

Myelosuppression

Associated With Novel Therapies

in Patients With Multiple Myeloma:

Consensus Statement of the IMF Nurse Leadership Board

**Teresa Miceli, RN, BSN, Kathleen Colson, RN, BSN, BS,
Maria Gavino, RN, BSN, Kathy Lilleby, RN,
and the IMF Nurse Leadership Board**

Novel therapies for multiple myeloma include the immunomodulatory drugs lenalidomide and thalidomide and the proteasome inhibitor bortezomib, which have increased response rates and survival times. However, the agents can cause myelosuppression, which, if not managed effectively, can be life threatening and interfere with optimal therapy and quality of life. The International Myeloma Foundation's Nurse Leadership Board developed a consensus statement that includes toxicity grading, strategies for monitoring and managing myelosuppression associated with novel therapies, and educational recommendations for patients and their caregivers. Although anemia, neutropenia, and thrombocytopenia are expected side effects of novel therapies for multiple myeloma, they are manageable with appropriate interventions and education.

Novel therapies for multiple myeloma include the immunomodulatory drugs lenalidomide (Revlimid®, Celgene Corporation) and thalidomide (Thalomid®, Celgene Corporation) and the proteasome inhibitor bortezomib (Velcade®, Millennium Pharmaceuticals, Inc.). The novel therapies have contributed to better response rates and survival times compared with conventional chemotherapy. However, the agents can cause side effects that, although predictable and manageable, have the potential to be life threatening and to interfere with adherence to optimal therapy and patient quality of life (Celgene Corporation, 2007a, 2007b; Fortner, Houts, & Schwartzberg, 2006; Fortner, Tauer, Zhu, Ma, & Schwartzberg, 2004; Ghobrial et al., 2007; Manochakian, Miller, & Chanan-Khan, 2007; Millennium Pharmaceuticals, Inc., 2006; Rajkumar et al., 2005; Richardson & Anderson, 2006; Richardson, Hideshima, Mitsiades, & Anderson, 2007). As with other treatments for multiple myeloma, the novel agents are associated with side effects in the myelosuppression category: anemia, neutropenia, and thrombocytopenia (Celgene Corporation, 2007a, 2007b; Millennium Pharmaceuticals, Inc.). The International Myeloma Foundation's Nurse Leadership Board, in recognition of the need for specific recommendations on managing key side effects of novel antimyeloma agents, developed a consensus statement for the management of myelosuppression associated with novel therapies to be used by healthcare providers in any type of medical institution (Bertolotti et al. 2007, 2008). The recommendations also are applicable to the management of myelosuppression associated with other therapies for myeloma.

At a Glance

- ◆ The immunomodulatory drugs lenalidomide and thalidomide and the proteasome inhibitor bortezomib can cause myelosuppression.
- ◆ Because anemia, neutropenia, and thrombocytopenia are expected side effects, patients should be monitored closely and educated about side-effect signs and symptoms.
- ◆ Anemia, neutropenia, and thrombocytopenia can be managed with a combination of therapies for side effects and appropriate dose reductions of novel therapies.

Teresa Miceli, RN, BSN, is an adult bone marrow transplant coordinator at the Mayo Medical Center in Rochester, MN; Kathleen Colson, RN, BSN, BS, is a multiple myeloma clinical research nurse at Dana-Farber Cancer Institute in Boston, MA; Maria Gavino, RN, BSN, is a clinical research nurse at the University of Texas M.D. Anderson Cancer Center in Houston; and Kathy Lilleby, RN, is a clinical research nurse at the Fred Hutchinson Cancer Research Center in Seattle, WA. Miceli has served as a speaker for the Oncology Nursing Society and is a member of the speakers bureau for Medical Education Resources. Colson and Gavino are members of the speakers bureaus for Celgene Corporation and Millennium Pharmaceuticals, Inc. Lilleby is a member of the speakers bureau for Millennium Pharmaceuticals, Inc. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Clinical Journal of Oncology Nursing* or the Oncology Nursing Society. (Submitted October 2008. Accepted for publication January 5, 2008.)

