

HOPA News



Volume 11, Issue 2, 2014



Salvage Therapies for Aplastic Anemia: An Updated Perspective

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A 67-year-old woman was diagnosed with aplastic anemia in August 2012. In June of that same year, she originally complained of fatigue, shortness of breath, and tachycardia. A complete blood count (CBC) revealed a white blood cell (WBC) count of 1.5 K/ μ L, hemoglobin count of 5.1 g/dL, and platelet count of 7 K/ μ L. She was referred to a private oncologist the first week of July, at which time a bone marrow biopsy revealed hypocellular bone marrow with erythroid hyperplasia, profound anemia, and marked leukopenia. A repeat bone marrow biopsy was performed at our clinic later that month and revealed 5% cellularity with decreased myeloid and erythroid lineage. Serum testing for hepatitis B and C as well as HIV was negative. Upon diagnosis with aplastic anemia, she was treated with a 5-day course of horse antithymocyte globulin (hATG), cyclosporine (CsA), and prednisone. She started maintenance therapy with CsA. From this, she obtained a complete response but then relapsed in June 2013. It was decided to begin treatment with eltrombopag 50 mg daily, which was increased to 75 mg daily on week 5 because of persistent thrombocytopenia. She was hospitalized again in December 2013 due to acute kidney injury and continued pancytopenia. What salvage therapies should be considered as a next course of treatment?

Aplastic anemia is a rare disorder that occurs when the bone marrow fails to produce hematopoietic precursor cells, resulting in pancytopenia.¹ Immunosuppressive therapy with hATG and CsA is the standard treatment for aplastic anemia in patients older than 40 years old and those younger than 40 years without a human leukocyte antigen (HLA) compatible sibling donor.¹ Refractory aplastic anemia occurs in about one-third of patients and is defined as a lack of response after one course of immunosuppression with persistence of severe pancytopenia observed at 6 months following therapy.^{2,3} Additionally, approximately one-third of responders are anticipated to relapse after initial immunosuppressive therapy.⁴ Predictors of nonresponse to immunosuppression include older age, low absolute reticulocyte count (<20 K/ μ L), low lymphocyte count (<1 K/ μ L), and disease severity.^{1,5} Matched unrelated donor (MUD) hematopoietic stem cell transplantation (HSCT) may be considered for patients younger than 50 years old or patients who are 50–60 years old with good performance status and are refractory to a first course of immunosuppression.¹ Unfortunately, 20%–40% of patients are ineligible for HSCT and continue to have severe cytopenias that put them at risk for hemorrhage from thrombocytopenia and infections from neutropenia.

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No standard treatment, other than supportive care measures, is recommended for patients with refractory aplastic anemia or relapsed disease who are ineligible for HSCT and do not respond to immunosuppressive therapies. Intensification of the immunosuppressive regimen with more potent agents, such as rabbit antithymocyte globulin (rATG), sirolimus, or mycophenolate mofetil (MMF), have not shown an improvement in the response rate.⁵ Patients with relapsed disease show a higher hematologic response rate to immunosuppression compared to HSCT.⁶ Therefore, HSCT is usually not recommended for treatment of older patients with relapsed aplastic anemia. Readministration of immunosuppressive therapy, an alternative immunosuppressive drug or novel agent, or experimental forms of transplantation are potential options to consider.

ATG-Based Regimens

Few studies have investigated salvage therapy with rATG for patients who fail to respond to an initial course of hATG. A second course of immunosuppression with rATG/CsA is associated with a variable response rate between 22% and 77%.⁷⁻⁸ A randomized controlled trial that compared rATG and CsA ($n = 27$) versus alemtuzumab ($n = 27$) in refractory disease found a comparable 6-month response rate (33% versus 37%, $p = 0.78$).⁹ Repeated treatment with hATG in 43 patients who did not respond to initial treatment or who relapsed after initial response was evaluated.¹⁰ Without resulting in increased risks of side effects, transfusion-independent hematopoiesis was achieved in 63% of patients with a survival probability of $52\% \pm 8\%$ at 10 years. Standard hATG plus CsA in patients who were refractory to initial rATG/CsA or cyclophosphamide (CY)/CsA resulted in a hematologic response in four of 19 (21%) patients who received rATG, compared to no patients in the CY group, by 3 months and in only one of six (17%) patients who received CY at 6 months.¹¹ These results suggest that the overall response rate is likely to be lower when hATG is used as salvage treatment compared to initial therapy. Administration of a third course of ATG, regardless of the animal source, was found to be ineffective in patients with refractory aplastic anemia.¹²

Further augmentation of response rates has been investigated with the addition of a third immunosuppressive agent or growth factor. Administration of rATG/CsA plus G-CSF at a dose of 5 mcg/kg on days 1–90 as salvage therapy after failed hATG/CsA in 30 cases resulted in a complete response rate of 30%, and transfusion independence was achieved in 77% of patients.⁷ A prospective randomized trial examined the addition of sirolimus to the combination of hATG/CsA, but there was no improvement in response rates observed in these patients.¹³ Other immunosuppressive agents such as MMF have been added to the ATG/CsA regimen, but no improvement in response or relapse rates have been observed when compared to ATG/CsA alone.¹⁴

Alternative Immunosuppressive Regimens

High-dose CY administered intravenously at 50 mg/kg for 4 days with intravenous mesna for prophylaxis of hemorrhagic cystitis or alemtuzumab given at various doses and schedules have been used as alternative immunosuppressive therapies in the treatment of refractory aplastic anemia. One study suggested high-dose CY showed comparable responses to hATG/CsA with fewer relapses; however, the 10-year follow-up data were disappointing as overall actuarial survival, response, and actuarial event-free survival rates were 62%, 48%, and 27%, respectively.¹⁵⁻¹⁶ Furthermore, a prospective study comparing high-dose CY with ATG/CsA in treatment-naïve patients was terminated prematurely due to excess deaths and increased incidence of fungal infections in patients treated with CY.¹⁷ Alemtuzumab, a humanized anti-CD52 IgG1 monoclonal antibody, was evaluated in a prospective clinical trial that included 25 patients with severe aplastic anemia ($n = 11$), pure red cell (PRCA; $n = 12$), or pure white cell aplasia (PWCA; $n = 2$).¹⁸ A response rate of 58% was observed when alemtuzumab was administered subcutaneously in a single course over 5 consecutive days at escalating doses of 3–10–30–30–30 mg to patients with severe aplastic anemia. Low-dose CsA (1 mg/kg) followed from day 7 and then adjusted according to blood levels. Early relapse rates were seen in five out of 11 patients with severe aplastic anemia, but three out of five patients achieved a complete response with retreatment of alemtuzumab. Alemtuzumab (60 mg and 90 mg)

in combination with CsA was examined in a dose-escalation study.¹⁹ A total of 19 patients were enrolled: 14 patients with severe/very severe aplastic anemia, three with transfusion-dependency, one with hypoplastic myelodysplastic syndrome (MDS), and one with PRCA. Response occurred in 35% (6 of 17) of patients with aplastic anemia, and all responses occurred in the 60-mg arm.

There have been several strategies aimed at preventing relapse after initial therapy with hATG/CsA. Continuation of full-dose CsA for 6–12 months with a slow taper afterward is a possible approach. A small retrospective study of 42 pediatric patients examined a CsA taper regimen that varied between patients.²⁰ Relapse was 7.6% in the “slower” CsA taper group (0.4–0.7 mg/kg/month) compared to 60% in the “rapid” taper group (0.8 mg/kg/month). A larger study found that 102 patients who received a hATG-based regimen achieved a cumulative incidence of relapse of 29% when the CsA dose was tapered by 25% every 3 months.²¹ The relapse rate was slightly higher at 32% when CsA was discontinued at 6 months.

Eltrombopag and Androgens

Eltrombopag (Promacta[®]) is an oral thrombopoietin agonist that increases platelet counts by binding to and activating the receptor c-MPL on megakaryocytes, resulting in platelet maturation and release.²² Eltrombopag produced hematologic responses in 11 of 25 refractory patients (44%) at 12 weeks with minimal toxic effects.²¹ Furthermore, eltrombopag may reduce transfusion requirements in patients with platelet transfusion-dependent aplastic anemia.^{23–24} The starting dose was 50 mg/day with doses increased in 25-mg increments in nonresponders every 2 weeks if the platelet count had not increased by 20 L/cumm up to a maximum dose of 150 mg/day. An additional 18 patients were included in long-term follow up, and the overall response rate was 40% (17 of 43 patients) at 3–4 months, including tri- and bi-lineage responses.²⁵ In the extension arm of responders remaining on eltrombopag, 14 of 17 patients continued to show hematologic improvement and seven eventually achieved significant increases in neutrophil, red blood cell, and platelet lineages.

Androgens, such as oxymetholone and danazol, have been studied and were used before ATG/CsA became the standard treatment of aplastic anemia.^{26–27} The results of these studies have not shown a significant impact on response or relapse rates or clonal growth. A recent study was conducted of 12 refractory and four relapsed patients who were alternately administered CsA (3 mg/kg and 5 mg/kg per day in adults and children, respectively) and levamisole (150 mg per day in adults or 2.5 mg/kg per day in children weighing less than 40 kg in three divided doses) every other day for 12 months, followed by a slow taper.²⁸ Of the 16 patients, five achieved a complete response at the last follow-up of a median 28 (range 4–53.5) months. Furthermore, CsA alternately combined with levamisole has promising results in patients with moderate aplastic anemia based on a recent study.²⁹

How Much Do You Know About Treating Aplastic Anemia?

Test your knowledge of aplastic anemia therapy by answering the following questions. The correct answers are provided on the next page.

