Spring 2020 NEWSLETTER

Official Newsletter of the ACCP Hem/Onc PRN

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Clinical Pharmacist
Bleeding Disorders, Malignant & Nonmalignant Hematology
CHS Specialty Pharmacy Services
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Charlotte, NC

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Clinical Pharmacist
Hematologic Malignancies/Bone Marrow Transplantation
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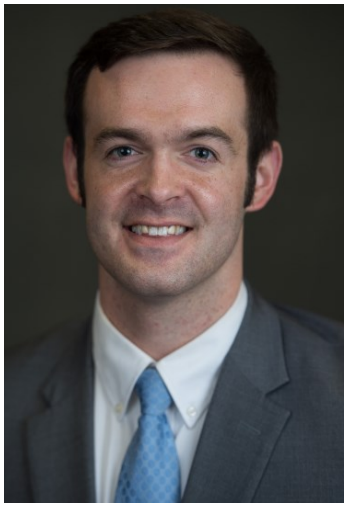
GREETINGS FROM THE CHAIR



Hi all, Our goal with the newsletter is to support the needs of the PRN membership, with biannual updates that will supplement the ACCP Spring and Fall PRN reports. This newsletter is a way to highlight our members and showcase a variety of practice areas and expertise.

2020 is certainly off to a crazy start as we now navigate patient and personal care in the setting of this COVID-19 crisis. Look for updated information, especially provided by the CDC, ASCO, and NCCN. Cancer patients have been rarely reported but are a recognized at-risk population (Liang et al, Lancet Oncol). Now is as important a time as ever to utilize your network, advocate for optimized care, and challenge the status quo to find the best care for patients and practice. Beyond COVID, I hope you will find this Spring newsletter informational and interesting!

In this issue:

American College of Clinical Pharmacy

Cancer Mortality Declines at an Unprecedented Rate

By: Adwoa Nyame, Virginia Commonwealth University School of Pharmacy , PharmD Candidate (Class of 2021)

Mentor: Erin Hickey, PharmD., BCOP

Over the past two decades, overall cancer mortality has declined. The American Cancer Society (ACS) annually compiles pooled incidence and mortality data, and reports that overall cancer mortality decreased by an average of 1.5% per year between 2008 and 2017.[1] In their most recent report, they announced the single largest yearly decline to date, a 2.2% decrease from 2016 to 2017.

The falling cancer mortality rate in the US has been exciting news for patients and providers alike. In 2016 there had been a 27% decline in cancer mortality from 1991, which was the peak in cancer mortality, which is an indicator of how far the field of oncology as progressed.[2] Although the ACS report cannot determine causal relationships between factors impacting mortality, there is debate on who deserves the credit. One point of discussion is whether or not the decreased mortality should be attributed to advances in cancer pharmacotherapy. As the declining rate is driven by a decrease in lung cancer mortality, many experts speculate that advances in treatment, including the introduction of precision and immunotherapy-based drugs, are now displaying large-scale progress.

Critics of the ACS report remind us that there are several other factors that may have more heavily influenced the decline in mortality. These include reduced smoking rates among both genders, improved supportive care, multimodal therapy (i.e. surgery and radiation techniques), and screening practices. For example, the incidence of tobacco use for men and women has decreased from 20.9% to 15.1% since 2005.[3] This decline in tobacco use in both men and women could be an integral part of the decline in cancer mortality because statistics show that the risk of developing lung cancer is 15-30 times higher in lifelong smokers as compared to nonsmokers.[4] Furthermore, it is unlikely that the anti-EGFR tyrosine kinase inhibitors approved in the early-mid 2000s (i.e. erlotinib, crizotinib) or immune checkpoint inhibitors in later lines of therapy for advanced disease are producing this improved decline. It remains to be seen whether the survival benefit of next generation targeted therapies or first-line combination chemoimmunotherapy will be reflected in future reports' mortality rates. [5]

Although the cancer mortality rate is declining at a faster rate than ever, the causal relationship is difficult to determine. As an oncology pharmacy community, we can carry this message to continue developing and expanding the role of the pharmacist to further the decline in cancer mortality, by optimizing pharmacotherapy as well as making use of the appropriate screening techniques. Regardless of the cause of the decline, cancer mortality is declining at an unprecedented rate and regardless of the cause, this is a victory that should be celebrated in the oncology field.

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Organization Meeting Updates:

American Society of Hematology 2019

By: Donald C. Moore, PharmD, BCPS, BCOP, DPLA

The 61st American Society of Hematology (ASH) annual meting was held December 7-10, 2019 in Orlando, Florida. Exciting updates in research for a variety of hematologic conditions are presented each year at this conference. Here are some highlights from across the spectrum of hematology that were presented at the most recent ASH meeting:

ELEVATE TN in CLL

A phase III trial randomized 535 patients with treatment-naïve chronic lymphocytic leukemia (CLL) in a 1:1:1 fashion to receive acalabrutinib, acalabrutinib/obinutuzumab (AO), or chlorambucil/obinutuzumab (CO). The primary endpoint was progression-free survival (PFS) with AO vs. CO. Secondary endpoints included PFS with acalabrutinib vs. CO and overall survival (OS). AO significantly prolonged PFS compared to CO (median not reached vs. 22.6 months; HR 0.10, 95% CI 0.06-0.18, p<0.0001). Acalabrutinib monotherapy also improved PFS compared to CO (median not reached, HR 0.20, 95% CI 0.13-0.31, p<0.0001). At a median follow-up of 28 months, median OS was not reached in any arm of the trial. The authors concluded that acalabrutinib-based therapy significantly improved PFS compared to CO.

