Safety Culture of Chemotherapy/Biotherapy
Michelle Ahnberg, BSN RN CPON®

Objectives:
At the completion of this self-learning module, the learner will be able to:

1. Define the role of the Pediatric Hematology/Oncology nurse in the culture of safety regarding administration of chemotherapy or biotherapy.
2. Describe three strategies to decrease errors in chemotherapy administration.

Key Points:
1. Multiple safety strategies may be used to decrease errors in chemotherapy administration.
2. Oral therapeutic medications are quickly becoming a safety challenge.
3. Safe practice policies or guidelines for the administration of vincristine are strongly recommended.

Over one million patients are diagnosed with cancer in the United States each year. Of those newly diagnosed patients, approximately 4% or 48,000 will be the victims of an adverse event related to their care. Roughly 20% of adverse events are directly related to the administration of medications (Dinning et al., 2005). It is the role of the pediatric oncology nurse to embrace the safe administration of chemotherapy and biotherapy. It takes the commitment of not only the nurse, but the pharmacist, physician and hospital administration to promote and provide safe medication administration.

Strategies to decrease chemotherapy administration errors include proper pre-treatment assessment, standardized chemotherapy order forms and proper patient identifiers. The nurse must ensure that the patient’s laboratory values and imaging studies are within guidelines to administer chemotherapy. In addition, the pretreatment assessment includes the calculation of current BSA by obtaining current height and weight. It also includes the administration of appropriate prehydration and antiemetics (Dinning et al., 2005; Roll, 2007; Schulmeister, 2006).

Standardized chemotherapy order forms have been shown to reduce chemotherapy errors. All chemotherapy orders should have the complete generic name of the medication rather than name brands. Chemotherapy orders should also include the current height, weight and body surface area. Administration guidelines such as drug dose, route, and rate of administration should also be included in the chemotherapy orders (Dinning et al., 2005; Schulmeister, 2006).

Appropriate patient identification must occur prior to the administration of chemotherapy or biotherapy. The patient’s full name in addition to a second identifier, such as a birth date or medical record number are required as part of the appropriate patient identification (Jacobson, 2009).
Oral therapeutic medications are quickly becoming a safety challenge. The process to check oral chemotherapy or biotherapy is much less scrupulous than the process used to check intravenous (IV) chemotherapy medications. A task force was developed by the National Comprehensive Cancer Network to assess the impact of oral chemotherapy/biotherapy administration and safety. It was found that there is a need for increased patient education regarding oral medication administration and adherence, but no formal guidelines were developed by the task force (Jacobson et al., 2009; Johnson et al., 2010).

In addition, the potential lack of adherence to treatment guidelines, leads to a potential risk of increasing treatment failure. When patients are being treated with oral medications, a shift in care occurs. There is a transfer of medication administration from the nurse to the patient whereby the patient self administers the chemotherapy/biotherapy medications. It is this transfer of responsibility that can potentiate a decrease in adherence (Jacobson et al., 2009).

The administration of vincristine continues to be one of great concern. On July 14, 2005, The Joint Commission released a sentinel event alert regarding the prevention of intrathecal vincristine administration. They suggested that vincristine be administered via mini bags. If the vincristine was to be administered via a syringe, the syringe must be labeled with the following statement “FATAL IF GIVEN INTRATHECALLY. FOR IV USE ONLY. DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION”. In 2007, the World Health Organization (WHO) recommended that vincristine should not be administered via a syringe, but rather from minibags. The WHO also recommended that the labeling of vincristine should include the following statement “FOR INTRAVENOUS USE ONLY- FATAL IF GIVEN BY OTHER ROUTES”. Note that while these two organizations agreed that vincristine should ideally be administered via mini bags, they did not agree on the language of the safety labeling for the vincristine (The Joint Commission, 2005; World Health Organization, 2007).

So, how did the Children’s Oncology Group (COG) respond to these reports? The COG pharmacy committee made the following recommendations in a memo released on November 9th, 2007.

- A multidisciplinary team (pharmacists, nurses, physicians, administrators) should meet at each institution to review vincristine policies and to seek ways to increase patient safety.
- Policies and procedures should be developed that define where vincristine may be stored and administered.
- A “Time Out” should occur prior to the administration of all intrathecal medication.
- All vinca alkaloids must have appropriate labeling “Fatal if Given Intrathecally. For IV Use Only”.

Each individual institution should form a multidisciplinary team to determine whether to administer vincristine via a syringe or mini bag. Ultimately, it is up to this team to determine what mode of vincristine administration works best for the institution. From there, policies and
procedures need to be in place to guide pharmacy and nursing to administer vincristine as safely as possible (Children’s Oncology Group, 2007).

A final recommendation for safe administration of chemotherapy and/or biotherapy is to include the stakeholder. Caregivers of children receiving chemotherapy or biotherapy have a vested interest in ensuring safe administration of medications. Educate caregivers about the treatment plan as well as the names and colors of the medications being administered. Caregivers can help prevent chemotherapy/biotherapy errors and can catch near misses if they observe something unusual or deviations from the standard of care (Schulmeister, 2005).

**Use of Chemotherapy & Biotherapy for Hematologic & Non-Oncologic Disorders**
Deborah J Lee, BSN RN CPON®

**Objectives:**
1. Describe the mechanism of action of hydroxyurea as a supportive therapy for Sickle Cell Disease.
2. Describe at least two nursing considerations for patients receiving hydroxyurea.
3. Identify two autoimmune disorders that respond to chemotherapy and/or biotherapy.
4. Describe the role of chemotherapy/biotherapy in at least 2 inflammatory diseases.

**Key Points:**
1. Chemotherapeutic agents may be beneficial for non-oncologic disorders.
2. Biotherapy is an emerging and effective therapy for patients with auto-immune disorders and inflammatory diseases.

Chemotherapy has been used since the 1940s to successfully treat and manage a variety of oncology disorders. The use of chemotherapy has advanced from single-agent therapy to more complex combinations and routes of administration. In recent years, biologic response modifiers have emerged as an approach to “target” therapy for a more defined approach. In addition to treating oncology disorders, we are now seeing chemotherapy agents and biologic agents being successfully utilized to treat and improve outcomes for non-oncologic disorders.

**Hematologic Disorders**

**Sickle Cell Disease (SCD)**

Sickle-cell disease (SCD) is an autosomal-recessive genetic hemoglobinopath resulting from a mutation in the normal DNA that determines hemoglobin production. Sickle hemoglobin (HbS) is formed by an amino acid substitution (glutamine is substituted with valine). This amino acid substitution causes HbS to polymerize causing the red blood cells to form into a crescent or sickle-shaped cell. Affecting more than 89,000 people, SCD is the most prevalent genetic blood disorder in the United States. Pain crises, or vaso-occlusive crises, are the hallmark of SCD and the primary reason patients with SCD are hospitalized. Pain is the most distressing symptom of SCD, and it may be acute, chronic, or a combination of both. Other complications of SCD
include but are not limited to avascular necrosis, dactylitis, priapism, cholelithiasis, aplastic crisis, acute chest syndrome, stroke and infections. Preventive care is essential for patients with SCD, but supportive therapy with medications is also beneficial (O’Brien-‐Shea, 2008, Speller-‐Brown, Eimicke, & Martin, 2008).

