CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Explain how graft-versus-host disease (GVHD) develops
- Discuss current first-line treatments for GVHD
- Describe the mechanism of action of rituximab in GVHD

Disclosure of Conflicts of Interest

The Nurse Practitioner Healthcare Foundation (NPHF) assesses conflict of interest with its instructors, planners, reviewers, and other individuals who are in a position to control the content of CE activities. All relevant conflicts of interest that are identified are thoroughly vetted by NPHF for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. NPHF is committed to providing its learners with high quality CE activities and related materials that promote improvements or quality in health care.

The **faculty**: Courtney Cook, BSN, RN, Jessica Mansour, BSN, RN, Joanne Nassar, BSN, RN, Brooke Nayak, BSN, RN, reported no financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CE activity.

The **planners, reviewers, and staff**: Fiona J. Shannon, MHS, FNP; Phyllis Arn Zimmer, MN, FNP, FAAN; Joyce Pagan; Kristen Childress, DNP, ARNP; Connie Morrison-Hoogstede, MN, ANP, AOCNP, Genean M. Page, RN, OCN, reported no financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CE activity.

Disclaimer

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of or imply endorsement by Nurse Practitioner Healthcare Foundation, American Nurses Credentialing Center, or Haymarket Media Inc.

As this article contains only a review, participants have an implied responsibility to use this newly acquired information while also consulting other appropriate sources of information in order to gain full understanding of the topic.

GVHD in pediatric HSCT patients: Clinical trials for rituximab

Courtney Cook, BSN, RN; Jessica Mansour, BSN, RN; Joanne Nassar, BSN, RN; Brooke Nayak, BSN, RN

STATEMENT OF NEED/PROGRAM OVERVIEW

Hematopoietic stem cell transplantation (HSCT) is a frequently used treatment option for malignant conditions. Graft-versus-host disease (GVHD) is a common adverse effect of HSCT. Its symptoms are similar to those of other autoimmune diseases, and its morbidity and mortality are high. The use of rituximab for GVHD in pediatric HSCT patients is still in clinical trials; thus, its availability as a treatment for steroid-refractory GVHD is not well-known. In order to incorporate research findings into treatment, nurses need to decide whether that research would be useful in their practice. Learning about the research behind a new treatment and the possibilities regarding that treatment are the first steps of incorporating new treatments into practice.

CE INFORMATION

Title: GVHD in pediatric HSCT patients: Clinical trials for rituximab
Release date: August 15, 2012
Expiration date: August 15, 2014
Estimated time to complete this activity: 54 minutes

Free continuing nursing education credit of 0.9 in **pharmacology** is available. After reading the article, go to **myCME.com** to register, take the posttest, and receive a certificate. A score of 80% is required to pass.

Please note that the posttest is available only on **myCME.com**. The article may also be viewed at OncologyNurseAdvisor.com and on the Nurse Practitioner Healthcare Foundation Web site: www.nphealthcarefoundation.org. For more information, contact Fiona Shannon at fiona@nphealthcarefoundation.org.

This continuing nursing education activity is provided by the Nurse Practitioner Healthcare Foundation (NPHF).

NPHF is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Target audience: This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

Media: Journal article and Web site (myCME.com; OncologyNurseAdvisor.com; nphealthcarefoundation.org)

Co-provided by the Nurse Practitioner Healthcare Foundation and Haymarket Media Inc.