QUAZAR AML-001

The international, randomized, double-blind, placebo-controlled phase III QUAZAR AML-001 trial evaluated CC-486, an oral formulation of azacitidine, as maintenance therapy for patients ≥55 years in first remission with intensive induction chemotherapy. Patients were randomized to CC-486 300 mg (n=238) or placebo (n=234) once daily on days 1-14 of a 28-day cycle; treatment was continued until progression, toxicity, or hematopoietic stem cell transplant. The primary endpoint of OS was significantly improved with CC-486 compared to placebo (median OS 24.7 months vs. 14.8 months; HR 0.69, 95% CI 0.55-0.86, p=0.0009). The adverse event profile of CC-486 was consistent with that of injectable azacitidine. The authors concluded that CC-486 maintenance therapy provided significant improvement in OS for patients with AML in first remission following induction chemotherapy with a manageable adverse event profile.

ICARIA-MM in older MM patients

A subgroup analysis of the phase III ICARIA-MM trial was conducted to evaluate efficacy and safety of isatuximab plus pomalidomide/dexamethasone (IPd) vs. pomalidomide/dexamethasone (Pd) in elderly patients (≥75 years) compared to younger patients. Included patients had relapsed/refractory multiple myeloma after ≥2 prior lines of therapy, including lenalidomide and a proteasome inhibitor. The overall population experienced an improvement in PFS with IPd compared to Pd (median 11.53 vs. 6.47 months; HR 0.596, 95% CI 0.436-0.814; p=0.001). Older patients had a similar median PFS (11.4 months) with IPd compared to Pd. The ORR for all patients was 60.4% and 35.3% with IPd and Pd, respectively. ORR for patients ≥75 was 53.1% with IPd and 31% with Pd. For safety, there were more grade ≥3 adverse events with IPd in patients ≥75 years (93.8%) compared to patients <65 years (85.2%). There were also more treatment discontinuations due to adverse events with IPd in patients ≥75 years (15.6%) vs. <65 years (7.4%). The authors concluded that the addition of isatuximab to Pd improved PFS and ORR and this benefit was consistent in older patients. There was a trend for higher rates of adverse events and treatment discontinuation for tolerability in older patients compared to their younger counterparts in this trial.

ACCP MeRIT Program Insight: Benyam Muluneh

The ACCP Foundation, a non-profit 501(c)(3) organization, is the charitable arm of the American College of Clinical Pharmacy (ACCP). The Foundation's mission is to improve human health by supporting research, scholarship, and practice. In its mission the Foundation offers the Focused Investigators (FIT), Mentored Research Investigator Training (MeRIT), and Futures Grants programs to foster scholarly activities among pharmacists. Our PRN recognizes the immense value of these programs and seeks to encourage engaging in these programs! Read below and on the next page the accounts of their involvement in the MeRIT program from Dr. Benyam Muluneh and Dr. Mitchell Hughes!

From: Benyam Muluneh, PharmD, BCOP, CPP; Clinical Assistant Professor, UNC Eshelman School of Pharmacy

American College of Clinical Pharmacy (ACCP) offers two training programs focused at developing junior investigators. The first is Focused Investigator Training (FIT) program which targets more experienced researchers who may have had difficulty attaining an NIH-level grant and get detailed feedback on their future grants. The second is the Mentored Research Investigator Training Program (MeRIT) program which is perfect for most clinical pharmacists and junior faculty who are interested in leading high quality and methodologically sound research.

I participated in the MeRIT program starting with a one week on-site primer in June 2018. The primary motivation for applying for the program was my interest in developing my research skills beyond what I was comfortable with in the past which were "one and done" resident projects with little thought to building a thematic area of expertise. I wanted to be intentional about building a research program while learning how to balance this with my other parts of my job. Two predictable barriers I encountered to pursuing this goal were time (since the MeRIT program requires 10% dedication) as well as money (the program costs upwards of $5,000). I approached my manager prior to applying to ensure I would have support to complete this program as part of my professional development. I also inquired about financial support and received partial institutional support. ACCP does offer a few grants including the ACCP Foundation Futures Grant (a mentored developmental research award). The application for this is typically due in September and awards are announced in November. Part of the grant request could include participation in this program. I would highly encourage anyone seriously considering FIT or MeRIT to speak with Sheldon Holstad who is the director of the ACCP foundation and primary contact for these programs.

My project focused on characterizing the complex and bidirectional relationship between adherence to oral oncolytics and health-related quality of life (HRQOL). Mentors are individually selected based on applicant project proposals so my mentor had expertise in practice-based research as well as survey methodology. Additionally, participants have an institutional mentor to guide them along the way who needs to be identified during the application process.