1. What is **not** a predictor of nonresponse to immunosuppressive therapy in a patient with refractory aplastic anemia?
 - a. Young age
 - b. Low absolute reticulocyte count
 - c. Low lymphocyte count
 - d. Disease severity
2. What is **not** a consideration when deciding whether to advise a transplant or nontransplant approach in a patient with refractory aplastic anemia or relapsed disease?
 - a. Patient age and comorbidities
 - b. Performance status
 - c. Availability of a suitably matched donor
 - d. Supportive care regimen
3. What is the standard treatment for patients with refractory aplastic anemia or relapsed disease who are ineligible for HSCT?
 - a. rATG+ CsA
 - b. Alemtuzumab
 - c. High-dose CY
 - d. There is no standard approach, and the treatments may be challenging.
4. What is the general dosing strategy for patients with refractory aplastic anemia who are treated with eltrombopag?
 - a. Initial dose is 25 mg once daily up to a maximum dose of 150 mg once daily, and dosage adjustment is based on platelet response after 2 weeks.
 - b. Initial dose is 50 mg once daily up to a maximum dose of 150 mg once daily, and dosage adjustment is based on platelet response after 2 weeks.
 - c. Initial dose is 50 mg once daily up to a maximum dose of 100 mg once daily, and dosage adjustment is based on platelet response after 12 weeks.
 - d. Initial dose is 25 mg once daily up to a maximum dose of 150 mg once, and dosage adjustment is based on platelet response after 4 weeks.

Aplastic Anemia Quiz Answers

1. Answer: a. Predictors of nonresponse to immunosuppression include older age, low absolute reticulocyte count (<20 K/mL), low lymphocyte count (<1 K/mL), and disease severity.
2. Answer: d. HSCT is indicated if patients are fit and have a suitably matched donor: either a sibling (>40–50 years) or unrelated donor. Patients lacking a fully matched donor should be considered for a second course of immunosuppressive therapy. Any supportive care is essential at all stages of disease. Best supportive care continues through initial therapies, whether with HSCT or immunosuppressive therapy. Because response to ATG is delayed until approximately 3 months, best supportive care is vital to ensure optimal outcomes.
3. Answer: d. No standard treatment is recommended for patients with refractory aplastic anemia or relapsed disease who are ineligible for HSCT and who do not respond to initial immunosuppressive therapies other than supportive care measures.
4. Answer: b. In patients with refractory aplastic anemia who are treated with eltrombopag, the starting dose is 50 mg/day with doses increased in 25-mg increments in nonresponders every 2 weeks if the platelet count has not increased by 20 K/mL up to a maximum dose of 150 mg/day.

Conclusion

The patient described in the vignette was treated with a repeat induction regimen of hATG, CsA, and prednisone during hospitalization. Follow-up clinic visits during the next 2 months revealed persistent pancytopenia resulting in the need for platelet and blood transfusions. Of note, her absolute neutrophil count was at the highest since relapse in July 2013 (1.32 K/ μ L in January 2014 versus 0.6 K/ μ L in July 2013), which may represent the onset of response.

Though aplastic anemia was a devastating diagnosis in the past, most patients can be treated effectively and expect long-term overall survival. The preferred therapy is immunosuppression with hATG/CsA in patients who are not candidates for a matched sibling donor HSCT. A MUD HSCT may be the preferred salvage therapy in younger patients with refractory aplastic anemia. A second course of immunosuppression should be offered if a MUD is unavailable. Mismatched unrelated, haploidentical, or umbilical cord HSCT are possible options but higher risks of GVHD, graft rejection, and infection should be considered. Other nonHSCT therapies, such as eltrombopag, androgens, or alternative immunosuppressants, may be appropriate options in patients who remain unresponsive or experience relapsed disease. 

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SAVE THE DATE

2nd Annual HOPA Fall Meeting

Oncology Pharmacy Practice Management Program

September 19–20, 2014 | Hyatt Regency O'Hare | Rosemont, IL
Registration opens in June.

Recommended Adult Immunization Schedule: 2013 Updates

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The Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) publish guidelines and recommendations to help practitioners manage vaccine administration. ACIP developed general guidelines based on age and preexisting conditions, while the IDSA's guidelines address vaccination in patients with a variety of immunocompromised states. IDSA guidelines define the level of immunosuppression to determine appropriate categorization and vaccination of patients receiving chemotherapy, with sickle cell disease, and undergoing hematopoietic stem cell transplantation (HSCT).

One of the updates included in the ACIP and IDSA guidelines was the addition of the pneumococcal conjugate 13-valent vaccine (Prevnar 13[®]) to the adult vaccination schedule. Data from the Centers for Disease Control and Prevention (CDC) suggest that 50% of invasive pneumococcal disease cases among immunocompromised adults in 2010 were caused by serotypes contained in Prevnar 13[®] (PCV13) and pneumococcal polysaccharide 23-valent vaccine (Pneumovax 23[®]), with an additional 21% caused by serotypes only contained in Pneumovax 23[®] (PPSV23).¹ A study assessed pneumococcal vaccine-naïve patients who were administered either PPSV23 alone or 1 year after a dose of PCV13. This study found that patients who had PPSV23 administered 1 year after PCV13 had a statistically significant increase in immunogenicity compared with those who received a single dose of PPSV23 based on opsonophagocytic activity and geometric mean antibody titers.¹ These results suggest that PCV13 augments the immune response to PPSV23. The authors felt this increase in immune response was due to the development of a memory response to the polysaccharide vaccine.

Oncology pharmacists frequently are asked when it is safe and effective to administer vaccinations in relation to chemotherapy. The IDSA guidelines recommend that inactivated vaccines be administered at least 2 weeks prior to chemotherapy and live vaccines be administered at least 4 weeks prior to chemotherapy.² IDSA also recommends that vaccines administered during chemotherapy should not be considered valid doses unless there is documentation of appropriate antibody levels. Inactivated vaccines and live vaccines for varicella and measles, mumps, and rubella should be administered as indicated according to the CDC adult schedule starting 3 months after chemotherapy.^{2,3} Vaccinations should be postponed for 6 months after chemotherapy if regimens include B-cell targeted therapy.²

ACIP now recommends that adults 19 years of age or older who previously have received one or more doses of PPSV23 and have immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants should be

given a PCV13 dose at least 1 year after the last PPSV23 dose was received.³ This recommendation also applies to patients with cancer, but ACIP does not address vaccination after HSCT. The IDSA guidelines include recommendations about vaccination of patients undergoing HSCT. The IDSA recommendations differ slightly from the guidelines published by the American Society for Blood and Marrow Transplantation (ASBMT). The ASBMT guidelines have not been updated since 2009; therefore, they include the pneumococcal conjugate 7-valent vaccine (PCV7) rather than the newer PCV13 vaccine. The ASBMT guidelines recommend administering a three-dose series of a pneumococcal conjugate vaccine with PCV7 prior to the administration of PPSV23 1 year after transplant. A fourth dose of PCV7 is recommended in patients with active graft-versus-host disease (GVHD) at the completion of the three-dose conjugate vaccine series rather than PPSV23.⁴ The IDSA currently recommends that patients receive three doses of PCV13 starting 3 months after HSCT. PPSV23 should be administered when the three PCV13 vaccine series is complete, unless patients have active GVHD. Patients with active GVHD should receive a fourth dose of PCV13.³ The IDSA guidelines address frequently asked questions related to certain chemotherapy regimens, hematologic versus solid tumor malignancies, vaccination of close contacts of immunocompromised patients, and a variety of other topics relating to vaccination. The citations for the ACIP and IDSA guidelines have been included for reference and will hopefully aid you with appropriate and safe vaccination of your patients.^{2,3} 

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Updates from the 2014 American Society for Blood and Marrow Transplantation Tandem Meeting

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Practitioners of all hematologic malignancy and bone marrow transplant disciplines convened for the 2014 American Society for Blood and Marrow Transplant (ASBMT) Tandem Meeting in Grapevine, TX, at the end of February. A myriad of concurrent meetings and workshops, including the primary scientific program, Foundation for the Accreditation of Cellular Therapy (FACT) accreditation workshop, and Fundamentals of Hematopoietic Stem Cell Transplantation course by the National Marrow Donor Program (NMDP), were held to address several unique subgroups, such as clinical trial network (CTN) coordinators and investigators, data managers, information technology (IT) professionals, pediatric transplant, pharmacists, nurses, and center administrators. The following are highlights from the pharmacists' portion of the meeting.

Update on the ASBMT Pharmacy Special Interest Group

Since its initiation in 2012, the Pharmacy special interest group (SIG) of ASBMT has played a major role in creating several new educational sessions at both the HOPA and ASBMT annual conferences. The boot camp course offered at the 2013 HOPA Annual Conference was met with great success with 77 registered participants. Of the boot camp attendees, 80% indicated that this conference provided information that would improve their clinical practice. The success of the fundamentals course offered in 2013 at the ASBMT annual meeting supported the continuation and expansion of this course at the 2014 meeting. The Pharmacy SIG also published a peer-reviewed article on pharmacist and physician collaborative practice agreements in the *Biology of Blood and Marrow Transplantation* journal. The other major achievement of the SIG was the inclusion of pharmacists in the FACT Accreditation Standards. Current initiatives include regularly publishing the Pharmacy SIG newsletter, increasing membership, establishing a Web page, and promoting pharmacy research and advocacy.

Best Pharmacy Abstracts

Four abstracts authors were selected to give an oral presentation of their research, with the best abstract selected later in the conference. Ashley Teusink, PharmD, Cincinnati Children's Hospital Medical Center, presented "Pharmacogenetic-Directed Dosing Leads to Optimized Voriconazole Levels in Pediatric Patients Receiving Hematopoietic Stem Cell Transplants," which was awarded best pharmacy abstract. Investigators evaluated 20 patients according to their CYP450-2C19 genotype and dosed their voriconazole using an algorithm designed to target those polymorphisms. Results indicated

a statistically significant improvement in the time to reach target levels (8 days versus 30 days, $p < .001$). "Intravenous (IV) Busulfan (BU) Pharmacokinetics Using Busulfan and Fludarabine (Flu) Conditioning in Institutions Where the Capability of Doing Pharmacokinetics Is Not Present," "Efficacy of Late Hematopoietic Stem Cell Mobilization 35-40 Hours After Administration of Plerixafor," and "Population Pharmacokinetic Modeling of Thymoglobulin in Children Receiving Allogeneic Hematopoietic Cell Transplantation (HCT): Towards Individualized Dosing to Improve Survival" were the other abstracts presented at the meeting.

