Cancer Chemotherapy Update

Ado-Trastuzumab Emtansine and Radium 223 Dichloride

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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, email: 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: Ado-trastuzumab emtansine

Synonyms: Trastuzumab emtansine, Trastuzumab-DM1, T-DM1, *Kadcyla*

COMMENT

Medication errors resulting from confusion between trastuzumab (*Herceptin*) and ado-trastuzumab emtansine (*Kadcyla*) have been reported. Some references, information systems, and Internet sites omit the “ado” portion of the generic name, resulting in confusion between the 2 drugs.^{1,2} Prescribers, pharmacists, and nurses should take precautions to ensure the proper drug is prescribed and dispensed.

MECHANISM OF ACTION

Ado-trastuzumab emtansine is a conjugate of trastuzumab with a cytotoxic (DM1) moiety. The conjugate combines the antibody-dependent cellular cytotoxicity of trastuzumab with the cytotoxic effect of DM1. DM1 functions as an antimitotic agent similar to the *vinca* alkaloids.³⁻⁵

PHARMACOKINETICS

At the recommended dose of 3.6 mg/kg every 3 weeks, the maximum serum concentration (C_{max}) is 74.3 ± 20.1 mcg/kg, the area under the time versus concentration curve (AUC) is 295.2 ± 65.4 mcg·d/mL, the terminal half-life ($T_{1/2}$) is 3.5 ± 0.8 days, and the volume of distribution (V_d) is 60 ± 13.6 mL/kg.⁵ At 2.4 mg/kg weekly, C_{max} is 54.8 ± 12.6

mcg/kg, AUC is 198.5 ± 54.5 mcg·d/mL, $T_{1/2}$ is 3.4 ± 1.1 days, and the V_d is 55.4 ± 13 mL/kg.⁶ The manufacturer reports C_{max} of the ado-trastuzumab conjugate and the DM1 component as 83.4 ± 16.5 mcg/mL and 4.61 ± 1.61 mcg/mL, respectively. The DM1 component is 93% bound to plasma proteins. The drug is metabolized in the liver by CYP3A4/5 to MCC-DM1, Lys-MCC-DM1, and DM1. The elimination $T_{1/2}$ is 4 days.⁷

Selected therapeutic regimens of ado-trastuzumab emtansine appear in **Table 1**.

PREPARATION

1. Follow institutional policies for preparation of hazardous medications when preparing ado-trastuzumab emtansine.
2. Use ado-trastuzumab emtansine powder for injection.
3. Reconstitute with sterile water for injection to a concentration of 20 mg/mL.
4. Dilute with 250 mL of 0.9% sodium chloride injection.
5. The product labeling states dextrose solutions should not be used to dilute ado-trastuzumab, but it does not explain the basis for this restriction.⁷

STABILITY

1. Reconstituted vials may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F).
2. Solutions diluted in 0.9% sodium chloride may be stored at 2°C to 8°C (36°F to 46°F) for up to an additional 24 hours.

Table 1. Selected therapeutic regimens of ado-trastuzumab emtansine

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
3.6 mg/kg ^a	IV	1	3 weeks	3.6 mg/kg	5,7-11
2.4 mg/kg	IV	1,8,15	3 weeks	7.2 mg/kg	6

Note: IV = intravenous.

^aConforms to dosing information listed in the manufacturer's labeling.

ADMINISTRATION

- Ado-trastuzumab emtansine is administered as an intravenous (IV) infusion.
 - Initial infusion: 90 minutes
 - Subsequent infusions: 30 minutes
- Ado-trastuzumab emtansine should be infused through a 0.22 micron polyethersulfone (PES) filter.

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%.

