

Understanding Doxil[®] in Myeloma



International Myeloma Foundation
12650 Riverside Drive, Suite 206
North Hollywood, CA 91607 USA

Telephone:

800-452-CURE (2873)

(USA & Canada)

818-487-7455

Fax: 818-487-7454

TheIMF@myeloma.org

www.myeloma.org



Table of Contents

Introduction	5
What Is Multiple Myeloma?	5
What Are the Stages of Multiple Myeloma?	7
What Is Doxil® and How Does it Work?	8
What Are the Possible Side Effects of Doxil® with VELCADE®?	9
Can Doses of Doxil® or VELCADE® Be Reduced If Necessary?	15
How Is Doxil® Plus VELCADE® Given?	15
Questions to Ask Your Healthcare Provider	15
About the IMF	17
Glossary	20
References	22



Introduction

You have been given this booklet to learn more about a new drug called Doxil® (doxorubicin HCl liposome injection). After reading this booklet you should know:

- What Doxil® is
- How Doxil® works
- The possible side effects of Doxil®
- Why Doxil® is administered in combination with VELCADE®
- The possible side effects of Doxil® given in combination with VELCADE® (bortezomib) for injection
- How Doxil® Plus VELCADE® is given

This booklet is meant to provide you with general information only. This booklet does not take the place of discussions with your doctor or nurse. Your doctor or nurse can answer questions related to your specific treatment plan. All words that appear in **bold** type are defined in the glossary at the end of the booklet.

What Is Multiple Myeloma?^{1,2}

Multiple myeloma (also known as myeloma and as **plasma cell neoplasm**) is a malignancy of the **immunoglobulin- (antibody)** producing **plasma cells** found in the **bone marrow**. It is a hematologic malignancy resembling leukemia. However, the malignant plasma cells, or myeloma cells, rarely enter the bloodstream as in a true leukemia.

Instead, the myeloma cells accumulate in the bone marrow, causing:

- Disruption of normal bone marrow function, most commonly giving rise to **anemia** (a low level of **red blood cells** in the bloodstream), although reduction in **white blood cell** and **platelet** counts can also occur
- Damage to bone surrounding accumulated myeloma cells
- Release of an abnormal protein, **monoclonal protein (M protein)**, into the bloodstream
- Suppression of normal immune function, observed as reduced levels of normal immunoglobulins and increased susceptibility to infection

Myeloma cells can also grow in the form of localized tumors or **plasmacytomas**. Plasmacytomas may be single or multiple and either medullary (confined within bone marrow and bone) or extramedullary (outside of the bone). When there are multiple plasmacytomas inside or outside bone, this condition is also called multiple myeloma.



The Stages of Multiple Myeloma^{2,3}

Stage I (low cell mass): Early disease. The bone structure appears normal or close to normal on x-ray images; the number of red blood cells and amount of calcium in the blood are normal or close to normal, and the amount of M protein is very low.

Stage II (intermediate cell mass): An intermediate stage between stage I and III

Stage III (high cell mass): More advanced disease. One or more of the following are present:

■ **Anemia**

- A high level of calcium in the blood
- More than 3 areas of advanced lytic bone lesions
- A high level of M protein in the blood or urine

Multiple myeloma is a serious malignancy, but it is treatable. Many patients experience a series of responses, relapses, and remissions. With new treatments, the average survival of 5 years for patients diagnosed with multiple myeloma may be extended.¹

Following diagnosis, several options are available for initial or frontline therapy. For patients who may be candidates for high-dose therapy with transplant, various induction regimens can be considered, including Thalomid® (thalidomide) with dexamethasone,⁴ dexamethasone alone, or other dexamethasone-containing

combinations.² The combination of the **alkylating agent** melphalan plus prednisone, a simple oral therapy, is an option for patients not considering bone marrow (stem cell) transplant with intravenous high-dose melphalan.² At the time of relapse, newer agents are frequently required to achieve further response. Revlimid® (lenalidomide) is available for use in this setting.^{2,5} VELCADE® (bortezomib) is also available for relapsed myeloma.^{2,6} VELCADE® is discussed in a separate booklet, **Understanding VELCADE®**, which is available from the International Myeloma Foundation.⁷ Doxil® given in combination with VELCADE® is an important new treatment option available.

What Is Doxil® and How Does it Work?

Doxil® is a prescription medication given to you by your doctor. Doxil® is a different form of the chemotherapy agent doxorubicin.

