Fall 2021 NEWSLETTER

Official Newsletter of the ACCP Hem/Onc PRN

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Thank you to our outgoing PRN officers for their hard work this year!

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GREETINGS FROM THE 2021-2022 CHAIR

Hello everyone, I hope you are all having a nice summer while continuing to stay safe amongst the ongoing COVID-19 pandemic.

Herein, you will find our biannual PRN newsletter that coincides with the ACCP Spring and Fall PRN reports. Our goal with this newsletter is to support the needs of our PRN, with drugs updates, articles on pertinent topics in hematology/oncology, and to highlight and showcase accomplishments and achievements of our PRN membership. Submissions for our newsletter may be made by clinicians, residents, fellows, or students. I hope that you will find the content in our newsletter interesting and meaningful to you as both a member of ACCP and of our Hem/Onc PRN.

A call for annual committee involvement will be going out at the beginning of October prior the Annual Meeting. If you are wanting to become more involved in the PRN, joining one of our several committees is a great place to start! Clinicians, students, residents, and fellows are all welcome.

ACCP recently announced the annual meeting this year will be held virtually again due to the ongoing COVID-19 pandemic. Some programming I would like to highlight at the upcoming meeting includes: Clinical Pharmacy Career Pathway Roundtable for students, residents, and fellows to learn more about different clinical specialties and practice settings, our Hem/Onc PRN Focus Session, our Hem/Onc PRN Business Meeting, and the BCOP Clinical Sessions. I hope to see you there (virtually)!

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American College of Clinical Pharmacy

Peripherally Acting Mu-Opioid Receptor Antagonists for Opioid-Induced Constipation in Patients with Cancer

By: Celina Hu, Pharm.D. Candidate Class of 2022, VCU College of Pharmacy, Richmond, VA
Mentor: Lisa Grate, Pharm.D., BCOP, BCPS, Heme/Onc/BMT Clinical Pharmacist at UC Health in Fairfield, OH

Constipation is a well-known adverse effect of opioid use. In patients with cancer, the use of opioids to treat cancer-related pain can cause constipation or worsen constipation that is present at baseline.[1] Currently, there is no consensus on the true prevalence of opioid-induced constipation (OIC) in patients with cancer, with estimates varying widely from 5-97% based on results from different studies. OIC may occur more frequently in patients with advanced or metastatic cancer as pain is most prevalent in this population, affecting 64% of patients with advanced cancer compared to 50.7% of patients with cancer at any stage.[2,3]

OIC is an important cause of morbidity and distress in patients with cancer.[4,5] The Rome IV criteria identify straining, hard stools, infrequent bowel movements (BMs), and the sensation of incomplete evacuation or blockage as potential symptoms of OIC.[6] Beyond this, OIC may also cause upper gastrointestinal (GI) symptoms, such as acid reflux, poor appetite, and nausea/vomiting.[4,7] A variety of complications may result, including intestinal obstruction or perforation, hemorrhoids, and urinary problems. In patients with cancer, OIC is associated with decreased quality of life, increased risk of hospitalizations and ED visits, and greater healthcare and societal costs.[2,7] OIC may also cause patients to reduce their opioid dose or discontinue opioid treatment, resulting in worsened pain control.[7]

Management of OIC is an important consideration when initiating opioid therapy. Non-pharmacologic methods for preventing OIC include improving toileting habits, maintaining hydration and adequate dietary fiber, and staying as physically active as possible. However, non-pharmacologic strategies may become less feasible as a patient's cancer progresses; moreover, there is a lack of evidence supporting the use of these methods in advanced cancer. Therefore, while non-pharmacologic measures may be helpful in some patients, they should be combined with conventional laxatives to effectively manage OIC. High quality evidence is lacking for the superiority of any individual laxative over others for treatment of OIC, but recent clinical guidelines from the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society for Medical Oncology (ESMO) favor the use of osmotic laxatives, primarily polyethylene glycol, and stimulant laxatives such as senna and bisacodyl.[4,7] While laxatives do target the symptoms of constipation, they are often incompletely effective for OIC because they do not counteract the constipating mechanism of opioids, which involves activation of mu-opioid receptors in the GI tract.[2] Activation of these mu-opioid receptors reduces propulsive intestinal motility, decreases mucosal secretions, increases water and electrolyte absorption, and increases anal sphincter tone, all contributing to constipation.[1,7] A survey of patients with OIC outside of the cancer setting found that 54% of patients receiving laxatives failed to achieve their desired treatment results half of the time.[2]

Peripherally acting mu-opioid receptor antagonists (PAMORAs) are a relatively new class of agents used for the treatment of OIC. PAMORAs directly reverse the constipating effects of opioids by competitively binding mu-opioid receptors in the GI tract. Due to their peripheral selectivity, PAMORAs theoretically should not interfere with opioid analgesia in the central nervous system (CNS), however these agents still carry a risk of precipitating opioid withdrawal and require monitoring.[1,2] The role of PAMORAs in treating OIC in cancer is still evolving, but recent clinical guidelines have addressed the use of these agents. The 2018 ESMO guideline on the management of constipation in advanced cancer states that PAMORAs may be useful after the failure of lifestyle modifications and laxatives.[4] The 2020 MASCC guideline more strongly recommends PAMORAs as a first-line treatment option in patients with OIC, with conventional and other laxatives such as lubiprostone used as second-line options after the failure of PAMORAs.[7]

Of the currently available PAMORAs in the US, only the SC formulation of methylnaltrexone (Relistor®) is FDA-approved for the treatment of OIC in patients with active cancer.[8] Other PAMORAs, including naldemedine (Symproic®), naloxegol (Movantik®), and the PO formulation of methylnaltrexone (Relistor®) are FDA-approved for the treatment of OIC in patients with chronic noncancer pain.[8-10] Lastly, alvimopan (Entereg®) is only FDA-approved for the short-term treatment of postoperative ileus in hospitalized patients.[11] Dosing and treatment considerations for methylnaltrexone, naldemedine, and naloxegol are listed in **Table 1**. Clinical trial evidence for these agents is summarized in **Table 2**.

Peripherally Acting Mu-Opioid Receptor Antagonists for Opioid-Induced Constipation in Patients with Cancer [Continued]

Methylnaltrexone (Relistor®)

Methylnaltrexone is a structural derivative of naltrexone with a quaternary N-methyl group, which prevents the drug from crossing the blood-brain barrier into the CNS.[1] The subcutaneous (SC) formulation is approved to treat OIC in "adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care." Both the SC and oral formulations are approved to treat OIC in "adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation."[8] The SC formulation of methylnaltrexone requires weight-based dosing. The oral formulation has a standard dose of 450 mg daily and should be taken on an empty stomach 30 minutes before breakfast. Both formulations require dose adjustment for renal and hepatic impairment. Unlike naldemedine and naloxegol, methylnaltrexone does not have any CYP450 drug-drug interactions. However, methylnaltrexone appears to be significantly more expensive than naldemedine and naloxegol based on average wholesale price (AWP).[12]