Hydroxyurea is an oral chemotherapeutic agent that has been found to be an effective therapeutic intervention for patients with SCD. By inducing the synthesis of fetal hemoglobin (HbF) with an associated increase of total hemoglobin, hydroxyurea successfully reduces hospitalizations by decreasing sickling and the number and severity of pain crises in patients with SCD. Hydroxyurea also reduces the white blood cell count and reticulocytes which are thought to be “sticky” cells and contributors to vaso-occlusion. Patients treated with hydroxyurea require fewer transfusions, experience fewer episodes of acute chest syndrome, and have improved survival. Sustained long-‐term benefit, as well as prevention or even reversal of chronic organ damage has been documented in patients treated with hydroxyurea (Bender & Hobbs, 2003; Mueller, 2008; Speller-‐Brown, Eimicke, & Martin, 2008; Strouse et al., 2008).

One of the concerns regarding the use of hydroxyurea is that it is a chemotherapeutic agent and could potentially be carcinogenic. Education about contraception should be provided to patients of child-‐bearing age due to the drug’s potential carcinogenic effect on the fetus (Speller-‐Brown, Eimicke, & Martin, 2008). Healthcare personnel should use personal protective equipment and safe handling precautions when handling the drug. Because of its myelosuppressive effects, it is important for patients to be closely monitored. A complete blood count should be assessed on a regular basis; dosing of hydroxyurea may need to be adjusted based on the results.

Nurses should teach patients and families the importance of adequate hydration, avoiding extreme temperatures, and avoiding activities that cause physical exhaustion. Compliance with therapy and follow-up appointments is often a challenge for patients and families with SCD. Nurses should provide education about the importance of follow-up appointments and adherence to the medication regimen.

The only cure for patients with SCD is an allogeneic hematopoietic stem cell transplant. However, not all patients can find a suitable donor, and patients and their families often choose not to undergo such a high-‐risk procedure due to the risk of death from regimen-‐related side effects (Speller-‐Brown, Eimicke, & Martin, 2008). Stem cell transplant is usually reserved for patients with significant complications from SCD (i.e. a history of cerebrovascular accidents or several episodes of acute chest syndrome) and who have a matched sibling donor. However, with new developments in stem cell transplantation, such as non-‐myeloablative regimens, improved immunosuppression and management of graft-‐vs-‐host disease, and availability of alternative sources of cells (i.e. umbilical cord blood), transplant may increasingly become an option for more patients with SCD (Bender & Hobbs, 2009).
Autoimmune Disorders

According to Garvey (2008), autoimmune disorders are characterized by the production of antibodies against ‘self’ antigens (autoantibodies). Several autoimmune hematological disorders are caused by the effects of autoantibodies against blood proteins or cells. Autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP) are two of the most frequently encountered immune-mediated hematological disorders. It is thought that B cells play a key role in the development of autoimmunity, so treatments that aid in B-cell depletion can be a valuable treatment option for patients with autoimmune disorders.

Auto-immune hemolytic anemia (AIHA)

In AIHA, auto-antibodies are directed against self red blood cells (RBCs) which results in severe anemia and hemolysis which may lead to significant morbidity and mortality. Most patients respond to therapy, but those who are refractory have a reduced quality of life and increased mortality. Corticosteroids are typically the frontline treatment for AIHA. Second-line treatment is usually a splenectomy, but patients are at increased risk for post-splenectomy sepsis as a result of encapsulated bacterial organisms. Other drugs, such as IVIG, cyclophosphamide, azathioprine, and cyclosporine, are used, but they are often associated with serious side effects (Garvey, 2008; Gupta et al., 2010).

Rituximab is a chimeric, human, monoclonal antibody (MoAb) specific for the CD20 antigen on the surface of the B lymphocytes that has demonstrated efficacy in patients with AIHA. The fact that rituximab can selectively target the B cells gives it an advantage over other less selective immunosuppressive agents used in the treatment of AIHA (Speller-Brown, Eimicke, & Martin, 2011). Patients may experience chills, fever, headache, dyspnea, hypotension, pruritis, serum sickness or angioedema during the infusion of rituximab, so pre-medication with antipyretics, antihistamines, and corticosteroids should be given to prevent these reactions (Garvey, 2008).

Immune thrombocytopenic purpura (ITP)

Immune thrombocytopenic purpura (ITP) (also known as idiopathic thrombocytopenic purpura) is an immune-mediated disorder characterized by a transient or persistent decrease in the patient’s platelet count. The exact cause of ITP in children is not understood. The onset often follows a viral infection, but it could also be drug-induced (i.e. sulfonamides, heparin, alcohol, or quinine) or as a result of immune disorders, such as systemic lupus erythematosus or HIV. Symptoms may include bruising, petechiae, oral bleeding, and possibly epistaxis. ITP is diagnosed by assessing the history and physical along with exclusion of other causes of thrombocytopenia. There is no definitive diagnostic test available. A child’s risk for bleeding does not necessarily correlate with a low platelet count; therefore, practitioners have to use their best judgment when deciding whether or not to treat patients. Many children do not require treatment. The disease simply runs its course, and education about bleeding
precautions is provided. Parents and patients are encouraged to avoid rough play to report signs/symptoms of bleeding (Truglia, 2008).

The primary reason to treat children with ITP is to prevent intracranial hemorrhage. Frontline therapies include corticosteroids, IVIG, and anti-D immune globulin (WinRho™) which help by preventing the attachment of antibodies to the platelets. There is an FDA boxed warning for anti-D immune globulin and it is used with extreme caution because of reports of fatal intravascular hemolysis (IVH) in patients treated for ITP. Administering platelets is not beneficial for these patients since the autoimmune antibodies would destroy the freshly administered platelets. When ITP does not respond or is refractory to these treatments, additional treatment is required (Truglia, 2008).

Studies have demonstrated that slow administration of vincristine (VCR), a vinca alkaloid, has been successful in increasing platelet counts, but experience with VCR as a therapy for ITP is limited (Dovat, Roberts, Wakim, Stiehm, & Feig, 1999). 6-Mercaptopurine (6-MP), an oral purine antimetabolite, suppresses B & T lymphocytes and may also be used as a second–line treatment for ITP. Advantages of 6-MP are that it is relatively inexpensive, has low toxicities, and it is easy for patients to take at home (not requiring a lengthy clinic or hospital stay). Studies have shown that 6-MP is also effective in reducing patients’ dependency on steroids, and this is a desirable outcome since chronic steroid exposure poses many risks for patients (Sobota, Neufeld, Lapsia, & Bennett, 2009). It is preferable for patients to take 6-MP on an empty stomach at bedtime (Sullivan, 2008).

For patients with ITP refractory to steroids, other medications, or splenectomy, rituximab is a promising alternative therapy. Rituximab’s mechanism of action in ITP is unclear, but it is thought that rituximab’s ability to deplete B cells decreases antibody production. In the few existing reports, rituximab appears to be a safe and effective treatment for autoimmune disorders, and it seems to be more effective for children than adults. However, more studies are needed, as there are currently no randomized placebo-controlled trials available for the use of rituximab in children (Giulino, Bussel, Neufeld, 2010; Munn, & Valdiviez, 2011).