CONTINUING EDUCATION

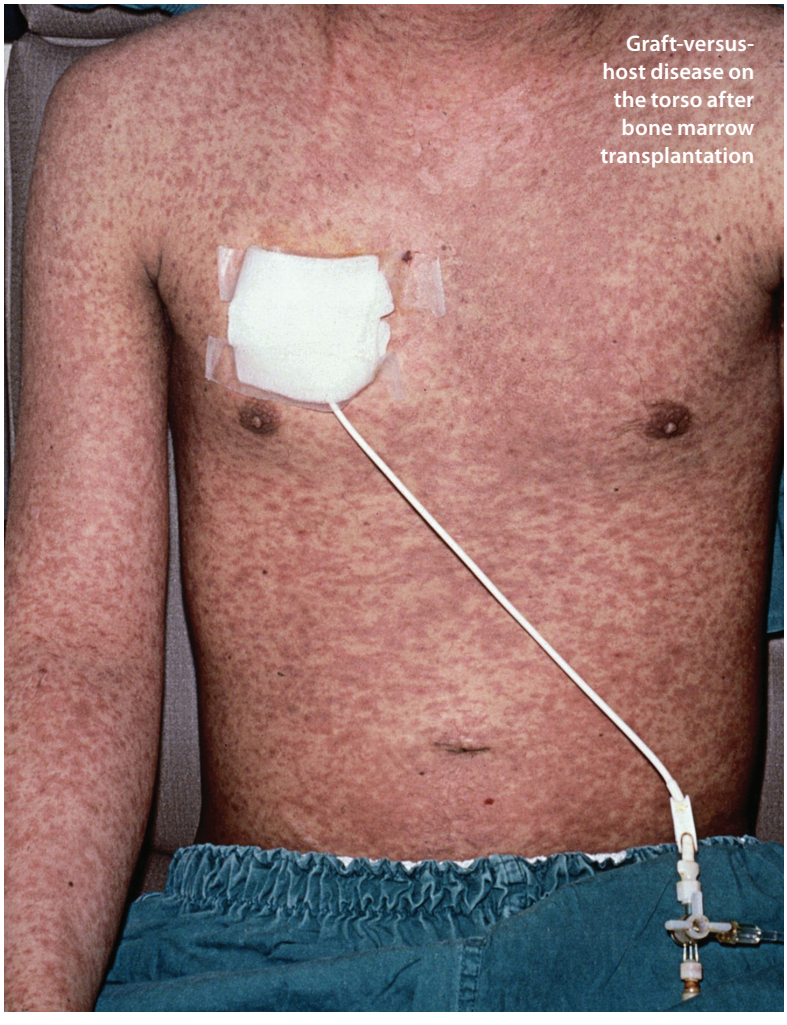
EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Explain how graft-versus-host-disease (GVHD) develops
- Discuss the current first-line treatments for GVHD
- Describe the mechanism of action of rituximab in GVHD

GVHD in pediatric HSCT patients: Clinical trials for rituximab

The CD20 antagonist is a potentially effective preventive and treatment for this common adverse effect of hematopoietic stem cell transplantation.



Graft-versus-host disease on the torso after bone marrow transplantation

COURTNEY COOK, BSN, RN;
JESSICA MANSOUR, BSN, RN;
JOANNE NASSAR, BSN, RN;
BROOKE NAYAK, BSN, RN

The most common adverse event following allogeneic hematopoietic stem cell transplantation (HSCT) is graft-versus-host disease (GVHD), which can increase morbidity and mortality in HSCT patients. The three sources of stem cells include bone marrow, umbilical cord blood, and peripheral blood.[1] HSCT is most commonly used as a treatment option for malignant conditions. Allogeneic transplants involve grafts from a genetically nonidentical donor of the same species and are the transplant type most often used in children. Chemotherapy, radiation, or both are initiated prior to transplantation to enable engraftment of the transplanted cells, decrease tumor size, and reduce immunoreactivity of the recipient.[2]

An environment for GVHD is formed when antigen-presenting cells are activated by the patient's disease and the pretreatment destruction of cells caused by chemotherapy and

TO TAKE THE POSTTEST FOR THIS CE ACTIVITY
and apply for 0.9 contact hours, please go to **OncologyNurseAdvisor.com/CEAugust2012**.