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Table 1. Risk of Grade 3 and 4 Hematologic Toxicities Associated With Novel Therapies for Myeloma

DRUG	PATIENT POPULATION	N	ANEMIA (%)	NEUTROPENIA (%)	THROMBOCYTOPENIA (%)
Thalidomide ^a	Newly diagnosed	102	16	13	4
Lenalidomide ^b	At least one prior therapy	346	8	21	10
Bortezomib ^c	One to three prior therapies	331	10	15	29

^a Administered in combination with dexamethasone; indicated in combination with dexamethasone for newly diagnosed patients with multiple myeloma

^b Administered in combination with dexamethasone; indicated in combination with dexamethasone for patients with multiple myeloma who have received at least one prior therapy

^c Indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy

Note. Based on information from Celgene Corporation, 2007a, 2007b; Millennium Pharmaceuticals, Inc., 2006.

Issue Statement

Myelosuppression is a common and expected side effect of novel therapies for multiple myeloma. As a result of myelosuppression, patients may experience anemia, neutropenia, and thrombocytopenia. Depending on their severity, the side effects can have a negative impact on patients' medical treatment and quality of life by interrupting or reducing therapy and causing life-threatening complications. Neutropenia can result in life-threatening infections (Marrs, 2006). In addition to such physiologic effects, myelosuppression may limit patients' ability to interact or work outside the home, resulting in depression, anger, financial burden, and a sense of social isolation (Fortner et al., 2004, 2006). Fatigue, the most common side effect of anemia and the most common complaint among patients with cancer, has a significant impact on patients' quality of life, ability to work, and physical and emotional well-being (Boyer, 2000; Foubert, 2006).

Novel Therapies and Myelosuppression

Anemia (hemoglobin \leq 12 g/dl) is present in 73% of patients at initial diagnosis of multiple myeloma. It can be seen in 97% at some time during the course of the disease. Leukopenia (white

blood cell count \leq 4 x 10⁹/L) is seen in 20% of patients at time of diagnosis. Thrombocytopenia (platelet count < 100 x 10⁹/L) is seen in 5% of patients at time of diagnosis (Kyle et al., 2003). Myelosuppression is a common and expected side effect associated with novel therapies for treatment of multiple myeloma. Table 1 summarizes the risks of grade 3 and 4 anemia, neutropenia, and thrombocytopenia that have been reported in patients with myeloma treated with the novel therapies lenalidomide, thalidomide, and bortezomib.

Myelosuppression Definitions

The National Cancer Institute ([NCI], 2007) defined myelosuppression as "a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets." Anemia was defined as abnormally low levels of red blood cells as measured by blood hemoglobin or hematocrit levels. As a result of an imbalance of production versus destruction or loss of red blood cells, the blood has decreased capacity for carrying hemoglobin and oxygen (Foubert, 2006). Neutrophils are the infection-fighting component of the total white blood cell count. Neutropenia is the reduction of circulating neutrophils in the bloodstream, leading to increased risk of infection (Held-Warmkessel, 1998; Marrs, 2006; West & Mitchell, 2004). Thrombocytopenia may result from a lack of production of megakaryocytes or an increase in use of platelets,

Table 2. National Cancer Institute Common Terminology Criteria for Adverse Events: Hematologic Toxicity Grades

ADVERSE EVENT	UNIT OF MEASURE	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE THREATENING OR DISABLING)
Anemia	Hemoglobin, g/dl	< lower limit of normal ^a to 10.0	< 10.0–8.0	< 8.0–6.5	< 6.5
Neutropenia	Absolute neutrophil count, x 10 ⁹ /L	< lower limit of normal ^a to 1.5	< 1.5–1.0	< 1.0–0.5	< 0.5
Thrombocytopenia	Platelet count, x 10 ⁹ /L	< lower limit of normal ^a to 75	< 75–50	< 50–25	< 25

^a Refer to the normal values established by the laboratory where the patient's blood is tested.

Note. Based on information from National Cancer Institute, 2006.

Table 3. Generally Accepted Practices to Manage Anemia

HEMOGLOBIN LEVEL	RECOMMENDATION
10–12 g/dl (grade 1)	Use of erythropoiesis-stimulating agents ^a (ESAs) is determined by clinical circumstances. A baseline erythropoietin level should be obtained prior to initiating ESA therapy to assist in selecting patients who are more likely to respond to the therapy (Spivak, 1994).
< 10 g/dl (grade 2)	ESAs recommended ^a
< 8.0 g/dl or symptomatic anemia (grade 3)	Red blood cell transfusion

