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## Posttransplant Cyclophosphamide: A Unique Approach for Prevention of Graft-Versus-Host Disease in Allogeneic Hematopoietic Stem Cell Transplantation

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The number of allogeneic hematopoietic stem cell transplants (HSCT) in the United States has steadily increased since the 1990s.[1] Allogeneic HSCT is a potentially curative treatment option for various malignant and nonmalignant hematologic conditions. Transplant has expanded as a treatment option for patients because of advancements in conditioning approaches and stem cell sources as well as graft versus-host-disease (GVHD) prevention strategies. Despite these improvements, GVHD remains a major source of posttransplant morbidity and mortality. Specific improvements in GVHD prophylaxis have positively affected acute GVHD, but incidence rates remain in the 20%–60% range.[2] Few improvements have been made on the incidence and severity of chronic GVHD, which is reported to occur in up to 80% of patients alive more than 100 days posttransplant. Chronic GVHD is a multisystem disease that can affect a wide variety of tissues. It may involve inflammation and fibrosis of the eyes, oral mucosa, skin, fascia, lungs, liver, gastrointestinal tract, joints, salivary glands, and genitourinary tract. Given all the organ systems potentially involved, it can have a major impact on quality of life. Chronic GVHD management continues to be a significant health-related problem in HSCT survivors because of the increased use of mobilized peripheral blood stem cells as a donor source, which has been associated with higher rates of chronic GVHD compared with bone marrow.[2]

Calcinuerin inhibitors (CNIs), such as tacrolimus or cyclosporine, combined with methotrexate (MTX) have been employed as GVHD prophylaxis for the past several decades and continue to be the most commonly utilized regimens by transplant centers in the United States. This strategy has resulted in satisfactory prevention rates and survival outcomes but is associated with treatment-related toxicity. Common side effects include nephrotoxicity, hypertension, neurotoxicity, and metabolic abnormalities. Improvements on standard CNI-based regimens for GVHD

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prophylaxis are needed to decrease GVHD rates and provide alternatives with a better side effect profile.[2]

## The Science Behind Posttransplant Cyclophosphamide

Cyclophosphamide (Cy) has been used for decades as a treatment for several malignancies and is tolerated in a wide range of dosages. It is broken down by the cytochrome P450 system into two metabolites: phosphoramide mustard (the active metabolite) and acrolein. Cy prevents cell growth by crosslinking DNA strands. It is effective throughout the cell cycle but is most effective during the G1 and S phases. Cells rapidly undergoing mitosis are uniquely sensitive to Cy's mechanism of action because of their reduced ability to replicate the damaged DNA. Aldehyde dehydrogenase is an enzyme required for conversion of phosphoramide mustard to an inactive metabolite, carboxycyclophosphamide. Hematopoietic stem cells possess this enzyme and are therefore resistant to Cy, allowing it to be used after HSCT without impairing engraftment.[3]

Immune reactions of donor T cells against contrasting host histocompatibility antigens lead to the development of GVHD after allogeneic HSCT. CNI-based GVHD prophylactic strategies weaken alloreactive T cell activation, proliferation, and interleukin-2 (IL-2) production and hinder the apoptosis of alloreactive T cells. The results of these actions cause widespread immunosuppression and delayed induction of transplant tolerance. Of the immunosuppressive agents currently employed, MTX and Cy can induce apoptosis of alloantigen-activated human T cells. Doses of MTX needed for the elimination of alloactivated T cells and tolerance induction cannot safely be given. Fortunately, Cy can be administered in the high doses required for the eradication of alloactivated T cells after allogeneic HSCT.[4]

Regulatory T cells (Tregs) also play an important role in the establishment of tolerance between the transplant recipient and donor-derived immunity. In animal studies, depletion of Tregs from the stem cell graft resulted in increased GVHD, and an increase in Tregs resulted in GVHD suppression posttransplant. When GVHD occurs in humans, Tregs are at a lower frequency than in patients without GVHD. It is thought that reconstitution of Tregs after HSCT is required to establish a well-balanced immune system that can maintain appropriate levels of tolerance between the transplant recipient and the donor-derived immunity. Studies show that CNIs have negative effects on Treg reconstitution, while mycophenolate mofetil (MMF) and sirolimus may promote posttransplant Treg recovery, making Cy used with either agent an attractive GVHD prophylaxis strategy.[2]

A three-step mechanism to explain the stimulation of early tolerance by posttransplant Cy has been postulated by scientists. In the first step, early proliferating alloreactive donor and recipient T cells are selectively destroyed by the administration of Cy. In the second step, the increased Tregs counterbalance the effect of any remaining alloreactive mechanisms. In the final step, the delayed but long-lasting intrathymic clonal removal of antihost T cells maintains long-term tolerance.[3]

Animal experiments also have shown that the timing of Cy administration is very important. In mice, administering Cy before or on the same day as the stem cell infusion resulted in suppressed antibody production but not the development of tolerance. The optimal time to administer Cy was identified as between graft administration and day +4 post-HSCT as evidenced by maximal effect in improving graft survival. The significance of timing has been carried over into clinical trials.[3] When patients do not receive immunosuppression for several days after graft infusion, they are at risk for "engraftment syndrome," especially with increases in human leukocyte antigen (HLA) mismatch. This may present as pulmonary edema, with or without fever, fluid retention, and renal failure.[4] It is important to closely monitor patients during this time.

## Haploidentical Transplant

The culmination of findings from animal experiments has been translated into GVHD prophylactic strategies performed in the setting of haploidentical HSCT in humans. Haploidentical HSCTs are an important option for patients because they expand the donor pool significantly

for patients unable to identify a matched related or unrelated donor. An early fundamental trial conducted at Johns Hopkins University treated patients with high-risk hematologic malignancies with T cell–replete haploidentical bone marrow transplants after receiving nonmyeloablative conditioning regimens (fludarabine 30 mg/m$^2$/day on days -6 to -2 and 2 Gray [Gy; a unit of ionizing radiation] total body irradiation [TBI] on day -1). The GVHD prophylactic strategy included Cy 50 mg/kg on day +3, MMF 15 mg/kg orally twice daily on days +4 to +35, and tacrolimus adjusted to achieve a therapeutic level of 5–15 ng/mL on day +4 to at least day +50. Two of the three first patients transplanted developed graft rejection; therefore, Cy 14.5 mg/kg/day was added on days -6 and -5 for the remainder of patients. With this improved regimen, eight of the following 10 patients transplanted achieved sustained engraftment. Among these patients, the median time to neutrophil recovery was 15 days and 14 days for platelets. Of the 13 patients transplanted utilizing posttransplant Cy, 46% developed acute GVHD at a median of 99 days posttransplant, with one patient developing fatal acute GVHD. Chronic GVHD rates were not captured in this trial.[5] The results of this study provided supporting evidence for further investigation of posttransplant Cy in haploidentical HSCT.

This method from Johns Hopkins was refined in a subsequent study attempting to identify the optimal dose of Cy to administer posttransplant. Patients with advanced hematologic malignancies ($n$ = 67) or paroxysmal nocturnal hemoglobinuria ($n$ = 1) received T cell–replete haploidentical bone marrow grafts after conditioning with Cy 14.5 mg/kg/day on days -6 to -5, fludarabine 30 mg/m$^2$/day on days -6 to -2, and 200 cGy of TBI on day -1. For GVHD prophylaxis, patients were administered one ($n$ = 28) or two doses ($n$ = 40) of Cy 50 mg/kg/day on day +3 or +3 and +4, respectively. In addition to posttransplant Cy, MMF at 15 mg/kg orally three times per day and tacrolimus adjusted to achieve a therapeutic level of 5–15 ng/mL were both started the day after completion of posttransplant Cy (day +4 or +5). MMF was continued until day +35 and tacrolimus was tapered off by day +180 unless the patient was experiencing active GVHD. Median time to neutrophil recovery was 15 days and 24 days for platelet recovery. Graft failure occurred in 13% of the evaluable patients (9 of 66). All but one of these patients experienced bone marrow recovery with a median time to neutrophil engraftment of 15 days and platelet engraftment of 28 days. For all patients, the cumulative incidence of treatment-related mortality (TRM) was found to be 15% with a relapse rate of 51% at 1 year. The 2-year overall survival (OS) was 36% and event-free survival (EFS) was 26%. The development of acute GVHD occurred in 34% of patients at grades 2–4 with 6% of patients at grades 3–4. The only important difference identified between the different Cy dosing groups was a trend toward decreased development of chronic GVHD in the two-dose Cy group (5% versus 25%; HR = 0.21; 95% CI: 0.04–1.01; $p$ = .05).[6] For adult patients with high-risk malignancies, this trial proved haploidentical HSCTs as a viable option with fairly low GVHD rates utilizing posttransplant Cy on days +3 and +4. Further investigation is needed.

A larger confirmatory trial conducted by Munchel and colleagues studied 210 patients with advanced hematological malignancies who received nonmyeloablative haploidentical HSCTs with posttransplant Cy as GVHD prophylaxis. Patients received the following preparatory regimen: Cy 14.5 mg/kg/day on days -6 to -5, fludarabine 30 mg/m$^2$/day on days -6 to -2, and 2 Gy of TBI on day -1. Grafts were bone marrow product with no manipulation to remove T cells. GVHD prophylaxis consisted of Cy 50 mg/kg/day on days +3 and +4, MMF 15 mg/kg orally three times per day on days +5 to +35, and tacrolimus targeting 5–15 ng/mL from days +5 to +180. Only 204 of the 210 patients included were evaluable for engraftment data. Thirteen percent of patients failed to engraft but nearly all had autologous reconstitution. The median time to neutrophil recovery was 15 days and 24 days for platelets. Acute GVHD occurred in 27% of patients as grade 2–4 and 5% as grade 3–4. The chronic GVHD incidence was low at 13%. The overall incidence of relapse mortality was 55% and nonrelapse mortality (NRM) was 18%. Patients experienced a 3-year OS of 41% and EFS of 32%. An interesting result was discovered with regard to HLA-antigen disparity among donors and recipients. This trial showed a trend toward improved EFS with increasing disparity with a 20% reduction in the risk of an event (death or relapse) for each increment of HLA mismatch (HR = 0.80; 95% CI: 0.66–0.96; $p$ = .02).[7] This larger trial provides additional support for the use of posttransplant Cy to prevent GVHD in haploidentical HSCTs.