In two double-blind randomized controlled trials of SC methylnaltrexone 0.15-0.3 mg/kg, patients receiving methylnaltrexone were significantly more likely to achieve a bowel movement within four hours after receipt of the drug (without the use of rescue laxatives) than patients receiving placebo.[13,14] The study by Thomas et al. also found that patients on methylnaltrexone had a shorter median time to laxation and were more likely to report subjective improvement in bowel status and constipation distress. The frequency of adverse events was similar between groups, but abdominal pain, flatulence, and dizziness were more common in patients receiving methylnaltrexone. Additionally, there was little change in pain severity or opioid withdrawal symptoms over the course of the study, with scores being similar between groups. In the three-month open-label extension study following this trial, the most common adverse events observed were abdominal pain and nausea/vomiting.[14]

Naldemedine (Symproic®)

Naldemedine is a structural derivative of naltrexone with an additional polar side chain that reduces its penetration across the blood-brain barrier.[9] It is approved to treat OIC in "adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation." Naldemedine is an oral agent typically dosed at 0.2 mg daily. Unlike oral methylnaltrexone and naloxegol, naldemedine can be taken without regard to food. It does not require renal dose adjustment but should be avoided in severe hepatic impairment. Naldemedine interacts significantly with CYP3A4 inducers and inhibitors as well as P-gp inhibitors.[15]

The COMPOSE-4 and COMPOSE-5 trials studied naldemedine 0.2 mg daily in patients with OIC and cancer pain. COMPOSE-4 was a double-blind randomized controlled trial testing efficacy while COMPOSE-5 was a 3-month open-label extension study focusing on safety. In COMPOSE-4, significantly more patients responded to naldemedine than placebo by 2 weeks, with a shorter median time to spontaneous BM. In addition, significantly more patients on naldemedine reported subjective improvement in constipation symptoms and quality of life.[16] Significantly more patients receiving naldemedine experienced treatment-emergent adverse events (TEAEs) resulting in discontinuation, with diarrhea as the most common of these adverse events. In COMPOSE-5, 80.2% of patients on naldemedine experienced TEAEs, the most common of which was diarrhea. Twelve patients discontinued treatment, including three patients who discontinued due to diarrhea. In both studies, no instances of opioid withdrawal occurred and there was little change in pain severity, which was similar between groups.[17]

Peripherally Acting Mu-Opioid Receptor Antagonists for Opioid-Induced Constipation in Patients with Cancer [Continued]

Naloxegol (Movantik®)

Naloxegol is a pegylated derivative of naloxone that undergoes P-gp efflux across the blood-brain barrier, limiting its penetration into the CNS.[1] Like naldemedine, naloxegol is approved to treat OIC in adults with chronic non-cancer pain who are on a stable dose of opioids. Naloxegol should be taken orally on an empty stomach one hour before breakfast. The tablets may be crushed and mixed with water for administration to patients with difficulty swallowing or for NG tube administration. The standard dose is 25 mg once daily, however the dose may be reduced to 12.5 mg daily to improve tolerability. Naloxegol requires renal dose adjustment and should be avoided in severe hepatic impairment.[10] Naloxegol may cause abdominal pain, nausea, vomiting, diarrhea, and flatulence. There have been case reports of severe abdominal pain and diarrhea requiring hospitalization.[18] Naloxegol interacts significantly with CYP3A4 inhibitors and inducers and patients should avoid consuming grapefruit and grapefruit juice while taking this medication.[10]

The KYONAL study was a prospective, observational study conducted over one year that assessed the efficacy and safety of naloxegol 6.25-25 mg PO daily. Naloxegol was associated with a significant improvement in constipation-related quality of life and constipation symptoms over baseline and this improvement was sustained over the one-year duration of the study. However, there was no change in overall health-related quality of life. Response to treatment was defined as ≥ 3 spontaneous BMs/week and an increase of ≥ 1 spontaneous BM/week over baseline. Response was 71.4% at 15 days, 74.6% at 1 month, 76.2% at 3 months, 77% at 6 months, and 77.8% at 12 months. Adverse events were mostly mild in severity and GI in nature. Of the six patients who discontinued treatment due to adverse effects, all discontinued due to abdominal pain, diarrhea, or nausea.[19]

Alvimopan (Entereg®)

Alvimopan is indicated for short-term use of < 7 days to treat postoperative ileus in hospitalized patients. Alvimopan at a dose of 0.5 mg BID has been associated with an increased risk of cardiovascular events over 12 months, which may reduce its utility for chronic use.[20] Alvimopan has been studied at doses of 0.5 mg daily or BID in two phase III randomized controlled trials for the treatment of opioid-induced bowel dysfunction in patients with chronic non-cancer pain. Both studies showed that more patients on naloxegol achieved SBM response compared with patients on placebo. Over 12 weeks, neither study saw excess cardiovascular risk with alvimopan. [20,21] Alvimopan has not been studied in patients whose primary illness requiring opioids for pain control is active cancer.

Conclusion

The body of evidence supporting the use of PAMORAs for the treatment of OIC in patients with active cancer is growing. They may be promising options for patients in whom conventional laxatives have proven ineffective or incompletely effective. Compared to placebo, SC methylnaltrexone is associated with an increased number of rescue-free BMs within four hours of the drug.[13,14] Naldemedine and naloxegol are associated with an increased number of spontaneous BMs per week.[16,17,19] All three agents are associated with subjective improvements in constipation symptoms and quality of life. None of these agents are associated with changes in pain score or symptoms of opioid withdrawal, suggesting that they do not interfere significantly with opioid analgesia in the CNS. All three agents are associated with a higher rate of GI adverse effects, such as abdominal pain, flatulence, and nausea/vomiting, when compared to placebo.[13,14,17,19] These adverse effects are mostly mild to moderate in severity, however they may be more severe with naloxegol.19 More research is needed to define the appropriate place in therapy for PAMORAs and to examine their long-term efficacy and safety when taken chronically for months to years.

Table 1 and 2 on subsequent pages.

Table 1. Characteristics of PAMORAs used for OIC

Agent	Methylnaltrexone SC (Relistor®)	Methylnaltrexone PO (Relistor®)	Naldemedine (Symproic®)	Naloxegol (Movantik®)
FDA indication	OIC in palliative care of advanced illness, including active cancer	OIC in chronic noncancer pain		
ROA	SC injection, prefilled syringe or single-dose vial	PO on empty stomach	PO without regard to food	PO on empty stomach; may be crushed and mixed with water
Dosing	Weight-based; 1 dose every other day, may increase to once daily < 38 kg: 0.15 mg/kg 38 to < 62 kg: 8 mg 61-114 kg: 12 mg > 114 kg: 0.15 mg/kg	450 mg daily	0.2 mg daily	25 mg daily, may reduce to 12.5 mg daily for tolerability
Renal/hepatic disease	CrCl < 60 mL/min: halve dose Severe hepatic impairment: consider halving dose	CrCl < 60 mL/min: 150 mg daily Moderate-severe hepatic impairment: 150 mg daily	No renal dose adjustment Severe hepatic impairment: avoid	CrCl < 60 mL/min: 12.5 mg daily Severe hepatic impairment: avoid
Contraindications	GI obstruction or risk for GI obstruction			
AEs	Abdominal pain, flatulence, nausea, vomiting		Abdominal pain, N/V/D, gastroenteritis	Abdominal pain, N/V/D, flatulence; abdominal pain and diarrhea may be severe
DDIs	Avoid other opioid antagonists (increased risk of withdrawal)		Avoid strong CYP3A4 inducers Caution with CYP3A4 and P-gp inhibitors	Avoid grapefruit Avoid strong CYP3A4 inhibitors and inducers Reduce to 12.5 mg daily with moderate CYP3A4 inhibitors
Cost (AWP)	$161.42 per 8 or 12 mg tablet – $2,421 per month (for a 70 kg patient)	$26.90 per 150 mg tablet – $2,421 per month	$15.84 per tablet – $475 per month	$14.64 per tablet – $439 per month