^a A goal of > 12.0 g/dl is not recommended because of risk of significant cardiovascular events. Concomitant use of ESAs with some antimyeloma therapies may increase the risk of thromboembolic events (Amgen Inc., 2007a, 2007b). Concomitant neutropenia is an independent risk factor for thromboembolism in hospitalized patients with cancer, including those with hematologic malignancies (Khorana et al., 2006). Rome et al. (2008) addresses these topics in detail.

leading to an abnormally low level of platelets (thrombocytes) in the circulating blood (Fukuyama & Itano, 1999). The severity of anemia, neutropenia, and thrombocytopenia can be quantified with the NCI Common Terminology Criteria for Adverse Events (CTCAE). The NCI CTCAE are used for identifying treatment-related adverse events to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures. The grades 1 through 5 (defined using unique clinical descriptions in the NCI CTCAE) refer to the severity of an adverse event; grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life threatening or disabling, and grade 5 is death related to the adverse event. Table 2 defines the NCI CTCAE version 3.0 hematologic toxicity grades 1–4 (NCI, 2006). The grades, along with nursing assessments, should be used to assist in monitoring hematologic toxicities related to novel therapies and to determine which medical and nursing management strategies are needed.

Management of Myelosuppression

General guidelines: Standardized precautions and interventions related to low blood counts vary among institutions.

Anemia: Management of anemia should take into account that some patients tolerate a greater degree of anemia than other patients. Assessment of anemia is more than a one-dimensional evaluation. In addition to the numeric value found in a complete blood count (CBC), symptoms that affect patients' quality of life also should be assessed (e.g., fatigue). A nursing interview that includes questions regarding performance status, shortness of breath, and chest pain on exertion will aid in determining the need for transfusions. Tools, such as the Brief Fatigue Inventory (Cleeland & Wang, 1999), can assist nurses in assessing patients' perceptions of fatigue. A patient's hemoglobin levels and symptoms of anemia leading to

a decision to transfuse must be balanced with the risks related to transfusions (i.e., transfusion-acquired infections, transfusion reactions, and transfusion-related lung injury) (Foubert, 2006). Table 3 lists generally accepted medical practices to manage anemia.

Transfusions are to be given at the discretion of a patient's healthcare provider. Blood products should be leukocyte-reduced to decrease the risk of febrile reactions, human leukocyte antigen alloimmunization, and cytomegalovirus infection (American Association of Blood Banks, America's Blood Centers, & American Red Cross, 2006). Transfusion policies and availability of blood products vary among institutions. General transfusion guidelines are available from the American Association of Blood Banks, America's Blood Centers, and American Red Cross and from Cable et al. (2002).

Neutropenia: Neutropenic patients are at greater risk of infection. Not all patients who are neutropenic become febrile. Handwashing by patients and all caregivers is the single most important factor for preventing infection (West & Mitchell, 2004). Nursing assessment and education of patients play a vital

Table 4. Generally Accepted Practices to Manage Neutropenia

PATIENT CHARACTERISTIC	RECOMMENDATION
Any grade of neutropenia	Initiate institutional precautionary standards for neutropenia, antifungal prophylaxis per institutional guidelines, antipneumococcal prophylaxis per institutional guidelines.
Febrile neutropenia	Treat per institutional guidelines, which may include, depending on symptoms <ul style="list-style-type: none"> • Blood and urine cultures • Chest radiograph • IV antibiotic therapy.
Prognostic factors predictive of poor clinical outcomes <ul style="list-style-type: none"> • Prolonged neutropenia (> 10 days) • Profound neutropenia (< 0.5 x 10⁹/L = grade 3 or 4) • Age > 65 years • Uncontrolled primary disease 	Granulocyte colony-stimulating factors (G-CSFs) should be considered. G-CSFs are not recommended for afebrile patients with mild neutropenia.
Previous activation of herpes simplex virus types I or II or varicella zoster virus, or receiving bortezomib	Antiviral prophylaxis. Use of live vaccines, including zoster vaccine live, is not recommended because it is a live vaccine (Centers for Disease Control and Prevention, 1996).
High risk for <i>Pneumocystis carinii</i> pneumonia (i.e., previous high-dose steroid therapy or immunosuppression)	<i>Pneumocystis carinii</i> pneumonia prophylaxis

Note. Based on information from Smith et al., 2006; Zitella et al., 2006.