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) conducted two parallel phase 2 clinical trials to study the reproducibility and applicability of the already published results with the goal of generating future phase 3 randomized controlled trials. BMT CTN 0604 evaluated the efficacy of double umbilical cord blood (dUCB) transplantation, while 0603 studied the efficacy of haploidentical bone marrow transplantation after reduced-intensity conditioning. Patients eligible for either trial needed to have advanced or high-risk leukemia or lymphoma. The conditioning regimen for the dUCB transplants included fludarabine 40 mg/m$^2$/day on days -6 to -2, Cy 50 mg/kg on day -5, and 2 Gy of TBI on day -1. GVHD prophylaxis included MMF given every 8 hours beginning on day -3 until day +30 or 7 days after engraftment (whichever was later) and cyclosporine dosed to achieve trough levels of 200–400 ng/mL until day +100 in the absence of GVHD. Patients undergoing haploidentical HSCTs received fludarabine 30 mg/m$^2$/day on days -6 to -2, Cy 14.5 mg/kg on days -6 and -5, and 2 Gy of TBI on day -1. GVHD prophylaxis for this regimen included Cy 50 mg/kg on days + 3 and +4, MMF three times per day on days +5 to +35, and tacrolimus dosed to achieve a target trough level of 5–10 ng/mL with the goal of discontinuation by day +180. Patients undergoing dUCB transplantation had a median time to neutrophil recovery of 15 days and 38 days for platelet recovery. Ten percent of patients experienced primary graft failure. After haploidentical bone marrow transplant, the median time to neutrophil recovery was 16 days and 26 days to platelet recovery. There was only one case (2%) of primary graft failure in this group. Acute GVHD occurred in 40% of patients at grade 2–4 and 21% of patients at grade 3–4 after dUCB transplant. In the haploidentical transplant group, acute GVHD occurred in 32% of patients at grade 2–4 and 0% of patients at grade 3–4. The cumulative incidence of chronic GVHD in dUCB transplant patients was 25% at 1 year and 13% for haploidentical HSCT patients. The 1-year cumulative incidence of NRM was 24% in dUCB transplant patients and relapse/progression of 31%. The 6-month survival for this group was 74% with a 1-year probability of progression-free survival (PFS) of 46% and OS of 54%. For the haploidentical

transplant group the 1-year cumulative incidence of NRM was 7% and relapse/progression was 45%. For this group the 6-month survival was determined to be 84% and 1-year probability of PFS was 48% and OS of 62%.[8,9] This trial reproduced results similar to those seen in previous clinical trials. The outcomes of these studies are comparable to high-risk patients transplanted with blood or marrow from matched unrelated donors after reduced intensity conditioning, confirming the utility of alternative donor transplants with unique GVHD prevention strategies. This study led to the development of the BMT CTN Trial 1101 to compare dUCB and haploidentical transplants in a larger phase 3 randomized trial that is still ongoing.[9]

## Use of Peripheral Blood Stem Cells as a Donor Source

Recently clinical trials have evaluated the use of peripheral blood stem cells as a graft source instead of bone marrow when utilizing haploidentical HSCTs with posttransplant Cy. The use of peripheral blood stem cells (PBSC) has been linked to a higher incidence of chronic GVHD but a decreased risk of relapse, leading to improved OS and EFS.[2] In the study by Solomon and colleagues, patients were deemed to be at high risk for relapse after nonmyeloablative haploidentical HSCT, therefore a myeloablative conditioning regimen was used. Twenty patients with hematologic malignancies were included in the study and received busulfan-based conditioning followed by T cell–replete peripheral blood stem cells from haploidentical donors. The first five patients received fludarabine 30 mg/m$^2$/day on days -7 to -2, IV busulfan 130 mg/m$^2$/day on days -7 to -4, and Cy 14.5 mg/kg/day on days -3 and -2. This regimen resulted in a notable amount of mucositis requiring dose reductions to the conditioning regimen for the following 15 patients to fludarabine 25 mg/m$^2$/day on days -6 to -2, IV busulfan 110 mg/m$^2$/day on days -7 to -4, and Cy 14.5 mg/kg/day on days -3 and -2. Posttransplant immunosuppression included Cy 50 mg/kg/day on days +3 and +4 and, starting on day +5, MMF 15 mg/kg three times per day, and continued until day +35, and tacrolimus with a goal level of 5–15 ng/mL continued until day +180. All 20 patients on the study experienced donor engraftment with a median time to neutrophil recovery of 16 days and 27 days for platelet recovery. The overall incidence of acute GVHD was 30% for grades 2–4 and 10% for grades 3–4. At a 20-month median follow-up time, the incidence of chronic GVHD was 35% (5% severe). There was 10% NRM at both 100 days and 1 year in this study. The 1-year estimate for OS was 69%, 50% for EFS, and 40% for relapse.[10] This study highlights the promising outcomes of utilizing a myeloablative conditioning regimen with PBSC as a donor source.

To further elucidate the impact graft source has on haploidentical HSCT, additional retrospective analyses have been conducted. Ciurea and colleagues completed a retrospective analysis of 65 consecutive haploidentical HSCTs for patients with hematologic malignancies. Patients received either T cell–replete peripheral blood stem cell transplants ($n$ = 32) or T cell–deplete bone marrow transplants ($n$ = 33), both following the same conditioning regimen. The preparative regimen contained melphalan 140 mg/m$^2$ on day -8, fludarabine 40 mg/m$^2$/day on days -6 to -3, and thiotepa 10 mg/kg on day -7. For the bone marrow group, GVHD prophylaxis contained rabbit antithymocyte globulin (ATG) dosed at 1.5 mg/kg/day on days -6 to -3. The PBSC group received Cy 50 mg/kg/day on days +3 and +4, with MMF starting on day +5 to +35 and tacrolimus continuing for at least 4 months posttransplant. For the last 11 patients in the PBSC group, MMF was continued until day +100 as a result of several initial patients developing acute GVHD. Neutrophil engraftment occurred in 94% of the PBSC patients and 81% of the bone marrow patients ($p$ = .10). Within 100 days, the cumulative incidence of acute GVHD grade 2–4 was 20% versus 11% ($p$ = .20) and grade 3–4 5% versus 9% ($p$ = .59) in the T cell–replete arm compared with the T cell–deplete arm, respectively. The rate of chronic GVHD was 7% in the T cell–replete arm and 18% in the T cell–deplete arm ($p$ = .03). The 1-year OS rate was 64% versus 30% ($p$ = .02) and PFS rate was 50% versus 21% ($p$ = .02) in the T cell–replete arm compared with the T cell–deplete arm. The 1-year NRM rates were significantly improved in the T cell–replete arm at 16% versus 42% in the deplete arm ($p$ = .02).[11]

Castagna also conducted a study comparing PBSC ($n$ = 23) and bone marrow ($n$ = 46) donor products for haploidentical HSCT, yet this time both products were T cell replete. Patients underwent a nonmyeloablative conditioning regimen including Cy 14.5 mg/kg/day on days -6 to -5, fludarabine 30 mg/m$^2$/day on days -6 to -2, and 2 Gy of TBI on day -1. The GVHD prophylactic regimen administered was Cy 50 mg/kg/day on days +3 and +4 and, starting on day +5, MMF at 15 mg/kg three times per day until day +35 and tacrolimus adjusted to maintain trough levels 10–20 ng/mL or cyclosporine adjusted to maintain levels between 100–200 ng/mL tapered by day +180. Patients receiving PBSC were given prophylaxis with cyclosporine, and patients receiving bone marrow were administered either tacrolimus ($n$ = 34) or cyclosporine ($n$ = 12). For the entire study population, the median time to neutrophil recovery was 20 days and 29 days for platelet recovery. Grade 2–4 acute GVHD occurred in 25% of patients receiving bone marrow (BM) and 33% of those receiving PBSC ($p$ = .43). The cumulative incidence of grades 3–4 acute GVHD was 14% and 3% in the PBSC and BM arms, respectively ($p$ = .10). The incidence of chronic GVHD was 13% regardless of stem cell source ($p$ = .21). The 2-year OS estimate was 68% and PFS was 62%. The 2-year overall NRM was 18%; 22% for BM source and 12% for PBSC source ($p$ = .96).[12] Several studies have analyzed the use of PBSC as a source for haploidentical HSCTs, showing that it is an alternative to bone marrow product.

## Matched Related and Unrelated Transplant

With the role of posttransplant Cy established in haploidentical HSCT with either PBSC or BM as a source, the use of Cy in the posttransplant setting was further evaluated in matched related and unrelated HSCTs. Patients with advanced hematologic malignancies who received matched related ($n$ = 78) or unrelated ($n$ = 39) donor transplants were included in this analysis by Lunzik and colleagues. The conditioning regimen utilized was myeloablative with busulfan 4 mg/kg/day orally or 3.2 mg/kg/day IV given in four daily divided doses for 4 consecutive days, followed by admistering Cy 50 mg/kg IV for 2 days. Busulfan doses were adjusted to achieve a target area under the curve (AUC) of 800–1400 µmol/L x min. Grafts were T cell–replete bone marrow product. GVHD prophylaxis was single-agent Cy given at a dose of 50 mg/kg/day on days +3 and +4 after transplant. Neutrophils recovered in a time of 23 days for related grafts and 25 days for unrelated grafts. Platelet recovery occurred in a median of 31 days for related donors and 34 days for unrelated donors. At

100 days posttransplant the cumulative incidence of grade 2–4 acute GVHD was 43% and of grade 3–4 was 10%. There was not a significant difference in grade 2–4 acute GVHD between related and unrelated donors (42% versus 46%; HR = 0.87; 95% CI: 0.50–1.54; $p$ = .64). The cumulative incidence of chronic GVHD for all patients was 10% with a median follow-up time of 26.3 months. The cumulative incidence of chronic GVHD at 2 years was not significantly different between related and unrelated donors (9% versus 11%; HR = 0.83; 95% CI: 0.25–2.88; $p$ = .79). The 2-year cumulative incidence of relapse was 44%. This was not significantly different when analyzed by donor type (HR = 1.4; 95% CI: 0.78–2.60; $p$ = .25). For related donor grafts the median follow-up on trial was 29 months and 24 months for unrelated donor grafts for surviving recipients. The OS and EFS also did not significantly differ by donor type (OS HR = 0.85; 95% CI: 0.49–1.50; $p$ = .58; EFS HR = 1.12; 95% CI: 0.68–1.86; $p$ = .65). The OS was found to be 36% at 1 year and 55% at 2 years. The 1-year EFS was 48% and at 2 years was 39%.[13] This trial revealed promising results for posttransplant Cy use in matched related and unrelated donors.