radiotherapy.[1] After transplantation, donor T cells are activated by antigen-presenting cells. Donor T-cells proliferate and inflammatory mediators are recruited. Cytotoxic T cells mount a response on the body and target recipient cells are lysed. This overactive immune response can cause significant damage to healthy tissue. GVHD can involve any organ; but the skin is the most affected organ, with the GI tract and liver also commonly involved organs.[1] A typical cutaneous reaction manifests as macular lesions first appearing on the upper back and lateral neck, jaw, ears, palms, and soles. A severe cutaneous reaction may include blisters with full-thickness necrosis. Diagnosis of GVHD is difficult because of its broad presentation that may manifest similar to other conditions such as drug reactions and viral infections.[2]

To date, no standard treatment is established for GVHD and no therapies are FDA approved for this indication in pediatric or adult patients.[3] Currently, prednisone in combination with cyclosporin or tacrolimus (Prograf, Protopic, generics) is used as a first-line preventive therapy. Treatment focuses on blocking the expansion of donor T cells, as GVHD develops from the expansion of these cells. Other treatments are extracorporeal photopheresis, pentostatin (Nipent, generic), tumor necrosis factor (TNF) antagonists, and CD20 antagonists. Extracorporeal photopheresis inactivates antigen-presenting cells and T cells, whereas TNF antagonists decrease cellular activation and local tissue damage. CD20 is an antigen expressed on the surface of B cells. CD20 antagonists deregulate B cells, which are believed to contribute to the pathogenesis of GVHD.[4] One of the primary pathways in which T cells are activated is through antigen-presenting cells such as B cells. When CD20 antagonists decrease the amount of circulating B cells, the body may not produce as many cytotoxic T cells that can potentially induce GVHD.[1]

Recent studies are investigating the efficacy of rituximab (Rituxan) for GVHD in pediatric HSCT patients. This article discusses the current status of clinical trials of rituximab to treat GVHD in the pediatric population.

HISTORY OF CLINICAL USE

Rituximab was developed in 1986 and received FDA approval for the treatment of B cell non-Hodgkin lymphomas in 1997. Rituximab attaches to the CD20 surface of mature B cells and destroys both normal and malignant B cells. The versatile drug is now also approved for the treatment of B-cell Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis in the adult population.

The package insert states that use of rituximab in children has not been studied;[5] however, it has been used to treat many pediatric hematologic conditions, including chronic immune thrombocytopenic purpura, posttransplant lymphoproliferative disease, juvenile rheumatoid arthritis, and other blood dyscrasias. Therapeutic response has been beneficial and resulted in successful treatment of these diseases.[6]

Several studies are analyzing the effectiveness of rituximab in improving morbidity and mortality in pediatric transplant patients. Although not a first-line treatment for GVHD, rituximab may offer an alternative treatment option for GVHD in pediatric patients.[6]

CLINICAL TRIALS

Several studies currently in progress analyze the effectiveness of rituximab on improving health outcomes in pediatric HSCT patients. The National Institutes of Health (NIH) references one such study in which rituximab improved symptom management in pediatric patients with chronic GVHD.[7] Participants received one dose of rituximab 375 mg/m^2 per week for the first 4 weeks of treatment, and those who did not respond well received an additional weekly dose. At 1-year follow-up, 70% of participants had improved symptoms. Two of the 21 participants had no signs of disease. Rituximab demonstrated the most benefit for patients who had GVHD of the skin. The NIH recommends further investigation of this medication as a prophylactic and initial treatment regimen.

Rituximab is a chimeric murine monoclonal antibody that binds to the CD20 antigen on B cells and facilitates apoptosis.

In addition to being a treatment option for GVHD, rituximab is also an antineoplastic agent. M.D. Anderson Cancer Center in Houston, Texas, is sponsoring a study to determine if cord blood is safe for transplantation in patients with leukemia or lymphoma.[8] In this study, which is not yet recruiting participants, researchers plan to use a rituximab dose of 375 mg/m^2 via intravenous (IV) route. This study will include participants aged 1 to 80 years, and completion is anticipated for April 2015.