Table 5. Specific Recommendations for Monitoring and Managing Myelosuppression in Patients Receiving Novel Agents for Treatment of Myeloma

AGENT AND MYELOSUPPRESSIVE SIDE EFFECT	RECOMMENDATIONS
Thalidomide Neutropenia	White blood cell count and differential should be monitored on an ongoing basis, particularly in patients prone to neutropenia. Treatment with thalidomide should not be initiated if a patient has an absolute neutrophil count of $< 0.75 \times 10^9/L$. If the absolute neutrophil count decreases to $< 0.75 \times 10^9/L$ while on treatment, the patient's medication regimen should be reevaluated. If neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.
Lenalidomide Anemia If grade 3 or 4 toxicity occurs that is judged to be related to lenalidomide	Hold treatment; restart at the next lower dose level when toxicity has resolved to grade 2.
Neutropenia If the absolute neutrophil count falls to $< 1.0 \times 10^9/L$	Interrupt lenalidomide treatment, consider granulocyte colony-stimulating factor, and follow complete blood counts weekly. When the absolute neutrophil count returns to $1.0 \times 10^9/L$ and neutropenia is the only toxicity, resume lenalidomide at 25 mg daily, or at previous dose if lower. However, do not dose below 5 mg daily. When the absolute neutrophil count returns to $> 1.0 \times 10^9/L$ and other toxicities are present, resume lenalidomide at 15 mg daily, or at previous dose if lower. However, do not dose below 5 mg daily.
For each subsequent drop of absolute neutrophil count to $< 1.0 \times 10^9/L$	Interrupt lenalidomide treatment. When the absolute neutrophil count returns to $1.0 \times 10^9/L$, resume lenalidomide at 5 mg less than the previous dose. However, do not dose below 5 mg daily.
Thrombocytopenia If platelet count falls to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment; follow complete blood counts weekly. When platelets return to $30 \times 10^9/L$, restart lenalidomide at 15 mg daily.
For each subsequent drop of platelets to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment. When platelets return to $30 \times 10^9/L$, restart lenalidomide at a dose that is 5 mg less than the previous dose. However, do not dose below 5 mg daily.
Bortezomib Anemia At the onset of any grade 4 hematologic toxicity, including anemia	Bortezomib should be held. Once toxicity has resolved, bortezomib may be restarted at a 25% reduced dose.
Neutropenia At the onset of any grade 4 hematologic toxicity, including neutropenia ^a	Bortezomib should be held. Once toxicity has resolved, bortezomib may be restarted at a 25% reduced dose.
Thrombocytopenia At the onset of any grade 4 hematologic toxicity, including thrombocytopenia ^b	Bortezomib should be held. Once toxicity has resolved, bortezomib may be restarted at a 25% reduced dose.
If the platelet count falls to $< 25 \times 10^9/L$	Bortezomib should be held. Transfusion is recommended for platelet counts $< 25 \times 10^9/L$ at the discretion of the physician, particularly with any signs of bleeding.

^a A decrease is anticipated in the neutrophil count during the treatment period (days 1–11), with rapid return to baseline during the rest period (days 12–21). No evidence exists of cumulative neutropenia (Lonial et al., 2005).

^b A decrease is anticipated in the platelet count during the treatment period (days 1–11), with return to baseline during the rest period (days 12–21). No evidence exists of cumulative thrombocytopenia (Lonial et al., 2005, 2007).

Note. Based on information from Celgene Corporation, 2007a, 2007b; Millennium Pharmaceuticals, Inc., 2006.

role in reducing the risk of febrile episodes, as does prompt intervention in the event of a febrile episode. In the absence of neutrophils, fever may be the only sign of an active infection. Multiple organ systems can be affected by infection, including respiratory, urinary, and gastrointestinal (Held-Warmkessel, 2000; Marrs, 2006). Assess patients for fever and associated symptoms such as chills, myalgias, malaise, nausea, hypoten-

sion, and hypoxia (Nunez & Liebman, 1999; West & Mitchell). Observe the oral mucosa and skin for any breaks in tissue and signs of infection. If a patient has a central venous access device, assess the exit site for erythema or exudate. A complete nursing assessment of all systems may reveal the source of a potential or actual infection (Held-Warmkessel, 2000). An accurate patient history also can provide information indicating

whether a patient is at high risk of infection when neutropenic. Previous exposures to bacteria, viruses, and fungal contaminants through travel, pets, and childhood infections can reactivate when patients are neutropenic. When a patient is at risk for neutropenia or becomes neutropenic, initiate institutional precautionary standards. Notify the patient's healthcare provider for medical intervention for neutropenia and neutropenic fever. Table 4 lists generally accepted medical management practices. If a neutropenic patient is found to be febrile, that is considered an emergency situation because the patient can progress quickly to septic shock (Burney, 2000; Turgeon-Lanes & Randolph, 2000). Administer prescribed antibiotics after blood cultures have been obtained and within one hour of presentation. IV hydration and antipyretics also should be administered in a timely manner if prescribed (Burney; Held-Warmkessel, 1998; Nunez & Liebman).