An additional multi-institutional trial utilized a myeloablative conditioning regimen of IV busulfan targeted to AUC and fludarabine at 40 mg/m$^2$/day on days -5 to -2 in patients with high-risk hematologic malignancies undergoing HLA-matched related and unrelated BM transplants. GVHD prophylaxis consisted of single-agent posttransplant Cy given on days +3 and +4 at a dose of 50 mg/kg/day. A total of 92 patients were transplanted during this analysis with 45 patients receiving related donor grafts and 47 patients receiving unrelated donor grafts. The median time to neutrophil engraftment was 21 days and platelet engraftment was 24 days. Grade 2–4 acute GVHD occurred in 51% of patients, with grade 3–4 in 15%. The cumulative incidence of chronic GVHD was 14% at 2 years. Approximately one-third of all patients (35%) never required additional immunosuppressive medication. NRM was 9% at day 100 and 16% at 1 year. OS was 67% at 2 years, and EFS was 62%.[14] This study also supports the efficacy of posttransplant Cy for myeloablative related and unrelated matched donor transplant.

A clinical trial in matched sibling and unrelated donor transplants compared posttransplant Cy with tacrolimus and minidose methotrexate as GVHD prevention. Patients on the study arm ($n$ = 49) received reduced-intensity conditioning with fludarabine at 40 mg/m$^2$ followed by IV busulfan targeting an AUC of 4,000 µmol/L x min on days -6 to -3. Patients receiving an unrelated donor graft also were given ATG on days -3 to -1 (total dose 4 mg/kg). Posttransplant Cy was given at a dose of 50 mg/kg/day on days +3 and +4. In the control arm ($n$ = 133) patients received the same reduced-intensity conditioning regimen of fludarabine with melphalan. GVHD prophylaxis for this arm included tacrolimus plus mini-MTX (10 mg/m$^2$ on day +1, then 5 mg/m$^2$ on days +3, +6, +11). Unrelated donor transplants also received anti-thymocyte globulin (ATG) in the control arm. A computer-generated algorithm identified matched controls for 37 of the study patients. More than half (59%) of patients in both arms had unrelated donors and required additional immunosuppression during conditioning with ATG. More patients in the posttransplant Cy arm received bone marrow product than in the control arm (70% versus 48%). The cumulative incidence of acute GVHD grade 2–4 occurred in 46% of the posttransplant Cy arm and 19% in the control arm (HR, 2.8; 95% CI, 1.1-6.7; $p$ = .02). The incidence of acute GVHD grades 3–4 was 14% in the study arm and 0% in the control arm ($p$ = .02). For chronic GVHD, the cumulative incidence was 14% versus 21% in the study arm compared with the control arm, respectively (HR = 0.8; 95% CI: 0.2-2.6; $p$ = .7). The OS, PFS, and NRM at 2 years were not significantly different between the groups with results of 26% versus 46% (HR = 1.8; 95% CI: 0.9-3.3; $p$ = .08), 22% vs 33% (HR = 1.3; 95% CI: 0.7–2.3; $p$ = .4), and 36% versus 16% (HR = 2.4; 95% CI: 0.8–6.7; $p$ = .1) for the posttransplant Cy arm compared with the control arm, respectively.[15]

Building on the results of the data for single-agent Cy posttransplant in matched related and unrelated donors, a trial by Solomon and colleagues evaluated a CNI-free GVHD prevention strategy. Patients were given a reduced-intensity conditioning regimen consisting of fludarabine 30 mg/m$^2$/day on days -9 to -6, IV busulfan 130 mg/m$^2$/day on days -5 to -4, and Cy 14.5 mg/kg/day on days -3 and -2 followed by administration of an unmanipulated peripheral blood stem cell graft on day 0. Immunosuppression consisted of Cy 50 mg/kg/day on days +3 and +4, then sirolimus began on day +5 and was discontinued day +90 to +100 without tapering in the absence of GVHD. Twenty-six patients with high-risk hematologic malignancies were treated in this trial. Seventeen patients had matched sibling donors, and the remaining nine patients had matched unrelated donors. All patients engrafted with a median time for neutrophil recovery of 15 days and 30 days for platelets. Acute GVHD grades 2–4 occurred in 46% of patients and 15% in grades 3–4. Thirty-one percent of patients experienced chronic GVHD. The 1-year cumulative incidence of NRM was 4%. Two-year estimated OS was 71%, EFS 64%, relapse 32%, and NRM 13% at a 20-month median follow-up period for surviving patients.[16] The results of this trial are promising, with a very low rate of NRM and an impressive 2-year OS.

## Conclusion

Posttransplant Cy is a safe and effective alternative to standard immunosuppression strategies. Cy administered early after HSCT leads to suppression of GVHD and graft rejection without compromising immune reconstitution. It has been utilized as a GVHD prevention strategy in HSCTs from bone marrow or peripheral blood as well as with various conditioning regimens and donor sources. Patients included in these studies had related, unrelated, matched, and mismatched donors, highlighting the versatility of posttransplant Cy. The BMT-CTN continues to explore this method of immunosuppression and has an ongoing trial, BMT CTN 1203, that is comparing novel approaches for GVHD prevention to contemporary controls in patients undergoing related or unrelated reduced-intensity conditioning transplants. In one arm of this trial, patients will receive posttransplant Cy at 50 mg/kg on days +3 and +4 followed by tacrolimus and MMF.[9] The results of this large multicenter trial are anticipated to confirm the data from the completed studies on using posttransplant Cy. Posttransplant Cy should continue to be evaluated as an immunosuppression option given its comparably low rates of acute and chronic GVHD and minimal side effects.

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# American Society of Hematology 2014 Annual Meeting Highlights

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The 56th American Society of Hematology Annual Meeting took place in San Francisco, CA, December 6–9, 2014. There were more than 20,000 attendees from across the world. In addition, more than 4,000 abstracts and six plenary sessions were presented. This report reviews key oral abstracts and plenary presentations regarding pharmacologic treatment of acute and chronic leukemia, myelodysplastic syndrome, and mantle cell lymphoma.

## Myelodysplastic Syndrome

### Abstract 0164: A Final Report: Phase I/II Study of Sequential Azacitidine and Lenalidomide in Patients with Higher-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

Azacitidine is a hypomethylating agent used as first-line treatment of higher-risk myelodysplastic syndrome (MDS) and in patients with acute myeloid leukemia (AML) who are unfit to receive induction chemotherapy. Furthermore, lenalidomide is increasingly studied in combination with azacitidine in patients with MDS and AML. A phase 1/2 study evaluated sequential azacitidine (75 mg/m$^2$ days 1–5) and lenalidomide in 88 patients with high-risk MDS and AML, including 23 patients with AML (>30% blasts). Lenalidomide was administered starting on day 6 per 28-day cycle. Following myelosuppression and infections observed with repeated cycles in the first 20 phase-2 subjects, the optimal lenalidomide dose was determined to be 25 mg on days 6–10. Rapid responses were obtained within median of two cycles. The overall response rate (ORR) was 35% with median overall survival (OS) of 33 weeks (range 1–172). Among the 40 patients administered the optimal lenalidomide dose, ORR was 55% with median OS duration of 75 weeks. Among 31 patients who responded to treatment, 42% of them proceeded to stem cell transplant. Therefore, this combination dose schedule was determined to be effective for patients with high-risk MDS and AML.

## Acute Myeloid Leukemia

### Abstract 0006: Sorafenib Versus Placebo in Addition to Standard Therapy in Younger Patients with Newly Diagnosed Acute Myeloid Leukemia (AML): Results from 267 Patients Treated in the Randomized Placebo-Controlled SAL-SORAML Trial

*In vitro* data and nonrandomized clinical studies have suggested that sorafenib as a multikinase inhibitor may be effective in the treatment of AML. This abstract was presented at the plenary session, which highlighted the results of the SORAML trial, a double-blind, placebo-controlled study that evaluated sorafenib in addition to standard induction and consolidation treatment in 267 AML patients who were 18–60 years old. All patients received two cycles of induction with daunorubicin 60 mg/m$^2$ days 3–5 and cytarabine 100 mg/m$^2$ days 1–7 followed by three cycles of consolidation with cytarabine 3 g/m$^2$ twice daily on days 1, 3, 5. Allogeneic stem cell transplantation was scheduled for all intermediate and high-risk patients. Patients were randomized to receive either sorafenib (800 mg/day) or placebo in addition to standard treatment. The primary endpoint, median event-free survival (EFS), was 9.2 versus 20.5 months in favor of sorafenib. Furthermore, there was a significant difference in 3-year relapse-free survival, which was 38% in the placebo arm and 56% with sorafenib. No differences in 3-year OS were reported, 56% in placebo arm and 63% with sorafenib, respectively. Similar EFS rates were observed among 46 FMS-like tyrosine kinase 3 internal tandem duplications (FLT3-ITD)-positive patients. Notably there was a higher incidence of fever, bleeding events, and hand-foot syndrome observed in sorafenib-treated patients.

## Acute Promyelocytic Leukemia

### Abstract 0012: Improved Outcome with ATRA-Arsenic Trioxide Compared to the ATRA-Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia (APL): Updated Results of the Italian-German APL0406 Trial on the Extended Final Series

Recently the randomized intergroup acute promyelocytic leukemia (APL) 0406 trial revealed the effectiveness of ATRA and arsenic trioxide (ATO) in combination compared with ATRA with chemotherapy for treatment of low-intermediate risk APL as defined by white blood cell count (WBC) <10x10$^9$/L (Lo-CoCo et al., *NEJM* 2013). Patients in the ATRA-ATO arm received ATO 0.15 mg/kg and ATRA 45 mg/m$^2$/day until complete remission (CR), then ATO 5 days/week, 4 weeks on and 4 weeks off, for a total of four courses and ATRA 2 weeks on and 2 weeks off for a total of seven courses. The primary study objective was EFS at 2 years. Follow-up results of an extended cohort of 254 additional patients demonstrated the 2-year EFS was 98% versus 84.9% in favor of ATRA-ATO. Furthermore, the ATRA-ATO arm was associated with superior 2-year OS (99.1% versus 94.4%) and 2-year cumulative incidence of relapse rates (1.1% versus 9.4%), and CR was achieved in every patient who received ATRA-ATO. This data further confirm the survival benefit of ATRA with ATO versus chemotherapy in the non-high-risk setting.

