Oncology Pharmacy Newsletter

Volume 1, Issue 11, December 7, 2015

# Thrombocytopenia in Cancer Patients

Almira Cecunjanin
UConn School of Pharmacy
Pharm. D. Candidate 2016

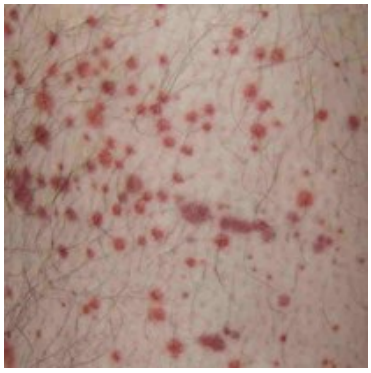
## Thrombocytopenia in Cancer Patients

Thrombocytopenia can occur when the body does not make an adequate amount of platelets, is losing platelets, or is destroying platelets. Thrombocytopenia is a common problem in many cancer patients. Chemotherapy can lead to a low production of platelets in the bone marrow. For some patients the bone marrow cannot make enough platelets because of cancers, such as leukemia. At platelet counts <100,000/uL, chemotherapy and radiation therapy are administered with caution due to the possibility of worsening the thrombocytopenia and increasing the risk of bleeding. Dose reductions and/or treatment delays are common ways of managing chemotherapy-associated thrombocytopenia. [3]

## What are symptoms?

Some patients may not experience any symptoms. However, if they do experience symptoms they may include:

- Bleeding in the mouth and gums
- Small purple or red spots under the skin (petechia)
- Nosebleeds
- Unexpected bruising
- Dizziness
- Severe headaches
- Blood in the vomit
- Black/bloody stool



## Is the thrombocytopenia caused by chemotherapy?

The frequency, severity, and duration of thrombocytopenia varies with the chemotherapy agents administered. This information can be found in the package insert or drug databases such as Lexicomp or Micromedex. Table 1. lists the platelet range for each grade severity.

**Table 1. Grades of Thrombocytopenia [2]**

| Grade | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Platelet count | <LLN- 75,000/µL | <75,000- 50,000/µL | <50,000-25,000/µL | <25,000/µL |

## Guidelines

Guidelines vary as to chemotherapy dose reductions or frequency in response to treating thrombocytopenia. How you approach this issue is multifactorial and very patient specific. It is vital to assess the underlying need for chemotherapy, goals of treatment (curative vs. palliative care), and bleeding risk. Reductions in chemotherapy dose and/or frequency are often made, especially if the goal of therapy is not of curative, and are based on package insert guidelines. [4] Platelet transfusion support should be used if maintenance of dose intensity is needed for response. Prophylactic platelet transfusions are indicated if bleeding occurs or if platelet counts are < 10,000/µL [5].

**Goals of treatment**

- Sustain a safe platelet count to allow successful treatment of the cancer
- Prevent bleeding complications
- Reduce the use of platelet product transfusions

**Patient Case example**

A metastatic rectal cancer patient is receiving:

capecitabine 850mg/$m^2$ PO twice daily, days 1-14
bevacizumab 7.5mg/kg IV on day 1
repeat every 3 weeks

*His platelet count on the day 1 of cycle 4 of therapy is 69,000/µL. Can you administer the bevacizumab and capecitabine?*

This patient has developed grade-2 thrombocytopenia while on therapy. Product labeling for capecitabine recommends that patients who develop grade-2 thrombocytopenia have a temporary discontinuation of therapy until the thrombocytopenia resolves to a grade 0 or 1. If this was the first appearance of thrombocytopenia then we would restart it at 100% of the original dose (850mg/$m^2$ PO twice daily) that was scheduled. However, dose adjustments and even possibly permanent treatment discontinuation can occur with future appearances of the same toxicity. [6]

Product information for bevacizumab, however, does not recommend dose adjustments for thrombocytopenia because it occurs in < 5% of patients [1]. Therefore, this patient may receive bevacizumab on day 1 and then once platelets recover to grade 0-1, re-administer the capecitabine at the original dose.

## Renal-Cell Carcinoma: Another New Indication for Nivolumab

In November, the FDA approved Nivolumab (Opdivo®) for use in previously treated, advanced renal-cell carcinoma. Similar to its use in other approved malignancies, the dose is 3 mg/kg every 14 days.

The CheckMate 025 study compared nivolumab 3mg/kg every 14 days to everolimus 10mg daily and demonstrated increased overall survival, increased objective response rates, slightly loner medial progression free survival, and lower incidence of grade 3-4 adverse events. This occurred even in the absence of tumor PD-L1 expression. Fatigue, nausea and pruritus were the most commonly reported adverse effects of nivolumab.