Thrombocytopenia: When platelet counts drop below normal (150–400 x 10⁹/L) to levels less than 100 x 10⁹/L, patients are classified as thrombocytopenic and are at greater risk of bleeding (Fukuyama & Itano, 1999). Life-threatening hemorrhage may occur when platelet levels decrease below 50 x 10⁹/L (grade 3 or 4). In addition to reviewing CBCs, nursing assessment should include a thorough patient history that covers any mucosal or gastrointestinal bleeding, increased bruising, or difficulty stopping bleeding. Physical examination should include evaluation of the mucous membranes and sclerae for signs of bleeding. Observe the skin for petechiae, multiple and large areas of bruising, and oozing from the exit site of a central venous catheter. A neurologic assessment also should be incorporated to monitor for symptoms of intracranial bleeding (Fukuyama & Itano; Held-Warmkessel, 1998, 2000). Generally accepted practices to manage thrombocytopenia include the following.

- Initiate institutional precautionary standards for thrombocytopenia.
- Minimize invasive procedures.
- Transfuse platelets prior to any necessary invasive procedures.
- Transfuse if signs of bleeding are present.

Recommendations for Monitoring Complete Blood Counts

All patients receiving novel therapies should have their CBCs monitored closely. Monitoring of serum creatinine levels also is important because decreased renal function may result in more severe anemia (Pandit & Vesole, 2003). If prolonged myelosuppression persists after dose modification or delay, further evaluation is recommended to rule out other possible causes, such as a reaction to another medication or progressive disease. The novel therapies bortezomib, lenalidomide, and thalidomide have specific recommendations for blood count monitoring, as follows.

- **Thalidomide:** Prescribing information recommends that blood count and differential be monitored on an ongoing basis, particularly in patients who may be prone to neutropenia (Celgene Corporation, 2007b).
- **Lenalidomide:** CBCs should be checked every two weeks for

- Patients should discuss any changes in prescribed medications with medical personnel prior to increasing or decreasing doses or stopping medications earlier than prescribed.
- Provide patients with indications for contacting medical personnel based on institutional policy and provide them with emergency contact numbers.
- Discuss the importance of blood count monitoring while receiving treatment, as indicated for the novel therapy prescribed.
- Outline the normal and critical values of blood counts as defined by the laboratory where the patient's blood is monitored.
- Explain the signs and symptoms of anemia that may indicate the need for a red blood cell transfusion.
- Discuss the risks and benefits associated with transfusions.
- Encourage patients to balance activity and exertion with available energy and to use assistive devices to spare energy (Boyer, 2000).
- Cover the signs and symptoms of infection.
- Neutropenic precautions and education should include the following.
 - Proper handwashing and good overall personal hygiene to reduce contact exposures
 - Proper skin care with lotion to keep skin moist and to reduce the risk of breaks in tissue (Held-Warmkessel, 2000)
 - Wearing a face mask during periods of neutropenia when the patient is outside of his or her own living space to reduce airborne infections
 - Avoidance of crowds and potential contagions
- Discuss the signs and symptoms of thrombocytopenia.
- Thrombocytopenic precautions and education include the following.
 - Avoid using aspirin, ibuprofen, or naproxen unless otherwise instructed (e.g., when aspirin is recommended for prophylaxis of thromboembolic events).
 - Avoid activities that can result in bruising or bleeding (e.g., blunt trauma, anal sex, body piercing or tattooing, contact sports).
 - Use an oral care regimen that includes soft sponges, nonabrasive toothpaste, and antimicrobial mouth rinses if bleeding occurs when brushing (Held-Warmkessel, 2000).

Figure 1. Recommendations for Patient and Caregiver Education

the first 12 weeks, then at least monthly thereafter (Celgene Corporation, 2007a).

- **Bortezomib:** Prescribing information recommends that blood counts be monitored prior to each dose of bortezomib (Millennium Pharmaceuticals, Inc., 2006).