## Acute Lymphoblastic Leukemia

### Abstract 0379: BLAST: A Confirmatory, Single-Arm, Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Leukemia (ALL)

Minimal residual disease (MRD) in acute lymphoblastic leukemia (ALL) refers to the presence of leukemic cells below the threshold

of detection by conventional morphologic methods despite achieving complete hematologic remission. Patients with persistent/recurrent MRD following induction therapy are at a higher risk of relapse. A phase 2 study evaluated 116 adult patients with MRD-positive ($\geq 10^{-3}$) B-precursor ALL who received blinatumomab after achieving hematologic complete remission, including 35% who were treated in second or later remission. The monoclonal antibody is a bispecific T cell engager that redirects CD3-positive T cells to CD19 target cells to ultimately cause lytic destruction of CD19-positive B cells. Notably patients with Philadelphia chromosome, central nervous system (CNS) involvement or extramedullary disease, or previous allogeneic stem cell transplant were excluded. Blinatumomab 15 µg/m$^2$/day was intravenously administered as continuous infusion for 4 weeks per 6-week cycle. Responders received up to four cycles of treatment or underwent stem cell transplant after completion of at least one cycle. Patients with hematologic relapse discontinued treatment. The primary study endpoint was rate of complete MRD response, which was achieved in 78% of patients after one cycle of treatment and 80% across all cycles. The most common adverse events observed (≥20%) included pyrexia (88%), headache (38%), tremor (29%), chills (25%), fatigue (24%), nausea (22%), and vomiting (22%). Serious adverse events that occurred in ≥5% of patients included pyrexia (15%), tremors (7%), aphasia (5%), encephalopathy (5%), and overdose (5%). Therefore, blinatumomab has the potential to improve patient outcomes, especially in those with MRD-positive ALL following intensive therapy, including second-line treatment.

## Chronic Myeloid Leukemia

### Abstract 0152: Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia (CML-CP) Trial (DASISION)

The recent 3-year follow-up results of the DASISION trial, a randomized phase 3 study, demonstrated improved efficacy and faster response at 3 months with dasatinib 100 mg daily ($n$ = 259) versus imatinib 400 mg daily ($n$ = 260) in treatment-naïve chronic-phase chronic myeloid leukemia (CML-CP) patients (Jabbour et al., *Blood*. 2014). Since then, the final 5-year analysis of DASISION has been completed. The primary endpoint was confirmed complete cytogenetic response (cCCyR). At the end of the study period, 61% of dasatinib-treated patients and 63% of the imatinib group were still receiving therapy. The rate of cCCyR by 5 years was 83% with dasatinib versus 78% with imatinib and increased rates of major molecular response (BCR-ABL ≤ 0.1%) were observed with dasatinib (76% versus 64%) by 5 years. Time to cCCyR (HR = 1.46; 95% CI: 1.20–1.77) and major molecular response (HR = 1.54; 95% CI: 1.25–1.89) were faster with dasatinib. There were no differences in 5-year, progression-free survival (PFS) and OS rates between both treatment arms. Although no new or unexpected safety events were identified in either treatment arm at 5 years, the total incidence of pleural effusion increased each year among the dasatinib group (29% overall). A majority of pleural effusion events were grade 1–2 (91%), and the median time to first grade 1–2 pleural effusion was 114 weeks (range: 4–299 weeks). Only 20% of dasatinib-treated patients who experienced a pleural effusion discontinued treatment. At 5 years, dasatinib 100 mg once daily has demonstrated superior outcomes compared with imatinib 400 mg once daily as initial therapy for CML, and the 5-year follow-up data confirm dasatinib should remain the standard of care in this setting.

## Chronic Lymphocytic Leukemia

### Abstract 0019: Frontline Chemoimmunotherapy with Fludarabine, Cyclophosphamide, and Rituximab (FCR) Shows Superior Efficacy in Comparison to Bendamustine and Rituximab (BR) in Previously Untreated and Physically Fit Patients with Advanced Chronic Lymphocytic Leukemia (CLL): Final Analysis of an International Randomized Study of the German CLL Study Group (CLL10 Study)

Among physically fit advanced chronic lymphocytic leukemia (CLL) patients with low comorbidity burden, fludarabine, cyclophosphamide, and rituximab (FCR) is considered the standard frontline regimen. The CLL10 study is a phase 3 study that compared bendamustine and rituximab (BR) with FCR in the frontline setting among 547 evaluable fit patients without del(17p) and who had a cumulative illness rating scale (CIRS) score ≤6 and creatinine clearance >70 ml/min. Patients were randomized to receive six courses of FCR ($n$ = 274; fludarabine 25 mg/m$^2$ days 1–3, cyclophosphamide 250 mg/m$^2$ days 1–3, rituximab 375 mg/m$^2$ day 0 at first cycle and 500 mg/m$^2$ day 1 all subsequent cycles every 28 days) or BR ($n$ =273; bendamustine 90 mg/m$^2$ days 1–2, rituximab 375 mg/m$^2$ day 0 at first cycle and 500 mg/m$^2$ day 1 all subsequent cycles every 28 days). The median CIRS score was 2 and a significantly higher proportion of patients 70 years or older was included in the BR arm (22% versus 14%, $p$ = .020). The ORR in both arms was 97.8%. The CR rate was 40.7% in favor of FCR compared to 31.5% with BR. Median PFS was 53.7 months in the FCR arm, which was significantly higher than 43.2 months in the BR arm (HR = 1.589; 95% CI: 1.25–2.079). Interestingly, among patients with unmutated IGHV status, median time to progression was 43.9 months after FCR compared with 34.0 months after BR ($p$ = .015). Physically fit subgroups (CIRS max 3, only one CIRS item, age <65 years) benefited most from FCR therapy. On the other hand, no differences in PFS were observed between both treatment arms in patients 65 years or older, CIRS 4–6 or >1 CIRS item. No difference in 3-year OS was observed between the two treatment groups (90.6% for FCR versus 92.2% for BR). There was a higher incidence of severe neutropenia observed in the FCR arm (87.7% versus 67.8%, $p$ < .001), but no significant difference in the incidence of anemia (14.2% versus 12.0%; $p$ = .46) or thrombocytopenia (22.4% versus 16.5%; $p$ = .096) was found. Severe infections occurred more frequently (39.8% versus 25.4%, $p$ = .001) in the FCR arm, especially in older patients (48.4% versus 26.8%; $p$ = .001). Treatment-related mortality was 3.9% (FCR) and 2.1% (BR), respectively. The final analysis of the CLL10 study demonstrates that FCR results in higher CR rates and longer PFS, especially in very fit CLL patients. However, BR should be considered as an alternative regimen in elderly fit patients or those with previous infections because increased toxicities were seen in older patients, which may have led to similar efficacy results between both arms.

## Mantle Cell Lymphoma

### Abstract 0149: Phase II Trial of R-CHOP Plus Bortezomib Induction Therapy Followed by Bortezomib Maintenance for Previously Untreated Mantle Cell Lymphoma: SWOG 0601

Currently there is no optimal induction regimen established for treatment of mantle cell lymphoma (MCL). Bortezomib, which is a 26S proteasome inhibitor, has been demonstrated to be active as monotherapy for treatment of MCL, and preclinical data suggest that synergism may be exerted by combination with other cytotoxic agents. Given that maintenance rituximab administration following rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was associated with a survival benefit, the SWOG cancer research cooperative group conducted a phase 2 study (S0601) to evaluate the safety and efficacy of combining bortezomib with R-CHOP for induction, followed by bortezomib maintenance for 2 years among 65 treatment-naïve adult patients with stage 3, 4, or bulky stage 2 MCL. Induction therapy included six cycles of R-CHOP (375 mg/m$^2$ rituximab, 750 mg/m$^2$ cyclophosphamide, 50 mg/m$^2$ doxorubicin, 1.4 mg/m$^2$ vincristine on day 1 and 100 mg prednisone daily for 5 days) plus bortezomib 1.3 mg/m$^2$ on days 1 and 4 of every 21 day cycle. Patients achieving at least stable disease after induction were eligible for bortezomib maintenance therapy 1.3 mg/m$^2$ days on 1, 4, 8, and 11 every 3 months for eight cycles. The primary endpoint was 2-year PFS rate. The 2-year PFS was 62% and 2-year OS was 85%. At 5 years the PFS was 28% and OS was 66%. Based on prior studies, the historical 2-year PFS rate for R-CHOP alone in this population is 30%. The Mantle Cell Lymphoma International Prognostic Index (MIPI) scores were significantly associated with outcome, with a 2-year PFS of 72%, 61%, and 25% for low-, intermediate-, and high-risk MIPI groups, respectively. Forty-eight percent of patients experienced grade 4 hematologic toxicities during induction therapy and 38.5% grade 3 nonhematologic and 6% grade 4 nonhematologic toxicities. During maintenance therapy, 13% of patients experienced grade 3 nonhematologic toxicities. Grade 3 peripheral neuropathy was experienced by 8% of patients during induction and 2% of patients during maintenance bortezomib, but grade 4 neuropathy was not reported. Combination R-CHOP with bortezomib followed by maintenance bortezomib appears to improve outcomes compared with historical data of R-CHOP alone, which suggests the addition of bortezomib to induction chemotherapy or maintenance should be further evaluated in a larger prospective study.