Highlights in Infectious Disease

During the past several years, it has been commonplace for new oncology agents to come to market; however, our infectious disease colleagues have not enjoyed a similar benefit with antifective agents. A few noteworthy agents that entered development this past year were discussed during the Highlights in Infectious Disease session. Ceftolozane/tazobactam is a novel, antipseudomonal cephalosporin and a well-established β -lactamase inhibitor in development for the treatment of complicated urinary tract infection, intraabdominal infections, and ventilator-associated pneumonia. Ceftolozane/tazobactam has activity against *E. coli*, *K. pneumoniae*, and *Pseudomonas aeruginosa*, including strains resistant to carbapenems, piperacillin/tazobactam, and other cephalosporins, as well as strains that are multidrug resistant. Tedizolid phosphate is an oral and intravenous agent related to linezolid that is being investigated in phase 3 trials for methicillin-resistant *Staphylococcus aureus* infections, and it likely results in much less myelosuppression. Clinical and Laboratory Standards Institute breakpoints for echinocandins have changed during the past year to better detect known resistance mechanisms. New breakpoints have markedly lower minimum inhibitory concentrations and are no longer uniform over the class but do differ based on the specific agent. Susceptible breakpoints for *albicans*, *tropicalis*, and *krusei* are now <0.25 (rather than <2), and susceptibility for *glabrata* is now <0.12 for anidulafungin and caspofungin and <0.06 for micafungin. This session concluded with the presentation of studies showing improved outcomes with combination therapy for invasive aspergillosis with voriconazole and an echinocandin.

Emerging Drugs for Hematopoietic Stem Cell Transplantation Conditioning

Several exciting studies utilizing newer agents in stem cell transplant

conditioning regimens were presented. The three drugs that were highlighted were clofarabine, bendamustine, and gemcitabine. Clofarabine can be advantageous in this setting because of its improved stability, increased intracellular retention, direct induction of apoptosis, synergy with alkylating agents, and increased potency and less neurotoxicity than fludarabine. Dose-limiting toxicities include hand-foot syndrome, liver function test abnormalities, and rarely capillary leak syndrome. Studies evaluating clofarabine in combination with a busulfan-based regimen showed high activity in high-risk patients and acceptable engraftment rates. Evaluated in combination with melphalan and alemtuzumab as a nonablative regimen, clofarabine showed immunosuppression and efficacy comparable to historical controls, although unexpectedly higher rates of renal failure occurred. Bendamustine has a unique mechanism of action and has shown great efficacy in its treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma. Studies evaluating bendamustine in combination with fludarabine and rituximab for conditioning of lymphoid malignancies show that it is well-tolerated, has low treatment-related mortality, and may lend itself well to outpatient conditioning or use in older patients as a nonablative preparatory regimen. Dose-limiting toxicities include thrombocytopenias and cardiotoxicity. Evaluation of the BEAM (BCNU, etoposide, Ara-C, melphalan) regimen with bendamustine replacing carmustine showed a very acceptable safety profile with no dose-limiting toxicities and was effective when compared against historical data. Gemcitabine shows a synergy with alkylating agents, increased potency compared with cytarabine, and minimal nonhematologic toxicities. Investigations of gemcitabine with melphalan and busulfan showed a maximal tolerated dose of gemcitabine of 2,775mg/m²/dose for two doses. Mucositis was the only dose-limiting toxicity, and rash and LFT elevation were common. Favorable results were shown in lymphoma patients compared with historical data. Most of the studies presented were single-arm studies compared with historical data with further phase 3 studies ongoing.

Stem Cell Transplant in HIV-Positive Patients

Patients infected with human immunodeficiency virus (HIV) have a higher incidence of cancer for both AIDS-defining and non-AIDS-defining malignancies. Prior to combination antiretroviral therapies (cARTs), HIV-positive patients diagnosed with lymphoma had poor outcomes including higher rates of relapse, increased opportunistic infections, and decreased overall survival. The incorporation of cART into HIV therapies has had a dramatic effect on outcomes. Patients diagnosed with lymphoma are now better able to tolerate standard chemotherapy, and their outcomes are similar to those of lymphoma patients who are HIV negative. Similarly, stem cell transplant has curative potential for many patients diagnosed with hematologic malignancies, but prior to cART, many HIV patients had poor outcomes associated with high-dose chemotherapy and transplant. With improved supportive care and cART, outcomes such as overall survival for HIV-positive patients postautologous stem cell transplant are similar to those of patients who are HIV negative. Allogeneic stem cell transplant can present greater challenges in the HIV-positive patient population, including chronic immunosuppression, risk of infection, and complex drug interactions between cART and

immunosuppressive agents. Currently, there is no evidence that cART adversely affects allogeneic transplant outcomes; however, each patient must be monitored for drug-drug interactions. Initial data in this unique patient population suggest that immune system reconstitution is satisfactory; however, opportunistic infections may be more common and necessitate post-HSCT surveillance. To ensure HIV-positive patients have optimal outcomes, it is essential that there be multidisciplinary management between oncologists, HIV physicians, and pharmacists.

Minimal Residual Disease After Stem Cell Transplantation

Minimal residual disease (MRD) is generally referred to as low levels of disease that are detected by nontraditional methods either during or after chemotherapy. Currently, there are two broad approaches for monitoring MRD that can detect abnormal genetic (polymerase reaction chain [PCR]) or phenotypic expression (flow cytometry). For some cancers, the presence of MRD is important because it can predict a higher relapse rate after chemotherapy or hematopoietic stem cell transplant. However, the prognostic value of MRD has not been clearly defined for each of the hematologic malignancies. MRD monitoring is well established in patients with chronic myelogenous leukemia (CML). PCR positivity in patients with CML can predict disease progression or relapse. Treatment initiated at the start of relapse has been reported to result in superior response rates and improved survival rates. In both adult and pediatric acute lymphoblastic leukemia (ALL), the monitoring of MRD is well established. In adults, it has been reported that MRD is an independent prognostic feature of disease-free survival (DFS) in nontransplant patients. There are fewer studies evaluating the role of MRD in the setting of allogeneic transplant for ALL patients. MRD that is detected before and after stem cell transplant in patients with ALL has been associated with a poor DFS. Monitoring for MRD in patients with AML can be more challenging. Unlike CML, which has the BCR-ABL mutation in the majority of patients, there are an abundance of cytogenetic and molecular mutations in patients with AML or advanced MDS that make standard surveillance more difficult. Several potential markers for these diseases have been identified and remain under investigation. MRD assessment is now routinely performed in the setting of many hematologic malignancies. Although its presence can predict disease recurrence, it has not been consistently reported in all patient populations. It is important to encourage patient enrollment in clinical trials to gain a better understanding of MRD in patients with hematologic malignancies.

Present and Future Trends in Immunosuppression

Patients undergoing an allogeneic stem cell transplant are at risk for graft-versus-host disease (GVHD) and require immunosuppression to prevent this complication. Many transplant centers rely on a calcineurin inhibitor (cyclosporine or tacrolimus) combined with methotrexate or mycophenolate mofetil (MMF) to prevent GVHD. Despite immunosuppression and improvements in identifying matched donors for recipients, GVHD remains a common complication post stem cell transplant. Novel prophylaxis combinations remain an active area of investigation for prevention of GVHD. The use of sirolimus as prophylaxis for stem cell transplant has several potential advantages including the promotion of T-regulatory cells and antiviral and

antineoplastic properties. The Blood and Marrow Transplant Clinical Trials Network published their results of the 0402 trial—a phase 3, randomized, multicenter prophylaxis trial of sirolimus and tacrolimus versus tacrolimus and methotrexate in patients with hematologic malignancies receiving a matched related peripheral blood stem cell transplant. In this trial, substituting sirolimus for methotrexate/MMF did not demonstrate superiority in progression-free survival or overall survival. However, the sirolimus group may have benefited in the incidence of grade II GVHD, but this was at the expense of toxicities such as thrombotic microangiopathy/thrombotic thrombocytopenia purpura and hyperlipidemia. Other novel agents have been investigated as prophylaxes against GVHD. One agent, vorinostat, was combined with tacrolimus/MMF in a phase 2 trial. The authors reported that when vorinostat was combined with standard of care the cumulative incidence of grade II-IV GVHD was reduced by day 100.¹ However, before any novel prophylaxis strategy can be incorporated into front-line therapy outside of a clinical trial, the results need to be confirmed by phase 3 prospective randomized trials. GVHD is a common complication after transplant and contributes to the morbidity and mortality of allogeneic transplant patients. The standard of care for the initial therapy of GVHD is still methyprednisolone or prednisone. Novel

GVHD therapy approaches that selectively inhibit T-cells remain under investigation. Graft manipulations, graft enrichment with regulatory T-cells, and photopheresis have shown promising results. In the past several years, there have been many advances in the understanding of immunology and cellular therapies. Novel approaches to GVHD prophylaxis and treatment are likely to yield more selective immunosuppression and positive outcomes for patients.

The 2014 ASBMT Tandem Meeting in Grapevine, TX, provided practitioners the opportunity to understand the newest advances in the field of stem cell transplant. This meeting provides education and updates for a variety of specialized fields and encourages interdisciplinary learning through its special interest group conferences. More information about the ASBMT Tandem Meeting and the Pharmacy SIG can be found on the ASBMT website at www.asbmt.org. 

Reference

1. Choi SW, DiPersio JF, Braun TM, et al. Targeting histone deacetylases as a new strategy for graft versus host disease prevention. *Blood* (ASH Annual Meeting Abstracts). 2012;120:740.

ONCOLOGY INTEREST GROUP

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Board Update

Michael J. Vozniak, PharmD BCOP, HOPA President



Now that spring has sprung, we can enjoy the freshness of the changing season, the blossoms of color, and renewed energy and growth. Every spring HOPA undergoes a similar resurgence as we convene for our annual conference, energized by educational and networking opportunities and transitions in our board and committees. Overall, this season serves as a time to review what we've accomplished and look forward to the work that still lies ahead to meet our strategic plan objectives.