Inflammatory Disorders

Juvenile idiopathic arthritis (JIA)

Juvenile idiopathic arthritis (JIA) is a collective term for seven or more clinical patterns of arthritis in children. All of the different patterns of arthritis are defined “as a chronic arthritis in a child 16 years of age or younger, lasting for 6 or more weeks in the absence of any known cause” (Haines, 2007, p. 205). JIA is an autoimmune disease characterized by chronic joint inflammation, and it is the most common rheumatic disorder found in children (Lovell et al., 2011).

Nonsteroidal anti-inflammatory drugs (NSAIDS) have typically been used in the initial treatment for JIA, but their efficacy is not high. Children may have trouble swallowing whole pills, and
they may frequently report side effects such as abdominal pain. More aggressive therapy may also be needed if the patients are experiencing contractures or muscle atrophy (Haines, 2007). When NSAIDS are ineffective or inappropriate for children with JIA, methotrexate (MTX) is the second-line drug of choice. MTX has a relatively rapid onset of action, and it achieves efficacy at relatively low doses. MTX can be administered orally with once-a-week dosing. It has been reported that low dose MTX lacks oncogenicity and sterility effects. Therapy should be continued for at least one year after remission is achieved. Toxicities are usually seen in the liver, bone marrow, and occasionally the lung. Gastrointestinal and mucosal irritation can be reduced by administering folic acid daily. Patients should be taught to take MTX on an empty stomach with clear liquids 45 minutes before breakfast. If the patient experiences nausea/vomiting or is not able to tolerate oral dosing, the MTX can be administered subcutaneously (Kim, 2010).

Etanercept, infliximab, and adalimumab are examples of biologic response modifiers that may be used in addition to MTX for patients with unremitting inflammatory disease. Biologic response modifiers work by reducing inflammation. Etanercept is often selected when arthritis is unresponsive to MTX. It is administered subcutaneously twice a week. Caution should be taken to not administer etanercept to any child with an active infection or history of recurrent infections, and there is also a risk of reactivation of tuberculosis (TB), granulomatous or fungal disease with this drug. Varicella infections can also be more severe in patients being treated with these disease-modifying anti-rheumatic drugs. Therefore, it is important to ensure patients are screened for TB and have their varicella and measles immunity checked prior to initiating etanercept. Adalimumab, a human, IgG, monoclonal anti-TNF antibody, has been approved by the FDA for the treatment of moderate to severe polyarticular juvenile arthritis in patients four years and older (Kim, 2010; Lovell et al., 2011; Pain & McCann, 2009). A study by Lovell et al. (2011) demonstrated that adalimumab, administered with or without concomitant methotrexate, reduced symptoms of JIA in children, and the disease flares were less common in the children receiving adalimumab than the placebo group. Common side effects include injection site burning or pain, headache, upper respiratory symptoms, pharyngitis, bruising, and viral infections, but adalimumab is generally well-tolerated (Passo, 2006).

**Crohn’s disease (CD)**

Crohn’s disease (CD) is a chronic inflammatory intestinal disorder characterized by patchy inflammation of any portion of the gastrointestinal tract from the mouth to the anus. Patients with CD experience recurrent exacerbations with symptoms such as abdominal pain, diarrhea, rectal bleeding, weight loss, growth failure, and pubertal delay. The etiology of CD is unknown, but it is thought that immune system dysfunction, environmental factors, infectious microbes, genetic susceptibility, and ethnicity play a role. There is not currently a cure for CD, so therapy is approached with a progressive course of treatment as the disease severity increases. The goal of treatment is to alleviate symptoms and improve quality of life (Lee, et al., 2010; Parashette, Makam, & Cuffari, 2010).
Patients are typically started on corticosteroids which are fast-acting and effective. However, many patients do not respond favorably, develop dependency, or experience detrimental impacts on growth and development as a result of long-term exposure to corticosteroids. Infliximab is an anti tumor necrosis factor-alpha monoclonal chimeric antibody that has demonstrated efficacy in the treatment of CD. Tumor necrosis factor alpha is a cytokine that plays a role in the inflammatory processes in diseases like CD. Early therapy with infliximab may reduce complications associated with conventional treatment and may improve the patient’s quality of life (Lee, et al., 2010). As with other biologic response modifiers, patients taking infliximab are at increased risk for TB, upper respiratory tract infections, and other symptoms caused by immunosuppression. Patients may also experience anaphylactic-type reactions during the infusion, so it is recommended to use pre-medications prior to infusion (Kim & Choe, 2010). Having emergency equipment and anaphylactic kits at the bedside is also recommended. Infusions are usually slowly titrated up, and vital signs are monitored throughout the infusion.

**Methotrexate and Ifosfamide Toxicities**
Joy Hesselgrave, MSN RN CPON®

**Objectives:**
1. Identify signs and symptoms of nephrotoxicity after high dose methotrexate administration.
2. Describe the nursing considerations related to glucarpidase administration.
3. Identify signs and symptoms of ifosfamide neurotoxicity.
4. Identify nursing interventions for ifosfamide neurotoxicity.
5. Describe medical management of ifosfamide neurotoxicity.

**Key Points:**
1. Nephrotoxicity is a potential side effect of high dose methotrexate.
2. Neurotoxicity is a potential side effect of ifosfamide.

**Methotrexate**

Methotrexate is an antimetabolite that is widely used in childhood cancer to treat leukemia, lymphoma and osteosarcoma. It is also used for non cancerous conditions such as histiocytosis, juvenile rheumatoid arthritis, Crohn’s disease and systemic lupus erythematosus (Widemann & Adamson, 2006; Buchen et al, 2005). Methotrexate is administered by a variety of routes including oral, intramuscular, subcutaneous, intravenous and intrathecal. It is safely given over a wide range of doses from 20 mg/m² for maintenance chemotherapy to high dose which may range from 1 gm – 12.5 gm/m² (Lexicomp, 2011). Methotrexate given at any dose of 1 gm/m² or greater is considered to be high dose and is usually administered over a long infusion followed by leucovorin rescue. These high doses of methotrexate may be administered safely as long as patients have a normal renal function, receive vigorous hydration with alkalinized fluids, methotrexate levels are monitored post infusion and they receive leucovorin rescue (Widemann & Adamson, 2006). However, there is still a 1.8% occurrence of nephrotoxicity.

Methotrexate binds to the enzyme dihydrofolate reductase (DHFR) preventing the formation of reduced folates and thymidylate synthetase which are ultimately necessary for DNA synthesis (Lexicomp, 2011). After infusions of high dose methotrexate, folic acid replacement must be administered to reverse the effects of methotrexate and prevent toxicity. Leucovorin, a folic acid analog, is used to rescue normal cells from the effects of methotrexate and must be administered according to the protocol schedule. Methotrexate is cell cycle specific for the S phase of the cycle. The primary side effects of methotrexate are myelosuppresion and oral-intestinal mucositis which occur 5-14 days after the dose is administered (Snyder, 2007). Side effects are related to the drug concentration and the duration of exposure.

