



THE ONCOLOGY BULLETIN



STUDENT ONCOLOGICAL ADVOCATES IN
PHARMACY (SOAP)
UGA COLLEGE OF PHARMACY

INSIDE THIS ISSUE:

Oncology Clinical
Pharmacist Spotlight: Dr.
Donald Harvey

Biology of Aging and Cancer

Olanzapine for CINV
Prevention

CRISPR: Therapeutic
Promises, Potential, and
Challenges

Breakthrough in Cancer
Therapy: Kymriah
(tisagenlecleucel)

Drug Spotlight: Yescarta
(axicabtagene ciloleucel)

E-Cigarettes and Cancer Risk

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Oncology Clinical Pharmacist Spotlight:

Dr. Donald Harvey

Written By Katie Fitton, Pharm.D. Candidate, Class of 2020



Dr. Harvey currently serves as the Director of the Phase I Clinical Trials Unit at the Winship Cancer Institute of Emory in Atlanta, GA. He is a Fellow of the American College of Clinical Pharmacy, a Fellow of the Hematology/Oncology Pharmacy Association, and Associate Professor in Hematology/Oncology at Emory University School of Medicine. Dr. Harvey received his BS Pharmacy and Doctor of Pharmacy from the University of North Carolina at Chapel Hill. He completed his PGY1 at the University of Kentucky Medical Center and his Oncology PGY2 at UNC hospitals and College of Pharmacy. Prior to coming to Emory, he served as faculty at UNC College of Pharmacy and as a clinical specialist and director of the Oncology PGY2 at Grady Hospital.

Dr. Donald Harvey, PharmD, BCOP, FCCP, FHOPA

What does your job as the Director of the Winship Cancer Institute's Phase I Clinical Trials Unit entail?

I have held this position for 10 years now. In taking this position, I have been responsible for creating a Phase I Unit for patients who are on early phase I clinical trials, creating an administrative program for research in the clinical trials unit, and staffing the clinical trials unit with employees who would be invested in taking care of the patients and performing research for the clinical trials unit. Currently, most of my time is spent in 3 main areas. A quarter of my time is spent seeing patients with advanced practice providers. We check on the side effects the patients are having, trials that are open for them, and how they are doing. Half of my time is spent in an academic setting writing or executing protocols, being a co-investigator on studies, papers, and grants, or collaborating in the lab. I have a significant academic expectation to write and publish studies. The other quarter of my time is spent training pharmacy residents and teaching graduate students in how drugs are developed and the pharmacology behind the hematology/oncology medications.

What do you enjoy most about your job? Are there any aspects of your job that you don't like?

Primarily, I enjoy the excitement with oncology drug development. There are always new drugs and new pathways being discovered and developed and always new questions to answer in the field. It is also remarkable to have these trials and drugs in portfolio in Atlanta and throughout Georgia because that isn't the case for every state. The challenging parts are the administrative parts and the difficulty in seeing patients failing treatments and their cancer progressing. In my administrative role, I have found that a better job needs to be done expediting the process of getting these innovative drugs to the patients.

Which one of your projects are you currently most excited about?

My pharmacology project – it is focused on how new immunotherapy drugs, especially new innovative approaches to treatment such as CAR T-Cell therapy, affect the hepatic metabolism of other drugs. While the patient is receiving the medication or therapy, we measure markers that indicate drug metabolism for that patient. I am also working on a project for globally understanding more about the clinical pharmacology and drug interactions with newly discovered therapies. New targets are very exciting, and as we become more adept at treating other diseases, there are more instances of cancer with more co-morbidities at advanced ages. With the patient being on multiple therapies for multiple diseases, there is a greater chance of drug interactions, and we are working on obtaining more data on the pharmacology and interactions of these therapies.

Would you say there are a significant number of pharmacist job openings in hematology/oncology?

Today and moving toward the future, oncology is a field where more and more drugs are being developed and approved. In the past year, there have been 17 total new approvals of molecular entities for cancer. These therapies require a specialized knowledge base, indicating a greater need for pharmacists to understand these drugs, how they work, and their drug interactions. At many academic institutions, time devoted to oncology has declined since they see it as a specialty; however, everyone needs to know the basics due to an increasing number of cancer patients with a rise in life expectancy.

What is a driving force for your passion for oncology research?

I had a professor at UNC who was very successful in motivating me. In addition, I always had an interest in research and how drugs are utilized in the population throughout pharmacy school. Oncology is a field where we can always make improvements in the way we treat our patients. Patient care, research, and good questions can come together and lead to a better degree of care for cancer patients. As I have gotten more involved in the field, I have also experienced more personal motivators for oncology research.