Annual Conference

Our 10th Annual Conference was a huge success! The conference had a record attendance of 873 attendees, and New Orleans served as a beautiful backdrop. It was highlighted by two preconference sessions, breakfast symposia, a new "How We Treat" series, corporate showcases, and a special John G. Kuhn Keynote Lecture during which John Kuhn, PharmD, himself was interviewed Larry King-style about the past, present, and future of hematology/oncology pharmacy and the formation of HOPA. In addition to the educational offerings, the exhibit hall offered attendees the opportunity to meet with representatives from a wide variety of pharmaceutical companies and learn more about their products and services. The Program Committee organized an exceptional meeting that provided a range of content to meet the needs of our diverse membership.

To celebrate HOPA's 10th anniversary, a gala was held during the annual conference. A task force of HOPA members, led by Susannah Koontz, PharmD BCOP, was organized shortly after last year's conference to orchestrate the festivities. I want to offer a huge thank you to all of the task force members. The event boasted great food and drinks, a fantastic live band, and a silent auction that benefited the HOPA Research Fund. It was a delightful engagement!

Health Policy

One of HOPA's strategic plan goal areas is advocacy. As many of you may know, HOPA hired the District Policy Group (DPG; a segment of Drinker, Biddle & Reath, LLP) a few years ago to help HOPA advance its advocacy agenda. The main focus during this partnership has been to inform legislators, coalitions, and healthcare organizations about HOPA and the work of hematology/oncology pharmacists. The HOPA Scope of Practice document also has been instrumental in increasing awareness of hematology/oncology pharmacists and the work they undertake.

Working closely with the DPG, HOPA's Health Policy Committee has been busy this past year composing issue briefs on biosimilars and pain management and commenting on several Centers for Medicare and Medicaid Services and U.S. Food and Drug Administration documents.

In early March, Niesha Griffith and I traveled to Washington, DC, to meet with our members of Congress and their staff to inform them about HOPA and the role of the hematology/oncology pharmacist and to urge their support of legislation regarding oral parity. I met with staff from the offices of U.S. Senators Pat Toomey (R-PA) and Bob Casey, Jr. (D-PA), and U.S. Representative Bob Brady (D-PA). The staffers were interested to learn about hematology/oncology pharmacists and the work we do on a routine basis. While there, I also discussed the importance of oral parity and how it impacts the patients we serve. Before this opportunity, I had never met with any legislators to discuss any issues. I certainly was anxious and apprehensive leading up to the day. However, it was phenomenal to see up close how our government runs and learn that any HOPA member can easily speak with legislators or their staff to advocate for our field and patients. I encourage all of our members to take advantage of any future opportunities to speak to your legislators about issues important to HOPA and the pharmacy profession.

Another important initiative of the HOPA Board of Directors and the Health Policy Committee is to advance the role pharmacists play in healthcare delivery. During the Annual Members' Meeting at the annual conference, it was decided that HOPA would fully support the initiatives set forth by the Patient Access to Pharmacists' Care Coalition (PAPCC), which is supported by American Society of Health-System Pharmacists and American Pharmacists Association, among other pharmacy organizations, and the Medicare Coverage Initiative, which represents the position of American College of Clinical Pharmacy and the College of Psychiatric & Neurologic Pharmacists. HOPA continues to have conversations with these groups and will work with them to learn how HOPA and its members can support the two initiatives and move the pharmacy profession forward.

What Lies Ahead

As I remarked at the annual conference, I am honored, humbled, and excited to serve as HOPA's president this year! HOPA is an exceptional organization that continues to build a superb reputation. The board of directors is composed of gifted individuals who will help guide HOPA to continued success. HOPA's biggest asset is its almost 2,000 members. HOPA members are engaged and have a strong desire to be active and contribute. We need to continue to capitalize on our committed membership and strive to meet the needs of our diverse and growing membership.

In the coming year, I encourage you to get involved with a committee or task force, attend a meeting, or participate in an educational offering. Most importantly, give HOPA feedback so it may continue to improve itself. We want to hear what we can do better so we may serve you better.

Have a safe and rejuvenating spring! 

HOPA 10th Anniversary Gala Summary

Susannah E. Koontz, PharmD BCOP, Gala Committee Chair

The “HOPA 10th Anniversary Gala: Celebrating Success!” was, indeed, an overwhelming success thanks to the enthusiastic support of so many individuals during the past several months. The gala was held to celebrate a decade of organizational accomplishment, recognize key people instrumental in HOPA’s founding, and raise money for the HOPA Research Fund. All of this (and more!) was achieved by the end of the evening—an evening that will not soon be forgotten.

More than 350 HOPA members and their guests embraced the suggested dress of “festive casual,” with many people arriving at The Chicory adorned in Mardi Gras beads and masks, feather boas, and brightly colored attire. Attendees enjoyed the opportunity to network with one another while listening to Dixieland jazz standards performed by the Gumbo Trio (by the end of the evening, dozens of guests were on the dance floor!). Everyone took a walk down memory lane, enjoying the display of items from HOPA’s archives and watching the DVD compilation that chronicled HOPA’s 10-year history. These features, in conjunction with the gala commemorative program, allowed us to highlight HOPA’s past accomplishments and acknowledge those members integral to our organization’s formation.

Equally successful were the fundraising efforts of the celebration, which raised nearly \$75,000 for the HOPA Research Fund! Contributing to the fund prior to the evening were a half-dozen corporate sponsors and several HOPA members. The generosity continued at the gala with numerous guests participating in the evening’s silent auction and “30 for 30” donor program (an opportunity for individuals to donate \$30 in honor of HOPA’s 30 founding and inaugural board members). Popular auction items included a painting by Hagop Kantarjian, MD, of MD Anderson Cancer Center and a private wine education event complete with dinner for eight hosted by HOPA member Jerry Siegel, PharmD.

On behalf of the Gala Committee, I extend deep gratitude to everyone for making this event such a success. What a terrific way to mark this, one of undoubtedly many more to come, important milestone in HOPA’s history! 

HOPA 10th Anniversary Gala by the Numbers

~\$75,000 raised for the HOPA Research Fund

357 guests attended the Gala

104 slides shown during the HOPA 10th anniversary history DVD

25 HOPA members, friends, and AMC staff planned and executed the event

17 items purchased in the silent auction, raising \$7,000

6 corporate sponsors supported the gala

2 commemorative gifts given to all gala attendees—a strand of customized Mardi Gras beads and a HOPA luggage tag

1 celebration for the ages!



Recalls, Withdrawals, and Safety Alerts from the FDA

Tina Gegeckas, RPh BCOP
Lee Memorial Health System
Fort Myers, FL

Iclusig (Ponatinib) Tablets

The boxed warning for ponatinib has been updated to include the risk of vascular occlusion, which has occurred in 27% of treated patients. This has included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for revascularization procedures. Patients with and without cardiovascular risk factors, including patients 50 years old and younger, have experienced these events. Ponatinib therapy should be stopped for vascular occlusions.

The warnings and precautions section also has been updated to include the vascular occlusion risk and the risk for heart failure, treatment-emergent hypertension, peripheral and cranial neuropathy, and ocular toxicities.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm380782.htm

Avastin (Bevacizumab)

The warnings and precautions for bevacizumab have been updated to detail the increased risk of arterial thrombotic events in patients with a history of arterial thromboembolism, diabetes, and an age greater than 65 years.

The adverse reactions section has been updated to include clinical trial information regarding the incidence of proteinuria, indicating that 5.4% of patients in a pooled analysis of seven randomized clinical trials who received bevacizumab in combination with chemotherapy experienced grade >2 proteinuria.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275758.htm

Taxotere (Docetaxel) Injection Concentrate

The warnings and precautions, adverse reactions, and patient information sections have been updated to include cystoid macular edema (CME), which has been reported in patients treated with docetaxel and other taxanes. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. If CME is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated. Alternative nontaxane cancer treatment should be considered.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm212079.htm

Yervoy (Ipilimumab) Injection

In a dose-finding trial, grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID).

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm328023.htm

Tafinlar (Dabrafenib) Capsules

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/

CYP1A2 substrate). Monitor international normalized ratio levels more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib. Coadministration of Tafinlar with other substrates of these enzymes, including dexamethasone or hormonal contraceptives, can result in decreased concentrations and loss of efficacy. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm380573.htm

Zofran (Ondansetron Hydrochloride) Tablets, Oral Solution, Orally Disintegrating Tablet, and Injection

The following has been added to the adverse reactions section of the ondansetron package insert: Stevens-Johnson syndrome and toxic epidermal necrolysis.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm230231.htm

Acetaminophen

The FDA is recommending that healthcare professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 mg of acetaminophen per tablet, capsule, or other dosage unit. There are no available data to show that taking more than 325 mg of acetaminophen per dosage unit provides additional benefit that outweighs the added risks for liver injury. Further, limiting the amount of acetaminophen per dosage unit will reduce the risk of severe liver injury from inadvertent acetaminophen overdose, which can lead to liver failure, liver transplant, and death.

Cases of severe liver injury with acetaminophen have occurred in patients who

- took more than the prescribed dose of an acetaminophen-containing product in a 24-hour period
- took more than one acetaminophen-containing product at the same time, or
- drank alcohol while taking acetaminophen products.

www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm381650.htm

IV Fluid Shortage

The FDA is aware of the shortage of intravenous (IV) solutions, particularly 0.9% sodium chloride injection¹ (i.e., saline), that are used to provide patients with the necessary fluids for hydration and other conditions. The shortage has been triggered by a range of factors including a reported increased demand by hospitals, potentially related to the flu season.

www.fda.gov/Drugs/DrugSafety/ucm382255.htm

http://www.fda.gov/Drugs/DrugSafety/ucm382255.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Vidaza (Azacitidine) for Injection

Changes to the package insert include the deletion of the statement, "Safety and effectiveness of VIDAZA in patients with MDS and renal

impairment have not been studied as these patients were excluded from the clinical trials,” and a new section has been added that states “Severe renal impairment has no major effect on the PK exposure of azacitidine after single and multiple SC administrations. Therefore, azacitidine can be administered to subjects with renal impairment without initial dose adjustment (see Clinical Pharmacology [12.3]).” www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289980.htm

ISMP Medication Safety Alerts

January 16, 2014 (Volume 19, Issue 1): The 2014–2015 ISMP Targeted Medication Safety Best Practices for Hospitals focuses on the following areas: IV vincristine, oral methotrexate, patient weights

in metric units, oral syringes, oral liquid dosing devices, and glacial acetic acid. ISMP encourages adoption of these practices in all U.S. hospitals. All are fully described on the website at www.ismp.org/tools/bestpractices.