A clinical trial at St. Jude Children's Research Hospital in Memphis, Tennessee, is investigating rituximab as a preventive agent in patients who underwent haploidentical blood and bone marrow stem cell transplant.[9] Investigators are recruiting patients with acute lymphocytic leukemia, acute myeloid leukemia, chronic myelogenous leukemia,

juvenile myelomonocytic leukemia, hemoglobinuria, paroxysmal nocturnal hemoglobinuria, Hodgkin lymphoma, non-Hodgkin lymphoma, or myelodysplastic syndrome. The interventions under investigation in this study are systemic chemotherapy and antibodies, including rituximab. The primary outcome is 1 year free of GVHD symptoms.[9]

Rituximab has been well tested in adults; current studies are investigating its potential for pediatric patients with GVHD. Shimabukuro-Vornhagen and colleagues summarized eight studies on the use of rituximab for the treatment of chronic GVHD in adults.[10] Of the studies noted, response rates varied between 43% and 80%. GVHD of the skin responded well to B cell depletion, whereas GVHD of organs such as the liver and GI tract did not respond as well.[10]

PHARMACOKINETICS AND PHARMACODYNAMICS

Rituximab is a genetically engineered chimeric murine monoclonal antibody that binds to the CD20 antigen on B cells and facilitates apoptosis. The drug is used to treat diseases that manifest as an overabundance of B cells or dysfunctional B cells. Rituximab destroys both normal and malignant B cells, allowing for the apoptosis of malignant B cells so new healthy B cells can develop from lymphoid stem cells.[6] Its effectiveness for treatment of non-Hodgkin B cell lymphoma and low risk of toxicity has made rituximab the standard medication in the protocol for B-cell lymphomas.

The drug is metabolized by the liver and is excreted mainly via the renal route. Rituximab distributes widely to the heart, liver, lungs, spleen, and kidneys. Although it has a low toxicity risk, renal and hepatic values should be monitored in patients taking rituximab because of their vulnerable states. Rituximab is administered intravenously once a week for 4 weeks. Dose is not based on pharmacokinetics; rather it is based on the patient's therapeutic response to the drug.[11]

B cells were found to play a vital role in the inflammatory process that contributes to the GVHD-associated effects of HSCT.

Rituximab in combination with other drugs has been shown to improve morbidity and mortality in patients with autoimmune diseases. It is used in combination with methotrexate for rheumatoid arthritis to relieve symptoms associated with the disease that have had a negative response to other therapies. Rituximab is also used in combination with other drugs such as immunosuppressants or steroids to manage refractory chronic GVHD in adults. Traditionally, medications for GVHD target the T-lymphocytes; however, studies have demonstrated B cells are involved in the immunopathophysiology of acute and chronic GVHD.[4] The role of B cells in GVHD combined with the action of rituximab against B cells are leading researchers to investigate a potential new indication for the drug.

Rituximab is packaged in single-use vials with concentrations of 100 mg/10 mL and 500 mg/50 mL. It is administered as an IV infusion and should never be administered as an IV push or bolus. The prescribed amount of drug should be drawn from the vial and diluted with 0.9% sodium chloride or 5% dextrose in water, and concentrations should be 1-4 mg/mL. No other medications should be mixed or diluted with this drug. Patients can be premedicated with an antihistamine or acetaminophen to prevent side effects.

Pregnancy category for rituximab is C: Data to support use of this medication in pregnant women is not sufficient. In studies, a small amount of rituximab was secreted in the milk of monkeys.[5] Whether the drug is secreted in human breast milk is not known because no studies have been done. No safety guidelines have been established for rituximab use in the pediatric population. No significant difference was recognized between the use of rituximab in geriatric patients and young adults. No long-term animal studies have been conducted to determine if rituximab increases the risk of cancer or any type of mutation.