Methotrexate is metabolized in the liver which is a minor route of elimination. About 90% of methotrexate is cleared by the kidneys. Acute renal failure during high dose methotrexate therapy is a medical emergency. The renal toxicity is caused by tubular obstruction from crystal deposits of methotrexate and its insoluble metabolites. This nephrotoxicity contributes to delayed methotrexate elimination (Buchen et al 2005; Nowicki et al, 2008). If not treated early, the high levels of methotrexate can damage the ability of normal cells to synthesize DNA leading to cell death, resulting in renal, liver and central nervous system toxicity (Nowicki et al, 2008). Vomiting, diarrhea and an elevated creatinine have been identified as early symptoms of methotrexate toxicity. Most patients with renal dysfunction may be initially asymptomatic but will eventually show a decrease in urine output and may have elevated AST, ALT, BUN and potassium levels (Nowicki, 2008; Widemann & Adamson, 2006). Hemodialysis has been effectively used to decrease methotrexate levels but dialysis must be done daily until levels are low enough and it is not without its own risks (Widemann and Adamson, 2006). There is evidence to suggest that using high dose leucovorin as a sole form of rescue has effectively been done (Flombaum & Meyers, 1999). Glucarpidase, previously known as carboxypeptidase G₂ (CPDG₂), has been effective in rapidly reducing blood levels of methotrexate. However, glucarpidase has no impact on intracellular concentrations of methotrexate or on renal function.

Rescuing patients with carboxypeptidase G₁ (CPDG₁) after high dose methotrexate was originally explored in the 1970’s. This non recombinant bacterial product was isolated from an enzyme from the strain of Psuedomonas stutzeri. The bacterial source was lost and no further patients were treated. Subsequently, carboxypeptidase G₂ (CPDG₂) or glucarpidase, a recombinant form of the bacterial enzyme was cloned (Snyder, 2007; Widemann & Adamson, 2006). Glucarpidase rapidly converts methotrexate into its inactive metabolites DAMPA and glutamic acid providing an alternate route of elimination to renal excretion (Widemann & Adamson, 2006). In a study of 21 patients treated on a NCI compassionate use protocol, glucarpidase lowered plasma methotrexate concentrations within 15 minutes of administration by >98% (Widemann & Adamson, 2006). A similar study on 82 European patients showed a decrease of methotrexate levels by 97% 15 minutes after administration of glucarpidase (Buchen, et al, 2005). Glucarpidase is not commercially available in the United States and
Europe but was granted orphan drug status in 2003. Glucarpidase is available for intravenous use under an open-label treatment protocol use through a 24 hour access call center Clinical Trials and Consulting Services, Inc. (Lexicomp, 2011). It is anticipated that FDA approval will be available in the near future making the drug commercially available. The following are suggested criteria for using glucarpidase (Snyder, 2007; Widemann et al, 2010):

- The plasma MTX concentration is >10μM/L 42 hours or more after the start of a high dose infusion.
- The patient has renal dysfunction such as a serum creatinine concentration of 1.5 times the upper limit of normal or a creatinine clearance of <60 mL/min/m² and the plasma methotrexate concentration was >2 standard deviations above the mean >12 hours after methotrexate administration.

Leucovorin calcium may compete with methotrexate for binding sites and glucarpidase protocols may require withholding leucovorin for 2-4 hours before and 1-2 hours after glucarpidase administration (Lexicomp, 2011). The drug is reconstituted immediately prior to use and administered via IV infusion over 5 minutes. IV dosing is 50 units/kg/dose (Buchen, 2005; Lexicomp, 2011). Glucarpidase is generally well tolerated with transient grade 1 adverse events such as flushing, warmth, tingling of fingers, head pressure, fever, shaking, burning sensation (face and extremities) and pruritis (Wiedemann et al, 2010; Lexicomp 2011; Snyder, 2007). In a study of 20 patients who received glucarpidase rescue, the symptoms resolved without intervention and patients had stable vital signs. Based on a study of one hundred patients over a seven year period indicated that second and third doses of glucarpidase did not result in substantial decreases in plasma methotrexate concentrations but that leucovorin should be continued according to protocol nomograms until plasma MTX concentration were less than 0.05 to 0.1 μmol/L (Widemann et al, 2010).

After a patient has experienced nephrotoxicity related to a high dose methotrexate infusion there are no clear recommendations about future cycles except that they should be introduced with caution and reduced dosing considered according to the protocol recommendations (Snyder, 2007).

Several drugs are associated with increasing the toxic side effects of methotrexate when co-administered. These drugs include probenacid, salicylates, penicillins, ciprofloxacin, nonsteroidal anti-inflammatory agents, trimethoprimsulfamethoxazole and proton pump inhibitors such as lansoprazole, omeprazole and pantoprazole (Widemann & Adamson, 2006; Snyder, 2007). Doses of methotrexate should be held or dose reduced for patients who have ascites, edema or pleural effusions as methotrexate easily enters body fluids and this may result in delayed clearance with these conditions.

Nephrotoxicity is a relatively rare side effect of high dose methotrexate administration in pediatric patients. It results in delayed methotrexate clearance which requires adequate alkalized hydration, leucovorin rescue and patients may benefit from the additional administration of glucarpidase.
Ifosfamide Toxicity

Ifosfamide is an alkylating agent widely used to treat pediatric malignancies. It is used in combination with other antineoplastics to treat neuroblastoma, nephroblastoma, rhabdomyosarcoma, acute lymphocytic leukemia, Ewing’s sarcoma, osteosarcoma Hodgkin’s and non-Hodgkin’s lymphoma (Ajithkumar, et al 2007; Lexicomp, 2011). Ifosfamide is a pro-drug that is metabolized by the cytochrome P450 system in the liver into ifosforamide mustard (Kerbusch, et al, 2001; Lexicomp, 2011; Patel, 2006). This alkylating agent prevents the double strand separation of DNA, thereby preventing replication and causing cell death. The primary dose limiting toxicity of ifosfamide is myelosupression. Hemorrhagic cystitis used to be a significant complication of ifosfamide. This side effect can be prevented with adequate hydration and the administration of mesna which binds to the by-product, acrolein. Pediatric patients are also at risk for developing ifosfamide induced nephrotoxicity which may lead to Fanconi syndrome. This results in polyuria, metabolic acidosis and renal phosphate wasting (Kerbusch, et al, 2001).

Central neurotoxicity is the non hematologic dose limiting toxicity of high dose ifosfamide (Kerbusch, et al, 2001). Some degree of CNS toxicity can occur in about 10-30% of patients after high dose ifosfamide intravenous infusions (Ajithkumar et al, 2007). Oral ifosfamide has a higher incidence of neurotoxicity than intravenous therapy (Patel, 2006; Kerbusch, et al, 2001). The most accepted hypothesis is that one or more of the ifosfamide metabolites cause the CNS symptoms. During hepatic metabolism chloroacetaldehyde is produced, structurally similar to alcohol and chloral hydrate, both central nervous system depressants. It can cross the blood brain barrier and may be responsible for the neurological symptoms. Another metabolite of ifosfamide S-carboxymethylcysteine may also contribute to neurotoxicity (Patel, 2007).

Neurotoxicity occurs during or shortly after the infusion. Confusion is the most common symptom followed by hallucinations or psychosis. Patients may also become incontinent, exhibit muscle twitching, extrapyramidal symptoms, cranial nerve abnormalities, diplopia, seizures, mutism and dysarthria (Ajithkumar et al, 2007; Lexicomp, 2011). In children, ifosfamide induced encephalopathy can lead to a loss of developmental milestones (Ames et al, 2009; Ajithkumar et al, 2007). Ifosfamide toxicities may be graded according to the National Cancer Institute Common Toxicity Criteria listed below.