January 30, 2014 (Volume 19, Issue 2): The quarterly action agenda included the problem of understanding and managing overflow, in which more than 1,000 patients received chemotherapy that was less potent than intended because overflow was not accounted for.

February 18, 2014 NAN Alert: The National Alert Network reported the potential inaccuracy of electronically transmitted medication history information used for medication reconciliation from Surescripts, a major provider of medication history services.

Resident's Cubicle Providing Useful Feedback

Alex Shillingburg, PharmD

Clinical Specialist BMT/Hematologic Malignancy

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Believe it or not, another residency year is nearing its end. For residents and program directors, ResiTrak®'s friendly and frequent reminders will begin pouring into inboxes. As you begin the task of working through the enormous pile of self-, experience, and end-of-year evaluations, it is important to ensure you are providing quality feedback.

Effective feedback is a two-way street; the preceptor and the resident must be able to both give and receive constructive comments. This article focuses on the aspect of providing feedback from two perspectives: the preceptor's perspective of appropriately evaluating the resident's performance and the resident's perspective of providing useful critiques for the preceptor, evaluating the learning experience, and appropriately self-evaluating.

Preceptors: Providing Feedback

A conventional approach to providing feedback is the “sandwich method,” which involves opening with positive comments, then discussing areas for improvement or any negative comments, and closing with something positive. Although this approach is not incorrect, it hardly scratches the surface of the components needed to provide quality feedback.

High-quality feedback should be concrete, specific, useful, timely, and frequent. Simply stating positives and negatives does not let residents know *what* they did well or in *what area* they can improve. The feedback should be actionable and useful. Comments such as “That was a really good job,” “Your presentation needs work,” and “You did that wrong” are not feedback at all because they will leave residents wondering, “What *specifically* should I do more or less of next time based on this information?” Residents won't know what was good or wrong about what they did and, most importantly, how to fix it.

In my experience, there are five common mistakes that even seasoned and effective preceptors make.

Making Observations

Observations and details about what the resident actually did are very important pieces of effective feedback; however, observations alone lack the most crucial aspect of feedback—assessment. If an entire evaluation is filled with statements like “The resident led three topic discussions with the team,” “The resident presented a patient case at medicine grand rounds,” and “The resident attended rounds daily,” there is no way to determine how well or poorly the resident performed. Each of these statements should be followed with an assessment of how well the task was performed by the resident and specifically identify positive accomplishments or areas that need improvement. For example, “The resident attended rounds daily and was punctual and prepared for every patient. He provided thoughtful suggestions and consistently picked up on key issues with very complicated patients. His follow-up post rounds improved greatly throughout the experience as he became more comfortable with the team's workflow. His communication with the team was excellent, and his input was very well received. He quickly became an effective member of the team.”

Making Assumptions

Making assumptions about why residents behave in a certain way can alienate or offend them. Receiving assumptions as feedback can result in residents reacting defensively or losing confidence. If a behavior needs to be corrected, it is best to state the actual behavior you observed and how that deviated from the desired behavior. For example, an ineffective statement would be “During the guest lecture, the resident was bored and uninterested.” This statement is a judgment, not an observation. A more effective and less subjective statement would be “During the guest lecture, I observed the resident displaying inattentive behaviors such as texting, staring around the room, and making eye contact with other residents/students. These behaviors display a lack of respect for the presenter and will not be tolerated in the future.”

Providing Only Summative Feedback

Feedback is most useful in changing and shaping a resident's performance if it is provided frequently and as close as possible to when the behaviors or tasks occurred. Receiving feedback only at the conclusion of a rotation is almost the same as if you went into your supervisor's office for your annual review and were informed that you are being fired because you have been incorrectly documenting your interventions for the past 10 months, even though you were never told that you were documenting incorrectly and would have corrected this practice immediately had it been brought to your attention. The same concept holds true for resident learning.

A good example of timely and frequent feedback can be seen in most video games. If you fail in Angry Birds or Guitar Hero, you can immediately start over—often from where you left off—improve your strategy, and try again. Games are built to reflect and adapt to our changing need, pace, and capacity to learn. Today's learners are accustomed to this type of rapid feedback and adaptation.

Giving Advice

As teachers and preceptors, we too often automatically give advice without first ensuring that the resident understands and accepts the initial critiques and feedback. In doing this, we often unintentionally cause residents to feel increasingly insecure about their own judgment and to become dependent on the advice of experts, which can result in panic about what to do when either varying advice is received from different people or no advice is available at all.

- You need more examples in your article.
- You might want to use a lighter baseball bat.
- You should have gone to PubMed for this question.

These three comments are not feedback; they are advice. Unanticipated advice like this seems unnecessary at best and unhelpful and annoying at worst. If the reason for the advice is not given first, the natural response of the resident would be to wonder, "Why are you suggesting this?"

To make the above statements more effective when providing feedback, make sure the resident understands the critique.

- The points in your article are unclear in some places. Maybe you could try adding a few more examples.
- You keep dropping your shoulder when you swing, causing you to hit pop-ups. You may want to try using a lighter baseball bat.
- The answer you gave is too vague. More specific data from primary literature are needed to properly answer this. Next time you might try using PubMed.

If your ratio of advice to feedback is too high, try asking the resident, "Given the feedback you received, what ideas do you have about how to improve?" This approach will help the resident build greater confidence and autonomy.

Grading or Evaluating Versus Giving Feedback

For the majority of our lives as learners, we have been programmed to rely on grades as a measure of our performance. Though it is important to assess the quality of the end product, it is most meaningful to understand why a grade was assigned, whether acceptable or unacceptable. Some examples of unhelpful evaluation statements to avoid include

- This presentation is weak.
- Good work!
- Your formulary review is better.
- I'm really pleased with your medication use evaluation poster.

These comments make value judgments. They assess, commend, or criticize what was done. There is little or no feedback provided and no actionable information about what occurred. As a result, the resident only knows that someone has placed a high or low value on what he or she did.

By adding additional detail to these comments, they can be reworked into effective feedback that the resident can use to progress.

- This presentation is weak. The topics you presented do not intuitively flow, making it difficult to follow. The evidence that you presented did not support your conclusions, and you missed a key factor in making treatment decisions.
- Good work! Your word usage was more precise in this paper than in the previous one, and I was able to clearly understand the reasoning for your treatment selection.
- Your formulary review is improved. You included logistic considerations and sought input from nursing and scheduling. You provided an accurate cost comparison with the two alternative treatments in this scenario. I appreciate that you formulated your own recommendation and supported it with your data and research.

The most common reason cited for not using the above methods to provide feedback is that there is no time for this extensive process. Essentially, "no time to give effective feedback" means "no time to promote learning."

Residents: Providing Feedback

All of the components of quality feedback previously discussed also apply to residents when they provide feedback to their preceptors and directors.

Evaluating Your Preceptor

The most difficult part for residents evaluating preceptors is to provide ongoing feedback. The relationship dynamic between the trainer and trainee does not often lend itself to the trainee providing any type of in-the-moment feedback about the preceptor's performance. One way to address this would be to focus on how the preceptor's performance affects the resident's personal experience rather than on his or her overall ability as a preceptor. For instance, to compliment without sounding condescending, talk about how certain things have specifically helped you improve your practice. To deliver critiques, make suggestions to correct behaviors that would help you to improve your learning, such as "I feel that more frequent topic discussions in the beginning of the rotation would help improve my understanding," or "Could you walk me through your prerounding process? I struggle learning new areas and find it helpful to hear my preceptors work through profiling their patients out loud because it shows me how to think about this special patient population."

When evaluating your preceptor at the end of the rotation, refrain from commenting on him or her as a person and instead focus on his or her precepting style, actions that you found helpful, and

actions that would benefit from improvement. Don't be afraid to provide constructive and useful comments; a wishy-washy evaluation is as ineffective for preceptors as it is for you. Be careful, however, not to critique things that are out of the preceptor's control, such as operational requirements. Be sure to point out times when the preceptor went above and beyond what you would have expected or when he or she failed to meet your expectations and why.

Learning Experience

I find the evaluation of the learning experience to be the most difficult. The structure of the experience is strongly dictated by the preceptor's position and the pharmacy practice model within the preceptor's institution or that particular area. Differentiating the experience from the preceptor also can be difficult when there is only one preceptor for a certain experience. Make an effort to focus on the pieces of the experience that can be manipulated, such as the content of topic discussions, the responsibilities you had, the activities you performed, and the goals and objectives of that rotation and whether they represent the experience you had expected. Do you feel that the things you learned and the experiences you had were representative of what that rotation should be? For example, a rotation in oncologic infectious disease should include several key pathogens and provide you with an adequate foundation for treating infections in immunocompromised patients regardless of which institution you are in or by whom you are taught.

Self-Evaluation

As a resident, one of the most crucial pieces of feedback is the self-evaluation. Self-reflection is vital to continuing your professional development beyond the residency training program. As a resident, you are evaluated constantly, but as a practitioner you receive formal feedback very infrequently. The task of evaluating your own performance and improving your practice relies on high-quality and accurate self-assessment. It is worth reiterating that the most important part is to assess how well you performed tasks, not simply

what you accomplished. The benefit of practicing self-assessment during residency is that this along with the preceptor's assessment of you will help you achieve a more realistic view of your actual performance. If the preceptor's and resident's assessments are similar, then the resident can be confident in knowing that he or she is able to accurately self-assess. The problem occurs when they differ from one another. If you find that your self-evaluation is rated consistently higher than your preceptor's, seek input from your preceptor to identify your deficiencies and develop a plan to improve the quality of your practice. If your evaluation is consistently lower than your preceptor's, then you may need to focus on building self-confidence. If your preceptor is impressed by your performance, ask what specifically motivated him or her to give you high marks and work to recognize your own strengths.