For me, the impact of the MeRIT program has been twofold. The mentors were very helpful in helping me develop my project, and, with monthly calls, ensured I was able to work through several barriers along the way. My project evolved significantly due to the targeted and individualized mentoring I received through this program. I also had never approached a project in a way that would prepare me to possibly write a competitive grant (which we had a chance to practice by writing parts of a grant). What I had not anticipated was the 1:1 opportunities to meet with as many of the mentors (even ones not assigned to me) and get guidance on a number of topics. I gained a tremendous amount of perspective on topics such as claims-based research, work-life balance, learning how to say "no", advocating for professional development, and more. Those conversations were truly created a paradigm shift in the way I viewed my long term career and helped me establish a clear vision for my future which I was able to discuss with my leadership upon my return. I highly recommend this program for clinicians wanting to sharpen their scholarship skills.

ACCP MeRIT Program Insight: Mitchell Hughes

From Mitchell Hughes, PharmD, BCPS, BCOP; Hematology/Oncology Pharmacist; University of Pennsylvania Health System

My name is Mitchell and I am one of the 2019 ACCP participants in the Mentored Research Investigator Training (MeRIT) program. I am fortunate to have been supported to attend the MeRIT program through the Hematology/Oncology Pharmacy Association (HOPA), which I would like to offer sincere gratitude to both HOPA and the ACCP Foundation for allowing me this opportunity and mentorship.

I am a clinical pharmacy specialist with the Lymphoma Program at the Hospital of the University of Pennsylvania (HUP). My current role is a hybrid position, integrating direct clinical care, infusion services, and specialty pharmacy support. Outside of my day to day responsibilities, I am passionate about incorporating translational research into practice. I wanted to challenge myself to develop a research question to submit as a grant proposal centered on observations of clinical toxicity patterns noticed in our patients from our practice team.

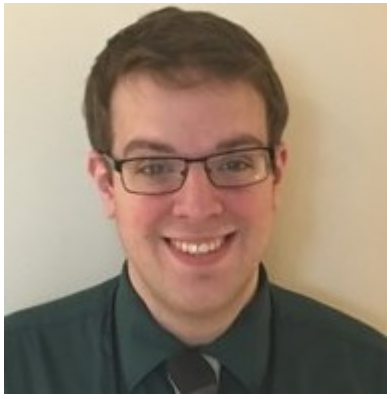
I submitted a letter of intent for the HOPA early career research grant titled, "A pharmacogenomics evaluation of ibrutinib for treatment of B-cell malignancies." I subsequently completed my first grant submission based on the aforementioned LOI and was awarded funding to design my research protocol. HOPA was exceedingly generous and offered the opportunity to apply my research proposal to the MeRIT program or Focused Investigator Training (FIT) program to help further refine my grant submission and connect me with research oriented mentors. Given I am not on a faculty track at the present moment, I applied to the MeRIT program since the FIT program supports the opportunity to improve competitiveness when submitting a K, R01, or similar NIH style grant.

The live-primer is a five-day program designed to provide a combination of didactic training and team-based thought groups with mentors and fellow MeRIT participants. The protected time and resources available at the live program is a refreshing and edifying experience. Mentors help guide early investigators and structure their question into a research proposal with a goal of applying for funding support. The mentors of the MeRIT program provide grounded analysis of proposals and assess feasibility based on their storied experience.

Challenges join every participant at one point or another; still, not everyone experiences them at the same stage, making everyone's experience unique. There are some who shift their entire research idea or develop a unique new idea during the live session. I personally changed my specific aims to my project and gained valuable insight to study design and education from mentors with pharmacogenomics experience. The most exciting part of the program is that there is no limit and nobody dissecting a research idea to say why it cannot work; to the contrary, mentors and mentees work together to strengthen ideas.

While I am in the midst of circumventing my own initial roadblocks, I am supported by my newfound mentors from the MeRIT program and my MeRIT class. I see the MeRIT program as an investment in developing my personal goal of training as an independent investigator and expanding my research experience outside of quality improvement and retrospective research protocols. The MeRIT program has offered me mentors who view things with a different lens than my predominantly clinical colleagues. I am grateful to have had the opportunity to learn and grow from my contemporaries in the program, from the ACCP mentors and staff, and the generous opportunity provided by HOPA. For those interested, please reach out to me if you have any questions at mitchell.hughes@pennmedicine.upenn.edu.

Consider these testimonies as you weigh the benefit of these programs for you own practice! Please reach out to anyone with experience in these programs, your PRN officers, or ACCP/ACCP Foundation staff as questions arise. Please refer to other resources provided by the ACCP Foundation to support your own research efforts!



Inaugural Virtual Rotations:

Transplantation & Cellular Therapy

In December of 2019 the ACCP Heme/Onc PRN coordinated two new "virtual rotation" experiences. This idea was presented and discussed at the ACCP Annual Meeting Hem/Onc Business Meeting, with calls for participation communicated through the PRN listserve shortly thereafter. Geared primarily towards learners and secondarily for interested practicing pharmacists, Dr. Justin Arnall and Dr. Katie Gatwood led a series of presentations, journal clubs, and other activities on bleeding disorders/factor stewardship and hematopoietic cell transplantation/CAR-T therapy respectively. These subjects were identified as those that many learners may not have readily available or offered by their programs. Students, residents, fellows, and practicing pharmacists participated in activities across 4-5 hour-long meetings via a Skype platform forum. Dr. Lauren Nice and student, Kathryn Fitton, offer testimony of their experiences below! We hope to continue this experience in the future as a novel opportunity to engage with our learners!