National Cancer Institute Toxicity Grading for Encephalopathy

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<tr>
<th>Toxicity Grade</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>1</td>
<td>None for encephalopathy</td>
</tr>
<tr>
<td>2</td>
<td>Mild signs and symptoms, no interference with activities of daily living</td>
</tr>
<tr>
<td>3</td>
<td>Signs and symptoms that interfere with activities of daily living, with hospitalization indicated</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening and/or disabling signs and symptoms</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
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Reported risk factors for neurotoxicity include a low serum albumin, elevated serum creatinine and the presence of a tumor in the pelvis or abdomen, prior therapy with cisplatin and prior central nervous system disease or cerebral metastasis (Ajithkumar et al, 2007; Kerbusch et al 2001; Patel, 2006). The encephalopathy does not seem to be dose related.

Ifosfamide encephalopathy usually reverses completely within 1-3 days after the drug’s infusion (Ajithkumar et al, 2007). Methylene blue has been used to treat and prevent ifosfamide encephalopathy. Based on published case reports and studies, the recovery from encephalopathy with methylene blue varies from 10 min to 8 days. Methylene blue is approved by the FDA for the treatment of methemoglobinemia and for relief of lower genitourinary tract discomfort (Patel, 2006). Its method of action in ifosfamide neurotoxicity is unclear; it may inhibit the formation of chloroacetaldehyde and restore a coenzyme (nicotinamide adenine dinucleotide) that allows oxidation of the toxic metabolites (Patel, 2006). Methylene blue may be given orally or intravenously. If given intravenously it may be administered over 5 minutes. Dosing for children > 12 years old is 50 mg every 6-8 hours and is continued until full recovery is observed (Lexicomp, 2011). Side effects of methylene blue are generally minor but may include dizziness, headache, confusion, hypertension, fecal and urine discoloration, nausea and vomiting. Methylene blue is contraindicated in patients taking psychiatric medications with serotonergic effects including SSRI’s, SNRI’s, tricyclic and MAOI antidepressants. It is also contraindicated in children with G6PD deficiency (Lexicomp, 2011). Other treatments that have been effective in decreasing symptoms of ifosfamide neurotoxicity include hemodialysis and thiamine infusions.
Biotherapy Agents- Molecular Targeted Therapies

Objectives

1. Describe common side effects of biotherapy agents.
2. Identify nursing interventions for select biotherapy agents currently in pediatric clinical trials.

Key Points

1. Pediatric patients receiving small molecule targeted therapies need to be closely monitored for adverse side effects.

One of the most rapidly evolving areas for cancer drugs is molecular targeted therapies. With a better understanding of tumor biology researchers have identified molecular pathways that are responsive to pharmacologic targeting (Bourdeau, et al, 2011). The benefit of small molecule drugs is that they can reach intracellular sites unlike the larger molecules of the monoclonal antibodies (Ruccione, 2011). The kinases are important because of the signaling pathways. By inhibiting their signaling function, cancer cell growth is deregulated. The small molecule kinase inhibitors generic names end in “ib” (Ruccione, 2011). There are also anti-angiogenesis drugs that target the vascular endothelial growth factor and receptors (VEGF and VEGFR) preventing new blood vessel growth. Additionally, drugs are being developed to interfere with the ubiquitin-proteasome system which inhibit cell proliferation, induce apoptosis and enhance chemotherapy (Ruccione, 2011).

Many of these new biotherapy agents are administered in conjunction with chemotherapy so there may be a wide variety of side effects that the nurse needs to monitor for. The targeted therapies require the nurse to be aware of unique administration considerations and to monitor for potential side effects and toxicities.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Classification &amp; Action</th>
<th>Route</th>
<th>Side Effects</th>
<th>Special Considerations</th>
<th>Nursing Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (Velcade™)</td>
<td>Proteasome Inhibitor Disrupting the proteasome pathway inhibits</td>
<td>Intravenous, subcutaneous</td>
<td>Common Bone marrow suppression- anemia, neutropenia and severe thrombocytopenia</td>
<td>One day before and 72 hours after bortezomib do not eat or drink items with antioxidants (vitamins, herbal supplements), green</td>
<td>Administer via rapid IV push (over 3-5 minutes) Monitor blood counts especially for anemia and</td>
</tr>
</tbody>
</table>
cellular proliferation and induces apoptosis

In Pediatrics – Current front line COG AML protocol

Has been used in relapsed Hodgkin’s, non-Hodgkin’s lymphoma and relapsed AML

| Gastrointestinal-nausea, vomiting, diarrhea or constipation CNS-psychiatric disturbance, fever, headache Neuromuscular – weakness, peripheral neuropathy Occasional Rash Arthralgias, bone pain, myalgias Cardiovascular – hypotension, syncope, prolonged QT syndrome Respiratory – dyspnea, cough Rare Acute liver failure Bleeding events Anxiety Heart failure, including pulmonary edema, congestive heart failure, hypotension Reversible posterior leukoencephalopathy syndrome | tea, vitamin C, ST John’s Wort. Avoid grapefruit or its juice for the duration of treatment | thrombocytopenia

Patient education regarding what foods and drinks should be avoided

Monitor for peripheral neuropathy and altered mental status
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Route</th>
<th>Common Adverse Events</th>
<th>Initial Dilution and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib</td>
<td>Tyrosine kinase inhibitor</td>
<td>Oral</td>
<td>Anemia, neutropenia, thrombocytopenia, diarrhea, nausea, fatigue, myalgia, headache, dyspnea, pleural effusion, fluid retention, macular-papular rash</td>
<td>Initial dilution is with apple juice but may be further added to other 100 % juices such as pineapple, grape, vegetable, cranberry and orange juice. Administer with food to decrease nausea and vomiting. Consider administration of 5-</td>
</tr>
<tr>
<td>Lestaurtinib</td>
<td>FLT 3 inhibitor</td>
<td>Oral</td>
<td>Nausea, diarrhea</td>
<td>Oral solution stable at room temperature, protect from light.</td>
</tr>
<tr>
<td>CEP-701</td>
<td></td>
<td></td>
<td>Occasional Vomiting, abdominal pain, constipation, dyspepsia, chills, fatigue, infection, neutropenia, chills, dizziness, headache, peripheral edema</td>
<td>Initial dilution of lestaurtinib is with apple juice but may be further added to other 100 % juices such as pineapple, grape, vegetable, cranberry and orange juice. Administer with food to decrease nausea and vomiting. Consider administration of 5-</td>
</tr>
</tbody>
</table>

Dasatinib (Sprycel™) is a tyrosine kinase inhibitor that binds to active and inactive ABL kinase targets. Kinase inhibition stops leukemia cell proliferation.

In pediatrics - used for CML and Philadelphia chromosome + ALL.