Precautions While rituximab has a low rate of toxicity, it does have some serious side effects and adverse reactions. As with all medications, allergic reaction is a severe side effect and rituximab should be stopped immediately if a patient reports any rash; hives; itching; difficulty breathing; swelling of the face, mouth, or lips. Less serious side effects include headache, light-headedness, mild fever and chills, mild muscle or joint pain, cold-like symptoms, diarrhea, and weakness.[2] Education, reassurance, and pharmacologic and nonpharmacologic treatments, when indicated, can assist the patient and family to cope with these possible side effects. Severe acute thrombocytopenia has also been reported with use of rituximab; therefore, any symptoms of internal bleeding such as bruising or unusual bleeding should be reported and the drug should be stopped immediately. Rituximab therapy should not be initiated if a patient reports a mouse or rat allergy because rituximab may contain a small amount of rat or mouse protein, which can cause a severe allergic reaction.[6]

Clinicians should be aware of the black box warning on the rituximab label.[5] Fatal infusion reactions are rare; however

if one were to occur, it would occur within 24 hours of the first dose. Tumor lysis syndrome; progressive multifocal leukoencephalopathy, a disease of the white matter of the brain; and severe mucosal reaction can occur and result in fatal outcomes.[5] If tumor lysis is suspected, clinicians should rapidly infuse IV fluids, administer antihyperuricemic agents, and monitor renal function. If progressive multifocal leukoencephalopathy is suspected, clinicians should discontinue rituximab and closely monitor the patient's neurologic status. Hepatitis B reactivation may occur in patients who are carriers of the virus. Patients who are carriers should be monitored for several months after infusion. Discontinue rituximab if reactivation occurs.

Live-virus immunizations should not be administered while the patient is taking this medication or before starting this medication. If infection develops, rituximab should be held and appropriate anti-infective medications given. Assess complaints of abdominal pain because of the possibility of bowel obstruction or perforation. Monitor patients with cardiac conditions closely, as life-threatening arrhythmias may occur. Monitor CBC weekly or monthly for severe cytopenia depending on each specific patient.

TABLE 1. What to tell your patient

Rituximab may take weeks to months to be therapeutic.
Rituximab is given intravenously (a tube in your vein) in a hospital or a doctor's office.
Rituximab is used to treat graft-versus-host disease (GVHD) to kill some of the cells that cause this problem.
Rituximab lowers your immunity, and acquired infections may become severe while you are taking this medication.
You should stay away from people with colds or the flu while you are taking this medication.
Rituximab may cause stomach upset or vomiting.
You may experience these side effects
• Cough • Dizziness • Fatigue • Flu-like symptoms • Headache • Swelling in your arms or legs • Nasal drainage
If you experience any of these side effects, call your doctor or oncology care provider immediately.
• Black tarry stools • Bruising or bleeding • Cyanosis • Difficulty breathing • Fever • Itching • Loose stools • Mouth or skin irritation • Swelling in your face, lips, tongue, or throat • Yellowing of your skin or eyes

PATIENT AND FAMILY EDUCATION

HSCT involves long hospital stays, and patients and families learn a great deal about their treatment. Powerful, high-dose medications such as rituximab may produce severe side effects; therefore, thorough patient education about these medications is necessary. Nurses should ask about allergies before administering any drug; in particular, nurses should ask the patient or family about a past allergic history to rituximab or mouse proteins.[7] **Table 1** lists additional teaching points for patients who are taking rituximab and their families.

Acetaminophen and diphenhydramine may be given before administration of rituximab to reduce fever and chills.[7] Rituximab should not be started if the patient currently has an infection. Patients should be tested for hepatitis before starting therapy because an infection could get worse after treatment initiation. If a pediatric patient is taking a blood pressure medication, it may need to be held the morning of treatment because rituximab may cause low or high blood pressure. Laboratory test results on the patient's blood need to be checked frequently because the drug can lower the white blood cell or platelet count. Nurses should obtain a current list of medications from the family or patient and advise against taking any products containing aspirin or ibuprofen, blood thinners, garlic, ginseng, gingko, or vitamin E without discussing it with their health care provider.