What changes would you like to see in the field of pharmacy in the next few years?

I would like to see us grow to meet the demand of the patient. More and more pharmacists are leaving direct patient care and moving into non-direct patient care roles. We need the patients to understand we are part of their care and publicize what we do because it is unique and important work. By doing more of this, we will increase our ability to meet the needs of patients. Provider status will also help cement our role as pharmacists in patient care. However, when the patient is no longer our central reason of existence, we are in trouble.

Would you say your PGY1 and PGY2 residencies at University of Kentucky and University of North Carolina set you up well for your pharmacy career?

They were critical for my pharmacy career for two reasons. First, my residencies taught me how to think and problem solve clinically, which was very important. For the oncology field, we need to understand normal physiology in order to understand what abnormal physiology in cancer is and decide how to target the abnormal parts with treatments. Second, my residencies really allowed me to see the depth of pharmacy patient care because I was able to experience situations and problems in a real-time basis with patients.

What would be your words of advice to students as they are looking to pursue a career in oncology/hematology? How would you tell them to approach the residency process?

Choose a residency that fits you best. Pick one that fits who you are and what you are trying to get out of a residency. In addition, don't specialize too early because general training and knowledge is very important. I personally did not do much oncology in my PGY1 because I knew I wanted to specialize in it and wanted a good broad knowledge base because cancer patients don't only have cancer. Also, be honest about what you are looking for in a residency when interviewing and applying to programs. Tell them if you aren't ready to commit to a specialty or if you have a specialty in mind, even if they don't have a PGY2 in that area.

How has your involvement in the Hematology/Oncology Pharmacy Association (HOPA) helped further develop you as a pharmacist?

It has helped me to be a networker. I love interfacing with others and learning about how people do things differently in different places. HOPA helped me learn and be introduced to others in the field. It invigorated my career because I was able to meet other people with the same passion. I was also able to mentor other individuals within HOPA. As a leader in the organization, I learned how to advance an agenda and think globally about the profession and accomplishing new goals. It was exciting to see how the organization could grow. I highly recommend becoming involved in organizations – specialized memberships like HOPA are very beneficial once you are specialized, but APhA and ACCP can offer a lot more to students and residents.

Biology of Aging and Cancer

Written By Laura Pyronneau, Pharm.D. Candidate, Class of 2020

Improvements in health care over the past century have resulted in an increased overall life expectancy in developed countries.¹ People are living longer today than ever before. As the population continues to increase, the number of older adults is expected to double.¹ According to the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER), 43% of men and 38% of women will develop a type of invasive cancer over their lifetime.³ More than half of cancers will occur in individuals over the age of 65 years.²

Aging is the most prominent unavoidable risk factor for cancer. Cancer is uncontrolled cell growth due to numerous mutations that fail to prevent cell replication.³ Older adults are believed to be more susceptible to cancer because aging is theorized to be an accumulation of damage to the body over time.¹ The underlying mechanism for both aging and cancer is time-dependent accumulation of cellular damage.¹

The normal aging process affects many important biological processes occurring in our bodies. The key difference between aging and cancer is in the type of mutations. Whereas aging is thought to be the process of many "loss of function" mutations over time, cancer, for the most part, is an accumulation of many "gain of function" mutations. Many biological mechanisms contribute to the increased incidence of cancer as we age. These mechanisms include genomic instability, telomere attrition, and altered cellular senescence.¹

DNA is replicated millions of times throughout a lifetime; with each replication, there is a risk of introducing an error into the genome.² Throughout life, DNA is also exposed to mutagens, exogenous, radiation, and free radicals. In the short-term, most of these inevitable mutations are harmless as the DNA repair system corrects the majority of them.² However, as time passes, the mutations accumulate and are more likely to bypass the repair system.

Telomeres, the end caps of the DNA, function like a "clock" for each cell. With each replication in somatic cells as we age, the telomeres are shortened due to a decrease in telomerase, the enzyme which replicates telomeres. Once telomeres are shortened to a certain extent, the cell either stops replication in a process called cellular senescence, or apoptosis occurs. This is thought to be a protective mechanism against cancer.¹ However, unlike in aging, accumulated mutations in cancer cells can cause telomerase to be upregulated when compared with normal tissues.² Due to this, in many cancers, these cells continue to replicate past their dividing limit, also known as the Hayflick limit, and are sometimes considered immortal.¹

Cellular senescence is the process in which a cell stops dividing yet remains metabolically active.² Senescence is an efficient protective mechanism against cancer. It causes cells that have the potential to be cancers to stop dividing. However, like all the above examples, accumulated mutations over time can cause the senescence mechanism to fail and cancer to arise.²

Cancer is associated with a number of events at the molecular and cellular level. Aging and cancer are interconnected, time-dependent occurrences. By understanding the complex changes that occur with increased age, we can begin developing interventions to better treat the cancers that arise with age.

