Cancer Chemotherapy Update

Blinatumomab and Pembrolizumab

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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.

Name: Blinatumomab

Synonyms: Blincyto, AMG103, MT-103

MECHANISM OF ACTION

Blinatumomab is a single-chain bispecific T-cell engager (BiTE) antibody with specificity for CD3 and CD19. BiTEs stimulate cytotoxic synapse formation between endogenous T cells and target tumor cells. Activation of T cells leads to granzyme-containing granules and pore-forming protein, perforin, fusion with the T-cell membrane, successive release of toxic matter, and lysis of the target cell.¹⁻⁴ Granzymes are proteases with serine esterase activities that represent most of the granule content of T cytotoxic cells.

PHARMACOKINETICS

Blinatumomab displays linear pharmacokinetics.⁴ Continuous intravenous (IV) infusion of blinatumomab 15 mcg/m²/day results in a mean steady-state serum concentration (C_{ss}) of 731 pg/mL $\pm$ 163 pg/mL that is achieved within a day.⁵ The mean area under the time versus concentration curve (AUC_{0-28}) is 19,659 $\pm$ 4,413 days•pg/mL, with a clearance of 22.3 $\pm$ 5.0 L/day/m².⁵ The volume of distribution (V_d) is 1.61 $\pm$ 0.74 L/m². The serum elimination half-life ($t_{1/2}$) is 1.250 $\pm$ 0.634 hours.⁵ The short serum half-life and

relatively high clearance suggest that blinatumomab is renally excreted.⁵ The metabolism of blinatumomab has not been identified.⁴ Selected therapeutic regimens for blinatumomab administration are listed in Table 1.

PREPARATION

- Follow institutional policies for preparation of hazardous medications when preparing blinatumomab.
- Blinatumomab should be prepared in a non-polyvinyl chloride (PVC) container.
- Add 5.5 mL of the solution stabilizer to 250 mL 0.9% sodium chloride (NS), and mix gently.
- Reconstitute the blinatumomab vial with 3 mL preservative-free sterile water for injection to a final concentration of 12.5 mcg/mL.
- Inject the sterile water slowly down the side of the vial to avoid excessive foaming.
- Dilute the drug in the NS solution previously prepared (step C above).

STABILITY

- The reconstituted vial is stable for up to 4 hours at controlled room temperature (23°C-27°C [73°F-81°F]) or up to 24 hours refrigerated (2°C-8°C [36°F-46°F]).
- Solutions diluted for infusion are stable for up to 48 hours at controlled room temperature

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Table 1. Selected therapeutic regimens of blinatumomab

Daily dose	Route of administration	Administered on day(s)	Cycle length, days	Total dose/cycle	Reference
9 mcg/day ^a 28 mcg/day 28 mcg/day	IV	Cycle 1, D1-D7 Cycle 1, D8-D28 Subsequent cycles, D1-D28	42	Cycle 1 = 651 mcg Subsequent cycles = 784 mcg	3,4
5-15 mcg/m ² /day	IV	D1-D28	42	140-420 mg/m ²	1,6,7
5-15 mcg/m ² /day	IV	D1-D28	35-42	140-420 mg/m ²	9
15 mcg/m ² /day	IV	D1-D28	42	420 mg/m ²	2,5,8
5 mcg/m ² /day 15 mcg/m ² /day 60 mcg/m ² /day	IV	D1-D7 D8-D14 D15-D28-56	28-56	35 mg/m ² 105 mg/m ² 840-2,520 mg/m ²	10

Note: IV = intravenous.

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

(23°C-27°C [73°F -81°F]) or up to 8 days refrigerated (2°C-8°C [36°F-46°F]).⁴

ADMINISTRATION

- To minimize infusion reactions, dexamethasone 20 mg IV should be administered 1 hour prior to the first dose of blinatumomab of each cycle, following interruptions of 4 hours or more in the infusion, and prior to dose increases.^{3,4}
- Blinatumomab is administered as a continuous IV infusion.
- Blinatumomab should be infused through low sorbing tubing and a low protein-binding, 0.2-micron filter.
- Do not flush the IV infusion line, as this will interrupt the infusion until the line clears.