# Highlights from the JADPRO Live at APSHO 2014 Conference

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The second annual *Journal of the Advanced Practitioner in Oncology* (*JADPRO*) Live conference was held in Orlando, FL, October 29–November 2, 2014. This meeting was held in conjunction with the first annual Advanced Practitioner Society for Hematology and Oncology (APSHO) meeting. The theme of this year's meeting was "Transition Oncology Practice" and focused on advanced practitioners and physicians coming together to discuss current treatment options and advances in the care of cancer patients, describe key legislative changes essential to the advanced practitioner, and identify means to improve collaboration—all with an ultimate goal of decreasing adverse events and improving patient outcomes. The first day of the 4-day conference consisted of multiple workshops, including writing for publication, decoding genetics, establishing a collaborative practice, interpreting an electrocardiogram (EKG) and pathology report, and a hands-on skills workshop reviewing bone marrow aspiration, lumbar puncture, Ommaya reservoir placement, punch biopsy, and suturing.

The remaining 3 days included more than 20 educational sessions on didactic, interactive, evidence-based content targeted to advanced practitioners in oncology including nurse practitioners, physician assistants, clinical nurse specialists, other advanced-degree nurses, hematology/oncology nurses, pharmacists, and physicians. Each presentation reviewed best practices involving a multidisciplinary setting.

The didactic grand round presentations were fantastic overviews of the disease states, diagnostics, identification of risk factors, and management options with both current and future treatment options. Each presentation included at least two speakers from different roles within the multidisciplinary team. The grand round presentations included effective strategies that practitioners could implement in their own institutions and clinics. The topics included non-Hodgkin lymphoma, chronic myelogenous leukemia, prostate cancer, breast cancer, basal cell carcinoma, chronic lymphocytic leukemia, gynecologic malignancies, and lung cancer.

One of the panel presentations, "Genetic and BRCA Mutations," addressed the controversies and challenges in genetic testing for breast cancer, including the social and ethical implications of testing for genetic mutations in this patient population. "Treatment and Disease-Related Cardiotoxicity in the Oncology Setting" provided the tools needed to apply the principles of risk analysis, prevention, early identification of signs and symptoms, and individualized treatment planning for cancer patients at risk of developing disease or treatment-related cardiac events. Cardiovascular disease is the second leading cause of death in cancer survivors, which explains the need for cardiologists and oncologists to collaborate throughout and after chemotherapy treatment. The presentation focused on the main medications that can result in cardiotoxicity, including anthracyclines, QTc prolongation medications, and tyrosine kinase inhibitors. Exciting new cancer therapies are being discovered; however, to maximize their potential, cardiac toxicities need to be identified and addressed upfront.

The program "Avoiding Common Drug Interactions and Reactions" not only reviewed the most frequent drug interactions and clinical impact in oncology and hematology, but also helped the audience develop ideas on how to create protocols to identify and minimize the risk of drug interactions by improving collaboration between all members of the healthcare team. At this program and throughout the entire conference, attendees received both quality education and practical resources that can be engaged and utilized in cancer centers throughout the country.

An additional program with pharmacy-related topics included "New Hematology/Oncology Drug Updates," which was a great review of pharmacology and indications of every new oncology/hematology drug approved in 2014. Recommendations for monitoring and management of toxicities also were addressed. This presentation emphasized the impact of each of these medications on advanced practitioners and explained how to utilize each medication in clinical practice.

Another highlight was the keynote presentation, "A Funny Thing Happened on My Way to Chemotherapy," by Dan Shapiro, PhD. Presented in first-person stories illustrating the complexity of front-line medicine, his talk emphasized the importance of connecting to others in the face of challenging regimens.

JADPRO Live at APSHO 2014 provided practitioners the opportunity to network with a multidisciplinary team and work together to better serve our patients. More information about joining APSHO and JADPRO Live can be found at www.jadprolive.com.

# Recalls, Withdrawals, and Safety Alerts from the FDA

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## Creative Compounds Recall in Oregon and Washington

Oregon Compounding Centers, Inc. has issued a voluntary recall of certain unexpired sterile products in Oregon and Washington due to issues with sterility assurance. This is a precautionary measure being taken by the company following a recent inspection. There have been no reports of adverse events or product contamination to date. Recalled products are labeled with the Creative Compounds name, have a lot number, and were made from July 1, 2014, through September 22, 2014. For a full list of recalled products and affected lot numbers, refer to the following website: www.fda.gov/Safety/Recalls/ucm418324.htm.

## Romidepsin (Istodax)

Serious and fatal infections, including sepsis, pneumonia, and viral reactivation (including hepatitis B and Epstein-Barr viruses), have been reported with romidepsin. Patients with disease involvement of the bone marrow and those who have received prior treatment with monoclonal antibodies directed against lymphocyte antigens may be at greater risk of developing life-threatening infections. Infections may occur during treatment and within 30 days after treatment. In a clinical trial that included patients with relapsed or refractory extranodal NK/T-cell lymphoma, Epstein-Barr viral reactivation leading to liver failure was reported. In clinical trials that included peripheral T cell lymphoma (PTCL) patients, hepatitis B reactivation was reported in 1% of the population. Consider monitoring for hepatitis B reactivation and administering antiviral prophylaxis in patients with evidence of prior hepatitis B infection.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360070.htm

## Capecitabine (Xeloda)

Updates have been made to the "Warnings and Precautions" section of the product labeling to include the risk of dehydration and renal failure, which can be fatal. Patients with nausea, vomiting, diarrhea, asthenia, anorexia, preexisting compromised renal function, or those receiving concomitant nephrotoxic agents are at higher risk. Dehydration should be corrected and prevented. In addition, therapy should be interrupted and dehydration corrected if grade 2 or higher dehydration occurs. Treatment may be restarted after the patient is rehydrated and precipitating factors have been controlled or corrected.

There is a risk of Stevens-Johnson syndrome and toxic epidermal necrolysis with capecitabine, which can be fatal. In patients who experience severe mucocutaneous reactions from capecitabine, therapy should be permanently discontinued.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm422806.htm

## Goserelin Acetate Implant (Zoladex) and Leuprolide Acetate (Eligard)

Updated warnings and precautions include the potential for androgen deprivation therapy to prolong the QT/QTc interval. Risks versus benefits should be considered in patients with congestive heart failure, congenital long QT syndrome, frequent electrolyte abnormalities, or taking concomitant medications known to prolong the QT interval. Correct electrolyte abnormalities and consider periodic monitoring of electrocardiograms and electrolytes.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm182245.htm
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm232194.htm

# HOPA Volunteer Activity Center Now Open!

Members interested in becoming involved in association activities or volunteering for one of the 2015–2016 committees or work groups can now visit the HOPA Volunteer Activity Center on the HOPA website to review current opportunities. Volunteers also may provide a list of their skills and interests that the organization will use when seeking participants for future opportunities. If you would like to serve on a 2015–2016 committee, visit today and tell us how you would like to be involved!

# Designing a Successful Presentation

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A large and often stressful component of residency programs today is providing education in the format of an oral slide show presentation. Residents and students often feel overwhelmed or lost about where to begin when composing a presentation, particularly on a subject with which they are unfamiliar. Some residents struggle with presenting in front of a group, but I have found that regardless of the resident's comfort level when speaking to groups, the presentation becomes significantly easier to deliver when the material is well put together and the resident is comfortable with the flow of information. This article will focus on the key elements of designing a successful presentation and discuss some common pitfalls that residents often make.

## Keys to a Successful Presentation

### Familiarize Yourself with the Topic

Unless you already have a good grasp on the topic, this often will be your first step. Most presentations throughout your residency, however, are on new topics or topics that were chosen with the intent that you gain knowledge. My suggestion is to find a good review article or a simple tertiary reference, such as UpToDate® or even (yes, I'm going to say it) Wikipedia. Most residents feel that because quality data should come from primary literature you should avoid these types of information at all costs, but that's not necessarily true. The purpose of these sites is a superficial, general overview, and at this stage of designing your presentation that is exactly what you need. I am not suggesting that you get your data from here or reference these sites; what you need is to get a feel for your topic. What are the critical points of interest? Is the diagnosis straightforward and simple? Does the controversy lie in staging or treatment? Or is the critical component the initial diagnosis, and the treatment is very standardized? This will allow you to determine the important aspects of your topic that need to be addressed in detail and which topics can be simply and briefly reviewed. Sites like these often are organized in a logical flow, which also will guide you as you begin the next important step in the process.

### Develop an Outline

This step is the most crucial step of creating any presentation. A good outline will guide you through the presentation from title slide to questions slide and keep you on track as you begin to add detailed information. There are many ways to compose an outline, none of which is right or wrong as long as it serves your purpose. You may want to put your outline in the presentation to guide the audience as well. I don't often use this technique, but some find it very helpful. Your outline can be scratched onto a Post-it® note, it can be a detailed Microsoft Word® document, or you can use the slides themselves and insert section header slides for all of the topics you want to cover. However you decide to create your outline is fine, but it should include the focus points of your topic and flow in a logical manner. If you present to a group that has never heard of your topic, you want to explain things to them one piece at a time with each bit of information building upon the last. You want to avoid saying, "I'll explain that part later in the presentation." The outline also will give you an idea of how much detail you are able to discuss on each topic. If you have six key topics for a 1-hour presentation, you could try to discuss each in less than 10 minutes, or you may decide that the treatment section deserves more weight, and thus you have to reduce the amount of time spent on earlier topics. By doing this you are able to avoid spending too much time on the beginning of your presentation and running out of time for the most important aspects that may be at the end of the presentation. A simple rule of thumb is one slide per minute. Some images or graphs may be much less, but discussing trials and treatment plans may be much more. Designing your outline also is a good time to write your learning objectives; these should flow together. You should strive to discuss each of your objectives and then circle back to them at the end to summarize. Learning objectives should be well-designed rather than an afterthought to meet the requirements for continuing education (CE); this will help provide purpose for your presentation, and the outline will serve as the structure and map to achieve that purpose.

### Fill in the Gaps with Data

Now that you have developed your road map, it's time to add in all those details! This typically is the step that most residents want to start with, but remember that there are mountains of data available, particularly when reviewing the history of treating a disease, and you can't present it all. What you need to present are the landmark trials and key references to support standards of practice or controversial issues that may have both positive and negative studies. Choosing the most important studies is another task which with residents struggle. My suggestion is to ask a question and then go find the answer. For example, let's say you are presenting on diffuse large B cell lymphoma (DLBCL) and you know that rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) are the standard first-line treatment. Ask yourself how that came about and look for a trial that established CHOP. Why did we add rituximab? Is there a trial to support that? Do we add rituximab for everyone? What about something better? Has R-CHOP been compared with anything else first line? Was it better or worse? Did some subgroups of patients gain benefit while others didn't? Is this good data? What are the flaws of this study? Put yourself in your preceptor's shoes and ask yourself all of the questions they will ask and then be ready to answer them. A quick helpful tip is to find a review article from a good clinical journal and see which trials are cited. Another valuable trick to save time is to just copy and paste the reference into the notes section below the slide each time you use a source. This will make it much easier to go back and put things into the correct citation format without disrupting you while in the presentation-making state of mind.