Consistently providing meaningful and effective feedback is crucial to the success and development of each resident and of the residency program. Although evaluations, rotations, or administrative responsibilities can be fatiguing and interfere with providing quality feedback, remember the tips discussed in this article and the vital role feedback plays in developing good clinical pharmacists, pharmacy preceptors, and healthcare professionals.

Special thanks to my residency program coordinator, Justin Hare, PharmD, for providing a preceptor development course on delivering feedback.



Suggested Reading

Wiggins, G. Seven keys to effective feedback. *Feedback for Learning*;2013;70(1):10-16.



HOPA Research Fund Grant \$50,000 available in funding

Call for proposals is now open.

Research grant information is now available on www.hoparx.org. Letters of intent are due June 16, 2014.

Crizotinib (Xalkori)

Class: Tyrosine kinase inhibitor

Indication: Treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by a U.S. Food and Drug Administration (FDA)-approved test

Dose: 250 mg orally twice daily, with or without food, swallowed whole

Dose modifications: Interrupt therapy for the following toxicities: grade 3 or 4 hematologic toxicity, grade 3 or greater nonhematologic toxicity. For grade 3 hematology toxicity, therapy can be resumed at the same dose when the counts recover to grade 2; for grade 4 hematologic toxicity, therapy should be restarted at 200 mg BID. Therapy should be discontinued if the patient develops treatment-related interstitial lung disease (ILD)/pneumonitis, a QTc of greater than 500 ms on two separate electrocardiograms (ECGs) after crizotinib has been dose reduced, a QTc change greater than 60 ms from baseline with the development of Torsade de pointes, polymorphic ventricular tachycardia or a serious arrhythmia, or if severe or life-threatening bradycardia occurs without a contributing concurrent medication.

Common adverse effects: Vision disorders, nausea, diarrhea, vomiting, constipation, edema, elevated liver transaminases, and fatigue

Drug interactions: Substrate of CYP3A4/5; avoid concurrent use with strong CYP3A inhibitors and inducers, medications known to prolong the QTc interval and cause bradycardia, and taking with grapefruit and grapefruit juice

Warning and precautions: Increased risk of hepatic dysfunction, pneumonitis, QT interval prolongation, and visual disorders

Crizotinib for Metastatic Non-Small Cell Lung Cancer

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During the past few years, the treatment of non-small cell lung cancer (NSCLC) has been revolutionized with the discovery of activating mutations in the kinase domain of the epidermal growth factor receptor (EGFR) gene, leading to novel treatments of molecular targeted therapies.¹ One of the newer mutations discovered is anaplastic lymphoma kinase (ALK). ALK activation is caused by a chromosomal rearrangement, which leads to the expression of an oncogenic fusion kinase, echinoderm microtubule-associated proteinlike 4-anaplastic lymphoma kinase (EML4-ALK).² Genetic alterations of ALK also have been found in anaplastic large-cell lymphoma, inflammatory myofibroblastic tumor,

and pediatric neuroblastoma.² ALK is activated in approximately 5% of all NSCLC tumors and defines a distinct molecular subtype of NSCLC. Risk factors for having an ALK mutation in patients with NSCLC are young age of onset, minimal or nonsmoker, and adenocarcinoma histology.^{2,3} According to the 2014 National Comprehensive Cancer Network (NCCN) Guidelines for the diagnosis and treatment of NSCLC, non-squamous and not otherwise specified histologies carry category 1 recommendation for molecular testing for ALK mutations.⁴

Crizotinib (Xalkori®, Pfizer) is a novel tyrosine kinase inhibitor that targets ALK, MET, and ROS1 tyrosine kinases.^{3,5} It is taken orally and is relatively well-tolerated. Crizotinib was approved in 2011 by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic NSCLC with ALK-positive tumors, as detected by an FDA-approved test.⁵ Current NCCN guidelines recommend the use of crizotinib for ALK-positive NSCLC as first- or second-line therapy (category 2a recommendation).⁴

Crizotinib gained accelerated approval by the FDA in August of 2011 based on the two phase 2 trials of patients with metastatic ALK-positive NSCLC. Camidge and colleagues developed a multinational, single-arm trial in patients with metastatic, ALK-positive NSCLC of which most patients received prior therapy.⁶ All patients received crizotinib 250 mg twice daily. The primary outcome was objective response rate (ORR). In the second trial, 119 patients were enrolled, and the median duration of treatment was 11 months. The ORR was found to be 61% (95% confidence interval [CI]: 52%–70%) with a median duration of response of 48 weeks.⁷ Crino and colleagues developed a multinational, single-arm trial in patients with metastatic, ALK-positive NSCLC of which 92% received prior therapy.⁶ All patients received crizotinib 250 mg twice daily. The trial included 136 patients with a median treatment duration of 9 weeks. The primary outcome was ORR. The ORR was 83%, and seven patients had objective disease progression.⁷

Regular approval for crizotinib was then granted in 2013 for locally advanced or metastatic NSCLC based on data showing improved progression-free survival (PFS) and ORR. Shaw and colleagues developed a randomized, multicenter, open-label, active-controlled trial of 347 patients who had received prior platinum therapy.⁸ Patients were randomized to either receive crizotinib 250 mg twice daily ($n = 173$) or chemotherapy ($n = 174$) with pemetrexed (500 mg/m²) or docetaxel (75 mg/m²) intravenously every 21 days. For the primary efficacy outcome of PFS, the median PFS was longer in the crizotinib group (7.7 months, 95% CI: 6.0–8.8 months), compared with the chemotherapy group (3 months, 95% CI: 2.6–4.3 months).³ In a subgroup analysis, the hazard ratio (HR) for disease progression or death comparing crizotinib with pemetrexed was 0.49 with a 95% CI of 0.37–0.64, $p < .001$.³ The HR for disease progression or death with crizotinib compared with docetaxel was 0.30 with a 95% CI of 0.21–0.43, $p < .001$.³ The response rate, based on the intention to treat population, was also significantly higher in the crizotinib group (65%) compared with the chemotherapy group (20%, 95% CI: 58–72; $p < .001$).³ Overall survival (OS) was not statistically different between the crizotinib and

chemotherapy groups (20.3 months and 22.8 months, respectively, HR 1.02, 95% CI: 0.68–1.54; $p = .54$). Notably, 64% of patients assigned to receive chemotherapy subsequently received crizotinib outside of the trial for a treatment duration of 58 months versus 17 months.

The primary end point of the previous trials is PFS, with OS as a secondary end point. The OS benefit of crizotinib will likely be confounded in both trials because of crossover; crossover is required because it would be unethical to have a randomized trial that deprived an ALK-positive patient of crizotinib.³ However, in a retrospective OS analysis of patients with ALK-positive NSCLC comparing those who received crizotinib in the phase 1 trial with those who never received crizotinib, treatment with crizotinib was associated with a substantial prolongation in OS. Shaw and colleagues designed a retrospective analysis to compare a group of advanced ALK-positive NSCLC patients who received crizotinib ($n = 82$) with a control group of advanced ALK-positive NSCLC patients who did not receive crizotinib ($n = 36$) and with a control group of patients with advanced NSCLC without an ALK-rearrangement ($n = 120$).² Baseline demographics were similar between the three groups with the exception of age and smoking history between the ALK-positive and ALK-negative cohorts. Patients in the ALK-positive group were significantly younger (age 51 years versus 63 years, respectively, $p < .0001$).² In the ALK-positive cohort, more patients had never smoked compared with the ALK-negative cohort (76% versus 33%, respectively, $p < .0001$).² Survival in the ALK-positive cohort who received crizotinib was significantly longer than the ALK-positive patients who did not receive crizotinib (median OS did not reach 95% CI, 14 months to not reached versus 6 months [4–17 months]). One year OS was 70% (95% CI: 50–83) in the crizotinib group versus 44% (95% CI: 23–46) in the noncrizotinib group, and 2-year OS was 55% (95% CI: 33–72) in the crizotinib group versus 12% (95% CI: 2–30) in the noncrizotinib group with an HR of 0.36 (95% CI: 0.17–0.75; $p = .004$).

Survival in the ALK-positive, crizotinib-treated group was similar to that of the ALK-negative, EGFR tyrosine kinase inhibitor-treated, EGFR-positive group with a 1-year OS of 71% (95% CI: 58–81) versus 74% (95% CI: 61–83), respectively, and a 2-year OS of 57% (95% CI: 40–71) versus 52% (95% CI: 38–65), respectively ($p = .786$).² Shaw and colleagues' results suggest that crizotinib therapy for patients with ALK-positive NSCLC is associated with improved OS compared with patients with ALK-positive disease who do not receive crizotinib. Overall, an ALK rearrangement is not a favorable prognostic feature in advanced NSCLC.

Crizotinib is relatively well tolerated.^{5,8–11} The most common adverse effects reported at a rate of $\geq 10\%$ are diarrhea, nausea, vomiting, constipation, edema, upper respiratory tract infections, dysgeusia, visual disturbances, and dizziness.² Crizotinib is moderately emetogenic, and the severity of nausea can be attenuated by taking crizotinib with food and premedicating with an antiemetic. Diarrhea tends to be mild and grade 1.^{5,8} Visual disorders such as impairment, photopsia, blurred vision, or vitreous floaters were reported in 55% of patients in a phase 2 trial, but the effects were not long lasting.¹⁵ These disorders did not

require dose adjustment or discontinuation and tended to occur during days 4–7 of the first week of therapy.⁵ Patients should be warned of this effect because they can occur suddenly but resolve quickly.