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 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 they 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:** Catheter thrombosis/medical device complication (port dislocation) (grade 3 or 4) 5%;² hypertension (all grades) 29%,⁶ (grade 3 or 4) 9%;¹ peripheral edema (all grades) 26%.³
- Central Nervous System:** Altered state of consciousness (grade 3) 1%;³ aphasia (grade 1 or 2) 3%,³ (grade 3) 1%;³ ataxia (grade 1 or 2) 3%,³ (grade 3) 1%;³ (grade 4) 1%;³ bradyphrenia (grade 1 or 2) 1%,³ (grade 3) 1%;³ cognitive disorder (grade 1 or 2) 1%,³ (grade 3) 1%;³ confusion (grade 1 or 2) 6%,³ (grade 3) 2%;³ convulsion (grade 1 or 2) 2%,³ (grade 3 or 4) 1% to 5%;^{2,3} dizziness (grade 1 or 2) 13%,³ (grade 3) 1%;³ encephalopathy (grade 1 or 2) 2%,³ (grade 3 or 4) 1% to 4%;^{1,3} febrile delirium (grade 4) 1%;³ headache (all grades) 34% to 39%,^{3,6,7} (grade 3 or 4) 5%;² hemiparesis (grade 1 or 2) 1%,³ (grade 3) 1%;³ mental status change (grade 1 or 2) 3%,³ (grade 3) 1%;³ seizure (grade 3 or 4) 3% to 5%;^{2,6} somnolence (grade 1 or 2) 4%,³ (grade 3 or 4) 1% to 5%;^{2,3} stupor (grade 3) 1%;³ syncope (grade 3 or 4) 1% to 5%.^{2,3}
- Constitutional:** Chills (all grades) 43%;⁸ fatigue (all grades) 30%;⁷ pyrexia (all grades) 62% to 100%,⁶⁻⁸ (grade 1 or 2) 53%,³ (grade 3 or 4) 4% to 7%.^{1,3}
- Endocrine/metabolic:** Blood albumin decreased (grade 3 or 4) 5%;² blood amylase decreased (grade 3 or 4) 5%;² blood immunoglobulin decreased (grade 3 or 4) 4% to 24%;^{1,2} C-reactive protein increase (grade 3 or 4) 4%;¹ cytokine release syndrome (grade 3 or 4) 2% to 4%;^{1,3} fibrin D dimer increase (grade 3 or 4) 4%;¹

hyperglycemia (grade 1 or 2) 5%,³ (grade 3) 8%³; hypokalemia (grade 1 or 2) 17%,³ (grade 3 or 4) 2% to 5%^{2,3}; hypophosphatemia (grade 1 or 2) 2%,³ (grade 3) 4%,³ (grade 4) 1%³; tumor lysis syndrome (grade 3 or 4) 4%.¹

E. Gastrointestinal: Constipation (all grades) 21%³; nausea (all grades) 24%.³

F. Hematologic: Anemia (all grades) 29%,⁶ (grade 1 or 2) 6%,³ (grade 3) 13%,³ (grade 4) 1%³; disseminated intravascular coagulation (all grades) 2%³; febrile neutropenia (grade 1 or 2) 3%,³ (grade 3 or 4) 1% to 24%^{1,3}; granulocytopenia (grade 3 or 4) 5%²; leukopenia (grade 1 or 2) 2%,³ (grade 3 or 4) 4% to 10%^{1,3}; lymphopenia (grade 3 or 4) 33%²; neutropenia (grade 1 or 2) 2%,³ (grade 3) 5%,³ (grade 4) 11%³; thrombocytopenia (grade 1 or 2) 3%,³ (grade 3 or 4) 1% to 9%.^{1,3}

G. Hepatic: Alanine aminotransferase (ALT) increased (grade 1 or 2) 6%,³ (grade 3 or 4) 1% to 6%^{2,3}; gamma-glutamyltransferase (GGT) increased (grade 3 or 4) 4% to 5%.^{1,2}

H. Infection: Catheter site infection (grade 3 or 4) 4% to 10%^{1,2}; pneumonia (grade 1 or 2) 1%,³ (grade 3 or 4) 1% to 7%^{2,3}; sepsis (grade 1 or 2) 1%,³ (grade 3 or 4) 2% to 5%^{2,3}; sinusitis (grade 3 or 4) 4%.¹