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Olanzapine for CINV Prevention

Written By Sydney Finder, Pharm.D. Candidate, Class of 2020

Chemotherapy induced nausea and vomiting (CINV) is a major side effect that reduces the quality of life in patients undergoing cancer treatment. Furthermore, CINV contributes to an increased return to the emergency department by chemotherapy-receiving patients, which is associated with average hospital visit costs of over \$5,000 per encounter.¹ CINV can occur at different times respective to time of treatment. Acute CINV occurs during the first 24 hours after chemotherapy, while delayed CINV generally occurs between 24-120 hours after chemotherapy.¹ Delayed CINV management, particularly nausea rates, has been the target of recent research efforts.

Historically, the management of highly emetogenic chemotherapies (HEC) included triplet prophylactic therapy with a neurokinin-1 receptor antagonist (NK1R), a 5-hydroxytryptamine (5HT-3) receptor antagonist, and a glucocorticoid.² HEC is defined as a 90 % risk of emesis and includes commonly used agents such as cisplatin, anthracyclines, carmustine, cyclophosphamide $\geq 1500\text{mg/m}^2$, and dacarbazine. Moderately emetic anthracyclines (daunorubicin, doxorubicin, epirubicin, and idarubicin) are also considered high-risk when combined with cyclophosphamide.² Even with the standard triplet emetogenic treatment, up to 75 % of patients on these chemotherapies will experience CINV during the course of treatment.¹

With CINV treatments leaving much to be desired, oral olanzapine has gained much interest as an antiemetic since the turn of the century.¹ Olanzapine is listed by the FDA as an atypical antipsychotic.¹ This drug antagonizes a wide variety of receptors, including the serotonin and dopamine receptors known to make up the vomiting center and chemoreceptor trigger zone. Based on this mechanism, olanzapine has been increasingly incorporated into CINV prophylaxis regimens, initially in combination with 5HT3 antagonist and glucocorticoid therapy and more recently in combination with NK1 based triplet therapy.¹

Initially, olanzapine was studied as a triplet regimen to prevent CINV for patients receiving HEC. In a study of 83 patients receiving a highly emetic anthracycline plus cyclophosphamide chemotherapy regimen comparing an olanzapine triplet (10 mg olanzapine on day 1, and 5 mg on days 2-4) to an aprepitant triplet, it was found that 85% of patients in the olanzapine arm achieved a complete response of no emesis or rescue medication compared to 81% of the aprepitant arm. While the differences were not statistically significant, this study suggested that oral olanzapine could replace the NK1R antagonist as a less expensive and non-inferior option in a 3 drug regimen.⁶ While the former study showed the olanzapine-based triplet is at least as effective as an NK1-based triplet, outcomes overall still warranted investigation of methods to improved CINV rates.⁶

While performing further research to optimize CINV for patient undergoing HEC, Navari and colleagues evaluated olanzapine in addition to NK1-based triplet prophylaxis (i.e., quadruplet prophylaxis). This study evaluated patients receiving single-day HEC who were treated with 10 mg of oral olanzapine or placebo on days 1-4 of chemotherapy treatment in combination with NK-1 based triplet therapy (a 5HT-3 receptor antagonist plus a NK1R antagonist plus a glucocorticoid). Those randomized to receive olanzapine experienced significantly less nausea and vomiting in the acute (74% vs 45%, $p=0.002$), delayed phase (42% vs 25%, $p=0.002$), and the overall period (64% vs 41%, $p<0.001$).³ A study of 101 patients receiving HEC and hematopoietic cell transplants found that a complete response of no emesis and minimal nausea was higher in patients receiving olanzapine in addition to fosaprepitant, ondansetron, and dexamethasone in overall level of nausea (55% versus 26%, $p=0.003$) and in the delayed phase of nausea (60.8% versus 30%, $p=0.001$) than those receiving only fosaprepitant, ondansetron, and dexamethasone.⁴ The results were not statistically significant for an improvement while using olanzapine in the acute phase ($p=0.13$).⁴ Similarly, a recent Cochrane analysis of 14 randomized controlled trials evaluating olanzapine for CINV prophylaxis concluded that 10 mg of olanzapine, administered on days 1-4 of chemotherapy, is a cost-effective way to reduce CINV in the delayed phase. A clear conclusion was not reached about the role of olanzapine in the acute phase of CINV.¹