Relistor (methylnaltrexone) [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals, July 2016.
Symproic (naldemedine) [package insert]. Florham Park, NJ: Shinogi Inc., March 2017.
Movantik (naloxegol) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, Feb. 2018.
Entereg (alvimopan) [package insert]. Research Triangle Park, NC: GlaxoSmithKline, May 2008.
Methylnaltrexone [monograph]. In: Lexicomp Online [database online]. Hudson, OH: Lexicomp. Accessed July 28, 2021.

Table 2. Summary of evidence for PAMORAs in the treatment of OIC in patients with active cancer

Study	Design	Population	Intervention	Primary Endpoint(s)	Results
Slatkin et al. 2009	Double-blind single-dose RCT	N = 154 Adults with OIC and advanced illness	Single dose of SC methylnaltrexone SC 0.15 mg/kg or 0.3 mg/kg vs. placebo Usual laxatives permitted except within 4 h before/after dose	Proportion of patients with rescue-free laxation within 4 h after dose	More patients on either dose of methylnaltrexone responded within 4 h after dose vs. placebo (62% on 0.15 mg/kg vs. 58% on 0.3 mg/kg vs. 14% on placebo, $p < 0.0001$ for each dose vs. placebo)
Thomas et al. 2008	Phase III double-blind RCT over 2 weeks, followed by 3-month open label extension study	RCT: N = 133 Open-label extension: N =89 Adults with OIC and advanced illness, including 78 with terminal cancer	RCT: methylnaltrexone SC 0.15 mg/kg every other day (could escalate to 0.3 mg/kg in week 2) vs. placebo Open-label extension: methylnaltrexone SC up to 0.3 mg/kg daily PRN Usual laxatives permitted except within 4 h before/after dose	Proportion of patients with rescue-free laxation (BM without use of rescue laxatives within 4 h before or after intervention) within 4 h after first dose Proportion of patients with rescue-free laxation within 4 h after ≥ 2 of first 4 doses	RCT: more patients on methylnaltrexone responded within 4 h after first dose vs. placebo (48% vs. 15%, $p < 0.001$) and after ≥ 2 of the first 4 doses vs. placebo (52% vs. 8%, $p < 0.001$) Median time to laxation after first dose: 6.3 h with methylnaltrexone vs. > 48 h with placebo ($p < 0.001$) Open-label extension: Response rate 45%, 58%, and 57% with methylnaltrexone vs. 48%, 48%, and 52% at months 1, 2, and 3, respectively
Katakami et al. 2017 (COMPOSE)	Phase III double-blind RCT over 2 weeks (COMPOSE-4), followed by 3-month open-label extension study (COMPOSE-5)	COMPOSE-4: N = 193 COMPOSE-5: N = 131 Adults with OIC and active cancer	COMPOSE-4: naldemedine 0.2 mg PO daily vs. placebo Usual laxatives permitted except within 24 h before/after first dose COMPOSE-5: naldemedine 0.2 mg PO daily	COMPOSE-4: proportion of patients with spontaneous BM response (≥ 3 spontaneous BMs per week AND increase of ≥ 1 spontaneous BM per week over baseline) COMPOSE-5: safety	COMPOSE-4: more patients on naldemedine responded by 2 weeks vs. placebo (71.1% vs. 34.4%, $p < 0.0001$) COMPOSE-5: 80.2% of patients experienced TEAEs, most commonly diarrhea (18.3%) 4 (3.1%) patients reduced dose to 0.1 mg daily and 12 (9.2%) patients discontinued treatment, of which 3 were due to diarrhea
Cobo Dols et al. 2020 (KYONAL)	Prospective observational study over 1 year	N = 126 Adults with OIC and active cancer after failure of laxatives Adults with cancer and OIC after failure of laxatives	Naloxegol 6.25, 12.5, or 25 mg PO daily Usual and rescue laxatives permitted	Impact on constipation-related quality of life via Patient Assessment of Constipation Quality of Life (PAC-QOL)	Significant improvement in PAC-QOL score from baseline sustained throughout the duration of the study ($p < 0.0001$ at all time points)

Peripherally Acting Mu-Opioid Receptor Antagonists for Opioid-Induced Constipation in Patients with Cancer [Continued]

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Tripling Down with Targeted Therapy: Exploring Three Generations of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia

By: Anna Sandler, PharmD Candidate Class of 2023, Rosalind Franklin University of Medicine and Science, Chicago, IL
Mentor: Marco Martino , Pharm.D., MBA, BCOP, BCPS, Medical Science Liaison at EMD Serono, Inc.

Introduction

Chronic myeloid leukemia (CML) is a devastating disease characterized by the uncontrolled production and proliferation of granulocytes, accounting for 15-20% of leukemias in adults.[1] The invasion of the bone marrow by these cells can result in fatigue, weight loss, and abdominal pain due to splenomegaly. CML is notorious for running a multiphasic course in which the chronic phase (CP) most commonly presents at the time of diagnosis and is easier to treat. However, when differentiation becomes impaired and the disease progresses to the accelerated phase (AP), it is more difficult to tame. The blast-crisis phase (BP), as its name suggests, is marked by a greater concentration of blood or bone marrow blasts (immature blood cells) and is the most aggressive form of CML.

Although disease progression is a major concern, the five-year survival rate has more than tripled from the mid -1970s to 2017 from 22% to 70.6% respectively with the advent of oral small molecule inhibitors directed against the underlying roots of the disease: the BCR-ABL tyrosine kinase.[2]

Uncontrolled growth begins with dysregulated intracellular signaling, and phosphorylation by protein kinases plays a vital role in the transmission of growth signals. The fusion of the BCR sequence from chromosome 22 upstream of the ABL gene on chromosome 9 produces the Philadelphia chromosome (Ph+) and a constitutively active tyrosine kinase termed BCR-ABL, powering granulocytes into unregulated growth in CML.

Historical treatments of CML included allogeneic hematopoietic cell transplantations, but those resulted in increased toxicity and early mortality.[3] The introduction of oral tyrosine kinase inhibitors (TKIs) revolutionized the treatment approach of CML, providing better long-term control.

Imatinib

Imatinib (GLEEVEC®) was the first TKI approved by the FDA in 2001 for the treatment of newly diagnosed Ph+ CML or Ph+ CML in AP, BP, or CP if interferon alfa therapy fails. Among its various pharmacological activities, imatinib targets the constitutively active BCR-ABL kinase that fuels CML.