There are several serious adverse effects associated with crizotinib use: hepatotoxicity, ILD/pneumonitis, QT interval prolongation, bradycardia, and embryofetal toxicity.⁵ Hepatotoxicity occurred in 9.2% of all patients but only 0.7% required permanent discontinuation of crizotinib.^{5,9} ILD/pneumonitis developed after 2 months of therapy in 2.5% of all patients, and 0.5% of the 2.5% who developed ILD had a fatal outcome.⁵ QT prolongation developed in 2.7% of all patients, and a QTc ≥ 500 ms occurred in 1.4% of all patients. Bradycardia occurred in 11% of all patients, and grade 3 syncope occurred in 2.9% of all patients.⁵ Crizotinib can cause fetal harm in pregnant women. There are no adequate and well-controlled trials in women; however, there was embryotoxic and fetotoxic exposure in nonclinical rat trials.⁵ Crizotinib is defined as pregnancy category D, and it is recommended that contraception be administered during therapy and for 90 days following the discontinuation of therapy.⁵

There are several dose reductions for crizotinib based on grade 3 and 4 severity adverse reactions as defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.⁵ The first dose reduction is to 200 mg twice daily, the second dose reduction is to 250 mg once daily, and the drug should be discontinued permanently if the patient is unable to tolerate the 250 mg once daily dose. If a patient develops a grade 3 hematologic toxicity, crizotinib should be held until counts recover to grade 2 or less and then resumed at the previous dose. If a patient develops a grade 4 hematologic toxicity, crizotinib should be held until counts recover to grade 2 or less and then resumed at the next lower dose. Crizotinib should be discontinued if the patient develops treatment-related ILD/pneumonitis, a QTc of greater than 500 ms on two separate electrocardiograms (ECGs) after crizotinib has been dose reduced, a QTc change greater than 60 ms from baseline with the development of Torsade de pointes, polymorphic ventricular tachycardia or a serious arrhythmia, or if severe or life-threatening bradycardia occurs without a contributing concurrent medication. Crizotinib should be dose adjusted for organ impairment. For patients with renal impairment (CrCl < 30 mL/min) who are not on dialysis, the dose should be adjusted to 250 mg orally once daily. For patients with hepatic impairment, crizotinib should be used with caution. If hepatic impairment develops while the patient is on treatment, crizotinib should be held and restarted at the next lowest dose when the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) recover to < 3 times the upper limit of normal (ULN). If AST/ALT are greater than 2.5 times ULN and the total bilirubin rises to > 1.5 times ULN, crizotinib should be permanently discontinued.⁵

Patients should be monitored closely, at first, while on crizotinib. Patients should have routine complete blood counts drawn, and their liver function should be monitored biweekly for the first month of treatment and then monthly thereafter.⁵ Patients should be monitored for symptoms of pneumonitis, and crizotinib should be permanently

discontinued if he or she is diagnosed with treatment-related pneumonitis.⁵ Due to the increased risk of QT interval prolongation in patients, those on treatment should have their ECGs and electrolytes monitored at baseline and then per the provider's discretion.⁵ More frequent monitoring is recommended for patients who are taking medications that are known to prolong the QT interval concomitantly with crizotinib.⁵ Because of the risk of vision disorders, ophthalmological evaluation should be considered if patients experience photopsia or new or increased vitreous floaters.⁵

Crizotinib is predominately metabolized by cytochrome P450 (CYP) 3A4/5 enzymes in the liver. The coadministration of strong CYP3A4 inhibitors and strong CYP3A4 inducers should be avoided. There currently are no recommendations for empiric dose reductions of crizotinib if the coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided. The coadministration of CYP3A4 substrates with narrow therapeutic indices with crizotinib should be avoided if possible; however, if a patient is required to take a medication with a narrow therapeutic index, it is reasonable to consider an empiric initial dose reduction of that agent.⁵ Other potential interactions discovered in *in vitro* studies with crizotinib are inhibition of CYP2B6 and P-glycoprotein. Crizotinib may increase the plasma concentrations of coadministered medications that are substrates of CYP2B6 or P-glycoprotein. Grapefruit and grapefruit juice should be avoided.^{1,5}

Crizotinib is an exciting option for patients with ALK-positive NSCLC. It is an oral agent and generally well tolerated. It has shown a benefit in PFS for the treatment of patients with ALK-positive NSCLC. Crizotinib is actively being studied in NSCLC and is being compared to current standard chemotherapy treatments. It may have future potential applications in the treatment of lymphomas and other ALK-mutation-driven cancers.

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Obinutuzumab (Gazyva™)

Class: Fully humanized monoclonal antibody targeting CD20

Indication: Treatment for previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil

Dose: Cycle 1: 100 mg intravenously on day 1; 900 mg on day 2; and 1,000 mg on days 8 and 15

Cycles 2–6: 1,000 mg administered intravenously every 28 days

Dose modifications: Obinutuzumab has not been studied in patients with a creatinine clearance (CrCl) < 30 mL/min or in hepatic impairment

Common adverse effects: Infusion-related reactions, neutropenia, thrombocytopenia, anemia, musculoskeletal pain, and fever

Serious adverse effects: Hepatitis B reactivation, progressive multifocal leukoencephalopathy

Drug interactions: No formal drug interactions studies have been conducted.

Obinutuzumab in Untreated CLL

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Chronic lymphocytic leukemia (CLL) is the most common leukemia affecting adults in the United States, with the American Cancer Society estimating 15,680 new cases and 4,580 deaths in 2013.¹ The average age at the time of diagnosis is around 72 years old.¹ CLL is characterized by a progressive accumulation of B lymphocytes in the blood, bone marrow, and lymphoid tissues. Although the majority of patients experience indolent disease, some present with aggressive disease.² The diagnosis of CLL is made when $> 5.0 \times 10^9$ L monoclonal B lymphocytes are present in the peripheral blood.³

Patients with CLL are treated based on prognostic factors that include the patient's age, performance status, stage of the disease, and symptoms on presentation. Patients may present with symptoms that include swollen lymph nodes, fever, chills, recurrent infections, or weight loss. In the majority of cases, patients present without symptoms and are diagnosed with CLL based on an elevated B lymphocyte count in their peripheral blood. Patients who are asymptomatic at presentation may have treatment deferred until symptoms occur.⁴

The treatment for CLL has evolved during the past several decades. Though monotherapy with alkylating agents was once the mainstay of treatment, treatment has progressed with the use of chemoimmunotherapy combinations, such as fludarabine, cyclophosphamide, and rituximab.⁵ Despite the fact that the treatment of CLL has advanced and overall survival is improving with new therapies, the disease remains incurable. Patients can receive numerous treatment regimens throughout the disease's course, but it almost always becomes refractory and relapse eventually follows.⁶ For these reasons, advancement

in therapy continues to be important. The success of rituximab in targeting cell surface antigen CD20 has fueled the advent of newer anti-CD20 antibodies, with different functional activity and potential improvement on rituximab's efficacy and safety profile. There are currently two types of U.S. Food and Drug Administration (FDA)-approved anti-CD20 monoclonal antibodies, and they differ based on their activity at the binding site. Obinutuzumab is a type 2 anti-CD20 monoclonal antibody that works by evoking homotypic adhesion and exhibits phagocytosis as well as nonapoptotic cell death mediated by lysosomes, cathepsin release, and a reactive oxygen species dependent pathway.⁷⁻¹⁰ Obinutuzumab is a type 2 anti-CD20 monoclonal antibody that works by evoking homotypic adhesion and exhibits phagocytosis as well as nonapoptotic cell death mediated by lysosomes, cathepsin release, and a reactive oxygen species dependent pathway.⁷⁻¹⁰ Obinutuzumab provides a new option to patients with CLL who are elderly or have significant comorbidities.⁵

On November 1, 2013, obinutuzumab (Gazyva™, Genentech) was approved for treatment of CLL in combination with chlorambucil in treatment-naïve patients.¹¹ This approval was based on the stage one results of a two-stage, randomized, open label, multicenter, international CLL (BO21004) phase 3 trial. All patients had previously untreated CLL. The study design allowed for inclusion of elderly patients with comorbidities because this represents patients in the general population treated for CLL. The median patient age was 73 years old, and comorbidities ranged from hypertension, coronary heart disease, heart failure, diabetes, musculoskeletal problems, to renal impairment. The first stage of the study consisted of patients randomized to obinutuzumab plus chlorambucil (G-Clb) or chlorambucil (Clb) alone for six cycles. In the second stage, rituximab was combined with Clb (R-Clb). Cycles were repeated every 28 days. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall response rate (ORR), overall survival (OS), safety, and minimal residual disease (MRD), defined as no detectable disease in the blood at the end of treatment courses.¹²

A total of 781 patients were enrolled in the study, of which 238 were in the G-Clb arm, 233 were in the R-Clb arm, and 118 were in the Clb arm. Compared with Clb monotherapy, chemoimmunotherapy with either G-Clb or R-Clb significantly prolonged PFS. The median PFS was 26.7 months for patients treated with G-Clb, 15.2 months in the R-Clb arm, and 11.1 months in the Clb arm ($p < .001$). Secondary endpoints also supported the use of chemoimmunotherapy with Clb rather than Clb monotherapy. Complete responses at the end of treatment were seen in 22.2% of patients in the G-Clb arm, 8.3% of patients in the R-Clb arm, and 0% in Clb alone ($p < .001$). MRD negativity in the bone marrow and the peripheral blood was achieved in a higher proportion of patients treated with G-Clb (19.5% and 37.7%, respectively) or R-Clb (2.8% and 2.0%, respectively) versus 0% and 0% of patients treated with Clb alone ($p < .001$). At the time of publication, OS medians had not been reached. However, in the most recent assessment of OS, G-Clb was shown to provide a significant benefit compared with Clb—the rate of deaths was 9% with G-Clb and 20% with Clb alone ($p = .002$). The rate

of death in the R-Clb arm was 15%, and there was no significant difference in survival with R-Clb compared with Clb ($p = .11$) and no significant difference between G-Clb and R-Clb ($p = .08$).¹²

The most common adverse reactions ($\geq 10\%$) reported in the trial with the G-Clb combination were infusion-related reactions (69%), neutropenia (41%), thrombocytopenia (15%), nausea (13%), anemia (12%), diarrhea (10%), pyrexia (10%), and cough (10%). The most common grade 3–4 adverse reactions ($\geq 10\%$) were infusion-related reactions, neutropenia, and thrombocytopenia. Grade 3 and higher infusion-related reactions occurred in more patients treated with G-Clb versus R-Clb (21.3% versus 4.0%); grade 3 and higher infusion-related reactions occurred during the first infusion only. Symptoms of the infusion-related reactions included nausea, vomiting, hypotension, pyrexia, chills, and flushing.¹² Obinutuzumab also has a black box warning for hepatitis B reactivation and progressive multifocal leukoencephalopathy.¹³

Dosing and Administration¹⁵

Cycle [†]	Day	Dose (mg)	Infusion rate**
1	1	100	25 mg/hr
	2	900	50 mg/hr, escalating by 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	8, 15	1,000	
2–6	1	1,000	100 mg/hr, escalating by 100 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr

[†]Do not administer obinutuzumab as an intravenous push or bolus.