Both the NCCN guidelines and ASCO guidelines now have an option including olanzapine with the common (fos)aprepitant, 5HT₃ antagonist, and dexamethasone regimen for the treatment of HEC.^{2,5} The NCCN guidelines strongly recommend a 4 anti-emetic drug regimen including olanzapine (category 1). An example regimen provided in this guideline includes fosaprepitant 150 mg IV once, ondansetron 16-24 mg PO or 8-16 mg IV once, dexamethasone 12 mg PO/IV once, and olanzapine 10 mg PO once on day one, then dexamethasone 8 mg IV/PO and olanzapine 10 mg PO on days 2-4.⁵ The ASCO guidelines recommend offering all patients on HEC therapy a regimen including a NK1 receptor antagonist, a 5HT-3 receptor antagonist, dexamethasone, and olanzapine. An example regimen from this guideline includes fosaprepitant 150 mg IV, ondansetron 8 mg PO twice daily or three 3 mg soluble films daily or 8 mg or 0.15mg/kg IV, and dexamethasone 12 mg PO/IV on day one, then olanzapine 10 mg orally on days 2-4, and dexamethasone 8 mg IV/PO on day 2, and then 8 mg PO/IV twice a day on days 3-4.²

Although data clearly supports the benefit of olanzapine in triplet or quadruplet regimens for CINV prophylaxis, further data is needed to elucidate the role of quadruplet therapy for multi-day chemotherapy, the extent of olanzapine's adverse effects during treatment, as well as the optimal dose of olanzapine to minimize adverse reactions. While each trial varied widely in the reported adverse events, the Cochrane review determined olanzapine probably increases risk of somnolence during treatment.¹ A study by Yanai et. al determined that 5 mg dose of oral olanzapine was non-inferior to a 10 mg dose in the delayed phase of CINV for patients receiving highly emetogenic chemotherapy, demonstrating a complete response of no emesis or use of rescue medications in 77.6% of patients taking 10 mg (p=0.01) and 85.7% of those taking a 5 mg dose (p<0.001). The 5 mg dose of olanzapine also showed reduced incidence of somnolence, occurring in 45.5% of those taking the 5mg dose and 53.5% of those taking the 10 mg dose. However, as most current studies were performed with a 10 mg dose, further research is needed to incorporate this reduced dose into practice.⁷ Olanzapine can cause other serious adverse effects, such as QTc prolongation, hyperglycemia, and hematological effects; however, while these were rarely seen in the Cochrane review, continued evaluation of these should occur in future research.¹

In conclusion, the evidence showing the benefit of oral olanzapine should be considered by institutions looking to reduce the incidence and burden of CINV on their patients undergoing HEC. Further studies are needed to determine optimal dosing. At the time of publication, 14 studies are listed in clinicaltrials.gov on this topic, which may provide clarification on olanzapine's exact role in CINV treatment.⁸

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CRISPR: Therapeutic Promises, Potential, and Challenges

Written By Lydia Lee, Pharm.D. Candidate, Class of 2022

Cancer is a genetic disease arising from changes in our genes that trigger uncontrollable cell division. When functioning normally, the human genome prevents uncontrolled growth with multiple checkpoints. Proto-oncogenes control the stimulating signals for cell growth, while tumor suppressor genes serve to protect the cell from replicating if there are dangerous mistakes in the genome, preventing the cells from turning cancerous. Disruption of any of these genetic checkpoints can lead to increased growth in our tissues and eventually to cancer.⁴ The advent of CRISPR/Cas9 and gene therapy, however, has led to the promise of a unique therapeutic opportunity to edit genomes for disease prevention, effectively rewriting our genomes to erase cancer at its very foundation.

The CRISPR/Cas9 system is composed of two parts: CRISPR, Clustered Regularly Interspaced Short Palindrome Repeats, short repeating DNA segments followed by a spacer, and Cas9, the CRISPR-associated endonuclease that cuts the DNA wherever it is targeted by the CRISPR sequence. The great achievement of CRISPR/Cas9 technology is that it can change the genetic code of a specific targeted area at the molecular level. Once the target is established, CRISPR binds and cleaves the DNA.¹ Then, a healthy engineered gene is used to repair the damage.¹ For cancer, it offers the opportunity to change problematic mutant genetic code into its wild type sequence. Take, for example, a single V600E mutation within the BRAF gene commonly found in melanoma. The patient's cancerous cells would simply need to be edited back into the wild type valine, and the cells would become harmless to the patient.

