Cancer Chemotherapy Update

Enzalutamide and Ruxolitinib

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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: Enzalutamide

Synonyms: MDV3100, *Xtandi*

MECHANISM OF ACTION

Enzalutamide acts as a pure androgen receptor antagonist that competitively inhibits the binding of androgen to androgen receptors. Enzalutamide also inhibits the nuclear translocation of the androgen receptor and DNA binding, resulting in decreased coactivator recruitment. This has been shown in vitro to reduce cell proliferation and increase apoptosis of prostate cancer cells.

PHARMACOKINETICS

Enzalutamide's kinetics can be described by a linear 2-compartment model with first-order absorption. Following the administration of a single oral dose, the volume of distribution (Vd) is approximately 110 L. Absorption is unaffected by meals; the area under the time-concentration curve (AUC) of enzalutamide and N-desmethyl enzalutamide both remain similar. Both enzalutamide and N-desmethyl enzalutamide are highly protein bound, approximately 97% to 98% and 95%, respectively. After oral administration, enzalutamide is rapidly absorbed, with a mean time to reach peak plasma concentration (C_{max}) of about 1 hour (range, 0.5 to 4 hours). With daily dosing, steady state is usually achieved by day 28. At steady state,

enzalutamide plasma concentrations have an average peak-to-trough ratio of 1.25. At steady state, the average peak plasma concentrations (C_{max}) for enzalutamide and its active metabolite, N-desmethyl enzalutamide, are 16.6 mcg/mL and 12.7 mcg/mL, respectively. The average minimum plasma concentrations (C_{min}) are 11.4 mcg/mL and 13.0 mcg/mL, respectively. Enzalutamide undergoes hepatic metabolism, primarily by CYP2C8 and CYP3A4. N-desmethyl enzalutamide (active metabolite) and a carboxylic acid metabolite (inactive metabolite) are the major metabolites. The estimated half-life of enzalutamide after a single dose is about 6 to 7 days (range, 3-13 days), with a mean terminal half-life for N-desmethyl enzalutamide of 8 to 9 days. Approximately 71% of the drug is excreted in the urine and 14% in the feces.

Selected therapeutic regimens of enzalutamide appear in Table 1.

PREPARATION

- Follow institutional policies for preparation of hazardous medications when dispensing enzalutamide.
- Enzalutamide is available as 40 mg liquid filled capsules.

STORAGE

- Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).
- Brief exposure to temperatures from 15°C to 30°C (59°F to 86°F) is acceptable.

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Table 1. Therapeutic regimen of enzalutamide

Dose	Route of administration	Administered on day(s)	Total dose/month	References
30 mg	PO	Daily	900 mg	1
60 mg	PO	Daily	1,800 mg	1
80 mg ^a	PO	Daily	2,400 mg	3
120 mg ^a	PO	Daily	3,600 mg	3
150 mg	PO	Daily	4,500 mg	1
160 mg ^a	PO	Daily	4,800 mg	2,3
240 mg	PO	Daily	7,200 mg	1

Note: PO = oral.

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

ADMINISTRATION

- A. Enzalutamide may be given without regard to food.
- B. Because the capsules are liquid filled, it is recommended that they be swallowed whole and not be opened, crushed, chewed, or dissolved.

3 or 4) 0.3%; seizure (all grades) 1%, (grade 3 or 4) 1% to 2%; spinal cord compression and cauda equina syndrome (grade 3 or 4) 7%.

- I. **Treatment-Related Death:** Infection or sepsis 1%; overall adverse events leading to death (all grades) 3%, (grade 3 or 4) 3%.