Specific recommendations for monitoring and managing myelosuppression associated with thalidomide, lenalidomide, and bortezomib are presented in Table 5.

Recommendations for Patient and Caregiver Education

Healthcare providers should educate patients and their caregivers on the basic concepts of myelosuppression (see Figure 1). Education should occur prior to patients becoming myelosuppressed and should be reinforced frequently (West & Mitchell, 2004).

Conclusions

Although anemia, neutropenia, and thrombocytopenia are expected side effects of novel therapies for multiple myeloma, they are manageable with careful monitoring of patients' blood counts, dose adjustments when indicated, prophylactic treatment, and concomitant therapies as necessary. Nursing assessment, intervention, and education of patients and caregivers play a vital role in promoting patient adherence and maintenance of prescribed therapy, thereby enhancing patient outcomes.

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Author Contact: Teresa Miceli, RN, BSN, can be reached at miceli.teresa@mayo.edu, with copy to editor at CJONEditor@ons.org

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Patient Education Sheet: Managing Myelosuppression From Novel Agents for Multiple Myeloma

KEY POINTS

Novel therapies used to treat multiple myeloma include thalidomide, lenalidomide, and bortezomib. The drugs can cause myelosuppression, which is a decrease in bone marrow activity, resulting in fewer red blood cells (anemia), white blood cells (neutropenia), and platelets (thrombocytopenia). The risk of side effects varies with each medication. Managing the side effects can reduce your discomfort, prevent serious complications, and allow you to receive the best treatment for your myeloma. Your healthcare provider may change your dose or schedule of medication to help manage your symptoms. Do not stop or adjust medications without discussing it with your healthcare provider.

ANEMIA

Anemia is a decrease in red blood cells, or hemoglobin, which carry oxygen in the blood. It may result from myeloma treatment, decreased kidney function, myeloma disease, or other medications.

Symptoms of anemia can include fatigue, low energy level, difficulty with normal daily activities, shortness of breath with activity, and chest pain with activity.

If you experience symptoms of anemia, contact your healthcare provider.

Try not to use too much energy in daily activities.

Your healthcare provider may prescribe a red blood cell supplement such as iron, erythropoietin, or a red blood cell transfusion. If necessary, changes may be made in medications you are taking.

NEUTROPENIA

Neutropenia is a decrease in white blood cells, which protect against infection. It may result from myeloma treatment, myeloma disease, or other medications.

Note. For more information, please contact the International Myeloma Foundation (1-800-452-CURE; www.myeloma.org). The foundation offers the Myeloma Manager™ Personal Care Assistant™ computer program to help patients and healthcare providers keep track of information and treatments. Visit <http://manager.myeloma.org> to download the free software.

Note. Patient education sheets were developed in June 2008 based on the International Myeloma Foundation Nurse Leadership Board's consensus guidelines. They may be reproduced for noncommercial use.

The greatest concern with neutropenia is infection. Symptoms can include fever of 100.5°F (38°C) or higher, shaking chills, dizziness, fainting, redness at a wound site, difficulty breathing, cough, or sinus congestion.

If you experience fever or symptoms of infection, contact your healthcare provider immediately.

To reduce your risk of infection, wash your hands carefully and often, avoid crowds, and take antibiotics as prescribed by your healthcare provider.

Your healthcare provider will check your blood counts regularly based on your plan of care and may prescribe antibiotics to prevent infection and growth factors to stimulate white blood cell growth. If necessary, changes may be made to medications you are taking.

THROMBOCYTOPENIA

Thrombocytopenia is a decrease in platelets that protect against bleeding. It may result from myeloma treatment, myeloma disease, or other medications. It may be associated more frequently with lenalidomide and bortezomib.

Symptoms of thrombocytopenia may include bruising, pink urine, nosebleeds, small red or purple spots on the body (petechiae), and bleeding that does not stop with pressure.

If you experience signs or symptoms of a low platelet count, contact your healthcare provider immediately.

To reduce your risk of bruising or bleeding, avoid taking aspirin, ibuprofen, or naproxen. Avoid activities that can cause bruising or bleeding, such as contact sports, anal sex, and heavy lifting. Participate in gentle exercise only.

Your healthcare provider will monitor blood counts regularly based on your plan of care and may prescribe a platelet transfusion. If necessary, changes may be made in medications you are taking.