Emerging proof of concept data on the use of CRISPR/Cas9 to cure genetic diseases has been very promising. For example, sickle cell disease (SCD) has shown potential to benefit greatly from CRISPR/Cas9 gene therapy. Sickle cells are not able to produce the WT β -globin that normal blood cells produce. Up until now, SCD had only one truly curative therapy, allogeneic hematopoietic stem cell transplantation, which is high-risk and works only in a small population of patients.⁷ With CRISPR/Cas9, researchers edited the mutated blood cells in order for the DNA to become a wild type and allow production of WT β -globin as in a normal blood cell.⁷ The corrected gene cells show evidence that if put in clinical trials, they would help treat SCD patients and also correct other inherited gene defects.

CRISPR/Cas9 has also been proven to help with other next generation therapies. The Gill lab at the University of Pennsylvania recently showed that edited myeloid CD33+ cells can protect against the myeloablative effects of CAR T33 therapy for acute myeloid leukemia (AML), the most common and deadly form of leukemia.⁶ Like sickle cell disease, AML has had to rely on allogeneic hematopoietic stem cell transplantation for the last 40 years, with no improvement on alternative therapies or patient prognosis. CAR T33 therapy has been effective at decreasing and eliminating AML disease, but the problem is that the therapy specifically targets and kills all myeloid-related cells. Patients lose the ability to produce red and white blood cells, a currently unmanageable side effect. To elude this side effect, researchers extracted myeloid stem cells and used CRISPR/Cas9 to knock out the CD33 protein to be then re-transplanted into both mouse and monkey models with the edited myeloid stem cells.⁶ After the transplantation of the CRISPR edited cells, no difference was found in the immune system function, and there was resistance to the toxic side effects of CAR T33 therapy. The AML cancer in their models could be cured without any evidence of defects in the blood cells. Due to these promising results, clinical trials for this strategy of CRISPR/Cas9 and CAR T therapy have already begun.

Although CRISPR may have benefits for cancer prevention and treatment and there are many promising future directions, recent problems with CRISPR have arisen. Not only does this technique have a site-specific targeted area for DNA cleavage, but it has been implicated in extensive off-target mutation and genetic damage. For example, large DNA mutations and deletions have been found downstream from the targeted area where Cas9 was editing, which could cause lesions that alter stem cells and could then have the potential to turn neoplastic.⁸ Two other studies were conducted using different approaches of gene editing with CRISPR and found that p53, a major tumor suppressor gene, was seriously affected and could turn the cells tumorigenic. The first study, focusing on Cas9 genome editing effects on retinal pigment epithelium, discovered the breakages of the double-stranded DNA eventually led to a dangerous inhibition of p53 function.³ The second study, evaluating the effects of genome editing in human pluripotent stem cells, found an increase in efficiency of the editing, but also revealed induced p53 mutations.⁵ Due to studies such as these, clinical trials of CRISPR for patients with inherited blood disorder β -thalassemia in the US were placed on hold by the FDA, which is a very rare move.⁵

Despite problems with the current technology, the development of CRISPR has paved a new road for genome editing as a viable therapy for diseases and cancer. As of October, the FDA decided to lift the hold. CRISPR Therapeutics and Vertex Pharmaceuticals plan for the first clinical trial (phase I/II) of CRISPR in SCD patients to start by the end of 2019.² With the hold being lifted on clinical trials, there will be more available resources to understand the potential of CRISPR in humans. The discovery of CRISPR/Cas9 and efficacy in improving SCD shows the potential of CRISPR to improve the site-specific correction of the genetic mutations in patients. Studies have also shown improvement of therapies by pairing them with CRISPR. The pairing of CAR T33 and CRISPR to enhance immunotherapy in AML leads the way for the possibility of expanding into other therapies. Researchers have also been actively working to improve CRISPR/Cas9 and, as a result, have developed a more effective and site specific CRISPR/Cas12a. CRISPR/Cas12a tightly binds and targets ssDNA and carefully checks each base pair to cut and edit.⁹ Cas12a can read up to 18 letters compared to Cas9, which can read about 8 letters with possible mistakes.⁹ Further research on CRISPR/Cas12a can offer a new direction in treating patients with disease or cancer without affecting off-target areas of the gene. Clinical trials in genetic disease are on-going and with more being performed and found successful, it shows promise for the potential of CRISPR in cancer in the future.