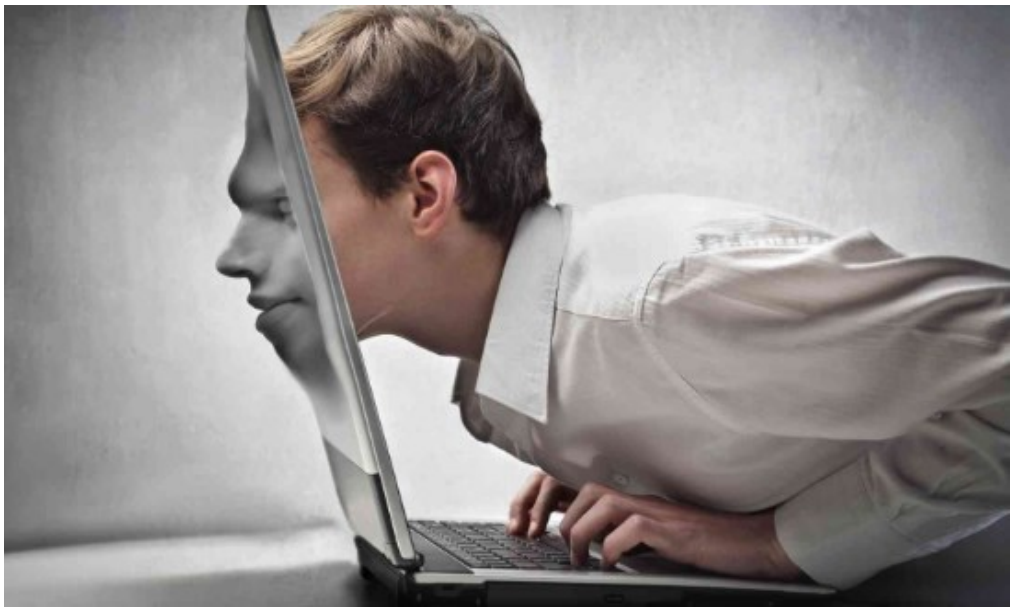
By: Laura Nice, PharmD, PGY2 Oncology Pharmacy Resident , University of Louisville Hospital

This past winter, students, residents, and fellows had the opportunity to participate in the inaugural ACCP hematology/oncology PRN virtual rotations. Led by experts in the field, virtual rotation topics included CAR-T, gynecologic oncology, and bleeding disorders. This created a fantastic opportunity for learners to gain additional knowledge in areas that may not be offered at their current institutions.

I was fortunate to participate in the CAR-T virtual rotation with four other pharmacy residents. The rotation consisted of four 1-hour virtual sessions, each with topics and readings about CAR-T and bone marrow transplant (BMT). Our sessions included CAR-T overview, infection prophylaxis, toxicity management, and advanced topics in BMT. Each learner was assigned a topic and led the first half of the discussion based on provided readings, followed by further discussion led by our facilitator.

Given my residency site does not currently treat patients with CAR-T, the sessions provided a solid foundation of knowledge with guidance from a pharmacist who had assisted in building a CAR-T program. It was also great to review topics in BMT, as I had completed my BMT inpatient rotation early in the residency year yet appreciated the additional information provided. It was especially beneficial to hear about these topics from our facilitator and residents at other sites to gain an understanding of how other sites treat this patient population. The virtual rotation has helped in my development as an oncology pharmacist, as I learned a lot about an area I had not experienced and was able to collaborate with oncology pharmacists from across the country.

Thank you to Katie Gatwood for volunteering their time and expertise in these areas!



Inaugural Virtual Rotations:

Bleeding Disorders & Factor Stewardship

By: Kathryn Fitton, PharmD Candidate, Class of 2020

In December of 2019, I had the privilege of participating in the ACCP Hem/Onc PRN Virtual Rotation on bleeding disorders and factor stewardship with four other students from various institutions and Dr. Justin Arnall. I was excited for this opportunity as it was something new and different. I also had an interest in hematology and oncology but unfortunately was not given an APPE rotation in these disciplines until March. Through this initiative, I was able to be proactive and obtain additional experience in non-malignant hematology prior to the residency application process.

Now, you may be asking, what is a virtual rotation? Similarly to any other rotation, we were given a document with what to expect and a rotation calendar. We were also given articles to read and assigned parts of the articles to present to the rest of the group. Unlike my APPE rotations, the virtual rotation was meant to supplement standard pharmacy training and was therefore divided into hour-long Skype sessions.