Doxil® is made by coating doxorubicin with **lipid** (fat). The fat bubble containing doxorubicin is called a liposome. The **liposome** is surrounded by another layer of a rubber-like material called methoxypolyethylene glycol (MPEG). This textured MPEG layer around the liposome may increase the time that Doxil® circulates in the bloodstream by protecting it from detection and destruction by the **immune system**. The FDA has recently approved Doxil® in combination with VELCADE® (bortezomib) to treat patients with



multiple myeloma who have not previously received VELCADE® (bortezomib) and have received at least one prior therapy.⁸

A large clinical phase III study looked at the safety and efficacy of Doxil® in combination with VELCADE® in 646 patients with myeloma who had not previously received VELCADE® and whose disease had progressed during or after at least one prior therapy. Patients were randomly assigned to receive either Doxil® plus VELCADE® (324 patients) or VELCADE® alone (322 patients). The **median time to disease progression** for patients treated with Doxil® plus VELCADE® was 9.3 months compared with 6.5 months for patients treated with VELCADE® alone.⁸

What Are the Possible Side Effects of Doxil® with VELCADE®?⁸

This is not a complete list of side effects. Talk to your doctor or nurse for more information,

or if you experience these or any other side effects.

Important Safety Information

You should not take Doxil® if you are nursing. If you are pregnant or are planning to become pregnant, inform your doctor.

Heart-related Side Effects – Cardiotoxicity

Symptoms of heart-related side effects may include the following:

- Irregular heartbeat
- Shortness of breath
- Fatigue
- Ankle-swelling, which is caused by excess fluid

In some cases, these heart-related side effects may be serious and possibly permanent. Serious and possibly permanent heart-related side effects which may lead to **congestive heart failure**.

Your doctor will monitor your heart function and closely watch the dosage of Doxil® and any related chemotherapy agents. Inform your doctor of any history of heart disease, radiation to your chest, or prior chemotherapy. **Notify your doctor or nurse immediately if you experience any of the above symptoms.**

Infusion-related Reactions

Infusion-related reactions have been seen in some patients treated with Doxil®, so you will be closely observed for reactions during your infusion. In some patients, infusion-related reactions can be managed by either

slowing or stopping the infusion. In some patients, these reactions may be serious or life-threatening. If a reaction occurs, it usually happens during the first infusion.

Let your doctor or nurse know if you experience any of these or other symptoms during your infusion.

- Flushed feeling
- Dizziness or light-headedness
- Shortness of breath
- Chills
- Back pain
- Facial swelling
- Tightness in the chest or throat
- Headache

Decreased Blood Cell Counts

You may experience significant reduction in the number of blood cells in your body. This can cause other unwanted effects. Decreased white blood cell counts (**neutropenia**) can lead to fever and infections. Decreased red blood cell counts (anemia) can make you feel tired and fatigued. Decreased platelet counts (**thrombocytopenia**) can lead to impaired blood clotting and prolonged bleeding. Your doctor will check all of your blood cell counts regularly, and may give you medication that may help increase blood cell counts. Your doctor may also manage your blood cell counts by delaying and/or reducing your Doxil® and VELCADE® doses.

Notify your doctor or nurse immediately if you develop a fever of 100.5° F or higher.

Skin-related Reactions

You may experience a skin reaction called **hand-foot syndrome (HFS)**, also called **palmar-plantar erythrodysesthesia (PPE)**. It usually occurs on the palms of the hands and soles of the feet. HFS is generally observed after 2 or 3 cycles of treatment, but may occur earlier. Skin-related reactions may also occur on other parts of the body where your clothes may be tight or where friction, pressure, rubbing, warmth, and/or sweating occur.

Another skin-related reaction is **stomatitis**, a mouth irritation characterized by inflammation or sores.

Hand-Foot Syndrome (HFS)

You or a friend or family member should check regularly for signs of skin irritation and hand-foot syndrome. If you already have **peripheral neuropathy** (numbness or tingling in the hands and feet), you may not feel the symptoms of HFS.

Notify your doctor or nurse if you experience any of the following common signs and symptoms of HFS:

- Redness
- Rash
- Pain or tenderness
- Swelling
- Tingling, burning, or itching
- Flaking or peeling of the skin
- Small blisters or small sores on the palms of hands or soles of feet



In most patients, the reaction is mild and improves in 1 to 2 weeks without a delay in Doxil® therapy. However, in some cases, hand-foot syndrome can be serious and may impact your daily activities, which may require either delaying or stopping Doxil® therapy.

Stomatitis

Stomatitis may be managed with proper care of your mouth and by avoiding certain foods and beverages. Your doctor or nurse can provide you with guidelines that may help control stomatitis. For example, you might be told to rinse your mouth daily with salt water.