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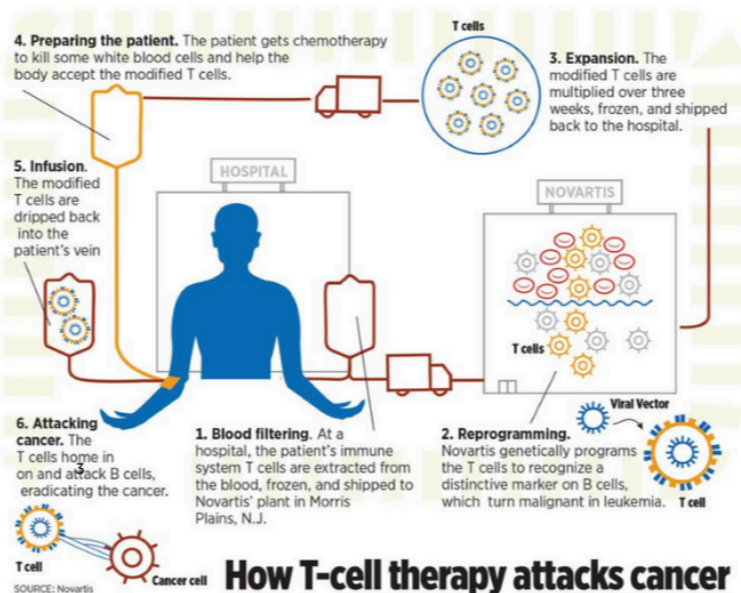
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Breakthrough in Cancer Therapy: Kymriah

Written By Brielle Scutt, Pharm.D. Candidate, Class of 2020, and Alia Reid, Pharm.D., Class of 2018

Noted as the most expensive cancer therapy treatment, Kymriah® (tisagenlecleucel) has global healthcare company, Novartis, putting their money where their mouth is. Novartis has promised eligible patients will not be charged the astonishing \$475,000 per treatment price tag if they do not respond within one month following therapy.² Tisagenlecleucel, a novel therapy, is a chimeric-antigen receptor therapy (CAR T) where a patient's own T-cells are removed and "reprogrammed" in the laboratory with a transgene to allow enhanced targeting of cancer cells. Specifically, tisagenlecleucel genetically programs the patient-specific T-cells to target cells expressing CD19 once reinfused. Once the tisagenlecleucel CAR T cells bind the malignant CD19 B-cells in the patient, the CAR signals trigger further T-cell production and persistence, which may allow for long-term remission of the cancer via enhanced and prolonged anti-tumor effects.

As seen in the picture provided, creating CAR T-cells is an extensive process that includes filtering of the patient's own blood to collect T-cells, reprogramming the T cells to create the CAR T-cells product in a central laboratory, followed by preparing the patient for re-infusion with conditioning chemotherapy, and then infusion of the individualized CAR T-cell therapy back into the patient. After re-infusion, patients are monitored for potential adverse events from the conditioning chemotherapy and the CAR T product itself.



The ELIANA phase II, single-arm, open-label, multi-center, international trial evaluated 75 patients who were given tisagenlecleucel.³ This trial

enrolled pediatric and young adult patients ages 3-23 years old (average age 11 years) who had a median of 3 prior therapies before the clinical trial and were currently diagnosed with relapse/refractory B-cell ALL with >5% lymphoblasts in bone marrow.⁵ Of the 75 patients who underwent infusion, 27 were discontinued (11 died, 9 had lack of efficacy, 5 underwent a new therapy for ALL while in complete remission, and 2 withdrew or were withdrawn by guardian) and 48 remained in the follow-up group. Of these patients with at least 3 months of follow-up, 81% went into remission (60% in complete remission and 21% in complete remission with incomplete hematological recovery).³ At 6 months post-infusion, the rate of event-free survival (EFS) was 73% and at 12 months EFS was 50% with the rate of overall survival at 12 months being 76%.³ Based on this data, tisagenlecleucel was FDA approved for patients up to 25 years of age with relapsed or refractory CD19+ B-cell acute lymphoblastic leukemia (B-ALL).

"FDA Approves First-Ever T-cell Cancer Treatment, Pioneered at Penn, CHOP. *The Inquirer*. Aug 30 2017.
<<http://www.philly.com/philly/health/health-news/fda-approves-novartis-t-cell-therapy-pioneered-at-penn-chop-20170830.html>>

Although treatment with tisagenlecleucel involves the use of one's own cells, this does not exclude the patient from experiencing numerous and potentially serious adverse drug reactions. Within the ELIANA trial, 73% of the patients experienced a grade 3 or 4 adverse event that was suspected to be related to tisagenlecleucel with 100% of patients experiencing an adverse event of any grade.³ Adverse drug reactions listed within the tisagenlecleucel package insert include but are not limited to reactivation of hepatitis B, hypersensitivity reaction, secondary malignant neoplastic disease, neutropenia, thrombocytopenia, and cytokine release syndrome.³

Cytokine release syndrome (CRS) and CAR T related encephalopathy syndrome (CRES) are the major life-threatening adverse drug reactions that must be monitored for in all patients undergoing tisagenlecleucel treatment. Monitoring for CRS includes evaluation of a fever, hypotension, requirement of oxygen or ventilator support, and various organ toxicity. CRES monitoring includes symptoms of somnolence, confusion, encephalopathy, dysphagia, seizures, incontinence or motor weakness, tremors, etc. Both CRS and CRES require emergent intervention and can be treated using the MD Anderson CARTOX guidelines.³ Pharmacists are well positioned within the multi-disciplinary team to aid providers in managing CRS and CRES toxicities.