Lestaurtinib (CEP-701) is a potent inhibitor of several tyrosine kinases including FLT3 and Janus kinase (JAK2). In leukemic cells, lestaurtinib inhibits FLT3 activity and induces apoptosis.
| **Pazopanib (Votrient™)** | Strong inhibitor of vascular endothelial growth factor (VEGF), tyrosine kinase inhibitor  
In Pediatrics – Phase 1 for refractory solid tumors including CNS tumors  
In adults – metastatic renal cell carcinoma, melanoma, breast cancer, prostate, thyroid, colon and lung cancer. | **Oral** | **Common**  
Anemia, neutropenia  
Diarrhea  
Fatigue  
Nausea  
Hepatotoxicity (elevated AST, ALT, bilirubin)  
Hypertension  
Hyperglycemia  
Depigmentation of hair  
**Occasional**  
Anorexia  
Vomiting  
Constipation  
**Rare**  
Gastrointestinal hemorrhage, perforation and fistula  
Electrolyte abnormalities  
Onset of hypertension can be sudden, occurring within hours or days of starting pazopanib.  
Pazopanib may be affected by various CYP34A inducers or inhibitors. (e.g. strong inhibitors ketoconazole or clarithromycin so consider dose reducing Pazopanib. Verify potential drug interaction with pharmacist.  
Take on an empty stomach either one hour before or two hours after a meal.  
Available in powder for reconstitution  
Avoid crushing tablet.  
Encourage dietary consult and advocate for appetite stimulant if significant anorexia.  
Monitor for signs of dehydration from diarrhea or vomiting – use 5-HT₃ (ondansetron, granisetron) for nausea  
Hypertension, monitor B/P and ensure patient taking antihypertensives if needed | **Rare**  
Dehydration, dyspnea, hypotension, confusion, vertigo, muscle weakness, GI hemorrhage, cerebral infarcts, congestive heart failure, sinus bradycardia, torsades de pointes, pulmonary emboli, hepatotoxicity, peripheral neuropathy | **HT₃** antagonist as antiemetic prior to administration of lestaurtinib |
| **Left ventricular systolic dysfunction**  
| **Prolonged QT interval**  
| **with risk of Torsades de pointes**  
| **Hand-foot syndrome** | **Diarrhea** – educate in use of antimotility agent such as loperamide, adequate fluid intake, monitor I & O  
| **Prepare patient for potential hair color changes, yellowing of original hair color, depigmentation of hair color** |
Pneumocystis carinii Pneumonia 
Prophylaxis: Current Therapies 
and Recommendations

Faith Crozier RN, BSN, MSN, CPNP-AC

Abstract

Pneumocystis pneumonia (PCP) can be life threatening for children receiving chemotherapy and immunosuppressive medication, including high-dose steroids. Although there are no current guidelines for prophylaxis in pediatric oncology patients, ongoing studies are evaluating the efficacy, side effects, ease of administration, and compliance of drugs used for PCP prophylaxis. Drugs currently being prescribed in practice include Bactrim, pentamidine, dapsone, and atovaquone. Bactrim remains superior for preventing PCP, but alternatives are being analyzed and investigated for those unable to tolerate Bactrim because of drug allergy or side effects. Educating patients and families about the importance of PCP prophylaxis and compliance should be a priority for all health care providers caring for children receiving immunosuppressive medications, including chemotherapy.

Keywords

Pneumocystis jiroveci, pneumocystis pneumonia, prophylaxis

Introduction

Pneumocystis jiroveci (formerly Pneumocystis carinii) pneumonia (PCP) was first described as a eukaryote with fungal and protozoa features in 1940 (Pyrgos, Shoham, Rolildes, & Walsh, 2009). Though the scientific name formally changed in the 1990s, most clinicians continue to refer to PCP as Pneumocystis carinii (Lindemulder & Albano, 2007) pneumonia. Transmission is not well understood, but PCP invades the respiratory tract causing an acute onset of respiratory symptoms with or without fever. It is diagnosed by bilateral infiltrates with a ground glass appearance on chest X-ray or computed tomography scan or by staining from a sputum sample or lung biopsy (Pyrgos et al., 2009; Shankar, S.M. & Nania, J. J., 2007). The first pediatric case was reported in 1956 (Madden, Pui, Hughes, Flynn, & Leung, 2007). Although PCP is clinically diagnosed most often in immunocompromised individuals, including those with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), most healthy people are colonized with PCP by 2 to 3 years of age (“Cotrimoxazole Is Generally Used to Manage,” 2008). PCP has a higher mortality rate in non–HIV/AIDS patients, and the risk factors for developing PCP in non–HIV/AIDS patients include high-dose steroid therapy, chemotherapy-induced immunosuppression, solid organ or bone marrow transplant, and primary immune deficiency (Pyrgos et al., 2009). Also, a recent study cautioned that children younger than 2 years may be at an increased risk for developing PCP after chemotherapy treatment and stem cell transplant (SCT) though this was noted in a small sample of patients (Kim et al., 2008).

High-dose, prolonged steroid use is now considered the highest risk factor for developing PCP in pediatric patients, whereas patients with primary immune deficiency have the lowest risk (Bollée et al., 2007; Pyrgos et al., 2009). One case study published by Aviles, Boyce, and Thompson (2004) described a 3-year-old with airway hemangiomas who was treated with high-dose steroids for 6 weeks prior to developing PCP. The article further described 105 non–HIV/AIDS patients who developed PCP; 90% of those patients were receiving high-dose steroids. High-dose steroids were defined as a range of 2 mg/
kg/d for 14 days to 30 mg/d for 12 weeks (Aviles et al., 2004). A systematic review by Green, Paul, Vidal, and Leibovici (2007b) also found a steroid dose of 30 mg of prednisone per day for 12 weeks as the number one risk factor for developing PCP. Pyrgos et al. (2009) further defined a prednisone dose of greater than 0.4 mg/kg/d over several months and greater than 20 mg/d for longer than 3 weeks as an increased risk for developing PCP with some clinical disease documented during steroid tapers.

In pediatric oncology patients, diagnosis, chemotherapy treatment, drug regimen, and need for SCT can increase the risk of PCP by 15% to 20% (“Cotrimoxazole Is Generally Used to Manage,” 2008), leading to mortality rates of 50% to 76% (Milstone, Balakrishnan, Foster, & Chen, 2006; Pyrgos et al., 2009). Children with high-risk leukemia have a 15% to 21% increased risk compared with 5% to 15% increased risk for those children 1 year post-SCT (Ohata et al., 2009). Pyrgos et al. (2009) listed patients with lymphoid malignancies as having the highest risk for PCP in addition to patients receiving the following drugs: fludarabine plus steroids, temozolomide, alemtuzumab, and antitumor necrosis factor. Another study by Prasad, Nania, & Shankar (2008) cited the intensity of the chemotherapy regimen, the underlying diagnosis, and the addition of steroids as increasing the risk for developing PCP. Leukemia and lymphoma patients may be at an increased risk because of the tumor burden present in the marrow or lymph system directly decreasing the functionality of granulocytes and lymphocytes produced. Of note, a study by Bollée et al. (2007) reported that PCP occurred in some leukemia patients prior to starting treatment; and of the 56 patients studied who developed PCP, none were neutropenic at clinical presentation. This study further supports the idea that a dysfunctional marrow may put patients at an increased risk for developing PCP.

Without PCP prophylaxis, the risk of developing PCP ranges from 22% to 45% (Pyrgos et al., 2009). Prophylaxis was first described in HIV/AIDS patients and was extrapolated to cancer in the 1970s when Bactrim was found to reduce the incidence of PCP by greater than 90% (Green, Paul, Vidal, & Leibovici, 2007a). Children at risk for developing PCP include those being treated for various malignant or nonmalignant tumors with treatment regimens containing steroids, chemotherapy, and SCT. Prophylaxis should be initiated for these identified high-risk populations by the advanced practice nurses caring for them. The most common drugs used and researched for prophylaxis in pediatric oncology patients are reviewed below.