One of the driving forces behind the drug's approval for CML stems from a phase 1 dose-escalating study in which 53 of the 54 patients treated under an intention to treat protocol with daily doses of 300 mg or more achieved complete hematologic responses four weeks after initiating imatinib in all but one patient.[4] A complete hematologic response was defined as a reduction in the white cell count to less than 10,000/mm3 and a reduction in the platelet count to less than 450,000/mm3. Both counts had to be maintained for at least four weeks.

The phase 1 study also evaluated cytogenetic responses (CRs) based on the percentage of bone marrow Ph+ cells. The absence of Ph+ cells constituted a complete CR, while the presence of 1-35% cells represented a partial response, and the presence of 36-65% of Ph+ cells was deemed a minor CR. Major (complete or partial responses) or minor CRs were exhibited by 29/54 (54%) of patients treated with 300 mg or more, and 7/54 (13%) of this cohort achieved complete cytogenetic remissions.[4] Obrien and colleagues further investigated imatinib in the IRIS study, demonstrating its superiority to interferon alfa plus cytarabine with respect to complete CRs (76.2% [95% confidence interval (CI) 29.3-40.0] versus (vs.) 14.5% [95% CI 10.5-18.5]; P< 0.001). It is also worth noting that imatinib resulted in significantly higher rates of freedom from progression to AP or BP (96.7% vs. 91.5%; P<0.001). The most common adverse effects included nausea, myalgias, edema/fluid retention and diarrhea but were mostly mild or moderate even at higher doses.[5]

Tyrosine Kinase Inhibitors in CML [Continued]

Imatinib (continued)

In the treatment of Ph+ CML, imatinib is dosed 400 mg once daily and can be increased to 600 mg if there is progression, usually defined as lack of a hematologic response after 3 months, lack of a CR after 6 to 12 months, or loss of previous hematologic or cytogenetic responses.[6-7] Monitoring parameters include CBCs that taper in frequency, baseline, and monthly liver functions tests (LFTs), as well as signs of heart failure (HF), bone marrow suppression, and GI toxicity (e.g., irritation or hemorrhage), the latter of which can be minimized with food and water. Imatinib is both a major substrate of CYP3A4 and a minor inhibitor, warranting clinical decision making when multiple interacting medications are at play.

Nilotinib

Despite imatinib's success, resistance via genetic and metabolic mechanisms became a concern, giving rise to second generation TKIs such as nilotinib (TASIGNA®), a more potent and selective TKI for BCR-ABL.[8]

Nilotinib was approved in 2007 for the treatment of AP- or CP-CML resistant to imatinib, or in patients intolerant to imatinib.[9] However, second generation TKIs are first line treatment options for high-risk CP-CML due to the likelihood of AP or BP progression. The on-boarding of a second generation TKI also increases the likelihood of eventually discontinuing treatment if certain criteria are met.[3] Nilotinib's efficacy is supported by a 2010 phase III, multi-center randomized control trial (RCT), evaluating rates of achieving 0.1% or less peripheral blood BCR-ABL transcript levels at 12-months, termed a major molecular response (MMR). This RCT showed 12-month major molecular responses (MMRs) in patients receiving 300 mg twice daily (44%) or 400 mg twice daily (43%) to be nearly twice as high compared to those taking imatinib 400 mg once daily (22%) ($P<0.001$ for both comparisons). Analysis of the secondary endpoint revealed significantly greater 12-month complete CRs in patients receiving the 300 mg (80%) or 400 mg (78%) twice daily doses of nilotinib compared with those randomized to imatinib (65%) ($P< 0.001$ for both comparisons).[10] Perhaps even more noteworthy is that there were significantly less AP or BP progressive events in both nilotinib cohorts compared to imatinib at 24 months, which had not been previously demonstrated even at 800 mg daily doses of imatinib.

Nilotinib is dosed 400 mg twice daily in AP-Ph+ CML and 300 mg twice daily in CP-Ph+ CML. but can be increased to 400 mg twice daily in resistant CP-Ph+ CML or if there if intolerance to prior treatments.[11] Dosing guidelines should be consulted in the context of hepatic impairment at baseline and/or during treatment. The drug should be taken on an empty stomach and separated from food two hours before and one hour after. Although all TKIs have reported cardiac toxicities, nilotinib has a black box warning (BBW) of prolonging the QT interval and is contraindicated in hypokalemia, hypomagnesemia and long QT syndrome.[11-13] Additional monitoring parameters include signs and symptoms of hepatotoxicity, fluid retention, ischemic heart disease and arterial occlusive events (AOEs). Like imatinib, nilotinib is a CYP3A4 substrate and inhibitor and should not be used together with strong CYP3A4 inhibitors.

Despite success with second generation TKIs, the environmental stress second generation TKIs placed on Ph+ cells spurred further genetic adaptations in favor of cell survival and the need to further drug development.

Ponatinib

All first and second generation TKIs are ineffective against the T315I BCR-ABL mutation, which effectively blocks TKI binding via steric hindrance.[14] In fact, 20% of patients resistant to imatinib possess this mutation. Ponatinib (ICLUSIG®) can overcome this molecular resistance. In the phase II PACE study, Cortes et al. revealed major cytogenic responses (MCyRs) and MMRs at the 5-year mark. A total of 159 (60%) and 64 (24%) CP-CML patients achieved MCyRs and MMRs respectively at any time during the trial. The durability of ponatinib is further evidenced by 5-year Kaplan-Meier estimates of progression free survival and overall survival, which were 53% and 73% respectively. The PACE trial was a major player in driving the 2012 approval of ponatinib as a second line option for Ph+ CP- CML patients harboring the T315I mutation and in those resistant or intolerant to at least two prior TKIs.[15] The efficacy of ponatinib in comparison to imatinib is yet to be elucidated due to early termination of the 2012 EPIC trial, evaluating ponatinib and imatinib in newly diagnosed CML over concerns regarding high incidences of serious AEOs in patients taking ponatinib (10 (6%) ponatinib patients vs. 1 (1%) imatinib patient; $P=0.010$).[16] However, ponatinib may make a comeback with more personalized approaches as some studies have suggested incorporating anti-platelet prophylaxis into the regimen and the fact that that 10 (91%) of the 11 total ponatinib patients who experienced an AEO in the trial had one or more cardiovascular risk factor or a history of cardiovascular disease.[16,17]

Tyrosine Kinase Inhibitors in CML [Continued]

Ponatinib [Continued]

Ponatinib is dosed starting at 45 mg once daily, with guided reductions based on BCR-ABL levels.[18] Dosing guidelines should be consulted in the context of baseline hepatic impairment and hepatotoxicity during treatment. Ponatinib carries a BBW for AEOs, serious HF, hepatotoxicity, and venous thromboembolic events. The TKI is also a CYP3A4 substrate and should be carefully evaluated when combining with CYP3A4 inhibitors or inducers.

Conclusion

The success of BCR-ABL TKIs in CML illustrates the impact of targeted cancer therapy but is just one piece of the puzzle. Novel TKIs inhibiting the pathogenesis of other cancers have emerged on the market. For instance, acalabrutinib (CALQUENSA®) approved in 2017 is a selective inhibitor of Bruton's tyrosine kinase, an essential player of the B-cell antigen receptor signaling cascade underlying the disease process of lymphocytic leukemia.