In preparation for the first session, I read the guidelines for the management of hemophilia (Srivastava, Brewer et al. 2013). During the video meeting, Dr. Arnall gave us an introduction into hemophilia, von Willebrand disease, and other rare bleeding disorders as well as their treatments including various factor concentrates. For the second session, I helped present the results of A Randomized Trial of FVIII & Neutralizing Antibodies in Hemophilia A (Peyvandi, Mannucci et al. 2016) and the background of the RODIN study (Gouw, van den Berg et al. 2013) with my peers. We utilized these articles to facilitate our discussion on chronic and acute management of bleeding in hemophilia patients. The last session included a presentation about inhibitor development in bleeding disorders and conversations on how to manage inhibitors and the potential impact of a factor stewardship program. Dr. Arnall also related each of the topic discussions back to patients in his clinical practice and tried to include patient cases for us when he could.

Overall, this experience was very beneficial for me to gain exposure to a topic I might not have had the opportunity to learn about otherwise. PGY2 standards for oncology pharmacy residents identify hematological disorders as elective considerations but discourage incorporating non-malignant hematology into a required focus area (ASHP). The ACCP Hem/Onc PRN offered a virtual rotation in bleeding disorders for residents as well due to the lack of exposure during residency training. While bleeding disorders represent a patient minority, blood factor concentrates often represent a major percentage of health-system pharmacy budgets. Therefore, specialized pharmacists can make a large impact with several novel factor medications in the pipeline and gaps in care for stewardship programs to fill. Despite the occasional video technology difficulties, virtual rotations have a place in education to fill niche specialties that may not be able to be prioritized in the average pharmacy curriculum.

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New Drug Update:

Trastuzumab-Deruxtecan (ENHERTU™)

By: Brennen Guzik, Shanada Monestime; Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC, University of North Texas Health Science Center, Fort Worth, TX

It is estimated that patients with metastatic breast cancer will have a 5-year overall survival of 27.4%.[1] In these cases, anywhere from 15% produce an overexpression of HER2+, and this overexpression allows for targeted agents to attack the cancerous cells.[2] Although those expressing HER2+ have an overall better prognosis than those not expressing HER2+, patients can relapse after first line therapy or develop resistance after second line therapy. Currently, third-line options on the market have limited benefit and response rates varies from 9 to 31% with a duration of progression-free survival of approximately 3 to 6 months.[3] The FDA approved a new third-line option to the market, trastuzumab-deruxtecan (ENHERTU™), in December 2019, for patients with unresectable or metastatic HER2+ breast cancer who have failed at least 2 prior treatments of anti-HER2 agents in the metastatic setting. Trastuzumab-deruxtecan is an antibody-drug conjugate designed to have anti-HER2+ activity. Differing from prior formulations of trastuzumab, is the addition of deruxtecan, a novel topoisomerase I inhibitor attached via a cleavable linker. This combination retains the traditional pharmacokinetic profile of trastuzumab, with a half-life of approximately 5.7 days.[4,5]

Efficacy

Trastuzumab-deruxtecan approval was based on the results of a two-part, open-label, single-group, multicenter trial consisting of 184 patients. Patients had a HER2 positive score of 3+ on immunohistochemical analysis or positive in-situ hybridization results. The primary endpoint was overall response. Secondary endpoints were the response duration, progression-free survival, overall survival, response rate according to investigator assessment, best percentage change in the sum of the diameters of measurable tumors, disease, clinical-benefit control rate, safety, and pharmacokinetics. Cohort 1 had tumor progression during or after receiving trastuzumab emtansine and Cohort 2 were patients who discontinued trastuzumab emtansine for reasons other than progressive disease. Of the 184 patients who received trastuzumab deruxtecan at 5.4mg/kg, overall response occurred in 60.9% of patients (95% CI, 53.4 - 68.0%) response duration was reported as 14.8 months (95% CI, 13.8 to 16.9). Median duration of progression-free survival was 16.4 months (95% CI, 12.7% to not reached) and overall survival was 86.2% at 12 months (95% CI, 79.8 to 90.7). Disease-control rate was documented at 97.3% (95% CI, 93.8 to 99.1) with clinical-benefit control rate at 76.1% (95% CI, 69.3 to 82.1).[4]

Safety

When administrating trastuzumab-deruxtecan, it is given at 5.4 mg/kg intravenous infusion every 3 weeks. The first infusion is given over 90 minutes, while subsequent infusions were given in 30-minute intervals. Common adverse events of grade 3 or higher occurring in 5% or greater of patients include decreased neutrophil count (20.7%), anemia (8.7%), nausea (7.6%), decreased lymphocyte count (6.5%), and fatigue (6.0%).[4]

Adverse events led to dose interruption in 65 patients (35.3%), dose reduction in 43 patients (23.4%), and discontinued treatment in 28 patients (15.2%). A total of 25 deaths were reported, in which 16 deaths were unrelated to trastuzumab deruxtecan. Among the three patients who experience an asymptomatic decrease in the left ventricular ejection fraction, none were less than 40%, experienced a decrease from baseline of 20% or more, or discontinued treatment due to a decrease in the ejection fraction.[4]

Of the 184 patients, 25 (13.6%) developed interstitial lung disease (ILD), in which 20 (10.9%) of these cases were grade 1 or 2, with one patient having grade 3. Four deaths were attributed to ILD. Providers and healthcare personnel need to monitor for signs of declining pulmonary function. If ILD is suspected, a consult to pulmonology and evaluation of pulmonary function, oxygen saturation, and CT scans are recommended. Treatment of ILD includes interruption of the drug regimen and prompt intervention with glucocorticoids when appropriate may help reduce the severity of this complication.[4]

CONCLUSIONS

Trastuzumab-deruxtecan has shown to be a viable option for patients with metastatic HER2+ breast cancer who have failed two prior anti-HER2 agents. Awareness and monitoring for symptoms of interstitial lung disease (fever, cough, or dyspnea) are recommended for early detection and treatment.