I. Neurologic: Dysarthria (grade 1 or 2) 3%,³ (grade 3) 1%³; dysesthesia (grade 1 or 2) 1%,³ (grade 3) 1%³; nervous system disorder (grade 3) 2%³; neurologic symptom (grade 3) 1%³; neurotoxicity (grade 1 or 2) 2%,³ (grade 3) 1%³; tremor (all grades) 30%,⁷ (grade 1 or 2) 17%,³ (grade 3 or 4) 1% to 9%.^{1,3}

DOSAGE MODIFICATIONS

A. Hepatic: There are no recommended dose adjustments for hepatic dysfunction due to lack of pharmacokinetic studies in patients with hepatic impairment.⁴

B. Renal: There are no recommended dose adjustments for renal dysfunction due to lack of pharmacokinetic studies in patients with renal impairment.⁴

Name: Pembrolizumab

Synonyms: Lambrolizumab, *Keytruda*, MK-3475

MECHANISM OF ACTION

Pembrolizumab is a humanized monoclonal antibody with activity against the inhibitory programmed death receptor-1 (PD-1) found on T cells. Binding of the PD-1 receptor to PD-1 ligands (PD-L1 and PD-L2) on the surface of tumor cells suppresses cytotoxic T-cell proliferation and cytokine release. Pembrolizumab inhibits this interaction by binding to PD-1 receptors, thus inhibiting interaction with the PD-1 ligands and impeding PD-1 pathway-mediated anti-tumor immune response.¹¹⁻¹³

PHARMCOKINETICS

An IV dose of pembrolizumab 2 mg/kg produced an area under the concentration versus time curve at steady state (AUC_{0-21}) of 0.643 g•day/L with a coefficient of variation (CV%) of 37%.¹¹ Following a single IV dose of pembrolizumab 3 mg/kg, the AUC_{0-28} was 90 µg•day/mL with a mean CV% of 23%.¹⁴ The clearance of pembrolizumab is 0.22 L/day based on doses of 1 to 10 mg/kg IV given every 2 weeks or 2 to 10 mg/kg IV given every 3 weeks.¹³ The mean CV% elimination serum half-life ($t_{1/2}$) was 26 days (24%).¹³ Selected therapeutic regimens for pembrolizumab administration are listed in **Table 2**.

PREPARATION

- Follow institutional policies for preparation of hazardous medications when preparing pembrolizumab.
- Reconstitute pembrolizumab 50 mg vial with 2.3 mL of sterile water for injection, USP by injecting the water toward the inside surface of vial for a final drug concentration of 25 mg/mL. Swirl the vial to mix. Do not shake. May require up to 5 minutes for bubbles to clear from vial.¹³
- Add reconstituted pembrolizumab to an IV bag containing 0.9% sodium chloride injection, USP. The concentration of the final solution should be between 1 mg/mL and 10 mg/mL.¹³

STABILITY

The reconstituted vial and diluted solutions of pembrolizumab are stable for up to 4 hours at room temperature (15°C-30°C [59°F-86°F]) or for up to 24 hours refrigerated (2°C-8°C [36°F-46°F]).¹³

ADMINISTRATION

- Pembrolizumab is administered as a 30-minute IV infusion.¹¹⁻¹³

Table 2. Selected therapeutic regimens of pembrolizumab

Daily dose	Route of administration	Administered on day(s)	Cycle length, days	Total dose/cycle	Reference
2 mg/kg ^a	IV	1	21	2 mg/kg	11-13,15-19
10 mg/kg	IV	1	14	10 mg/kg	12,15,16,19
10 mg/kg	IV	1	21	10 mg/kg	11,12,15,17-19

Note: IV = intravenous.