TKIs have demonstrated the impact of small molecule inhibitors on individualizing cancer therapy and the value of better comprehending the molecular biology of cancer.

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Review of Biosimilars for the Oncology Pharmacist

By: Paul Christopher Parish, Pharm.D. Candidate Class of 2022, UNC Eshelman College of Pharmacy, Chapel Hill, NC
Mentor: Matthew Sugidono, Pharm.D., Lead Clinical Scientist at Genentech in San Francisco, CA

As of July 2021, seventeen biosimilar products indicated for oncology-related treatment or supportive care have been approved by the Food and Drug Administration (FDA), half of which were approved since the beginning of 2019.[1] With this recent acceleration in biosimilar approvals, it is essential for oncology pharmacists to understand the process by which biosimilars are approved, the relationship between biosimilars and their reference products, and the current challenges facing the widespread utilization of biosimilars.

Biosimilar, Generic, and Interchangeable

The category of *biosimilar* or *biosimilarity* was first created within the Biologics Price Competition and Innovation (BCPI) Act of 2009 as an expedited approval pathway for biological products that are similar to an existing (or *reference*) biologic.[2] For a product to be considered biosimilar, it must be "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and there must be "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product".[2–4] Importantly, the evidence required for regulatory approval of a biosimilar differs from generic small molecules, as the structural complexity of biologics and the manufacturing modalities required for their synthesis make it unfeasible to demonstrate the same degree of similarity that must be proven for generics.[3] Instead, a "totality of evidence" presented by a manufacturer of a biosimilar to the FDA, including a combination of *in vitro* and *in vivo* studies, is considered in the review of a biosimilar product.[3,5] Analytical studies, usually involving structural characterization techniques and *in vitro* activity assays, confirm the molecular similarity of the reference product and the biosimilar. Animal studies are performed to ensure that the safety profile of the biosimilar product is similar to the reference product in a living organism. Once these assessments have been made, the biosimilar is tested in human subjects. These clinical studies involve efficacy, safety and immunogenicity, pharmacokinetic, and pharmacodynamic assessments of the biosimilar.[6] For example, Ruxience (rituximab-pvvr), a biosimilar of rituximab, was approved based on a phase III randomized, controlled trial showing no clinically meaningful differences in safety and efficacy to the reference product, Rituxan (rituximab) in first-line treatment of patients with CD20-positive low-tumor burden follicular lymphoma.[7]

Biosimilar products that meet additional requirements outlined by the BCPI Act can be considered for "interchangeability". Interchangeable products can be freely substituted for the reference product without prescriber approval, dependent on state law. The FDA requires that manufacturers perform *switching studies* that demonstrate noninferior clinical outcomes in patients who switch between the reference and biosimilar products in order to prove interchangeability.[8,9] Currently, no biosimilar products have been deemed interchangeable by the FDA, meaning that all biosimilar products currently available must be specifically prescribed in order to be dispensed.[8]

Extrapolation: How Biosimilars Get Their Indications

There are several factors that determine the degree of overlap in FDA-approved indications between a reference product and a biosimilar. The FDA allows for biosimilars to have extrapolated indications beyond the populations and indications in which they were initially studied if there is sufficient "scientific justification", which includes potential pharmacokinetic and pharmacodynamic features of the medication in the populations of interest, mechanism of action in treating the proposed indication, and "any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought".[6,9–11] For example, all FDA-approved biosimilars of filgrastim were granted an identical list of indications as the reference product, Neupogen, when initially approved, even though they were not specifically studied for each of the indications they were granted.[10,12–14]

Review of Biosimilars [Continued]

Exclusivity rights also play a role in the FDA's decisions surrounding labeled indications. To carry our previous example forward, Neupogen (filgrastim) was granted orphan drug designation in 2015 for its indication in treating radiation-induced myelosuppression following a radiological/nuclear incident.[15] No filgrastim biosimilar shares this indication due to this unexpired orphan drug exclusivity. Other oncology reference products, including Rituxan (rituximab) and Avastin (bevacizumab), also have unique indications that their biosimilar competitors lack due to exclusivity rights.[16,17]

Labeling and Naming of Biosimilars

The current naming convention for biosimilars is based on a FDA guidance recommendation released in 2017.[18] Each biosimilar contains two parts– a core name (based on the reference or originator product's name) and a suffix. This suffix must be composed of four lowercase letters (three of which are unique) and must be devoid of meaning. Biosimilars released prior to the release of this guidance in 2017 were not required to adhere to these stipulations (ex. Filgrastim-sndz, manufacturer Sandoz). While this naming convention does provide needed standardization to nomenclature within the biosimilar marketplace, clinicians must exercise caution when prescribing and dispensing these products, as the suffixes are all composed of random letters and may be easily confused (ex. Rituximab-arrx vs. pvvr vs. abbs).

Appropriate labeling of biosimilars is complicated by the fact that indications for biosimilars are most frequently extrapolated based on similarity to the reference product. As a result, the FDA recommends that all data regarding clinical efficacy, potential toxicities, and other drug information contained in the medication labeling should be derived from the reference product of a biosimilar unless "necessary to inform safe and effective use by a health care provider, including administration, preparation, storage, or safety information".[19] Therefore, most clinical efficacy data found in the labeling of biosimilars is derived from the clinical studies for the biosimilar's reference product, while several key operational recommendations are biosimilar-specific.[8,11] For example, Rituxan's package insert states that "Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature [after refrigeration for 24 hours]".[20] In contrast, the package insert for Ruxience, the aforementioned rituximab biosimilar, states that administration should be completed within 8 hours of removal from refrigeration.[21] It is essential that the appropriate biosimilar package insert be consulted for potential operational differences as highlighted in this example regarding administration and storage.

Barriers to Widespread Biosimilar Use in Oncology

Barriers that hinder the widespread adoption of biosimilars in clinical practice generally fall into two broad categories: fiscal/insurance coverage issues and concerns about the safety and efficacy of biosimilars. Regarding financial barriers, a recent study of US commercial health plans showed that biosimilars were granted preferred coverage in only 14% of coverage decisions, and 33% of coverage decisions for biosimilars were granted nonpreferred status.[22] Additionally, the cost of biosimilar development vastly exceeds the cost of development of generic small molecule medications. The cost savings from switching to a biosimilar, typically estimated between 15% and 35%, will therefore be more modest than cost savings seen from generic medications, which can exceed 80%.[23,24] As a result, it is estimated that biosimilars will result in an estimated 2.8% in direct cost savings in biologic sales in the US between 2017 and 2026, with only approximately 23% of those cost savings being derived from oncology indications.[11,25] Therefore, the hope of substantial cost savings from the entrance of biosimilars onto the marketplace will be dependent on the competitive landscape, costs of the reference and biosimilar products, and sales.

Review of Biosimilars [Continued]

Studies have also shown that prescribers have varying levels of concern about the safety and efficacy of biosimilar products. A recent meta-analysis evaluated provider perceptions and knowledge about biosimilars and identified several primary areas of concern, including extrapolated indications and potential immunogenicity of biosimilar products. Additionally, prescribers were more hesitant about switching patients from a reference product to a biosimilar than starting a therapy-naïve patient on a biosimilar.[26] Together, these data suggest that interchangeable products approved in the future will likely have to overcome another barrier to be used widely: prescriber perceptions about the appropriateness of biosimilar therapy.