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Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

Journal Club: N Engl J Med 2020; 382:140-151

Summarized by MinhThi Nguyen, PharmD Candidate, Class of 2020

Reviewed by Justin Arnall, PharmD, BCOP

Background:

The MEDALIST is the trial investigating the efficacy of luspatercept, a first-in-class erythroid maturation agent, in non-del(5q) lower-risk myelodysplastic syndromes with ring sideroblasts patients (MDS RS+). This patient group has had limited treatment options once refractory to erythropoiesis-stimulating agents and when chronic RBC transfusion has exposed them to morbidity. The safety data of this trial has been described as being consistent with its preceded phase 2 PACE-MDS study.

Methods:

This trial was a double-blind, placebo-controlled, phase 3, 2:1 ratio randomization, multicenter study assigning patients 18 years of age or older who were MDS RS+. Patients had SF3B1 mutation with at least 5% blasts and < 15% RS+ were also eligible. Patients in the treatment arm were given 1 mg/kg luspatercept subcutaneously every 3 weeks for 24 weeks. Patients included in the trial were those who had more than 2 units of red blood cell transfusions per 8 weeks and were refractory to prior erythropoietin stimulating agent (ESA) use or had epoetin levels (EPO) > 200 IU/L. Those who had been treated with hypomethylating agents or lenalidomide or received more than 2 units of RBC transfusion per 8 weeks. Del(5q) lower risk MDS patients were excluded. The primary efficacy endpoint aimed to investigate the proportion of patients who became red blood cell (RBC) transfusion independent for every 8 weeks during the first 24 weeks. Key secondary endpoint was transfusion independence (TI) for 12 weeks or longer, which was evaluated during both the first 24 weeks and 48 weeks.

Results:

The study recruited 229 patients. The median transfusion burden over an 8-week period during the 16 weeks before treatment was 5 units per 8 weeks. The results were based from a high fraction of patients (95%) who had received ESA prior to this trial. For primary endpoints, during the first 24 weeks, TI for 8 weeks or longer was higher in the treatment arm (38% v 13%; P<0.001). Primary endpoints were archived in 62% of patients in the treatment group, in which they had at least two response intervals of TI lasting 8 weeks or longer. Compared to baseline, TI for 8 weeks or longer in the treatment group had a rate of 80%. SF3B1 allelic burden did not interfere with the rate of patients who had a response to treatment. For the key secondary endpoint, more patients in the luspatercept arm had transfusion independence for more than 16 weeks or longer during the first 24 weeks based on the new 2018 International Working Group (IWG) response criteria (19% v 45%). Mean increase in hemoglobin of at least 1.0 g/dL was observed in 35% of patient in the interventional group during the first 24 weeks. Incidence of grade 3/4 events was similar in both arms (42% v 45%). Same trend was seen in serious adverse events (31% v 30%). The most frequent reported adverse events were fatigue, diarrhea, headache, and dizziness, which tended to occur during the first four cycles of treatment but were either self-limiting or no dose adjustment required.

Application in clinical practice:

Red blood cell transfusion dependence with its considerable risks of iron overload and hospitalization clearly affect a patient's quality of life. And are often realities of even low-risk MDS patients. While ESAs are generally considered as the first line treatment for non-del(5q) lower risk MDS patients with eligible EPO cutoff, retrospective studies have shown limited response rates. Results of this study demonstrate the avoidance of red blood transfusions for lower and very low risk MDS patients and thus present an opportunity or at least a novel addition to consider in the current treatment protocol for MDS RS+ patients. This agent might serve as a treatment of choice to replace lenalidomide when patients seem to experience adverse events such as thrombocytopenia and neutropenia. As this enters practice, considerations are warranted regarding its application along MDS algorithms, incurred cost, and combinations with other agents (i.e. ESAs).