TOXICITIES

- A. **Cardiovascular:** Any cardiac disorder (all grades) 6%, (grade 3 or 4) 1%; hot flush (all grades) 20%; hypertension (grade 3 or 4) 2%; myocardial infarction (all grades) <1%, (grade 3 or 4) <1%; peripheral edema (grade 3 or 4) 1%.
- B. **Constitutional:** Dizziness (all grades) 0.5%; fatigue (all grades) 34%, (grade 3 or 4) 6% to 11%.
- C. **Gastrointestinal:** Diarrhea (all grades) 21%, (grade 3 or 4) 1%.
- D. **Hematologic:** Anemia (grade 3 or 4) 3%; epistaxis (grade 3 or 4) 0.1%; hematuria (grade 3 or 4) 2%; neutropenia (all grades) 15%, (grade 3 or 4) 1%; thrombocytopenia (grade 3 or 4) 0.5%.
- E. **Hepatic:** Abnormal liver function tests (all grades) 1%, (grades 3 or 4) <1%; alanine aminotransferase elevation (all grades) 10%, (grade 3 or 4) 0.3%; bilirubin elevation (all grades) 3%.
- F. **Infection:** Lower respiratory tract infection (grade 3 or 4) 2%.
- G. **Musculoskeletal:** Arthralgia (all grades) 14%, (grade 3 or 4) 1% to 3%; asthenia (grade 3 or 4) 2% to 9%; back pain (grade 3 or 4) 5%; muscle stiffness (grade 3 or 4) 0.3%.
- H. **Neurologic:** Anxiety (grade 3 or 4) 0.3%; hallucinations (all grades) 2%; headache (all grades) 12%, (grade 3 or 4) 1%; hypoesthesia (grade 3 or 4) 0.3%; mental impairment disorders (grade

Name: Ruxolitinib

Synonyms: INCB018424, *Jakafi*

MECHANISM OF ACTION

Ruxolitinib is a strong, selective ATP-competitive inhibitor of the Janus associated kinases (JAK) 1 and 2 enzymes. These enzymes are responsible for mediating cytokine and growth factor signaling, which play a significant role in hematopoiesis and immune function. Signal transducers and activators of transcription (STATs) are recruited through JAK signaling. The binding of STATs to cytokine receptors causes activation and eventual migration of STATs to the nucleus, which allows for modification or mutation of gene expression.

PHARMACOKINETICS

Ruxolitinib has good oral bioavailability (greater than 95%) and is rapidly absorbed. It usually reaches peak concentrations (C_{max}) within 2 hours of administration. The C_{max} and total exposure (AUC) of ruxolitinib increase linearly with the dose. Steady state is usually reached by day 2, regardless of dose. Ingestion of ruxolitinib is not greatly affected by food. C_{max} decreases approximately 24% when taken with a high-fat meal versus fasting; there is little affect on the AUC. The volume of distribution (V_d) is estimated to range from 53 to 97 L. Ruxolitinib is 97% protein bound, primarily to albumin. Ruxolitinib is largely

metabolized by CYP3A4 into multiple active metabolites. The average half-life of ruxolitinib and ruxolitinib plus its metabolites is 2 to 3 hours and 6 hours, respectively. Approximately 74% of the drug is excreted (as the metabolites) in the urine and 22% in the feces. Less than 1% (~0.11%) is excreted as unchanged drug.

Selected therapeutic regimens of ruxolitinib appear in **Table 2**.

PREPARATION

- A. Follow institutional policies for preparation of hazardous medications when dispensing ruxolitinib.
- B. Ruxolitinib is available as 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets.

STORAGE

- A. Ruxolitinib tablets should be stored at room temperature (20°C to 25°C [68°F to 77°F]).
- B. Brief exposure to temperatures from 15°C to 30°C (59°F to 86°F) is acceptable.

ADMINISTRATION

- A. May be given orally without regard to food.
- B. To give via nasogastric tube:
 1. Crush the tablet(s) to a fine powder.
 2. Mix with 40 mL of water.
 3. Stir until the particles are well dispersed.
 4. Following administration of the drug, flush the tube with 75 mL of water.
 5. Administer within 6 hours.