### Tell a Story and Make it Make Sense

As an audience member, you will stay interested and retain much more information if the presentation continues to build upon itself and is not just a constant stream of data and information. Every topic has a story and has interesting facts along the course of that story. For a

disease state, start with defining the disease and how to identify it. Is it important to separate out the disease into subclasses or stages or risk groups? How do we treat this disease, and did we always treat it that way? How did the treatments evolve to where they are now, and could they be better? What other options are available? For a drug: Where did it originate and how did it come to be a medication? What were its successes and failures? How has it evolved over time, treating different indications or different dosage forms or in different combinations? What is its current role and what could be its future? If you make the topic interesting for yourself, then it will be interesting to your audience, as well.

### Practice Your Flow and Transitions

Congratulations! At this point your presentation should be complete, and now it's time to walk through it. Whether you feel the need to stand up and practice it out loud or just simply read through it in your head, it is important to go through the entire presentation from beginning to end at least once. Make sure that each slide logically follows the one before it, and move things around as necessary. You should be able to add a few bits of information here and there without struggling or pausing too much. It can be useful to put some reminders or details in the notes section below the slide. You should know what is coming on the next slide (because you prepared such a great outline) and be able to smoothly transition and keep folks interested. This also is one last chance to review for any spelling or grammar errors and address the visual appeal of your slides, as well.

## Common Mistakes

### Trying to Pull All of Your Literature First

This is a mistake that residents often make in an attempt to streamline and save time, when in fact it is a very inefficient use of time. Ultimately you will spend hours pulling an excessive amount of articles, printing or saving them to a drive, and then frantically sifting through them looking for relevant information to insert into your presentation. The error here is starting with mountains of data and trying to shove it into your presentation rather than starting with your outline and intended objectives and finding data to support those. This often leads to "data overload" with an enormous amount of numbers crammed into every space and a disjointed presentation that seems to jump from one section to the next.

### Going too Far Down a Rabbit Hole

What I mean by this is spending a great deal of time and effort researching one small facet of a presentation. For example, data on identifying, characterizing, and quantifying minimal residual disease in leukemia and how it should influence practice continues to emerge at a rapid rate. There are many articles about each aspect that discuss which markers to use and what quantity signifies what, and so on and so forth. But for a presentation that is meant to focus on acute leukemias, this topic should merit a few bullet points with some interesting facts and what we currently know and use. That is all! If you explain every aspect of this topic, you will quickly lose your audience and never have time to discuss treatments and other extremely important topics. If you find yourself pulling more than a handful of articles on one topic or making three or more slides on one topic, you should step back from the computer and get a cup of coffee and then go back to your outline to determine if this is a main focus point and how much valuable PowerPoint® real estate this topic warrants. It is very easy to fall into this trap, particularly if you find yourself extraordinarily interested in the topic, but you should always keep one eye on the big picture and remember to focus on the objectives of your presentation.

### Forcing in a Patient Case

Patient cases are great additions to presentations if done correctly. They can illustrate a common presentation of a disease, help to develop a differential of important things to consider, or showcase a rare diagnosis. What you want to avoid is an excessively long case with too much information that doesn't add to the purpose of your presentation. The common idea is to present a patient at the beginning, discuss the disease of interest and its treatments, and end with the patient case and what happened. This design can work in some presentations, but it does not work for all, and it is obvious when it is forced into this format. A case can be seamlessly inserted anywhere into the presentation, but it should always compliment the topic you are discussing at that point. Use cases to clarify concepts that are difficult to explain or how one finding could have multiple causes or implications and why that is important. After you insert your case, always ask if it adds value to the point you are trying to make and whether it fits into the flow you designed with your outline. If not, then consider moving it, revising it, or deleting it!

### Reading from Your Slides

Reading from slides makes the presenter sound like a robot and puts the audience to sleep, but it is so easy to do! How can you avoid this? This article does not focus on how to deliver a presentation, but this common pitfall in delivery is derived from poor slide preparation. The simplest answer is to know your material very well and don't overcrowd your slides with text. Your slides should be simple and read quickly. This will allow the audience to focus on what you are saying. If you put every piece of information you know on the slide, then you have to read it because you don't know anything else! Use short phrases and elaborate with what you know, highlight important numbers and data, and use your slides to put up information that you don't want to have to say. How many times have you zoned out during a presentation when someone starts with, "In this phase three, randomized, placebo-control, international, multicenter, cooperative group trial of..."? That is information that can be placed on the slide and allows you the ability to speak about the important aspects of the trial, such as, "This trial evaluated more than 300 patients and included patients with renal dysfunction and those older than the age of 60, so it is more applicable to the actual patient population we see. They assigned patients to [list assignment] and what they found was [list result]". Discussing clinical trials is difficult, but remember to focus on the take-home point of each and not just what the authors concluded. Is this good data and can they be applied to our patients? Why or why not? Be sure to know the studies you present beyond simply reading the abstract.

There are many different types of presentations and even more ways to go about presenting them, so deciding where and how to begin often can be very daunting, but I hope you are able to use the suggestions given here as a guide to getting started and staying focused. As you continue to develop your skills as a presenter, you will find your

own style of composing an effective presentation. Always seek the feedback of those whose opinions you trust on how you can improve your presentation, and review the comments that often are sent back in aggregate form from the Accreditation Council for Pharmacy Education (ACPE) programs. Both of these suggestions can help you identify deficits that you may not have recognized and fine-tune areas of improvement. You have all the tools you need to design a successful presentation, and with enough hard work and a little bit of confidence, you will be sufficiently prepared to educate and impress your audience.

## Board Update

*Michael Vozniak, PharmD BCOP, HOPA President*

March is always an exciting month for HOPA! This March marks HOPA's 11th Anniversary since our founding in 2004. In addition, our Annual Conference is held later this month. I am looking forward to seeing everyone in Austin, TX, for our 11th Annual Conference. HOPA President-Elect Scott Soefje lives in Austin, and it will be a terrific setting for him to begin his presidential term! I have heard great things about Austin, and I can't wait to see it for myself.

HOPA was extremely excited to announce in February that 39 members were awarded a HOPA travel grant to attend the Annual Conference this month. We received a record number of applications, and a big thank you goes out to our Membership Committee for overseeing the program and making it successful.

In January the board of directors held a strategic planning meeting. This meeting served as an opportunity to pause and reflect on the progress HOPA has made on its current strategic plan and to identify the goals and objectives HOPA should undertake moving forward. Work on finalizing the 2015/2016 HOPA Strategic Plan continues, and goals will be shared with the membership in Austin. After the goals, objectives, and strategies are finalized, the completed document will be announced and posted on the HOPA website. We expect this to happen sometime in May 2015.

In January the House of Representatives reintroduced the Pharmacy and Medically Underserved Areas Enhancement Act (H.R. 592) legislation, and the Senate introduced a companion bill (S. 314) for the first time. On the same day H.R. 592 was introduced, I, along with our health policy advisor, Jeremy Scott, met with the office of newly elected Congressman and pharmacist Buddy Carter (R-GA) in Washington, DC. It was a terrific introductory meeting! We had the opportunity to share information about our organization, our members, our Scope of Practice document and to offer our support for H.R. 592. HOPA will continue to actively participate in the Patient Access to Pharmacists' Care Coalition (PAPCC) and lend our support until these bills are passed. HOPA will be working to advance our Health Policy Agenda by having a HOPA Hill Day at the end of April. HOPA's Board of Directors and Health Policy Committee members will travel to Washington, DC, for 2 days of planning meetings and Hill visits. Our aim is for each participant to meet with his or her state's Senators and district's representative. For more information on these bills, please visit the Health Policy & Advocacy page on the HOPA website.

### New HOPA Central Online Community is Here

I hope you have had a chance to log in and test out the new HOPA online discussion forum, HOPA Central. Recognizing that the HOPA listserv is one of our most valuable member benefits, we realized that the listserv platform was old, provided limited functionality, and presented numerous challenges for searching the archives. HOPA Central is a much needed upgrade providing the functionality we have all come to expect but in a more user friendly interface along with better search capabilities. The Resource Library also allows for larger document uploads. Please help us keep a high standard of professional dialogue by reviewing the Code of Conduct and refraining from posting surveys, position announcements, and educational events.

### A Goodbye and a Hello

In January we formally said goodbye to Mary Beth Benner. Mary Beth had served as HOPA Director of Operations since 2010, when HOPA became a client of Association Management Center (AMC). Mary Beth remains with AMC, however she will be focusing her efforts on another association. I had the privilege of working with Mary Beth on the Standards Committee and as a board member. Behind the scenes, I credit Mary Beth for transforming HOPA's policy and procedures into living and breathing documents and, even more importantly, for helping identify the policies and procedures we needed. Mary Beth is engaging, insightful, helpful, and professional in everything she does. HOPA owes Mary Beth a big thank you for moving our organization forward. Thank you Mary Beth, and we wish you the best!

Kris Cichowski assumed the role of HOPA's Director of Operations in January. Kris most recently was the executive director of the Rehabilitation Institute of Chicago (RIC) Women's Board and Associate Board. Kris has deep experience in customer service as well as outcomes management having designed and implemented a corporate-wide knowledge management system to access customer satisfaction and functional outcomes. Welcome, Kris! We look forward to working with you.

## The Final Lap

In distance-running races, a bell is sometimes rung to signify the last lap of the race. Runners will quicken their pace leading up to an all-out sprint for the finish line. As your HOPA President, I feel the bell is about to be rung. I have found myself going through countless emails to determine what I still need to complete or if I may have missed something I should have already done. While I am looking forward to the Annual Conference at the end of the month, it also signifies passing the presidential responsibilities over to HOPA President-Elect Scott Soefje. It truly has been a privilege and an honor to serve HOPA this past year. As with all presidents before me, we all hope to leave HOPA in a better place than when we started. I feel confident our association is in a better place, and the credit truly goes to the dedicated board of directors who volunteer countless hours and the HOPA staff who help make our vision a reality. Finally I want to thank the HOPA membership for all the support, dedication, time, and effort they give. HOPA is successful because of its tremendous membership!