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

- B. Pembrolizumab should be infused through a low protein-binding, 0.2-micron to 5-micron filter.¹³

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 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 they 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:** Dehydration (all grades) 1%,¹¹ face edema (all grades) 2%,¹¹ hypertension (all grades) 5%,¹² peripheral edema (all grades) 5%.¹¹
- B. Central Nervous System:** Confusion (grade 3 or 4) 1%,¹¹ dizziness (all grades) 2%,¹¹ encephalopathy (grade 3 or 4) 1%,¹¹ headache (all grades) 5%.^{11,12}
- C. Constitutional:** Asthenia (all grades) 6%¹¹; chills (all grades) 5% to 8%^{11,12}; fatigue (all grades) 9% to 33%,^{11,12} (grade 3 or 4) 6%¹¹; influenza-like illness (all grades) 1%¹¹; lethargy (all grades) 5%¹¹; night sweats (all grades) 5%¹¹; pain (all grades) 2%¹¹; pyrexia (all grades) 3%¹¹; tumor pain (all grades) 1%.¹¹
- D. Dermatologic:** Dry skin (all grades) 2%¹¹; erythema (all grades) 5%^{11,12}; pigmentation disorder (all grades) 2%¹¹; pruritus (all grades) 18% to 26%,^{11,12} (grade 3 or 4) 5%¹²; rash (all grades) 14% to 18%,^{11,12} (grade 3 or 4) 5%¹²; rash, generalized (all grades) 1%¹¹; rash, maculopapular (all grades) 2%¹¹; vitiligo (all grades) 5% to 9%.^{11,12}
- E. Endocrine/Metabolic:** Amylase increased (grade 3 or 4) 1%¹¹; blood thyroid-stimulating hormone (TSH) increased (all grades) 1%¹¹; hyperglycemia (all grades) 5%¹²; hyperthyroidism (all grades) 1%¹¹; hypophysitis (all grades) 2%,¹¹ (grade 3 or 4) 1%¹¹; hypothyroidism (all grades) 5% to 6%^{11,12}; thyroxine decreased (all grades) 1%¹¹; weight decreased (all grades) 3%.¹¹
- F. Eye Disorders:** Dry eye (all grades) 2%,¹¹ visual impairment (all grades) 2% to 5%.^{11,12}
- G. Gastrointestinal:** Abdominal discomfort (all grades) 2%,¹¹ abdominal pain (all grades) 1% to 3%,^{11,12} constipation (all grades) 5%,¹¹ decreased appetite (all grades) 5% to 9%,^{11,12} diarrhea (all grades) 11% to 27%,^{11,12} dysgeusia (all grades) 5%,¹² gastroesophageal reflux disease (all grades) 3%,¹¹ mucosal inflammation (all grades) 1%,¹¹ nausea (all grades) 8% to 9%,^{11,12} vomiting (all grades) 2%.¹¹
- H. Hematologic:** Anemia (all grades) 3%,¹¹ (grade 3 or 4) 1%¹¹; leukopenia (all grades) 5%¹²; thrombocytopenia (all grades) 9%.¹²
- I. Hepatic:** ALT increased (all grades) 5%¹¹; aspartate aminotransferase (AST) increased (all grades) 3% to 5%^{11,12}; autoimmune hepatitis (grade 3 or 4) 1%.¹¹
- J. Infection:** Influenza (all grades) 1%¹¹; pneumonitis (all grades) 2%,¹¹ (grade 3 or 4) 1%.¹¹
- K. Musculoskeletal:** Arthralgia (all grades) 5% to 12%^{11,12}; back pain (all grades) 3%¹¹; muscle spasms (all grades) 2% to 5%^{11,12}; muscular weakness (any grade) 3%,¹¹ (grade 3 or 4) 1%¹¹; myalgia (all grades) 5% to 6%^{11,12}; pain in extremity (all grades) 5%¹²; pain in jaw (all grades) 1%.¹¹
- L. Neurologic:** Hypoesthesia (all grades) 3%,¹¹ peripheral motor neuropathy (grade 3 or 4) 1%.¹¹

M. Respiratory: Cough (all grades) 9%,¹² exertional dyspnea (all grades) 1%,¹¹ dyspnea (all grades) 5% to 8%.^{11,12}

DOSAGE MODIFICATIONS

- A. Hepatic:** There are no recommended dose adjustments for hepatic dysfunction. No significant differences in clearance were observed in patients with mild hepatic impairment, and no studies have been performed in patients with moderate to severe hepatic impairment.¹³
- B. Renal:** There are no recommended dose adjustments for renal dysfunction. No significant differences in clearance were observed in patients with renal impairment.¹³

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