Notify your doctor or nurse if you experience any of the following:

- Mouth sores
- Dry, swollen tongue
- Dry, cracked lips
- Pain or burning in the mouth

- Inability to eat or drink
- Difficulty swallowing

Talk to your healthcare provider for suggestions that may help manage hand-foot syndrome or stomatitis.

Nausea and Vomiting

Nausea and vomiting are usually mild and may be managed with medication. Notify your doctor or nurse if you experience either of these symptoms.

Fluid Discoloration

Because of its color, Doxil® may cause urine and other body fluids to turn reddish-orange. This side effect is nontoxic and will disappear as Doxil® is eliminated from the body.

Other Most Common Side Effects

Notify your doctor or nurse if you experience any of the following:

- Nausea
- Vomiting
- Tiredness
- Weakness



Can Doses of Doxil® or VELCADE® Be Reduced If Necessary?

Possible dose reductions of your medication(s) are decisions best made by your physician. Therefore, it is important to communicate openly with your doctor or healthcare professional and keep regular appointments to maintain your treatment schedule. Your doctor may choose to modify your dose of either Doxil® or VELCADE® or both drugs as part of an overall plan to manage a particular side effect that you experience.⁸

How is Doxil® Plus VELCADE® Given?

Both Doxil® and VELCADE® are given as **intravenous (I.V.) infusions**, and must be administered by a healthcare professional in a supervised environment, such as a doctor's office or clinic. VELCADE® is administered on days 1, 4, 8, and 11 of a 21-day cycle. Doxil® is administered on day 4 only of the VELCADE® schedule, and is given after the VELCADE® dose.⁸

[Doxil Prescribing Information Section 2.4]

Questions to Ask Your Healthcare Provider⁹

- How can I prepare for my treatment?
- Why do you recommend Doxil® plus VELCADE®

- Will my treatment keep me from doing certain things?
- Will I be able to work and exercise during treatment?
- How often will I need to be checked after my treatment?
- Can I go back to my normal daily activities after treatment?
- What can I do to manage side effects?
- Can I talk to any of your patients who are currently receiving this treatment?
- What other drugs or treatments might I have to take?
- What symptoms or problems should I report right away?

IMF Hotline:

USA & Canada only: 800-452-CURE (2873)

Elsewhere: 818-487-7455

IMF Web site: www.myeloma.org

About the IMF

*"One person can make a difference,
Two can make a miracle."*

Brian D. Novis
IMF Founder

Myeloma is a little-known, complex, and often misdiagnosed bone marrow cancer that attacks and destroys bone. Myeloma affects approximately 75,000 to 100,000 people in the United States, with more than 20,000 new cases diagnosed each year according to recent data. While there is presently no known cure for myeloma, doctors have many approaches to help myeloma patients live better and longer.

The International Myeloma Foundation (IMF) was founded in 1990 by Brian and Susie Novis shortly after Brian's myeloma diagnosis at the age of 33. It was Brian's dream that future patients would have easy access to medical information and emotional support throughout their battle with myeloma. He established the IMF with the 3 goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients, their families, friends, and health care providers. Although Brian died 4 years after his initial diagnosis, his dream didn't. Today the IMF reaches out to an international membership of more than 165,000. The IMF was the first organization dedicated solely to myeloma, and today it remains the largest.

The IMF provides programs and services to aid in the research, diagnosis, treatment, and management of myeloma. The IMF ensures that no one must brave the myeloma battle alone.

We care for patients today, while working toward tomorrow's cure.

How Can the IMF Help You?

PATIENT EDUCATION

INFORMATION PACKAGE

Our free IMF InfoPack provides comprehensive information about myeloma, treatment options, disease management, and IMF services. It includes our acclaimed *Patient Handbook*.

INTERNET ACCESS

Log on to www.myeloma.org for 24-hour access to information about myeloma, the IMF, education, and support programs.

ONLINE MYELOMA FORUM

Join the IMF Internet Discussion Group at www.myeloma.org/listserve.html to share your thoughts and experiences.

MYELOMA MINUTE

Subscribe to this free weekly email newsletter for up-to-the-minute information about myeloma.

PATIENT & FAMILY SEMINARS

Meet with leading experts in myeloma treatment to learn more about recent advances in therapy and research.

MYELOMA MATRIX

On our website and in print, this document is a comprehensive guide to drugs in development for myeloma.

MYELOMA TODAY NEWSLETTER

Our quarterly newsletter is available free of charge by subscription.

SUPPORT

MYELOMA HOTLINE: 800-452-CURE (2873)

Toll-free throughout the United States and Canada, the IMF Hotline is staffed by trained information specialists and is in frequent interaction with members of our Scientific Advisory Board.