See you in Austin!

# HOPA Investigational Drug Service Best Practice Standards WEBINAR

## May 5, 2015, from 2–3 pm Eastern

***Barry R. Goldspiel, PharmD BCOP BCPS***
***Sapna R. Amin, PharmD BCOP***
***Joyce S. Lee, PharmD BCOP BCPS***

Learn how the *HOPA Investigational Drug Service Best Practice Standards* addresses the pharmacist's crucial role in investigational studies across the life cycle of a protocol, the investigational drug service's roles and responsibilities, and special circumstances related to medication therapy access on protocols.

Visit HOPA U for details at **www.hoparx.org.**

# Drug Updates

## Bevacizumab (Avastin®)

**Class**: Vascular endothelial growth factor (VEGF) inhibitor[1,2]
**Indications:** Treatment of persistent, recurrent, or metastatic cervical cancer in combination with paclitaxel and either cisplatin or topotecan; first- or second-line treatment of metastatic colorectal cancer (CRC) in combination with fluorouracil-based chemotherapy; second-line treatment of metastatic CRC in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line treatment containing bevacizumab; progressive glioblastoma; first-line treatment of unresectable, locally advanced, recurrent or metastatic nonsquamous non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel; platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, doxorubicin (liposomal), or topotecan in patients who received no more than two prior chemotherapy regimens; and metastatic renal cell carcinoma (RCC) in combination with interferon alfa.[1,2]
**Dose**: Indication and regimen dependent. 5 or 10 mg/kg every 2 weeks or 7.5 or 15 mg/kg every 3 weeks. No dosage adjustments provided in manufacturer's U.S. Food and Drug Administration (FDA)-approved package insert for renal/hepatic dysfunction. See package insert for discontinuation suggestions for adverse effects.[1,2]
**Common adverse effects:** (Serious adverse effects appear in bold)
*Cardiovascular*: Hypertension (12% to 34%; grades 3–4: 5% to 18%), venous thromboembolism (secondary: 21%; with oral anticoagulants), peripheral edema (15%), hypotension (7% to 15%), **venous thromboembolism** (8% to 14%; grades 3–4: 5% to 15%), **arterial thrombosis** (6%; grades 3–4: 3%)[1,2]
*Central nervous system*: Fatigue (33% to 80%; grades 3–4: 4% to 19%), pain (8% to 62%; grades 3–4: 8%), headache (22% to 37%; grades 3/4: 3% to 4%), dizziness (19% to 26%), taste disorder (14% to 21%), anxiety (17%), peripheral sensory neuropathy (grades 3–4: 17%)[1,2]
*Dermatologic*: Alopecia (6% to 32%), exfoliative dermatitis (>10%), xeroderma (>10%)[1,2]
*Endocrine and metabolic*: Ovarian failure (34%), hyperglycemia (26%), hypomagnesemia (24%), weight loss (15% to 21%), hyponatremia (19%; grades 3–4: 4%), hypoalbuminemia (16%)[1,2]
*Gastrointestinal*: Abdominal pain (61%; grades 3–4: 8% to 12%), vomiting (47% to 52%; grades 3–4: 11%), anorexia (35% to 43%), constipation (40%; grades 3–4: 4%), decreased appetite (34%), diarrhea (21%; grades 3–4: 1% to 34%), stomatitis (15% to 32%), **gastrointestinal hemorrhage** (19% to 24%), dyspepsia (17% to 24%), nausea (grades 3–4: 12%), **gastrointestinal perforation, sometimes fatal** (0.3% to 3.2%), gastrointestinal (GI) fistula (case reports)[1,2]
*Genitourinary*: Proteinuria (4% to 36%; grades >2%: grades 3–4: ≤7%; median onset: 5.6 months; median time to resolution: 6.1 months), urinary tract infection (22%; grades 3–4: -8%), pelvic pain (14%; grades 3–4: 6%)[1,2]
*Hematologic and oncologic*: **Hemorrhage** (40%; grades 3–4: ≤7%), leukopenia (grades 3–4: 37%), pulmonary hemorrhage (4% to 31%), neutropenia (12%; grades ≥3: 8% to 27%, grade 4: 27%), lymphocytopenia (12%; grades 3–4: 6%)[1,2]
*Infection*: Infection (55%; serious: 7% to 14%; pneumonia, catheter infection, or wound infection)
*Neuromuscular and skeletal*: Myalgia (19%), back pain (12%; grades 3–4: 6%)[1,2]
*Renal*: Increased serum creatinine (16%)[1,2]
*Respiratory*: Upper respiratory tract infection (40% to 47%), epistaxis (17% to 35%), dyspnea (25% to 26%), rhinitis (3% to >10%)
*Miscellaneous*: **Postoperative wound complications** (including dehiscence, 1% to 15%)[1,2]
**Drug interactions**
*Antineoplastic agents (anthracycline, systemic)*: May enhance the cardiotoxic effect of antineoplastic agents (anthracycline, systemic). Risk C: Monitor therapy[1].
*Belimumab*: Monoclonal antibodies may enhance the adverse/toxic effect of belimumab. Risk X: Avoid combination.[1]
*Bisphosphonate derivatives*: Systemic angiogenesis inhibitors may enhance the adverse/toxic effect of bisphosphonate derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. Risk C: Monitor therapy[1].
*Clozapine*: Myelosuppressive agents may enhance the adverse/toxic effect of clozapine. Specifically, the risk for agranulocytosis may be increased. Risk X: Avoid combination.[1]
*Dipyrone*: May enhance the adverse/toxic effect of myelosuppressive agents. Specifically the risk for agranulocytosis and pancytopenia may be increased. Risk X: Avoid combination.[1]
*Irinotecan*: May enhance the adverse/toxic effect of irinotecan. Risk C: Monitor therapy.[1]
*Sorafenib*: May enhance the adverse/toxic effect of sorafenib. Specifically the risk for hand-foot skin reaction may be increased. Risk C: Monitor therapy.[1]
*Sunitinib*: May enhance the adverse/toxic effect of bevacizumab. Specifically the risk for a specific form of anemia, microangiopathic hemolytic anemia (MAHA), may be increased. Bevacizumab may enhance the hypertensive effect of sunitinib. Risk X: Avoid combination.[1]

# Bevacizumab for Platinum-Resistant Ovarian or Cervical Cancers

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After a recent Priority Review of bevacizumab (Avastin®) the FDA granted the drug two new indications—platinum-resistant ovarian cancer and cervical cancers—in combination with chemotherapy.[1-4]

Bevacizumab is a humanized monoclonal antibody that binds to and inhibits vascular endothelial growth factor (VEGF), preventing its association with the Flt-1 and KDR endothelial receptors. The drug was already FDA approved for several indications including first- or second-line treatment of metastatic colorectal carcinoma, in combination with 5-FU-based chemotherapy; second-line treatment of metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliptan-based chemotherapy in patients who have progressed on a first-line bevacizumab-containing regimen; first-line treatment of unresectable, locally advanced, recurrent, or metastatic nonsquamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel; treatment of glioblastoma with progressive disease following prior therapy as a single agent; and the treatment of metastatic renal cell carcinoma in combination with interferon alfa.[2]

The new approvals were the result of two clinical trials published in 2014.[3,4] The first trial—published in *The New England Journal of Medicine* in February—was a randomized, four-arm trial of bevacizumab in combination with chemotherapy for the treatment of persistent, recurrent, or metastatic cervical cancer.[3]

The trial included 452 patients in a four-arm, 2x2 factorial design. In this study bevacizumab was administered at 15 mg/kg every 3 weeks in combination with paclitaxel and cisplatin or paclitaxel and topotecan. Control arms consisted of cisplatin plus paclitaxel or topotecan plus paclitaxel. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal.[3]

The median survival was 17 months for those patients who received bevacizumab and 13.3 months for patients who received chemotherapy alone ($p$ = .004). In total, 97% of patients discontinued study treatment, most commonly due to disease progression (51% chemotherapy alone; 38% chemotherapy plus bevacizumab).[3]

Discontinuation due to adverse events also was higher for patients who received bevacizumab (25% versus 16%). Adverse reactions more common in patients who received bevacizumab included grade 2 or higher hypertension (25% versus 2%; $p < .001$); grade 3 or higher gastrointestinal or genitourinary fistulas (6% versus 0%; $p$ = .002), and grade 3 or higher thromboembolic events (8% versus 1%; $p$ = .001).[3]

A second trial—published in the *Journal of Clinical Oncology* in May—compared bevacizumab plus chemotherapy with chemotherapy alone in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[4]

The open label, phase 3 AURELIA trial included 361 patients who received bevacizumab at 10 mg/kg every 2 weeks plus single-agent chemotherapy. Chemotherapy choice was made at the discretion of the investigator. Acceptable agents included paclitaxel, pegylated liposomal doxorubicin, or topotecan. Again, treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients assigned to chemotherapy alone could cross over to single-agent bevacizumab 15 mg/kg every 3 weeks after progression.[4]

Primary endpoint was progression-free survival (PFS). Median PFS was 3.4 months for patients who received chemotherapy alone versus 6.7 months in those who received bevacizumab plus chemotherapy ($p < .001$). Overall response rate was 12.6% with chemotherapy alone versus 27.3% with the addition of bevacizumab ($p$ = .001). There was no statistically significant difference in overal survival (OS) between treatment arms. Median OS was 13.3 months for chemotherapy alone compared with 16.6 months for the bevacizumab group.[4]

Adverse effect profile was similar in this trial. Hypertension of grade 2 or greater occurred more commonly in the bevacizumab-treated group (7% versus 20%). Proteinuria was also more common with bevacizumab (0% versus 2%). GI perforation of grade 2 or above occurred in 2.2% of bevacizumab-treated patients. Fistulas of grade 2 or above also occurred in 2% of bevacizumab patients.[4]

For more information and full prescribing information, visit www.avastin-hcp.com.