- Cardiovascular:** Edema (peripheral) (all grades) 4% to 10%^{5,11}; hypertension (all grades) 4%⁵; hypotension (all grades) 4%⁵.
- Central Nervous System:** Depression (all grades) 10%,⁹ (grade 1) 5%,⁹ (grade 2) 3%,⁹ (grade 3) 3%⁹; dizziness (all grades) 4%⁵; headache (all grades) 8% to 41%,^{5,6,8,9,11} (grade 1) 18%,⁹ (grade 1 or 2) 40%,⁸ (grade 2) 4%⁹.
- Constitutional:** Abdominal pain (all grades) 8% to 9%,^{5,9} (grade 1) 6%,⁹ (grade 2) 2%,⁹ (grade 3) 1%,⁹ (grade 4) 1%⁹; arthralgia (all grades) 8% to 23%,^{5,6,8,9,11} (grade 1) 10%,⁹ (grade 1 or 2) 21%,⁸ (grade 2) 3%,⁹ (grade 3) 1% to 2%^{8,9}; back pain (all grades) 18% to %, ^{9,11} (grade 1) 12%,⁹ (grade 2) 4%,⁹ (grade 3) 3%,⁹ ($\geq$ grade 3) 1%¹¹; chills (all grades) 4% to 11%^{5,6}; fatigue (all grades) 35% to 65%^{5,6,8-11} (grade 1) 30%,⁹ (grade 1 or 2) 61%,⁸ (grade 2) 27%,⁹ (grade 3) 5% to 7%,^{6,8,9} ($\geq$ grade 3) 2% to 4%^{10,11}; infusion reactions (all grades) 4% to 1%,^{5,9} (grade 1) 8%,⁹ (grade 2) 6%⁹;

muscle spasms (all grades) 8% to 11%,^{5,9} (grade 1) 8%,⁹ (grade 2) 3%⁹; myalgia (all grades) 8% to 14%^{5,9}; (grade 1) 13%,⁹ (grade 2) 1%,⁹ pain in extremity (all grades) 14% to 22%,^{8,9} (grade 1) 10%,⁹ (grade 1 or 2) 22%,⁸ (grade 2) 2%,⁹ (grade 3) 2%⁹; pyrexia (all grades) 8% to 41%^{5,6,8,9,11}; (grade 1) 14%,⁹ (grade 1 or 2) 34%,⁸ (grade 2) 8%,⁹ (grade 3) 1%^{8,9}; tumor pain (all grades) 4%⁵; weight loss (all grades) 11%,⁹ (grade 1) 7%,⁹ (grade 2) 3%,⁹ (grade 3) 1%⁹.

- Dermatologic:** Alopecia (all grades) 4%¹¹; onychoclasis (all grades) 4%⁵.
- Electrolyte/endocrine abnormalities:** Hyperglycemia (all grades) 7%,⁹ (grade 1) 5%,⁹ (grade 3) 3%⁹; hypocalcemia (all grades) 4%⁵; hypokalemia (all grades) 4% to 24%,^{5,8-10} (grade 1) 19%,⁹ (grade 1 or 2) 15%,⁸ (grade 2) 1%,⁹ (grade 3) 1% to 9%,^{8,9} ($\geq$ grade 3) 2%¹⁰; hypomagnesemia (all grades) 4%⁵.
- Gastrointestinal:** Anorexia (all grades) 13% to 21%^{5,6,9}; (grade 1) 13%,⁹ (grade 2) 7%,⁹ (grade 3) 1%⁹; constipation (all grades) 8% to 30%^{5,6,8,9}; (grade 1) 20%,⁹ (grade 1 or 2) 30%,⁸ (grade 2) 3%,⁹ (grade 3) 1%⁹; diarrhea (all grades) 13% to 26%,^{6,8-11} (grade 1) 9%,⁹ (grade 1 or 2) 26%,⁸ (grade 2) 9%,⁹ ($\geq$ grade 3) 2%¹⁰; dry mouth (all grades) 4% to 32%^{5,6,9}; (grade 1) 17%,⁹ (grade 2) 3%⁹; dysgeusia (all grades) 4% to 11%^{5,6}; dysphonia (all grades) 4%⁵; mucosal inflammation (all grades) 4% to 7%^{5,10}; ($\geq$ grade 3) 0.2%¹⁰; nausea (all grades) 25% to 51%^{5,6,8-11}; (grade 1) 26%,⁹ (grades 1 or 2) 50%,⁸ (grade 2) 10%,⁹ (grade 3) 1%^{8,9}; ($\geq$ grade 3) 1% to 3%^{10,11}; vomiting (all grades) 13% to 25%,^{5,6,8-11} (grade 1) 11%,⁹ (grade 1 or 2) 23%,⁸ (grade 2) 6%,⁹ (grade 3) 1%⁸; ($\geq$ grade 3) 1% to 3%^{10,11}.
- Hematologic:** Anemia (all grades) 10% to 29%,^{5,6,8-11} (grade 1) 7%,⁹ (grade 1 or 2) 18%,⁸ (grade 2) 11%,⁹ (grade 3) 2% to 7%,^{6,8,9} ($\geq$ grade 3) 3%^{10,11}; epistaxis (all grades) 13% to 36%^{5,6,8,9,11}; (grade 1) 19%,⁹ (grade 1 or 2) 34%,⁸ (grade 2) 3%,⁹ (grade 3) 1% to 2%^{8,9}; leukopenia (all grades) 8% to 24%,^{5,6,11} ($\geq$ grade 3) 2% to