SUPPORT GROUPS

A worldwide network of more than 100 myeloma support groups hold regular meetings for members of the myeloma community. The IMF conducts annual retreats for myeloma support group leaders.

RESEARCH

BANK ON A CURE®

This DNA bank will provide genetic data research in new drug development.

THE INTERNATIONAL STAGING SYSTEM (ISS)

This updated staging system for myeloma will enhance physicians' ability to select the most appropriate treatment for each patient.

RESEARCH GRANTS

Leading the world in collaborative research and achieving extraordinary results, the IMF Grant Program supports both junior and senior researchers working on a broad spectrum of projects. The IMF has attracted many young investigators into the field of myeloma, and they have remained in the field and are actively pursuing a cure for this disease.

Glossary^{9,10}

Alkylating agent: A chemotherapy agent that prevents the growth and division of new cancer cells by inhibiting their ability to replicate DNA.

Alopecia: Hair loss.

Anemia: A low level of red blood cells in the bloodstream.

Antibody: A protein produced by some of the body's white blood cells that helps fight infection.

Bone marrow: A soft, spongy tissue found in most large bones that produces red and white blood cells and platelets.

Cardiotoxicity: Side effects affecting the heart.

Chemotherapy: Use of chemicals to treat or control cancer.

Congestive heart failure: Also known as heart failure; a condition in which the heart is unable to pump blood to the body's organs effectively.

Deep vein thrombosis (DVT): A blood clot in the deep veins of the lower part of the body

Hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia (PPE): a skin irritation typically occurring on the palms of the hands and soles of the feet or other parts of the body where friction, rubbing, or sweating occurs.

Immune system: The system of white blood cells and their products that helps the body resist infection and some cancers.

Immunoglobulin: An antibody.

Intravenous (I.V.) infusion: Delivery of a drug or fluid into the body using a needle inserted into a vein.

Lipid: Fat.

Liposome: Fat bubble containing a drug or other substance.

Lysis (lytic): Dissolution or destruction of cells.

Median: In the middle; the middle value of a series of values in order from lowest to highest.

Monoclonal protein (M protein): An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. A high level of M protein indicates that myeloma cells are present in large numbers.

Multiple myeloma: A cancer arising from the plasma cells in the bone marrow. The plasma cells in patients with multiple myeloma form abnormal antibodies, possibly damaging the bone, bone marrow, and other organs.

Neoplasm: Cancer.

Neutropenia: A low level of white blood cells in the bloodstream.

Peripheral neuropathy: Numbness, tingling, and/or pain in the hands, feet, legs, and/or arms.

Plasma cell: A type of white blood cell that produces antibodies.

Plasmacytoma: A tumor made up of cancerous plasma cells.

Platelet: An element in the blood that helps with clotting, which in turn helps repair damaged blood vessels.

Pulmonary embolism (PE): A blood clot that circulates in the bloodstream and ends up in the lungs.

Red blood cell: A blood cell that carries oxygen from the lungs throughout the body.

Side effect: An effect caused by treatment with a drug. The term usually refers to an unwanted effect, but some side effects may be beneficial.

Stage I (low cell mass): Early myeloma disease.

Stage II (intermediate cell mass): Stage of myeloma disease intermediate between stages I and III.

Stage III (high cell mass): More advanced myeloma disease.

Stomatitis: Mouth discomfort, including inflammation or sores in the mouth.

Thrombocytopenia: A low level of platelets in the blood. These low levels can cause bruising or bleeding as well as delay in the injury healing process.

Time to disease progression: The length of time from the beginning of treatment until the disease begins to get worse.

White blood cell: A cell made by the bone marrow that helps fight infection and/or disease.

References

1. Kyle RA, Rajkumar SV. Multiple myeloma. *New Engl J Med* 351:1860-1873
2. Durie BGM, Kyle RA, Belch A, et al. Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *The Hematology Journal* 4:379-398, 2003
3. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 36:842-854, 1975
4. *Thalomid® (thalidomide) Prescribing Information*, Celgene Corporation, 2006
5. *Revlimid® (lenalidomide) Prescribing Information*, Celgene Corporation, Thompson PDR, 2007
6. *Velcade (bortezomib) for Injection® Prescribing Information*, Millennium Pharmaceuticals, 2006
7. *Understanding Velcade (bortezomib) for Injection*; International Myeloma Foundation, 2006
8. *Doxil (doxorubicin HCl liposome injection) for intravenous infusion Prescribing Information*, Ortho Biotech, May 2007
9. *Questions and Answers About Doxil*; Ortho Biotech, 2007
10. *Stedman's Medical Dictionary*, 26th Ed. 1995