**Cancer and Prophylaxis: Review of the Literature**

There are no current, evidence-based guidelines for PCP prophylaxis in non-HIV pediatric patients (Green et al., 2007b). Bactrim (trimethoprim/sulfamethoxazole or cotrimoxazole) remains the gold standard for both prophylaxis and treatment of PCP (Shankar, S.M. & Nania, J. J., 2007). The first study examining the clinical efficacy of Bactrim was published in 1977 by Hughes and colleagues (Lindemulder & Albano, 2007). With compliance, the prevention rate for PCP with Bactrim is 93% to 100% (“Cotrimoxazole Is Generally Used to Manage,” 2008; Lindemulder & Albano, 2007; Ohata et al., 2009; Prasad et al., 2008; Pyrgos et al., 2009). Several studies have looked at the timing of medication administration for prophylaxis. When compared with daily dosing, twice-daily dosing on 2 consecutive days a week, 2 non-consecutive days a week, and 3 nonconsecutive days showed no difference in prevention rate (Green et al., 2007a; Lindemulder & Albano, 2007; Ohata et al., 2009; Pyrgos et al., 2009). Intermittent dosing was studied not only for efficacy but for side effect and compliance prevalence as well. Ohata et al. (2009) reported that 13.7% of patients were noncompliant even with 2 day nonconsecutive, twice-daily dosing however, neutropenia was reduced with intermittent dosing. In addition to preventing PCP, Pyrgos et al. (2009) noted that Bactrim could also cover additional bacterial infections and toxoplasmosis. Side effects that required switching from Bactrim to alternate forms of prophylaxis include drug allergy, gastrointestinal upset, rash, myelosuppression, compliance, and oral formulation (“Cotrimoxazole Is Generally Used to Manage,” 2008; Lindemulder & Albano, 2007; Ohata et al., 2009; Prasad et al., 2008; Pyrgos et al., 2009; Shankar, S.M. & Nania, J. J., 2007).

Pentamidine is often used as the alternative to Bactrim for PCP prophylaxis and is given monthly via inhalation or intravenous (IV) routes. Studies (Pyrgos et al., 2009) report pentamidine as having a successful treatment rate of 40% when compared with Bactrim (93%) and atovaquone (80%). One retrospective review (Kim et al., 2008) looked at 232 immunocompromised patients who received IV pentamidine for prophylaxis over 5 years, and 3 of the children (1.3%) developed PCP. Two of the patients were younger than 2 years and had received a bone marrow transplant. This is the only study that examined IV pentamidine use in pediatrics for PCP prophylaxis. Side effects associated with IV pentamidine administration include hypotension when administered rapidly, long QT syndrome, arrhythmias, renal dysfunction, nausea and vomiting and perioral numbness that resolves when the infusion is complete (Milligan & Phillips, 2007; Pyrgos et al., 2009). In addition, there was a case report of a 21-month-old receiving IV pentamidine for prophylaxis who developed PCP after 2 unrelated SCTs (Milstone et al., 2006). The implications of age on developing or preventing PCP with pentamidine are not well-defined, and further controlled studies are needed to evaluate IV pentamidine for PCP prophylaxis in pediatric oncology patients (Prasad et al.,
Inhaled pentamidine is also used for prophylaxis, though there are limited studies in pediatrics evaluating the efficacy and long-term side effects of this route of administration (Kim et al., 2008). Inhaled pentamidine should not be used in children younger than 5 years (Pyrgos et al., 2009) or those who are unable to breathe in the inhaled medication properly because of concern for adequate distribution. Side effects for the inhalation route include coughing, wheezing, nausea and vomiting, and bronchospasm (“Cotrimoxazole Is Generally Used to Manage,” 2008). Bronchospasm may be prevented or minimized with the use of age-appropriate albuterol prior to administration of pentamidine.

For children unable to tolerate Bactrim or pentamidine, dapsone may be used as the next line of treatment. Dapsone can be given orally daily or 3 times a week, and both schedules are equally effective (Williams, MacDonald, Hoyer, Barr, & Athale, 2005). Prevention of PCP with dapsone is similar to prevention of PCP with Bactrim (Sangiolelo et al., 2005). One retrospective study reported that out of 223 children, 1 of the 36 patients (2.7%) taking dapsone developed PCP (Prasad et al., 2008). Most research on dapsone has been related to potential adverse events including methemoglobinemia, rash, hemolytic anemia, liver dysfunction, and agranulocytosis (“Cotrimoxazole Is Generally Used to Manage,” 2008). Williams et al. (2005) did a 10-month retrospective study evaluating the incidence of methemoglobinemia in 15 children with acute lymphoblastic leukemia. He found that there was a correlation with cytochrome b5 reductase (Cb5R) enzyme levels in the patients who received Dapsone prophylaxis daily on Monday, Wednesday and Friday weekly. Three of the patients developed symptomatic methemoglobinemia and all patients had oxygen saturations greater than 95%. The study concluded that heterozygosity for the cytochrome b5 reductase gene may affect the incidence of methemoglobinemia and that hemolytic anemia associated with dapsone use worsens with increased age. When dapsone was stopped, the symptoms resolved (Williams et al., 2005). A case report of a patient who died from sulfone syndrome after receiving dapsone prophylaxis post-SCT reported the patient had fever, methemoglobinemia, hemolytic anemia, exfoliative dermatitis, and transaminits that lead to multisystem organ failure (Abidi, Kozlowski, Ibrahim, & Peres, 2006). These side effects can occur at various doses, most often occur within 2 months of starting the drug, and can even appear as late as 2 weeks after discontinuing the drug (Abidi et al., 2006). With an increased risk of sulfone syndrome and potential oxidative drug interactions (Williams et al., 2005), dapsone should not be used in patients with glucose-6-phosphate dehydrogenase deficiency (“Cotrimoxazole Is Generally Used to Manage,” 2008).

Atovaquone is currently being studied for efficacy in preventing PCP in the pediatric population and may be an effective second-line therapy, but it has only been studied in small samples (Kim et al., 2008). Atovaquone is an oral medication taken daily. Madden et al. (2007) retrospectively examined 86 patients with leukemia receiving atovaquone because of intolerance to Bactrim and none of the patients developed PCP. The study additionally looked at the interaction of atovaquone with etoposide. There was a slight increase in the concentration of the metabolite from etoposide with concurrent atovaquone administration when compared with Bactrim. Diarrhea and rash were reported as the most common side effects (Madden et al., 2007). Green et al. (2007b) also reported no significant difference for prevention of PCP compared with Bactrim, but atovaquone could provide some gram negative bacterial coverage that Bactrim would likely not because of increased antibiotic resistance to Bactrim. Another study reported that atovaquone was better tolerated but less effective than Bactrim (“Cotrimoxazole Is Generally Used to Manage,” 2008), indicating studies with larger sample sizes are needed to further examine the efficacy, side effects, and potential drug interactions related to atovaquone.

**Implications for Practice**

A summary of current recommendations for PCP prophylaxis, route of administration, administration frequency, side effects, monitoring parameters, and additional considerations is provided in Table 1. Educating families about the need for PCP prophylaxis can be overlooked at time of diagnosis when patients and families are overwhelmed with consents and information for chemotherapy, surgery, or radiation. However, PCP education should be a priority because of the fatality risk associated with PCP in children undergoing cancer treatment.