Conclusion

Biosimilars provide a unique opportunity for oncology pharmacists to be involved with patient and provider education, especially as the number of biosimilar products available for oncology indications continues to rapidly increase. While there are currently several limiting factors to the development and uptake of biosimilars, including biologic patents, financial concerns, and patient/provider hesitancy, the regulatory and clinical landscape continues to develop in the US. Oncology pharmacists can play an instrumental role in addressing confusion around biosimilars and participate in shaping both institutional and national policies that govern biosimilar utilization.

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Review of Biosimilars [Continued]

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Highlighting the Differences in Intravenous vs Orally Administered Drugs: Inqovi® and Onureg®

By: Linda Allworth, Pharm.D. Candidate Class of 2023, UNC Eshelman College of Pharmacy, Chapel Hill, NC
Mentor: Grace Hwang, Pharm.D. , Hematology/Oncology Clinical Pharmacist at Baylor St. Luke's Medical Center

Last year, the FDA approved Onureg® (azacitidine) and Inqovi® (decitabine and cedazuridine). The approval of these tablets was significant because both drugs were previously only available as intravenous (IV) or subcutaneous (SQ) formulations. The convenience of tablets is impactful for patients as it can increase overall quality of life and reduce their need to go to an infusion clinic on a daily basis. However, it is important to keep in mind that various dosage forms may not always be interchangeable. The ability to substitute one dosage form for another depends on how each drug has been studied. In this article we will highlight the studies that led to the FDA approval of Onureg® and Inqovi® and compare the approved indications and bioavailability.

Onureg® has been studied in a phase 3 randomized double-blind placebo-controlled trial as maintenance therapy for acute myeloid leukemia (AML) patients in remission with or without complete blood cell count recovery after intensive chemotherapy. Patients included in the study were at least 55 years of age. Patients were excluded if they were considered potential candidates for hematopoietic stem cell transplant (HSCT). Patients were randomized to receive Onureg® 300 mg or a placebo once daily for the first 14 days of a 28-day cycle. It was concluded that Onureg® maintenance therapy resulted in significantly longer overall survival (24.7 months vs. 14.8 months; $P<0.001$) and relapse free survival (10.2 months vs. 4.8 months, $P<0.001$) when compared to placebo.[1]

The package insert contains a warning to not substitute Onureg® for the other dosage forms, since the drugs are not bioequivalent for two reasons. First, since Onureg® was not directly compared with intravenous or subcutaneous azacitidine, the different dosage forms cannot have the same indication. As studied, Onureg® is only indicated for maintenance therapy of AML patients in complete remission while IV/SQ azacitidine is indicated for the treatment of MDS as well as AML. Second, the oral bioavailability of azacitidine is limited due to rapid inactivation by cytidine deaminase (CDA) in the gastrointestinal (GI) tract and liver. High oral doses of azacitidine (up to 600 mg) are required to achieve modest systemic exposure (maximum 20% bioavailability) but are associated with significant GI toxicity (grade 3/4 diarrhea in 12% of patients) and high variability in systemic exposure.[2] Onureg® 300 mg once daily has a similar side-effect profile as injectable azacitidine, with nausea, vomiting, and diarrhea reported most commonly and decreasing in frequency after the first two cycles of treatment.[1]

Inqovi® was studied in a phase 2 randomized crossover study that was designed to compare the systemic decitabine exposure, pharmacodynamics, and safety of the combined tablet to the intravenous dosage form.[3] The oral bioavailability of decitabine is also limited, similar to azacitidine; however, cedazuridine is a CDA inhibitor that has been found to safely and effectively increase oral decitabine exposure.[4] The patient population included adults with intermediate or high-risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML). Patients were randomized to receive either 35 mg of decitabine and 100 mg of cedazuridine orally or 20 mg/m^2 of intravenous decitabine daily for 5 days. After cycle 1, patients received the other dosage form for cycle 2, and everyone received the oral dosage form for cycle 3 and beyond. This design was studied in a dose confirmation and fixed dose cohort. The dose confirmation cohort was studied first and received the 35 mg of decitabine and 100 mg cedazuridine as separate pills. Once that dose was confirmed to have comparable systemic exposure to 20 mg/m^2 decitabine, the fixed dose cohort received a single tablet containing decitabine and cedazuridine together. This study concluded that systemic decitabine exposure, pharmacodynamics, and safety are similar for oral decitabine/cedazuridine and intravenous decitabine.[3]

Highlighting the Differences in IV vs PO Drugs: Inqovi® and Onureg® [Continued]

Since Inqovi® was studied in comparison with decitabine, both the oral and IV dosage forms are indicated for the treatment of adults with myelodysplastic syndrome. Notably, approximately half of the patients that were transfusion dependent at baseline became transfusion independent while taking Inqovi®. Given that gastrointestinal adverse events were reported similarly between the IV and oral dosage form groups, there is no indication of additional gastrointestinal toxicity with the oral dosage form.[3] Overall, Inqovi® presents as an equally effective alternate therapy for patients who would prefer not to receive intravenous decitabine.

While the approval of new tablets will certainly increase the quality of life for many patients, it is important to keep in mind which dosage forms are truly interchangeable. Labeled indications are dependent on clinical trial design. As discussed here with Inqovi® and Onureg®, it is important to investigate these studies and to understand the intricacies of each new drug. Future studies also promise innovative approaches to therapy. Injectable azacitidine in combination with venetoclax has been shown to increase overall survival (14.7 months vs. 9.6 months, P<0.001) and increase the incidence of remission (66.4% vs. 28.3%; P<0.001) when compared to azacitidine alone in previously untreated AML patients.[5] Currently, studies are planned to assess the potential therapy of Onureg® or Inqovi® in combination with venetoclax in setting of the newly diagnosed and relapsed/refractory AML, respectively. The results of these studies will bring further insight into the use of Onureg® and Inqovi® and will undoubtedly impact the practice of AML treatment.

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What's in the Tea?: Herbal Supplement Drug Interactions Commonly Seen in the Oncology Setting

By: Mary Vogel, Pharm.D. Candidate Class of 2022, University of Maryland School of Pharmacy, Baltimore, MD
Mentor: Laura Cannon, Pharm.D., MPH, BCOP, Clinical Assistant Professor at the University of Texas at Austin College of Pharmacy and Clinical Pharmacist at Livestrong Cancer Institutes, Austin, TX

Questions regarding the use of herbal supplements with concurrent chemotherapy regimens are not uncommon for pharmacists, and often these scenarios present a challenge due to ambiguity of herbal supplements' effectiveness and the potential for drug-drug interactions. In a comprehensive national study, 12% of participants with a history of cancer reported use of herbal supplements.[1] Most importantly, almost 4% of patients did not disclose their use of herbal supplements to their physician.[1] Herbal supplements are products that are derived from plants and/or their oils, seeds, berries, flowers, or roots.[2] The US Food and Drug Administration (FDA) does not have the authority to review dietary supplement products for safety and efficacy prior to marketing, adding more uncertainty to their use. The clinical effects of supplements are often difficult to predict due to the lack of human data and the inability to standardize dosing between different product forms and manufacturers.[3] Similarly, the potencies of herbal supplements are influenced by the plant parts used, harvesting and processing methods, and varying amounts of active compounds that are absorbed into the body.[3] The use of dietary supplements, specifically herbal supplements, in cancer patients is important to be aware of as they have potential to interact with common cancer treatments. When asked about current medications, patients may not report herbal supplements or understand their potential to interact with their cancer treatment.