TOXICITIES

- A. **Cardiovascular:** Cardiac murmur (all grades) 2%; edema (all grades) 2%; peripheral edema (all grades) 3% to 22%.
- B. **Constitutional:** Dizziness (all grades) 3% to 18%, (grade 3 or 4) 1%; fatigue (all grades) 4% to 25%, (grade 3 or 4) 1% to 5%; insomnia (all grades) 2% to 12%, (grade 3 or 4) 0% to 1%; pyrexia (all grades) 2% to 11%, (grade 3 or 4) 1%.
- C. **Dermatologic:** Pruritus (all grades) 5%.
- D. **Endocrine/Metabolic:** Weight gain (all grades) 7%, (grade 3 or 4) 1%.
- E. **Gastrointestinal:** Abdominal pain (all grades) 10% to 11%, (grade 3 or 4) 3%; constipation (all grades) 13%; diarrhea (all grades) 6% to 23%, (grade 3 or 4) 0% to 2%; flatulence (all grades) 2% to 5%; nausea (all grades) 2% to 15%, (grade 3 or 4) 0% to 1%; vomiting (all grades) 12%, (grade 3 or 4) 1%.
- F. **Hematologic:** Anemia (all grades) 96%, (grade 3 or 4) 45%; bruising (all grades) 23%, (grade 3 or 4) 1%; ecchymosis (all grades) 19%; epistaxis (all grades) 2%; esophageal varices (all grades) 2%; neutropenia (all grades) 19%, (grade 3 or 4) 7%; thrombocytopenia (all grades) 70%, (grade 3 or 4) 13%.
- G. **Hepatic:** Alanine aminotransferase abnormalities (grade 1) 25%, (grade 2 or greater) 2%; aspartate aminotransferase abnormalities (grade 1) 17%, (grade 2) 1%; cholesterol abnormalities (grade 1) 17%, (grade 2) 1%.

Table 2. Therapeutic regimen of ruxolitinib

Dose	Route of administration	Administered on day(s)	Total dose/month	References
5 mg	PO	Daily	150 mg	7
10 mg	PO	Daily	300 mg	7
15 mg	PO	Daily	450 mg	7
20 mg	PO	Daily	600 mg	7
25 mg	PO	Daily	750 mg	7, 8
50 mg	PO	Daily	1,500 mg	7, 8
100 mg	PO	Daily	3,000 mg	7, 9
10 mg ^{a,b}	PO	Daily	300 mg	11
20 mg ^{a,b}	PO	Daily	600 mg	9, 11
30 mg ^{a,b}	PO	Daily	900 mg	5, 7, 9, 10, 11
40 mg ^{a,b}	PO	Daily	1,200 mg	5, 10, 11
50 mg ^{a,b}	PO	Daily	1,500 mg	4, 5, 7, 9, 11

Note: PO = oral.

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

^bThe individual dose is half the daily dose (eg, 20 mg/day = 10 mg twice a day). Care should be taken ensure the intended daily dose is not taken twice a day.

- H. **Infection:** Nasopharyngitis (all grades) 16%; pneumonia (all grades) 1%; urinary tract infection (all grades) 3% to 9%.
- I. **Musculoskeletal:** Arthralgia (all grades) 2% to 12%, (grade 3 or 4) 0% to 2%; asthenia (all grades) 2% to 18%, (grade 3 or 4) 1% to 2%; back pain (all grades) 10%, (grade 3 or 4) 2%; pain in extremity (all grades) 3% to 12%, (grade 3 or 4) 0% to 1%.
- J. **Neurologic:** Anxiety (all grades) 2%, (grade 3 or 4) 1%; headache (all grades) 3% to 15%, (grade 3 or 4) 0% to 1%; peripheral neuropathy (all grades) 2%.
- K. **Respiratory:** Cough (all grades) 14%; dyspnea (all grades) 3% to 17%, (grade 3 or 4) 0% to 1%.
- L. **Treatment-Related Death:** Intracerebral hemorrhage without thrombocytopenia 1%.
- M. **Other:** Herpes zoster (all grades) 2%.

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