CONCLUSION

Rituximab has existed for years as a treatment for many disorders, but recently its benefits in the prevention and treatment of GVHD were discovered. The drug attaches to the CD20 surface antigen of B cells and destroys the cells. B cells were found to play a vital role in the inflammatory process that contributes to the GVHD-associated effects of HSCT. This discovery has prompted researchers to study the effectiveness of rituximab for GVHD in pediatric patients. Research is focusing on determining the appropriate dose and frequency for therapeutic effect in this patient population. Health care providers should keep their knowledge of treatment options for patients undergoing stem cell transplantation current to improve morbidity, mortality, and quality of life for patients. The use of rituximab to treat GVHD in pediatric patients is showing promise. ■

Courtney Cook is a staff nurse at Children's Hospital of Michigan, Detroit. **Jessica Mansour** is a nurse in pediatrics at William Beaumont Hospital in Royal Oak, Michigan and a former instructor at Madonna University in

Livonia, Michigan. **Joanne Nassar** is an ICU nurse at Oakwood Hospital Medical Center, Dearborn, Michigan. **Brooke Nayak** is a nurse at Mott Children's Hospital, Ann Arbor, Michigan. The authors are also NP graduate students at Wayne State University, Detroit, Michigan.

REFERENCES

1. Goddard DS, Horn BN, McCalmont TH, Cordoro KM. Clinical update on graft-versus-host disease in children. *Semin Cutan Med Surg.* 2010;29(2):92-105. doi:10.1080/14622200410001676305.
2. Choi SW, Levine JE, Ferrara JL. Pathogenesis and management of graft-versus-host disease. *Immunol Allergy Clin North Am.* 2010;30(1):75–101. doi:10.1016/j.iac.2009.10.001.
3. Inamoto Y, Flowers ME. Treatment of chronic graft-versus-host disease in 2011. *Curr Opin Hematol.* 2011;18(6):414–420.
4. Pérez-Simón JA, Sánchez-Abarca I, Díez-Campelo M, et al. Chronic graft-versus-host disease: Pathogenesis and clinical management. *Drug.* 2006;66(8):1041–1057.
5. Highlights of prescribing information [Rituxan]. Genentech Web site. http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf. Accessed July 3, 2012.
6. Giulino LB, Bussel JB, Neufeld EJ; Pediatric and Platelet Immunology Committees of the TMH Clinical Trial Network. Treatment with rituximab in benign and malignant hematologic disorders in children. *J Pediatr.* 2007;150(4):338–344, 344.e1.
7. Medications: What you should know. Rituximab. KidsHealth from Nemours Web site. http://kidshealth.org/parent/medications/rituximab.html#cat18. Accessed July 23, 2012.
8. Cord blood fucosylation. http://www.clinicaltrials.gov/ct2/show/NCT01471067?term=cord+blood+fucosylation&rank=1. Accessed July 3, 2012.
9. Mismatched Family Member Donor Transplantation for Children and Young Adults With High Risk Hematological Malignancies. http://www.clinicaltrials.gov/ct2/show/NCT00566696?term=mismatched+family+member+donor&rank=1. Accessed July 23, 2012.
10. Shimabukuro-Vornhagen A, Hallek MJ, Strob RF, von Bergwelt-Baildon MS. The role of B cells in the pathogenesis of graft-versus-host disease. *Blood.* 2009;114(24):4919–4927.
11. Bates JS, Engemann AM, Hammond JM. Clinical utility of rituximab in chronic graft-versus-host disease. *Ann Pharmacother.* 2009;43(2):316–321.

TO TAKE THE POSTTEST FOR THIS CE ACTIVITY
and apply for 0.9 contact hours, please go to
OncologyNurseAdvisor.com/CEAugust2012.