While there are numerous supplements available, some common herbal supplements that patients and healthcare teams may inquire about in the cancer treatment setting, either due to their potential anti-cancer effects or to alleviate side effects of treatment, include the following:

- **Turmeric**. Used in traditional Chinese and Indian medicine, it has been used for its anti-inflammatory, neuroprotective, and cancer-preventative effects.[4] Curcumin, the active compound derived from turmeric, gives the supplement its classic yellow color.[4] In laboratory studies, turmeric has been found to induce apoptosis in cancer cells and may inhibit angiogenesis.[5,6] Importantly, turmeric has very low oral bioavailability and is often formulated with piperine, a major component of black pepper that inhibits hepatic and intestinal glucuronidation of turmeric.[7] Other ways to improve oral bioavailability of turmeric include administration with a fatty meal or liposomal formulations.[4] Turmeric is generally well tolerated and side effects are mainly gastrointestinal, including constipation, flatulence, and yellow hard stools.[8] The most notable drug-drug interactions arise because turmeric inhibits CYP1A1, 1A2, 3A4, and P-glycoprotein.[4,8] Additionally, turmeric's antioxidant effects interfere with alkylating agents, topoisomerase inhibitors, and antitumor antibiotics.[4]

- **Ginseng**. Ginseng encompasses 13 different species, but the term 'ginseng' is typically associated with the species Panax ginseng, a slow-growing deciduous plant that grows in Korea, northeastern China, and far-eastern Siberia. Panax ginseng has been used as a calming agent in traditional Chinese medicine to resist physiological and psychological stress. Patients take ginseng to assist with cancer-related fatigue, to improve athletic performance, strength and stamina and as an immunostimulant.[9] Most notably, ginseng has been investigated for its anti-cancer potential as well and its active constituents have shown antiproliferative effects in vitro.[10] Insomnia, tachycardia, and nervousness are common side effects, and use of ginseng has also been associated with rare side effects such as anaphylaxis, arrhythmia, ischemia, and Stevens-Johnson Syndrome. Important drug-drug interactions may arise due to ginseng's induction of CYP3A4, which may increase the clearance of some drugs. Additionally, use of ginseng with the tyrosine kinase inhibitor imatinib may increase the risk of hepatotoxicity.[9,10]

Herbal Supplement Drug Interactions in Oncology [Continued]

- **Astragalus**. Astragalus is a genus of flowering plants used for centuries in traditional Chinese medicine to help the body resist physiological and psychological stress.[11] Astragalus may be used in oncology patients to alleviate chemotherapy-induced nausea and vomiting, to strengthen the immune system, to increase stamina and strength, to reduce cancer-related fatigue, and as an anti-cancer agent. Astragalus is typically administered as the dried root, liquid extract, or through intravenous formulations and its use is associated with common side effects of malaise, headache, hypotension, or fatigue.[11,12] Astragalus may interfere with the effectiveness of cyclophosphamide therapy and has been found to affect the pharmacokinetics of gemcitabine in animal models.[11,13] Additionally, astragalus can inhibit P-glycoprotein, which can increase the cytotoxicity of chemotherapy drugs such as doxorubicin, etoposide, and vincristine.[14] Antioxidant and estrogenic properties may interfere with certain hormonal therapies and chemotherapies, respectively.[12]
- **Green Tea**. Green tea is a beverage made from unfermented tea leaves. Green tea extract is marketed as a dietary supplement to regulate blood sugar, cholesterol, blood pressure, and for weight loss and cancer prevention. The active components of green tea include EGCG, or epigallocatechin-3-gallate, caffeine, and theanine.[15] Green tea extracts have been used for cancer prevention in patients with oral pre-malignant lesions and in high risk liver and colorectal patients, and has been reported to produce beneficial responses in patients with chronic lymphocytic leukemia.[16-19] Common side effects associated with its use include bloating, dyspepsia, flatulence and nausea.[20] Rare side effects associated with prolonged use include hepatoxicity, specifically elevated transaminase enzymes.[15] Notably, green tea supplements may not be labeled appropriately with the total caffeine content. Green tea naturally contains caffeine, and often only the amount of added caffeine to the supplement is stated on the product label. Caffeine consumption greater than 600 mg daily is associated with tachyarrhythmias and sleep disturbances. Notable drug-drug interactions include reduced therapeutic effect of bortezomib and imatinib, increased oral bioavailability of tamoxifen, and increased side effects with 5-fluorouracil and irinotecan.[20] Active constituents in green tea may inhibit CYP3A4.[15] Green tea contains small amounts of vitamin K which may interfere with warfarin therapy.[20]
- **Cat's Claw**. This herb is derived from a woody vine native to the Amazon Rainforest and tropical areas of South and Central America.[21] Cat's claw has been observed to stimulate phagocytes and T-helper cells in laboratory studies. It is thought that Cat's Claw may slow inflammatory processes, enhance DNA repair, and that it can alleviate side effects of chemotherapy, such as protection from low white blood cell counts. Reported side effects are generally mild and include nausea, diarrhea, and stomach discomfort.[22] Cat's Claw inhibits CYP3A4 enzymes, which can interfere with intracellular levels of drugs metabolized by this enzyme. Additionally, the alkaloids present in Cat's Claw may lead to increased bleeding risk in patients being treated with anticoagulant or antiplatelet therapy.[21]
- **Turkey Tail**. Turkey tail, or Coriolus versicolor, is a mushroom used in traditional Chinese medicine as a tonic. Studies indicate that turkey tail may have immunostimulant and anti-tumor properties. Polysaccharide K (PSK) and polysaccharide-peptide (PSP) are derivatives from turkey tail that are commonly marketed as supplements for this purpose.[23] PSK has been used in Japan as a biological response modifier in cancer chemotherapy regimens and when used as an adjuvant, PSK appears to improve survival rates for patients with gastric and colorectal cancers.[24-26] A meta-analysis found that turkey tail may have potential benefits in cancer patients' overall survival and quality of life.[27] Side effects reported with use are mild and include dark colored stools and fingernails' gastrointestinal side effects, hematological abnormalities, and liver dysfunction.[23, 24] This agent is often used in conjunction with chemotherapy, making it difficult to discern whether these side effects are due to the chemotherapeutic agents or the supplement itself.[23] Important drug interactions include increased exposure of cyclophosphamide and inhibition of CYP2C9.[24]