6%¹¹; neutropenia (all grades) 4% to 16%^{5,10,11}; ($\geq$ grade 3) 2% to 6%^{10,11}; thrombocytopenia (all grades) 28% to 54%,^{5,6,9-11} (grade 1) 13%,⁹ (grade 2) 16%,⁹ (grade 3) 7% to 4%,^{5,6,9} ($\geq$ grade 3) 7% to 13%,^{10,11} (grade 4) 2% to 8%.^{5,6,9}

H. Hepatic: Abnormal liver function tests (all grades) 3% to 18%,^{6,9} (grade 2) 1%,⁹ (grade 3) 2%⁹; increased alanine aminotransferase (ALT) (all grades) 11% to 26%,^{6,9-11} (grade 1) 8%,⁹ (grade 2) 3%,⁹ (grade 3) 3% to 4%,^{6,9} ($\geq$ grade 3) 3% to 10%^{10,11}; increased aspartate aminotransferase (AST) (all grades) 22% to 44%,^{6,9-11} (grade 1) 12%,⁹ (grade 2) 12%,⁹ (grade 3) 3% to 11%,^{6,9} ($\geq$ grade 3) 4% to 9%^{10,11}; increased alkaline phosphatase (all grades) 4% to 11%,^{5,9} (grade 1) 8%,⁹ (grade 3) 2%,⁹ increased lactate dehydrogenase (all grades) 8%⁵; increased transaminase enzymes (all grades) 42%.⁵

I. Infections: Cellulitis (all grades) 6%,⁹ (grade 2) 3%,⁹ (grade 3) 3%,⁹ (grade 4) 1%⁹; oral candidiasis (all grades) 4%.⁵

J. Neurologic: Hypoaesthesia (all grades) 4%⁵; neuropathy (all grades) 8%⁵; palmar-plantar erythrodysaesthesia (all grades) 1%¹⁰; peripheral neuropathy (all grades) 18%,⁹ (grade 1) 13%,⁹ (grade 2) 6%⁹; peripheral sensory neuropathy (all grades) 11%.⁶

K. Ophthalmic: Conjunctivitis (all grades) 4%,⁵ dry eye (all grades) 11%,⁶ photophobia (all grades) 4%,⁵ swollen tear ducts (all grades) 4%.⁵

L. Pulmonary: Cough (all grades) 18% to 28%,^{8,9,11} (grade 1) 13%,⁹ (grade 1 or 2) 28%,⁸ (grade 2) 6%⁹; dyspnea (all grades) 15% to 43%,^{6,8,9,11} (grade 1) 10%,⁹ (grade 1 or 2) 18%,⁸ (grade 2) 4%,⁹ (grade 3) 3%^{8,9}; pneumonia (all grades) 4% to 9%,^{9,11} (grade 1) 1%,⁹ (grade 3) 2%,⁹ ($\geq$ grade 3) 6%¹¹; pulmonary hypertension (grade 1) 4%.⁵

M. Treatment-Related Mortality: Pneumonia 1%.⁹

Name: Radium-223 dichloride

Synonyms: *Alpharadin*, Radium chloride, Radium Ra 223 dichloride, Radium 223 chloride, Radium-223, Ra 223, *Xofigo*

MECHANISM OF ACTION

Radium-223 dichloride emits alpha particles that cause double-strand DNA breaks, which the cell is incapable of repairing.¹²⁻¹⁴ Radium is reported to selectively incorporate into bone at regions of active

bone turnover, maximizing the radiation dose given locally and reducing the effects on normal tissue.¹⁵⁻¹⁹

PHARMACOKINETICS

Radium-223 dichloride is 61% distributed to bone within 4 hours. The drug is excreted fecally (13%) and renally (2%) within 48 hours. Sixty-three percent of a dose is excreted within 7 days.¹⁹

Selected therapeutic regimens of radium-223 dichloride appear in **Table 2**.

PREPARATION

1. Follow institutional policies for preparation of radioisotopes and hazardous medications when preparing radium-223 dichloride.
2. Use radium-223 dichloride injection, 27 $\mu\text{Ci/mL}$ (at the reference date).
3. Dispense in a syringe.

ADMINISTRATION

Radium-223 dichloride is administered as a slow IV injection over 1 minute.