^{**}Obinutuzumab is given for six 28-day cycles.

Prior to infusion of obinutuzumab on days 1 and 2 of cycle 1, premedicate patients with 20 mg of dexamethasone or 80 mg of methylprednisolone, 650–1,000 mg of acetaminophen, and an antihistamine (e.g., diphenhydramine 50 mg). If no infusion-related reaction occurs, all future doses may be premedicated with acetaminophen only. Premedication protocols for patients experiencing an infusion-related reaction can be found in the package insert. Patients experiencing neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period, and antiviral and antifungal prophylaxis also should be considered.¹⁵

Obinutuzumab is supplied as a 1,000 mg/40 mL (25 mg/mL) single-use vial containing preservative-free solution and is stable at 2 °C–8 °C (36 °F–46 °F). Vials should be protected from light. Obinutuzumab has not been studied in patients with hepatic impairment or CrCl < 30 ml/min. No formal drug interaction studies have been conducted with obinutuzumab.¹⁵

Obinutuzumab is an anti-CD20 monoclonal antibody that is approved for use in patients with untreated CLL in combination with chlorambucil. Obinutuzumab's approval for use in CLL treatment is based on a randomized, open-label, multicenter trial that showed improved PFS and other secondary endpoints for obinutuzumab in combination with chlorambucil compared with chlorambucil monotherapy. Based on these results, the National Comprehensive Cancer Network recommends obinutuzumab as the preferred regimen in patients older than 70 years with comorbidities as well as frail patients unable to tolerate purine analogs.⁵ Obinutuzumab provides a new option for patients that necessitate anti-CD20 monoclonal antibodies as part of treatment. For patients who are not able to tolerate standard first-line regimens, such as fludarabine, cyclophosphamide, and rituximab, obinutuzumab provides a superior option to chlorambucil alone.

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Sorafenib (Nexavar®)

Class: Tyrosine kinase inhibitor; vascular endothelial growth factor (VEGF) inhibitor

Indication: Advanced renal cell carcinoma, unresectable hepatocellular carcinoma, and late-stage (metastatic) differentiated thyroid cancer

Dose: 400 mg orally twice daily on an empty stomach (1 hour before or 2 hours after a meal)

Dose modifications: Modify or hold dose based on toxicity. Refer to the package insert for specific dose changes.

Dose reduction	Dose modification
First dose reduction	400 mg and 200 mg, 12 hours apart
Second dose reduction	200 mg twice daily
Third dose reduction	200 mg once daily

Common adverse effects: Fatigue, weight loss, rash, hand-foot-skin reaction, alopecia, diarrhea, anorexia, nausea, and abdominal pain

Serious adverse effects: Cardiac ischemia/infarction, bleeding, dermatologic toxicity, QT prolongation, hypertension, and gastrointestinal perforation

Drug interactions: Sorafenib is a minor substrate of CYP3A4 and UGT1A9. Avoid concurrent use with strong CYP3A4 inducers. Use caution when administering sorafenib with drugs that are metabolized predominantly via UGT1A1. Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer.

Monitoring parameters: Thyroid-stimulating hormone, blood pressure, complete blood count with differential, electrolytes, and liver function tests, and monitor for hand-foot syndrome

Sorafenib (Nexavar®): Now Approved for Advanced Differentiated Thyroid Cancer

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Thyroid cancer has become the fastest-increasing cancer worldwide.¹ The incidence of thyroid carcinoma increased almost 310% between 1950 and 2004.² In the United States, there are an estimated 534,973 people currently living with thyroid cancer.³ The main histologic types of thyroid carcinoma include differentiated (e.g., papillary, follicular, and Hürthle), medullary, and anaplastic.² Differentiated thyroid cancer (DTC) accounts for approximately 90% of all thyroid cancers.⁴ The standard treatment for DTC includes surgery whenever possible,

followed by radioactive iodine for selected patients and thyroid hormone suppression therapy in most patients.² Although the majority of DTCs are curable, radioactive iodine (RAI)-refractory locally advanced or metastatic disease is more challenging to treat and is associated with a lower patient survival rate.^{5,6} Systemic therapy can be considered for advanced DTCs that are not responsive to standard treatment.² Traditional cytotoxic chemotherapy has minimal efficacy in the setting of metastatic DTC.⁷ In recent years, new targeted agents for the treatment of advanced thyroid cancer have been developed.²

Sorafenib is an oral tyrosine kinase inhibitor (TKI) that blocks multiple intracellular (c-CRAF, BRAF, and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, RET/PTC, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-β). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib has been approved by the U.S. Food and Drug Administration (FDA) under the brand name Nexavar® for the treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma.⁸

In November 2013, the FDA granted approval of sorafenib for the treatment of locally recurrent or metastatic progressive DTC refractory to RAI treatment. The approval was based on the results of the DECISION trial, a randomized, double-blind, placebo-controlled multicenter phase 3 study conducted in 417 patients with advanced DTC that had progressed within the prior 14 months on RAI.⁹ Patients were randomized to receive 400 mg of oral sorafenib twice daily (207 patients) or matching placebo (210 patients). Of the 417 patients randomized, 48% were male, the median age was 63 years, 60% were Caucasian, 62% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and 99% had undergone thyroidectomy. Metastases were seen in 96% of patients: lungs in 86%, lymph node in 51%, and bone in 27%. The majority of patients in the study population had papillary carcinoma (57%), followed by follicular, including Hürthle cell (25%), poorly differentiated carcinoma (10%), and other (8%). The primary endpoint of the study was progression-free survival (PFS), as defined by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included overall survival (OS), time to progression, response rate, and duration of response. Safety and tolerability were also evaluated.⁹

The median PFS was 10.8 months with sorafenib compared to 5.8 months with placebo (hazard ratio [HR] = 0.59; 95% confidence interval [CI]: 0.46–0.76; $p < .001$). OS was not statically significant. No complete response was seen in the study. Partial responses (PR) were observed in 12% of patients receiving sorafenib compared with 0.5% in the placebo arm ($p < .0001$). Median duration of PR was 10.2 months.⁹

The most common adverse reactions were palmar-plantar erythrodysesthesia syndrome, diarrhea, alopecia, weight loss, fatigue, hypertension, rash, decreased appetite, stomatitis, nausea, pruritus, and abdominal pain. Dose interruptions from adverse reactions occurred in 66% of patients receiving sorafenib, and 64% had dose reductions. Discontinued therapy due to adverse reactions occurred in 14% of sorafenib-treated patients compared with 1.4% of those receiving placebo.⁹ At present, sorafenib offers an FDA-approved therapeutic

option for patients with locally recurrent or metastatic, progressive DTC that is refractory to radioactive iodine treatment. However, the impact of sorafenib on OS still remains to be seen.

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HOPA 10th Annual Conference: Big Success in the Big Easy

Celebration was in the air at the recent HOPA 10th Annual Conference in New Orleans, LA, as members old and new gathered to mark this important milestone in HOPA's history! We were pleased to welcome more than 870 pharmacists and allied health professionals—the most attendees ever at a HOPA conference. More than 50 exhibitors and 25 industry supporters also participated in the event.

The conference kicked off with the John G. Kuhn Keynote Lecture by the session's namesake. Moderator Kevin O'Connor led an informal conversation with John G. Kuhn, PharmD, about his involvement in founding HOPA, as well as his professional journey, insights into oncology pharmacy practice, personal reflections on working with cancer patients, and lessons learned throughout his life. Attendees also had an opportunity to ask Dr. Kuhn questions and engage in the conversation.

Many of the nation's leading experts in hematology/oncology pharmacy shared their knowledge by presenting interactive sessions that covered topics such as new and emerging therapies and reviews of recent developments in medical literature regarding advanced treatments. In addition, the number of concurrent educational breakouts rose to more than 36 sessions. Breakout sessions addressed chemotherapy dosing in obese patients, updates on closed-system transfer devices, and the use of chemotherapy during pregnancy, among other subjects. Six BCOP sessions provided opportunities for attendees to earn important recertification credits. Another popular session was the Health Policy Update, presented by Jeremy Scott and Erin Morton, HOPA's health policy consultants from the District Policy Group. Scott and Morton detailed the work of the Health Policy Committee on Capitol Hill as well as involvement with coalitions that are working toward advancing the goals of hematology/oncology pharmacists. Members were able to offer feedback and ask questions during the session.



During the Annual Members' Meeting, an update on the state of HOPA and its accomplishments from the past year was presented and award and grant winners were recognized.

Networking events provided attendees an opportunity to expand their professional contacts. The exhibit hall was filled with the premier providers of pharmaceutical products, devices, and delivery systems. The latest in Completed Research and Research-in-Progress posters rounded out the conference.

Celebrating Success: HOPA 10th Anniversary Gala was a tremendous success, raising nearly \$75,000 in ticket sales, industry support, and silent auction items. The sold-out event treated the crowd to great conversation and networking, delicious food, and music by a local jazz band. HOPA's important work in research funding was highlighted and research grant recipients were recognized for their work to improve hematology/oncology research.

We hope to see you next year at the HOPA 11th Annual Conference in Austin, TX, March 25-28, 2015.

Congratulations to the 2014 HOPA Award Winners



Rowena (Moe) Schwartz, PharmD BCOP
HOPA Award of Excellence Recipient



Robert Mancini, PharmD BCOP
HOPA New Practitioner Award Recipient



Ali McBride, PharmD BCOP BCPS
Oncology Pharmacy Practice Literature Award Recipient



Casey Williams, PharmD BCOP
HOPA Basic Science and Clinical Research Literature Award Recipient



Sarah Hudson-DiSalle, PharmD RPh
HOPA Patient Advocacy Award Recipient