Table 1: Herbal Supplement Interactions

Herbal Supplement	Interacting Drug	Description of Interaction
Turmeric	Alkylating Agents Antitumor Antibiotics Topoisomerase I Inhibitors	Turmeric has antioxidant effects and may reduce the activity of chemotherapy drugs that generate free radicals.[4]
	CYP 1A1, 1A2, 3A4 Substrates	Inhibition of these enzymes may affect serum levels of these substrates.[4]
	P-glycoprotein substrates	Inhibition of P-glycoprotein may affect serum levels of these substrates.[4]
	Anticoagulant and Antiplatelet Drugs	Turmeric's antiplatelet effect may increase the risk of bleeding.[4]
Ginseng	Anticoagulants	Ginseng may have anticoagulant effects that increase the risk of bleeding.[9]
	Imatinib	May increase the risk of hepatotoxicity.[9]
	CYP 3A4 Substrates	Ginseng may induce 3A4, leading to increased clearance of 3A4 substrates.[9]
Astragalus	Cyclophosphamide	May interfere through reversal of cyclophosphamide-induced immunosuppression.[11]
	Gemcitabine	Pretreatment with an astragalus extract was found to affect pharmacokinetics of gemcitabine in animal models.[12]
	Hormonal therapies	Astragalus and its constituents have estrogenic properties.[12]
	Anticoagulants	Additive anticoagulant effects may increase the risk of bleeding.[11]
	P-glycoprotein substrates	Astragalus can inhibit p-glycoprotein, increasing cytotoxicity of chemotherapy drugs such as doxorubicin, etoposide, and vincristine.[12]
Green Tea	Iron	Tannin content in green tea may reduce the bioavailability of iron. Separate iron administration by 2 hours before or 4 hours after green tea administration.[15]
	Bortezomib Imatinib	May inhibit therapeutic effect of these agents.[20]
	Tamoxifen	EGCG increases the oral bioavailability of tamoxifen.[15,20]
	Irinotecan	EGCG may inhibit the transport of irinotecan and its metabolite SN-38 into biliary elimination, prolonging its half-life.[15,20]
	Atorvastatin	Inhibition of organic anion-transporting polypeptide substrates (OATPs) results in reduced plasma concentration of atorvastatin.[20]
	CYP3A4 substrates	Inhibition of CYP3A4 affects intracellular concentrations of these substrates.[15,20]
	Warfarin	Green tea contains a small amount of vitamin K. Drinking green tea in moderation is unlikely to cause a significant interaction.[15,20]
Cat's Claw	Anticoagulants/ Antiplatelet drugs	Cat's Claw contains alkaloids that may inhibit platelet aggregation. Combination with anticoagulants can lead to increased risk of bleeding.[21]
	Antihypertensives	Use with Cat's Claw may increase the risk of hypotension.[21]
	CYP3A4 Substrates	Cat's Claw inhibits CYP3A4, which can affect intracellular concentrations of CYP3A4 substrates.[21]
	Immunosuppressants	Cat's Claw has immune-stimulating activity that may stimulate phagocytosis and mobility of leukocytes.[21]
Turkey Tail	Cyclophosphamide	Polysaccharide-peptide (PSP) may increase exposure to cyclophosphamide up to 50% and increase the half-life up to 43%.[24]
	CYP2C9 Substrates	Polysaccharide-peptide (PSP) may inhibit CYP2C9 and may interfere with substrate drug levels.[24]

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Coriolus Mushroom. Food, Herbs & Supplements. [updated 2020 Dec 17; cited 2020 Jul 20]. In: Natural Medicines [Internet]. Stockton, CA: Natural Medicines. Available from https://naturalmedicines.therapeuticresearch.com/about-us/contact-us.aspx

Herbal Supplement Drug Interactions [Continued]

The use of herbal supplements is often discouraged when undergoing cancer treatment because of ambiguity surrounding potential drug-drug interactions. Despite this, it is common for patients to inquire about using herbal supplements in the ambulatory setting. Open dialogue is recommended when engaging with patients about supplement use – the potential benefits, potential risks, and a review of the evidence regarding their use. Often, the use of herbal supplements in patients who are undergoing cancer treatment represents a need for personal empowerment.[28] Other reasons for use may include dissatisfaction with conventional treatment due to adverse effects, as well as alignment with their personal values and beliefs as the use of 'natural' or 'organic' remedies may give patients a feeling of wellness that aligns with their personal philosophy.[28] The entire journey of cancer, from diagnosis through treatment, is fraught with feelings of uncertainty, loss of independence, and lack of control. Much of a cancer journey involves learning about an entirely new disease process and bombardment with various chemotherapy drugs that are foreign, scary, overwhelming, and accompanied by numerous side effects. In this case, herbal supplements may offer a patient solace and a feeling of personal control over their cancer diagnosis. Whether it is a quest for independence or merely curiosity about alternative medicines, every patient should receive accurate information to make an informed decision with their healthcare team. After careful weighing of risk versus benefit, including the value of patients' playing an active role in their care, you may conclude that permitting use of herbal supplements will foster a more trusting patient-provider relationship and give patients a sense of ownership over their disease and disease-related side effects.

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PRN ACTIVITIES AND ANNOUNCEMENTS

MEMBER SPOTLIGHT

Publications

Congratulations to several of our members for notable publications in the 6 months: Ahmed H, Alhammad AM, Arbruster D, Arnall JR, Moore DC, Bubalo JS, Burkhard A, Cannon LA, Chan A, Crona DJ, Cuellar S, DeRemer D, Elder CT, Farris KB, Figg WD, Glode AE, Goodner JA, Gulbis AM, Haaf CM, Hanks CR, Hicks JK, Holle LM, Schwartz R, Soberiaj D, Hossain S, Huang E, Kolesar JM, Lao P, Lester PA, Lin K, McAlister R, McCormick J, McLean E, Mcleod HL, Monestime S, Nakashima L, Nedved AN, O'Hara W, Ononogbu O, Po-Hung Li L, Palkimas S, Rice ML, Schmitz NS, Seddon AN, Wojenski D, Sun L, Thackray J, Buege MJ, Buie LW, Tossey JC, Walko CM, Gatewood T, Walters JH, Ward DA, Weilnau J, Williams C, Wu D, Yee GC.

Promotions

Ashley Glode: Associate Professor at the University of Colorado Skaggs School or Pharmacy and Pharmaceutical Sciences

Jennifer Thackray: Promoted to Clinical Pharmacy Specialist III at Memorial Sloan Kettering Cancer Center

Awards

Ashley Glode: ASCO Advocacy Champion at the Senator's Club level and University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences Excellence in Precepting Award for Ambulatory Care Pharmacy

Jennifer Thackray: 2021 Ralph D. Bienfang Outstanding Practitioner Award by the University of Oklahoma College of Pharmacy Alumni Association

If you would like to see your achievements or a colleague's recognized within our PRN group, please reach out to our PRN leadership.

PRN OFFICERS FOR 2021-2022

Congratulations to our officers for the coming year!

Chair: Don Moore, PharmD, BCPS, BCOP, DLPA
Chair-Elect: Erin Hickey, PharmD, BCOP
Secretary/Treasurer: Farah Raheem, PharmD

FACEBOOK & TWITTER PAGEs

Please send Don, Erin and I (shelbylmerchant@gmail.com) 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 or email (shelbylmerchant@gmail.com). If you would like to be featured in the fall 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!