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: Chest pain 3%²¹; dehydration (severe) 3%²¹; myocardial infarction (severe) 3%.²¹

B. Central Nervous System: Confusion (mild) 3%.²¹

C. Gastrointestinal: Constipation (mild) 18%,²¹ (moderate) 15%,²¹ (severe) 3%²¹; diarrhea 40%,²⁰ (grade 3) 10%,²⁵ (mild) 18%,²¹ (moderate) 9%²¹; nausea (grade 3) 10%,²⁵ (mild) 18%,²¹ (moderate) 9%²¹; nausea and vomiting (grade 3) 4%²⁰; vomiting (mild) 12%,²¹ (moderate) 21%.²¹

D. Hematologic: Anemia (grade 1) 40% to 79%,^{20,21} (grade 2) 12% to 26%,²⁰⁻²² (grade 3) 3% to 10%^{21,22,25}; (grade 4) 1%²²; leukopenia (grade 1) 20% to 27%,^{21,23} (grade 2) 3% to 28%,²⁰⁻²³ (grade 3) 1% to 12%,²⁰⁻²³ (grade 3 or 4) 10%²⁵; neutropenia (grade 1) 8% to 32%,^{20,21,23} (grade 2) 6%

Table 2. Selected therapeutic regimens of radium-223 dichloride

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
5 kBq/kg (0.14 μ Ci/kg)	IV	1	Did not repeat	5 kBq/kg	22
1.35 μ Ci/kg ^a (49.95 kBq/kg)	IV	1	4 weeks	1.35 μ Ci/kg	19
25 kBq/kg (0.68 μ Ci/kg)	IV	1	Did not repeat	25 kBq/kg	22
25 kBq/kg (0.68 μ Ci/kg)	IV	1	6 weeks	25 kBq/kg	23
46 kBq/kg (1.24 μ Ci/kg)	IV	1	4 weeks	46 kBq/kg	20
50 kBq/kg (1.35 μ Ci/kg)	IV	1	4 weeks	50 kBq/kg	21, 24
50 kBq/kg (1.35 μ Ci/kg)	IV	1	6 weeks	50 kBq/kg	23
50 kBq/kg (1.35 μ Ci/kg)	IV	1	Did not repeat	50 kBq/kg	22, 23 ^b
80 kBq/kg (2.16 μ Ci/kg)	IV	1	6 weeks	80 kBq/kg	23
93 kBq/kg (2.51 μ Ci/kg)	IV	1	4 weeks	93 kBq/kg	20
100 kBq/kg (2.7 μ Ci/kg)	IV	1	Did not repeat	100 kBq/kg	22, 23 ^b
163 kBq/kg (4.41 μ Ci/kg)	IV	1	4 weeks	163 kBq/kg	20
200 kBq/kg (5.4 μ Ci/kg)	IV	1	Did not repeat	200 kBq/kg	23 ^b
213 kBq/kg (5.76 μ Ci/kg)	IV	1	4 weeks	213 kBq/kg	20
250 kBq/kg (6.76 μ Ci/kg)	IV	1	4 weeks	250 kBq/kg	20

Note: IV = intravenous; kBq = kilobecquerel; μ Ci = microcurie.

^aConforms to dosing information listed in the manufacturer's labeling.

^bA 50 kBq dose was allowed at week 6.

to 28%,²⁰⁻²³ (grade 3) 1% to 10%,²⁰⁻²⁵ (grade 3 or 4) 2%²⁴; (grade 4) 2%²²; thrombocytopenia (grade 1) 10% to 19%,^{20,21,23,25} (grade 2) 2% to 3%,^{22,23} (grade 3) 2% to 4%,^{22,23} (grade 3 or 4) 6%,²⁴ (grade 4) 1% to 2%.^{22,23}

E. Infection: Pneumonia (moderate) 3%,²¹ (severe) 3%²¹; pseudomonas (severe) 3%²¹; sepsis (severe) 3%.²¹

F. Metabolic: Bone pain (mild) 6%,²¹ (moderate) 21%,²¹ (severe) 3%²¹; bone pain/ "flare" 36%,²⁰ fatigue 20%²⁰; (mild) 9%,²¹ (moderate) 15%²¹; myalgia (mild) 9%,²¹ (moderate) 6%²¹; tumor flare (mild) 6%,²¹ (moderate) 9%,²¹ (severe) 3%.²¹

G. Pulmonary: Exacerbation of chronic obstructive airway disease (severe) 3%.²¹

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