Tisagenlecleucel offers a novel mechanism for the treatment of relapse/refractory B-ALL; however, the financial cost and potential detrimental adverse reactions warrant further study of long-term outcomes. This high cost of initial treatment due to individual cellular product being created is increased further by the cost of close monitoring of adverse reactions and strict interventions to enhance patient outcomes. Therefore, the need for more cost-effective and safer treatment options for patients with relapse/refractory B-ALL is still a pertinent issue.

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Drug Spotlight: Yescarta

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The introduction of chimeric antigen receptor T-cell (CAR T) therapy has been an exciting development in the race to cure cancer. CAR T-cell therapy is a type of targeted specific immunotherapy that can revolutionize the way we treat a variety of cancers by enhancing an individual patient's immune response to their cancer. CAR T involves retrieving the patient's own T cells from their blood via leukapheresis. Subsequently, in the laboratory setting, a gene for the specific receptor that binds certain proteins on the cancer cells is then added to the T cells allowing these T cells to target the specific cancer cells for destruction by the immune system. The new CAR T-cells are then given back to the patient via an infusion.¹ Before a patient is given Yescarta® (axicabtagene ciloleucel), they will receive chemotherapy to reduce the non-CAR T-cells and the immune system so that the new CAR T-cells can flourish. This cellular product is infused over 30 minutes via an intravenous catheter. Patients are monitored daily for at least 7 days after the infusion has occurred and must plan to stay in the area for at least 4 months for regular follow up visits and blood tests to evaluate for adverse reactions.²

Currently, only two CAR T products are FDA approved. One of these CAR T-cell therapies is called axicabtagene ciloleucel. Axicabtagene is FDA approved for patients with non-Hodgkin lymphoma that have failed at least two other kinds of treatment. Axicabtagene is a one-time therapy that resulted in complete remission in 51% patients from the ZUMA 1 trial. The ZUMA 1 trial was a phase I/II, open label, single arm, multicenter study evaluating the safety and efficacy of axicabtagene in 111 patients with refractory aggressive non-Hodgkin lymphoma. The trial patients received a single intravenous infusion of axicabtagene at a target dose of 2×10^6 CAR-positive viable T cells/kg. All patients were hospitalized for a minimum of 7 days for monitoring. Results of this trial revealed 82% of patients responded to therapy (overall response rate) including a 58% of patients who had no detectable cancer remaining. Adverse reactions observed in these patients included pyrexia (85%), grade 3 or higher neutropenia (78%), anemia (43%), and thrombocytopenia (38%).³

The two most commonly observed toxicities with CAR T therapies are cytokine release syndrome (CRS) and a CAR T-cell related encephalopathy syndrome (CRES). CRS is characterized by high fever, hypotension, hypoxia, and/or multi organ toxicity. CRES is characterized by encephalopathy presenting as confusion or delirium, and occasionally seizures and cerebral edema. In the ZUMA 1 trial, grade 3 or higher cytokine release syndrome (CRS) occurred in 13% patients with symptoms of pyrexia (11%), hypoxia (9%), and hypotension (9%). CRES was found in 28% of patients with grade 3 or higher encephalopathy (21%), confused state (9%), aphasia (7%), and somnolence (7%). These are life-threatening toxicities, which require monitoring to ensure patient safety. Monitoring should include assessment of vital signs, review of organ systems, physical examinations, complete blood counts with differential, complete metabolic profile, measurement of serum CRP and ferritin levels, and neurologic work up (specifically if there is a concern for CRES). Daily fluid balance and body weight should be monitored as well as provision of maintenance intravenous hydration. In Grade 2 or higher CRS/CRES, pharmacologic therapy with tocilizumab and/or corticosteroids are being used as management options per guidelines.⁴