Bruton Tyrosine Kinase (BTK) Inhibitors in Chronic Lymphocytic Leukemia

By: Laura Roccograndi, PharmD, PGY1 Resident, MD Anderson Cancer Center
Mentor: Caitlin Rausch, PharmD, Clinical Pharmacy Specialist—Leukemia, MD Anderson Cancer Center

Background: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia with approximately 20,000 new cases reported annually.[1] CLL is a clonal disorder arising from mature B lymphocytes with constitutive activation in B cell receptor (BCR) signaling.[2] It is characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow and lymphoid tissue. Patients are often diagnosed at an older age (≥ 65 years) and do not require therapeutic intervention until symptomatic. At the time of therapy initiation, a patient's age, comorbidities, and genotypic features inform treatment choice. For initial therapy of CLL, treatment approaches have progressed from traditional chemotherapy to chemo-immunotherapy including CD20 monoclonal antibodies, and more recently targeted therapies including PI3 kinase inhibitors, the BCL-2 inhibitor, venetoclax, and Bruton's tyrosine kinase (BTK) inhibitors. This shift in treatment paradigm has improved survival, especially for patients not eligible for intensive chemotherapy. BTK expression and activity plays an essential role in B-cell receptor signaling, cellular homing, and adhesion.[3] Ibrutinib, acalabrutinib, and zanubrutinib are small molecule irreversible BTK inhibitors, binding to cysteine 481 of BTK, blocking autophosphorylation on tyrosine 223 and phosphorylation of downstream substrates including phospholipase C-g2 (PLCg2).

Clinical Trials: Ibrutinib is a first-in-class BTK inhibitor established in both the frontline and salvage therapy settings in CLL. Originally approved in relapsed/refractory (R/R) patients, ibrutinib was shown to be superior to ofatumumab in both progression free survival (PFS) and overall survival (OS).[4] More recently, the efficacy and safety of ibrutinib monotherapy in patients ≥ 65 years old with untreated CLL without del(17p) has been established in phase III trials. RESONATE-2 randomized 269 patients ≥ 65 year old with untreated CLL to receive ibrutinib or chlorambucil.[5] After a median follow-up of 5 years, ibrutinib therapy resulted in a significantly higher overall response rate (92% vs 37%; P<0.001) and significantly longer PFS (70% vs, 12%; P <0.001). The ECOG-ACRIN cancer research group showed that ibrutinib + rituximab was more effective than fludarabine + cyclophosphamide + rituximab (FCR) in patients ≤ 70 years old without del(17p).[6] From a recent follow-up of 48 months, the results continued to show sustained PFS and OS benefits of ibrutinib + rituximab. The second-generation BTK inhibitor acalabrutinib was developed to increase selectivity and decrease off-target effects. It was granted breakthrough designation in CLL based on the results of the ASCEND and ELEVATE-TN phase III trials. The ASCEND trial compared acalabrutinib monotherapy (n =155) to rituximab plus idelalisib (n=119) or bendamustine (n=36).[7] At a median follow-up of 16 months, patients treated with acalabrutinib had significantly prolonged PFS (median not reached vs. 16.5 months); representing a 69% risk reduction of disease progression or death. The ELEVATE-TN randomized 535 treatment-naïve patients to the combination of acalabrutinib + obinutuzumab, obinutuzumab + chlorambucil, or acalabrutinib monotherapy.[8] At a median follow-up of 28 months, the acalabrutinib + obinutuzumab led to a 90% risk reduction of disease progression or death compared with obinutuzumab + chlorambucil. When used as monotherapy, acalabrutinib also showed a significant benefit in PFS (HR, 0.20; 95% CI, 0.13-0.30; *P* <.0001). Zanubrutinib is the newest BTK inhibitor approved by the FDA for the treatment of mantle cell lymphoma (MCL), with a similar mechanism to ibrutinib and potentially fewer off-target effects. ALPINE is an ongoing phase II trial evaluating non-inferiority of zanubrutinib versus ibrutinib monotherapy in patients with R/R CLL.[9]

Safety: Given the average age of diagnosis is 70 years old, patients with CLL often have comorbidities and may be unfit for chemo-immunotherapy, necessitating novel treatments with limited side effects. Despite ibrutinib's efficacy, its off-target effects lead to increased rates of atrial fibrillation, hypertension, rash, and bleeding compared to second-generation inhibitors. New-onset atrial fibrillation was reported in up to 10% of patients treated with ibrutinib, with non-warfarin anticoagulation recommended in select patients. Additionally, new-onset or worsening hypertension (grade ≥3) is reported in 20% of patients, with peak hypertensive effects found 6 months post-initiation.[2-3,10] In comparison, the rate of atrial fibrillation for acalabrutinib is closer to 5%, and hypertension between 3-12%.[3] Serious bleeding events (grade ≥3 or central nervous system hemorrhage) were observed in 4% of patients on ibrutinib and 2% for acalabrutinib.[2-3] Retrospective analysis demonstrate that most patients who suffered major bleeding were also treated with an anti-coagulant and/or anti-platelet medication.[11] Of note, patients on warfarin were excluded in the trials. Patients on oral anticoagulation should be monitored for bleeding. Current guidelines recommend holding ibrutinib 3 days before and after minor surgery and 7 days before and after major surgery.[2] Similarly, acalabrutinib should be held for 3 days pre- and post- surgery. Due to these safety considerations, a Phase II study of patients transitioned to acalabrutinib from ibrutinib demonstrated tolerability and efficacy.[12] As real-world experience with acalabrutinib increases, higher rates of these adverse events of interest may be observed. In addition, results from ongoing head-to-head trials may better elucidate the potential differences in safety profiles. There are several class adverse effects of BTK inhibitors. Early lymphocytosis is an expected on-target effect of BTK inhibitors and is not considered a sign of progression.[2] Additionally, increased risk of opportunistic infections has been reported with all approved BTK inhibitors, including invasive fungal infections as well as *Pneumocystis jirovecii* pneumonia (PJP).[13] At this time, routine antimicrobial prophylaxis is not recommended.[2]

Bruton Tyrosine Kinase (BTK) Inhibitors in Chronic Lymphocytic Leukemia

Conclusions: BTK inhibitors are critical treatment options for frontline and R/R CLL patients. While exact differences in efficacy and toxicity profile are difficult to discern, ongoing head-to-head phase III trials versus ibrutinib will better inform treatment options for patients.