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## Ramucirumab (Cyramza®)

**Class:** Vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist
**Indication:** Advanced gastric or gastroesophageal junction adenocarcinoma, as a single agent or in combination with paclitaxel, after prior fluoropyrimidine- or platinum-containing chemotherapy.
**Dose:** 8 mg/kg intravenous infusion over 60 minutes every 2 weeks either as a single agent or in combination with weekly paclitaxel. When given in combination, ramucirumab should be administered prior to paclitaxel. Premedication with a histamine H1 antagonist is recommended. In the event of an infusion reaction, the addition of dexamethasone and acetaminophen should be used prior to each ramucirumab infusion.
**Dose modifications:** No dose adjustments necessary for patients with renal impairment or in those with mild hepatic impairment based on population pharmacokinetic analyses. No recommendations are provided for dose adjustment in moderate to severe hepatic impairment. Clinical deterioration has been reported in patients with Child-Pugh B or C receiving ramucirumab. Dose reductions or treatment interruptions may be warranted in the setting of infusion-related reactions, severe hypertension, or proteinuria (urine protein levels > 2 g/24 hours). Therapy should be held prior to surgery and may be resumed once the surgical wound is fully healed. Therapy should be permanently discontinued in the setting of nephrotic syndrome, arterial thrombosis, gastrointestinal perforation, grade 3 or 4 bleeding, or reversible posterior leukoencephalopathy syndrome (RPLS).
**Common adverse effects:** Hypertension, diarrhea, anemia requiring red blood cell transfusion, and infusion-related reactions. In combination with paclitaxel, additional adverse effects include fatigue, neutropenia, epistaxis, and stomatitis.
**Serious adverse effects:** Hemorrhage, arterial thrombotic events, gastrointestinal perforation, impaired wound healing, and RPLS. Febrile neutropenia and sepsis were seen when given with paclitaxel.
**Drug interactions:** Ramucirumab may enhance the adverse/toxic effects of belimumab, so this combination should be avoided. It may also increase the risk for osteonecrosis of the jaw if used concurrently with bisphosphonate derivatives.
**Monitoring parameters:** Blood pressure should be monitored every 2 weeks or more frequently if indicated. Other monitoring parameters include liver function tests, urine protein, signs and symptoms of arterial thrombotic events, hemorrhage, gastrointestinal perforation, wound healing impairment, and RPLS. Signs and symptoms of an infusion reaction should be monitored during infusion.

## Ramucirumab (Cyramza®) Now Approved in Combination with Paclitaxel for Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

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The incidence of gastric cancer in the United States has been declining during the past several decades, and it is now considered one of the least common cancers in North America—roughly 1.3% of new cancer diagnoses.[1,2] It is estimated that 22,200 new cases were diagnosed in 2014 in the United States, with almost 11,000 people having succumbed to the disease.[2] Unfortunately, for many other countries gastric cancer remains highly prevalent and is considered the fifth most common cancer and the third leading cause of cancer death worldwide.[3] Many cases are diagnosed in advanced disease stages, requiring treatment with cytotoxic chemotherapy.[1] Preferred first-line treatments include fluoropyrimidine- or platinum-based two- or three-drug combination regimens, with or without radiation or surgery. Single-agent regimens are less preferred because of their limited efficacy benefit and generally are reserved for patients with poor performance status who are unlikely to tolerate more aggressive therapy. For patients who progress despite first-line treatment, there are limited options for second-line therapies, and prognosis generally is poor in this setting.

To improve second-line treatment options, targeted therapies have been evaluated for safety and efficacy as monotherapy and in combination regimens. Vascular endothelial growth factor (VEGF)- and vascular endothelial growth factor receptor-2 (VEGFR-2)-mediated signaling are understood to play a role in the pathogenesis of gastric cancer. Ramucirumab (Cyramza®) is a human IgG1 monoclonal antibody VEGFR-2 antagonist that binds to the VEGFR-2 and inhibits the binding of VEGFR ligands, resulting in disruption of angiogenesis.[4] Ramucirumab received U.S. Food and Drug Administration (FDA) approval in April 2014 as a single-agent treatment for advanced gastric cancer or gastroesophageal junction adenocarcinoma after prior fluoropyrimidine- or platinum-based chemotherapy. The approval was based on the results of the REGARD trial, in which ramucirumab demonstrated a statistically significant overall survival (OS) of 5.2 months compared with 3.8 months observed in the placebo group receiving best supportive care (hazard ratio HR = 0.776; 95% confidence interval [CI]: 0.603–0.998; $p$ = .047).[5]

To further increase survival, ramucirumab also has been studied in combination with paclitaxel and recently received additional FDA approval on November 5, 2014, for use in combination with paclitaxel for the treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma after prior fluoropyrimidine- or platinum-based chemotherapy. The approval was based on the results of the RAINBOW trial, an international, phase 3, randomized, double-blind,

placebo-controlled study.[6] In this study Wilke and colleagues assessed the safety and efficacy of ramucirumab plus paclitaxel compared with paclitaxel alone in 665 patients. Patients 18 years and older with metastatic or nonresectable locally advanced gastric or gastroesophageal junction adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 were eligible for the study. Included patients also needed to have documented disease progression during or within 4 months of the last dose of first-line therapy with platinum or fluoropyrimidine, with or without anthracycline. Exclusion criteria included squamous or undifferentiated gastric cancer; gastrointestinal perforation, fistulae, or any arterial thrombotic event within the past 6 months; any significant or gastrointestinal bleeding within the past 3 months; or poorly controlled hypertension.

Eligible patients were randomized in a 1:1 ratio to receive paclitaxel (80 $mg/m^2$ intravenously on days 1, 8, and 15 of a 28-day cycle), plus either ramucirumab (8 mg/kg intravenously days 1 and 15) or placebo, and continued until disease progression, unacceptable toxicity, or consent withdrawal. Cross over to the ramucirumab arm was not allowed. The study's primary endpoint was OS, and secondary endpoints included progression-free survival (PFS), objective tumor response, disease control, patient-reported outcomes, ramucirumab immunogenicity (assessed by antiramucirumab antibodies), and safety. Patient baseline characteristics were well balanced between the two groups. Of the 665 patients randomized, 71% were male, the median age was 61 years, 61% were Caucasian, and 35% were of Asian descent. A large proportion of patients in both arms had poor prognostic factors, including poorly differentiated tumors (56%), disease progression within 6 months from the start of previous therapy (76%), three or more metastatic sites (34%), peritoneal metastases (47%), and presence of ascites (36%).[6]

Study enrollment occurred from December 23, 2010, through September 23, 2012. Follow-up assessment was completed July 12, 2013, with a median follow-up for OS of 7.9 months. The median OS for ramucirumab plus paclitaxel was 9.6 months versus 7.4 months in the placebo group ($p = .017$). Median PFS was 4.4 months in patients receiving ramucirumab and paclitaxel, versus 2.9 months in patients receiving placebo plus paclitaxel ($p < .0001$). A greater proportion of patients receiving ramucirumab plus paclitaxel achieved an objective response, as well as disease control, compared with the placebo plus paclitaxel group, 28% versus 16% ($p = .0001$) and 80% versus 64% ($p < .0001$), respectively.[6] The median duration of response also was noted to be longer in the ramucirumab arm than the placebo arm—4.4 months versus 2.8 months, respectively. The median treatment duration for those receiving ramucirumab plus paclitaxel was 18 weeks compared with 12 weeks observed in patients receiving paclitaxel alone.[6] The most common reason for treatment discontinuation in both treatment arms was disease progression. The median relative dose intensity (RDI) for ramucirumab was similar to placebo (99% versus 100%, respectively), as was the RDI for paclitaxel (88% in patients receiving ramucirumab versus 93% in patients receiving placebo). Ramucirumab and placebo dose reductions occurred in 5% and <1% of patients, respectively. Paclitaxel dose reductions occurred in 24% of patients receiving ramucirumab plus paclitaxel and in 7% of patients receiving placebo plus paclitaxel. Antiramucirumab antibodies were detected in five (2%) patients receiving ramucirumab and in one (<1%) patient receiving placebo.[6] No patient in either arm developed ramucirumab-neutralizing antibodies. For patient-reported outcomes, global quality of life was similar between both treatment arms and was assessed using the EORTC QLQ-C30 and EQ-5D-3L questionnaires.[6]

The most common adverse reactions (any grade) among both treatment arms were fatigue, neuropathy, nausea, and diarrhea. Incidence of grade 3 or 4 adverse events was higher in patients receiving ramucirumab plus paclitaxel, including grade 3 or 4 neutropenia (41%), leucopenia (18%), grade 3 hypertension (14%), fatigue (12%), neuropathy (8%), and abdominal pain (6%).[6] There was no significant difference in the incidence of grade 3 or higher febrile neutropenia between patients receiving ramucirumab or placebo (3% versus 2%, respectively). Less common adverse effects (grade 3 or higher) associated with ramucirumab included bleeding or hemorrhage (<5%), proteinuria (1%), and stomatitis (<1%).[6] Additional adverse effects (any grade) in patients receiving ramucirumab included decreased red blood cells requiring transfusion, epistaxis, headache, and infusion-related reactions. Rates of grade 4 or 5 adverse reactions were low in both groups, with similar incidence of gastrointestinal hemorrhage and a slightly higher incidence of gastrointestinal perforation in the ramucirumab group. No patients receiving ramucirumab experienced grade 4 or 5 hypertension.[6]

A preplanned subgroup analysis of the RAINBOW trial demonstrated a geographical difference in OS, specifically in patients of Asian descent. The median OS in patients receiving ramucirumab plus paclitaxel was 8.5 months for non-Asian patients and 12.1 months for Asian patients. In patients receiving paclitaxel plus placebo, the median OS was 5.9 months and 10.5 months for non-Asian and Asian patients, respectively. Wilke and colleagues speculated this nonsignificant difference may be attributed to the higher use of poststudy treatment in Asia than other regions, which incorporates cultural differences in health care, use of third- and fourth-line treatments, and management of end-of-life patients.[6]

Based on the results of the REGARD and RAINBOW trials, ramucirumab is supported by the National Comprehensive Cancer Network treatment guidelines as monotherapy or in combination with paclitaxel for second-line treatment of patients with advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma who have progressed following fluoropyrimidine- or platinum-containing therapy.[1] Ramucirumab is being studied in other malignancies and also is approved for use in combination with docetaxel for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy.

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