The cost of CAR T-cell therapies like axicabtagene can pose a huge financial burden on the patient and the healthcare system. Treatment with Yescarta costs approximately \$373,000, while some patients may end up spending close to \$1 million dollars with ancillary medical costs surrounding the treatment and follow-up care. This high cost has generated much discussion by legislative personnel and primary insurers who have posed a skeptical outlook on the sustainability of such costs. Most large insurers have developed methods to handle treatment requests; however, smaller insurers as well as state Medicaid programs may not cover these novel therapies at all. While successful targeted immunotherapies are revolutionizing the way we treat cancer, moving forward efforts to create affordable methodologies is necessary.⁵

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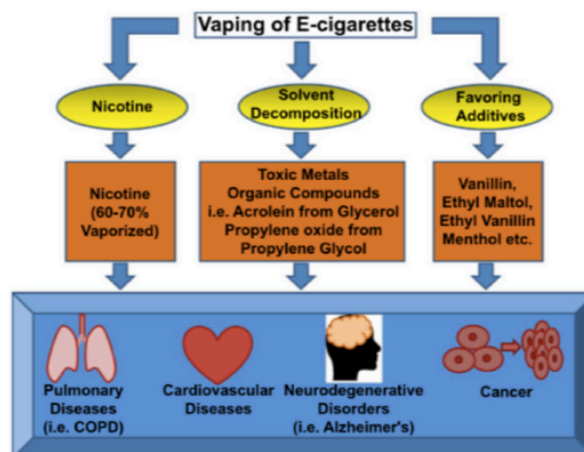
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E-Cigarettes and Cancer Risk

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E-cigarettes are popular devices used to deliver nicotine, flavorings, and other excipients via inhaled aerosols. Use of these new products is growing exponentially despite potential long-term health effects (Figure 1). The industry has grown to \$2.5 billion and e-cigarettes are currently the most commonly used form of tobacco smoked by youth in the U.S. Usage of both e-cigarettes and conventional cigarettes, also known as dual use, is also common among adults aged 18-25 years.² E-cigarettes are a growing public health concern due to the harmful ingredients, such as cancer-causing chemicals (formaldehyde, acetaldehyde, and acrolein)⁵ and nicotine present in these devices.

Figure 1: Health problems associated with e-cigarette use (Cai & Wang, 2017)



Pharmacists are uniquely positioned in the community setting to educate patients on the potential risks of e-cigarette use and to clarify misconceptions regarding these devices. For example, ingredients may be misrepresented on e-cigarette packaging. There have been documented cases of e-cigarette products being marketed as nicotine-free; however, when tested in labs, nicotine was found in the aerosols.² Further, some believe e-cigarettes are less harmful and less likely to cause cancers compared to other tobacco products. This widespread belief is possibly one of the driving factors for e-cigarette popularity.⁴ It is well known that aerosols are not harmless.² When nicotine is inhaled, the compound is metabolized mainly to cotinines, which is noncarcinogenic; however, a small amount is metabolized to nitrosamines, which have been shown to induce multiorgan tumors.³

Studies have shown the detrimental effect of e-cigarette smoke. Recently, a study found mice exposed to e-cigarette smoke had increased mutagen susceptibility, reduced DNA repair activity, and impaired DNA in the lung, heart, and bladder tissues.³ Research has also pointed to this phenomenon of DNA repair activity reduction and tumorigenic transformation in human lung and bladder epithelial cells exposed to e-cigarette smoke.³ As pharmacists, informing the public about the ingredients contained in these devices and their possible role in cancer development is imperative.

Substantial controversy surrounds the use of e-cigarettes in smoking cessation due to its associated health risks and lack of supporting evidence. Notably, the FDA has not approved these devices as smoking cessation aids.² Few studies suggest e-cigarettes may be used to completely substitute all tobacco products.² Two randomized controlled trials from a Cochrane Review showed that using e-cigarettes with nicotine increased the chances of smoking cessation compared to using e-cigarettes without nicotine.²

There was a trial comparing how well people stopped smoking on e-cigarettes with nicotine versus nicotine patches; however, due to the low number of participants and wide confidence intervals, good quality results could not be drawn from the research findings.² More research with larger sample sizes and smaller margins of error around the estimates are needed to define the place in therapy for e-cigarettes in smoking cessation.²

Despite lack of proven efficacy for reducing smoking habit, many adults still use e-cigarettes for this indication.² Unfortunately, this practice can lead to dual use, which is a danger to health quality as it increases the level of nicotine and other potentially harmful substances in the body.

As e-cigarette use is continuously increasing, especially among young populations, more research is needed on the long term effects these devices have on health outcomes. Furthermore, the role of e-cigarettes in smoking cessation is unclear; therefore, more studies are also needed to establish or refute its efficacy in reducing nicotine addiction. Since pharmacists are heavily integrated into their communities, spreading knowledge about these products to patients will build healthy awareness and, ideally, reduce the use of these products.

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