Although Bactrim remains the gold standard, providers may choose to alter the prophylactic regimen based on drug allergies, age at diagnosis, intensity of chemotherapy, and steroid use. Some patients are allergic to sulfa medications and therefore cannot be placed on a Bactrim regimen. Children younger than 2 years may be at an increased risk for developing PCP and should be placed on Bactrim unless clinically contraindicated. PCP should be included in the differential diagnosis for immunocompromised children younger than 2 years presenting with symptoms of pneumonia or respiratory failure.

Initiation of prophylaxis is provider dependent, but care should be taken to not start more than one drug at a time to accurately evaluate side effects. If a patient is not beginning chemotherapy but is on postoperative steroids for a prolonged period of time, PCP prophylaxis may need to be initiated (see Table 2). The intensity of the
chemotherapy regimen based on diagnosis and the expected length of neutropenia can also influence when PCP prophylaxis is initiated. Prophylaxis should be initiated for anyone who is expected to be neutropenic or functionally neutropenic (prolonged steroid use, relapsed leukemia, or other marrow disease) to minimize the risk of developing PCP. In addition to starting prophylaxis, there is also discussion of when to discontinue prophylaxis. Most studies recommend continuing prophylaxis for 3 to 6 months posttherapy or until immune function is fully recovered (“Cotrimoxazole Is Generally Used to Manage,” 2008; Shankar, S.M. & Nania, J., 2007; Suryaprasad & Stone, 2008).

Patient compliance is an important consideration when prescribing prophylactic medications. A 2 days or 3 days a week regimen may be better tolerated, but it could be more difficult to remember to take a drug consistently if it is only taken 2 or 3 days a week. Conversely, it might be easier to remember to take a pill every day, but the patient may experience more side effects from this dosing regimen. Providers may feel more confident knowing a patient receives pentamidine once a month, even though it may be less effective, instead of risking poor compliance to oral regimens.

When patients are receiving multimodal drug therapy, potential drug interactions need to be identified. For example, Bactrim should be held with high-dose methotrexate until methotrexate is cleared because of potential drug interactions (Libecco & Powell, 2004). In addition, Bactrim should be used cautiously in patients receiving temodar because of an increased risk of myelosuppression when the drugs are used concurrently (Bachuss, 2008).

Another provider concern requiring patient and family education is antibiotic resistance. Some studies have shown that prophylaxis with Bactrim increases the resistance of certain strains of bacteria. Other studies conclude that Bactrim not only works for PCP prophylaxis but may suppress other bacterial infections as well. With high mortality rates associated with PCP infection, the risk of resistance is minimal compared with the benefit of preventing clinical infection (Green et al., 2007a).

In addition to taking the medications as prescribed, patients must be monitored closely for side effects. The number one reason for switching from Bactrim to an alternate form of PCP prophylaxis is thrombocytopenia and neutropenia (“Cotrimoxazole Is Generally Used to Manage,” 2008). This should be monitored with complete blood counts, though there is no time line for monitoring the complete blood counts. Pentamidine administration may require premedication with albuterol for the inhaled formulation and Zofran for intravenous doses to minimize

Table 1. Common Prophylaxis Regimens and Guidelines

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Route of Administration</th>
<th>Administration Frequency</th>
<th>Potential Side Effects</th>
<th>Monitoring Parameters</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bactrim</td>
<td>Oral</td>
<td>BID, 2 or 3 days/week</td>
<td>Rash, N/V, allergy, drug interactions (MTX, Temodar)</td>
<td>CBC for myelosuppression</td>
<td>Compliance with intermittent dosing</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>IV or IH</td>
<td>Once every 30 days</td>
<td>IH: Bronchospasm</td>
<td>Respiratory status</td>
<td>Older than 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV: Hypotension</td>
<td>BP monitoring</td>
<td>Over 1-2 hours</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Oral</td>
<td>Once daily or BID 3 days/week</td>
<td>IV: Arrhythmias</td>
<td>Oxygen saturation</td>
<td>Not for G6PD, caution with Cb5R-positive patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dapsone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Oral</td>
<td>Once daily</td>
<td>Hemolytic anemia, Hepatic damage, rash</td>
<td>CBC, LFTs</td>
<td>Currently not well studied</td>
</tr>
</tbody>
</table>
| Abbreviations: BID, twice daily; N/V, nausea and vomiting; MTX, methotrexate; CBC, complete blood count; IV, intravenous; IH, inhalation; BP, blood pressure; CR, cardiac/respiratory; G6PD, glucose-6-phosphate dehydrogenase; LFT, liver function test; Cb5R, cytochrome b5 reductase; N/D, nausea and diarrhea.

Table 2. Consider Prophylaxis for Patients Who:

- Are receiving high-dose steroids for >2 weeks
- Are children younger than 2 years receiving immunosuppressive therapy
- Are receiving high-dose, immunosuppressive chemotherapy
- Have primary or acquired immune deficiency
- Are receiving the following medications: fludarabine and steroids, temozolimide, alemtuzumab, or antitumor necrosis factor
side effects. Intravenous pentamidine should be administered with blood pressure and cardiac/respiratory monitoring for potential side effects (Kim et al., 2008). With methemoglobinemia being the most concerning adverse event associated with dapsone use, patients should have weekly oxygen saturation monitoring and an arterial blood gas for symptomatic or suspected methemoglobinemia (Williams et al., 2005). Since atovaquone is currently being studied, the nursing and monitoring parameters may change as more information becomes available on the drug. All side effects should be reported according to institution policy for data collection and adverse drug event reporting.

Nurses and health care providers play an important role in PCP prevention through patient and family education. Without proper education, patients and families may not understand the implications of acquiring PCP. After initial education, families require follow-up to ensure that the medication is being administered properly and potential side effects are being monitored for. If patients and families are not asked about side effects related to the medication, they may not be distressing enough to bring up during routine visits. Support from health care providers is important to increase compliance of medication administration. Additionally, health care providers are responsible for recognizing signs and symptoms of PCP. Families put a significant amount of trust in health care providers to prescribe medication that will not cause harm, but medication alone cannot prevent PCP in children. A mutual effort between health care providers and patients and families is imperative for PCP prevention.

**Conclusion**

As more children are being treated with immunosuppressive medications, including chemotherapy and high-dose steroids, increasing their risk for developing PCP pneumonia, it is imperative for health care providers to include PCP prophylaxis in treatment regimens. In addition to prescribing, providers and nurses play a vital role in increasing patient compliance to prophylactic regimens through patient and family education. Ongoing and future studies are needed to compile evidence-based guidelines for PCP prophylaxis for children receiving chemotherapy, transplants, and high-dose steroids that will outline who needs prophylaxis, how often, and for how long and what drugs are most effective with the least amount of toxicities.

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Bio

Faith Crozier received a master’s degree in nursing from the University of Pennsylvania, specializing in pediatric oncology with a minor in palliative care. She received a BS in biomedical science from Texas A&M University and a BSN from Valparaiso University. She has worked as a pediatric oncology nurse for 6 years at various institutions, including camps for children with chronic and life-threatening illnesses and is currently working at Children’s National Medical Center, D.C.
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Methotrexate Toxicity


**Ifosfamide Toxicity**


**Biotherapy**


PCP prophylaxis

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Joy Hesselgrave, MSN RN CPON®
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Michelle Ahnberg, BSN RN CPON®
Deborah J. Lee, BSN RN CPON®
Nancy Kline, PhD RN CPNP FAAN
Joan O’Hanlon Curry, RN CPNP CPON®