	Ibrutinib (Imbruvica)[14]	Acalabrutinib (Calquence)[15]	Zanubrutinib (Brukinsa)[16]
FDA indications in CLL	CLL with or without 17p deletion – treatment naïve or relapsed/refractory	CLL – treatment naïve or relapsed/ refractory	Not currently approved for CLL; approved for patients with MCL who received ≥1 prior therapy
Dose	420 mg taken orally once daily with or without food	100 mg orally every 12 hours with or without food	160 mg orally twice daily or 320 mg orally once daily with or without food
Dose Adjustments	Monitor for adverse effects in CrCl < 25 ml/min Dose adjust in Child –Pugh Class A and B Avoid use in Child-Pugh Class C	Monitor for adverse effects in CrCl < 30 ml/min Avoid in severe hepatic impairment	Monitor for adverse effects in CrCl < 30 ml/ min Dose modifications in severe hepatic impairment
Drug-drug interactions	3A4 Inhibitors: Strong: Avoid other than those below (if short course < 7 days may consider holding ibrutinib) Voriconazole: 140 mg PO daily Posaconazole: 70 mg PO daily Moderate: 280 mg PO daily	3A4 Inhibitors: Strong: Avoid Moderate: 100 mg PO daily 3A4 Inducers: 200 mg PO daily Gastric acid reducing agents: Avoid co-administration with proton pump inhibitors Stagger dosing with H2-receptor antagonists and antacids	3A4 Inhibitors: Strong: 80 mg PO daily Moderate: 80 mg PO twice daily 3A4 Inducers: AVOID concomitant use
Emetogenicity	Low	Minimal	Not categorized by NCCN
Adverse effects	• Cardiac arrhythmias* • Infections* (e.g. *Pneumocystis jirovecii* pneumonia (PJP) invasive fungal infections) • Hemorrhage* • Hypertension* • Tumor lysis syndrome* • Rash • Diarrhea	• Atrial fibrillation and flutter* • Serious opportunistic infections* • Hemorrhage* • Cytopenias* • Headache • Diarrhea • Increased weight • Hypertension	• Cardiac arrhythmias* • Hemorrhage* • Hold 3-7 days prior to and after major surgery • Cytopenias * • Rash • Bruising • Diarrhea • Upper respiratory tract infections
Mechanisms of resistance	Amplifies the the IL 4R - IL-4 Axis (not seen in other BTK inhibitors) Mutations in C481S in BTK and downstream target PLCg2	Mutations in C481S in BTK and downstream target PLCg2 Increased CD49d expression	Currently being studied

*Black Box Warning

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PRN ACTIVITIES AND ANNOUNCEMENTS

COVID-19

Along with other pharmacy organizations, ACCP is engaged in a call to action to recognize pharmacists as frontline care providers. See the joint statement and consider reaching out to your federal representatives.

2020 ACCP VIRTUAL POSTER SYMPOSIUM

Investigators in the field of clinical pharmacy and clinical pharmacology, will present findings during the ACCP Virtual Poster Symposium, May 25-31, 2020. Consider presenting your research on this innovative platform! Abstract submissions, for all except Research in Progress, are due by March 30, 2020. Research in Progress submission deadline is April 27, 2020. For more information: https://www.accp.com/abstracts/2020vps/

ANNUAL CONFERENCE

The 2020 ACCP Annual Meeting will take place on October 24-27 in Dallas, Texas. Registration is not open at this time. Abstract submissions (except Research-in-progress) deadline is June 15, 2020.

HEME/ONC PRN FOCUS SESSION

The Heme/Onc and Pharmaceutical Palliative Care PRN will be putting on the PRN Focus Session on the topic of opiate pain management in cancer patients and opiate use disorder mitigation strategies. The proposal is being reviewed by the Education Committee. More details to come closer to time.

PRN ELECTIONS

Look for details regarding nominations for PRN elections to come around late spring/ early summer! If you or other PRN members are interested in running for office, please do not hesitate to reach out to current or past officers for insight! PRN leadership is a great step towards greater organizational involvement!

FACEBOOK & TWITTER PAGEs

Please continue to send Katie, Don, and me articles and ideas you would like to see posted! If you have ideas for greater social media engagement we would especially enjoy hearing from you!

IDEAS FOR THE NEWSLETTER

Please submit any ideas you may have for improving the newsletter to the PRN leadership. if you would like to be featured in the summer edition, whether it be a member spotlight, or a clinical write-up, let us know!

THANK YOU!

The PRN leadership thanks everyone who has served on our various committees as well as our members who engages with the PRN on a regular basis!