).[10,11]
J. **Infection:** Catheter-related infection (13%),[10] infection (3% to 39%).[10,12]
K. **Pain:** Neuropathic (13% to 87%).[10-12]
L. **Pulmonary:** Hypoxia (5% to 13).[10,12]

DOSAGE MODIFICATIONS

A. **Hepatic:** No information available.[1]
B. **Renal:** No information available.[1]

Name: Panobinostat

Synonyms: Farydak, LBH589

MECHANISM OF ACTION

Panobinostat is a pan-deacetylase inhibitor with activity against histone deacetylase (HDAC) I, II, and IV enzymes.[16] Panobinostat inhibits enzymatic activity of HDACs resulting in increased acetylation of histone proteins.[17] Accumulation of acetylated histones results in relaxing of chromatin, leading to transcriptional activation and cell cycle arrest and/or apoptosis.[17]

PHARMACOKINETICS

Oral panobinostat is 21.4% bioavailable.[17,18] The time to maximum concentration (T_{max}) is within 2 hours of oral administration.[17] Following ingestion after a high-fat meal, the C_{max} and area under the time versus concentration curve (AUC) were 44% and 16% lower, respectively, compared to fasting.[17] Panobinostat is highly (90%) bound to plasma protein and is a P-glycoprotein substrate.[17]

Panobinostat is extensively metabolized via reduction, hydrolysis, oxidation, and glucuronidation.[16,17]

Following a single oral dose of [^{14}C] panobinostat, 29% to 51% of administered radioactivity is excreted in the urine and 44% to 77% in the feces.[19] Median clearance of panobinostat is L/h; interindividual variability in clearance is 65% to 74%.[14,15] Terminal $T_{1/2}$ is 30 to 37 hours.[16,19] AUC decreases from 104 to 88 µg•h/mL as BSA increases from 1.8 to 2.1 m^2.[18] AUC decreases from 102 to 95 µg•h/mL as age increases from 51 to 70 years.[15]

In patients with mild, moderate, and severe renal failure, panobinostat $AUC_{0\text{-inf}}$ is 64%, 99%, and 59% of the non-impaired group.[20] $AUC_{0\text{-inf}}$ is increased 43% and 105% in patients with mild and moderate hepatic failure compared with normal patients.[17]

Selected therapeutic regimens of panobinostat are shown in **Table 2**.

PREPARATION

A. Follow institutional policies for preparation of hazardous medications when dispensing panobinostat.
B. Panobinostat is available as 10 mg, 15 mg, and 20 mg capsules.
C. The manufacturer recommends the capsules not be opened, crushed, or chewed.[17]

STABILITY

A. Panobinostat should be stored at 20°C to 25°C (68°F-77°F).
B. Brief (less than 24 hours) exposure to temperatures up to 30°C (86°F) is acceptable.

ADMINISTRATION

A. Panobinostat should be taken by mouth once a day.
B. Panobinostat can be taken with or without food.
C. If a dose is missed, it can be taken up to 12 hours after the scheduled dose time.

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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for

Table 2. Selected therapeutic regimens of panobinostat

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/ cycle	References
10-20 mg	PO	Three times/week for 3 to 6 doses	28 days	30-120 mg	26
10-30 mg	PO	1, 3, 5, 8, 10, 12, 15, 17, 19	21 days	90-270 mg	31
10-30 mg	PO	Three times/week	28 days	120-360 mg	32
10-30 mg	PO	Three times/week for 6 doses	21 days	60-180 mg	34
10-40 mg	PO	Three times/week for 7 doses	28 days	70-280 mg	33
20 mg[a]	PO	1, 3, 5, 8, 10, 12	21 days	120 mg	17, 21, 22, 30
20-30 mg	PO	1, 3, 5, 15, 17, 19	28 days	120-180 mg	25
20-30 mg	PO	Three times/week for 3 weeks	29 days	180-270 mg	27
20-40 mg	PO	Three times/week	28 days	240-480 mg	24
20-40 mg	PO	Three times/week for 2 weeks	21 days	120-240 mg	28
30 mg	PO	Three times/week	28 days	360 mg	20
30 mg	PO	1, 3, 5, 15, 17, 19	28 days	180 mg	29

Note: PO = oral.
[a]Conforms to dosing information listed in the manufacturer's labeling.