## Yervoy®—Bigger Doses, Longer Treatments and Combination Therapy

Four doses is no longer the only the story with ipilimumab (Yervoy®) which may now be used as adjuvant treatment of melanoma at a dose of 10mg/kg every 3 weeks for 4 doses, and continued up to 3 additional years every 12 weeks. Doses are skipped if toxicity occurs until the symptoms resolve.

In addition, unresectable melanoma may now be treated with combination therapy with ipilimumab 3mg/kg and nivolumab 1mg/kg every 21 days for the first 4 cycles, before discontinuing ipilimumab and continuing nivolumab at 3mg/kg/day every 14 days. Note the reduced dose and prolonged cycle for nivolumab during the initial 4 treatments. Nivolumab is continued as single agent therapy until disease progression or unacceptable toxicity is experienced.

# Brentuximab Vedotin (Adcetris®)

Brentuximab vedotin is a conjugated antitumor drug, consisting of monomethyl auristatin E (MMAE), that impairs microtubule function and inhibits cell division, a cleavable joining molecule, and a CD-30 antibody that targets this protein found on malignant lymphoma cells. Once bound to the cell, brentuximab vedotin is internalized, then the MMAE is cleaved off and disrupts microtubule function, leading to apoptosis.

**Use:**

Brentuximab vedotin is used in refractory Hodgkin lymphoma, for patients who have failed at least two therapies or relapsed after transplant, high risk Hodgkin lymphoma that has failed one or more prior therapies, or anaplastic large cell lymphoma following primary treatment failure. It is also used in maintenance therapy following autologous stem cell transplant, starting within 4-6 weeks of transplant.

**Dose:**

All three indications are dosed the same way: 1.8mg/kg every 21 days until disease progression or toxicity. For stem cell transplant patients, who do not progress or have toxicities, the maximum number of cycles is 16. All doses are capped at 180mg/dose. For severe renal impairment with CrCl<30 or Child-Pugh class B or C, brentuximab vedotin should be withheld. Reduced dosing of 1.2mg/kg may be appropriate in Child-Pugh class A patients (mild hepatic impairment).

**Monitoring:**

CBC with diff, BUN/Cr, and LFTs should be done before each cycle. Patients should be monitored for infusion reactions, tumor lysis syndrome, symptoms of infection, mental status changes, neuropathy, respiratory changes, and rashes.

**Adminsitration:**

Brentuximab is mixed in 100ml NS and infused over 30 minutes. Reconstitution requires some care, as the 50mg vial is diluted with 10.5ml which should not be injected directly into the drug cake to avoid foaming. The vial should be swirled, and not shaken, to dissolve. The resulting solution will be 5mg/ml. It should be diluted as soon as it is reconstituted, but may be refrigerated for up to 24hrs.

**Adverse Effects:**

Brentuximab vendotin may cause severe infusion reactions or anaphylaxis. In case of infusion reactions, the infusion should be immediately stopped, but may be continued at a slower rate once the patient has been treated and has improved. Nausea and vomiting can occur so antiemetics should be available as prn, and our order sets use premedication with dexamethasone and ondansetron. Brentuximab is considered to have low emetic potential.

Other side effects include bone marrow suppression, severe rash (including potentially fatal exfoliative reactions), opportunistic infections, tumor lysis syndrome, pruritis, alopecia, pulmonary toxicity (so concomitant use with bleomycin is contraindicated), peripheral neuropathies (some reversible), neutropenia and thrombocytopenia, hepatotoxicity, diarrhea, constipation, abdominal pain, peripheral edema, fever, cough, and dyspnea.

Brentuximab carries a black box warning concerning progressive multifocal leukoencephalopathy that has been seen in patients who have received brentuximab and can be fatal.

**Drug Interactions:**

There are many drug interactions with brentuximab vendotin. These include other immunosuppressant drugs and monoclonal antibodies, which can combine to cause more severe immunosuppressive impact, and vaccines, skin tests, BCG, or sipuleucel-T, which may elicit lessened response due to brentuximab vendotin's suppression of immune response. Additive pulmonary toxicity may be seen with concomitant use of bleomycin.

http://adcetrisconsolidation.com/doc/adcetris-pi-with-aethera-data.pdf

http://online.lexi.com brentuximab vedotin, Accessed 12/7/15

http://www.micromedexsolutions.com brentuximab vedotin, Accessed 12/7/15