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:** Hypotension (all grades) 14% to 20%,[21,22] (grade 3) 2% to 5%,[21,22] (grade 4) 1% to 4%.[21,22]
B. **Central Nervous System:** Dizziness (all grades) 6% to 19%,[21,23] (grade 3) 3%,[21] (grade 3 or 4) 32%[23]; headache (all grades) 14%,[21] (grade 3) 3%,[21] (grade 4) 1%[21]; insomnia (all grades) 19%,[21] (grade 3) 5%[21]; pain in extremity (all grades) 10%,[21] (grade 3) 1%[21]; syncope (all grades) 9%,[22] (grade 3) 9%.[22]
C. **Constitutional:** Asthenia (all grades) 20% to 57%,[21-23] (grade 3) 9% to 23%,[21,22] (grade 4) 1%,[21] (grade 3 or 4) 26 %[23]; fatigue (all grades) 53%,[23] (grade 3 or 4) 11%[23]; fever (all grades) 26%,[21] (grade 3) 6%,[21] (grade 4) 1%,[21] (grade 3 or 4)[23]; peripheral edema (all grades) 29%,[21] (grade 3 or 4) 2%[21]; weight decreased (all grades) 12%,[21] (grade 3) 2%.[21]
D. **Endocrine/Metabolic:** Dehydration (all grades) 16%,[22] (grade 3) 4%,[22] (grade 4) 2%[22]; hypokalemia (all grades) 22% to 29%,[21,22] (grade 3) 4%,[22] (grade 4) 4%,[22] (grades 3 or 4) 11%[23]; hypophosphatemia (all grades) 5%.[22]
E. **Gastrointestinal:** Abdominal distention (all grades) 11%,[21] (grade 3) 7%[21]; anorexia (all grades) 28% to 45%,[21-23] (grade 3) 3%,[21] (grade 3 or 4) 2%[23]; constipation (all grades) 27% to 29%[21,23]; diarrhea (all grades) 68% to 73%,[21-23] (grade 3) 18% to 24%,[21-23] (grade 4) 1% to 2%[21-23]; dyspepsia (all grades) 12%,[21] (grade 3) 1%[21]; flatulence (all grades) 11%,[22] (grade 3) 5%[22]; nausea (all grades) 36% to 61%,[21-23] (grade 3) 5% to 11%[21,22]; vomiting (all grades),[21,22] (grade 3) 7%,[21] (grade 3 or 4) 5%.[23]
F. **Hematologic:** Anemia (all grades) 18% to 62%,[21-23] (grade 3) 9% to 15%,[21,22] (grade 3 or 4) 18%[23]; lymphopenia (all grades) 83%,[21] (grade 3) 42%,[21] (grade 4) 12%[21]; thrombocytopenia (all grades) 65% to 98%,[21-23] (grade 3) 13% to 33%,[21,22] (grade 4) 35% to 51%,[21,22] (grade 3 or 4) 81%.[23]

G. **Infection:** Herpes zoster (all grades) 5%,[21] (grade 3) 1%,[21] (grade 4) 1%[21]; nasopharyngitis (all grades) 13%[21]; neutropenia (all grades) 74% to 75%,[21,23] (grade 3) 28%,[21] (grade 4) 7%,[21] (grade 3 or 4) 60%[23]; pneumonia (all grades) 16% to 17%,[21,22] (grade 3) 10% to 11%,[21,22] (grade 4) 3% to 4%[21,22]; sepsis (all grades) 9%,[22] (grade 3) 4%,[22] (grade 4) 5%[22]; septic shock (all grades) 5%,[22] (grade 4) 5%[22]; upper respiratory infection (all grades) 18%,[21] (grade 3) 2%.[21]

H. **Neurologic:** Peripheral neuropathy (all grades) 61%,[21] (grade 3) 17%.[21]

I. **Pulmonary:** Cough (all grades) 21%,[21] (grade 3) 5%,[21] (grade 4) 1%[21]; dyspnea (all grades) 15%,[21] (grade 3) 2%,[21] (grade 4) 1%.[21]

J. **Pain**: Abdominal pain (all grades) 13% to 16%,[21,22] (grade 3) 2% to 5%[21,22]; back pain (all grades) 13%,[21] (grade 3) 1%[21]; upper abdominal pain (all grades) 12%,[21] (grade 3) 1%.[21]

DOSAGE MODIFICATIONS

A. Hepatic[17]:
   1. Mild impairment: Reduce starting dose to 15 mg.
   2. Moderate impairment: Reduce starting dose to 10 mg.
   3. Severe impairment: Avoid use.

B. **Renal:** No information available[17].

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