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Benzodiazepine Overdose: The Possible Opioid Cocktail Crisis

By: Emily Saso

Benzodiazepines (BZD) are the most widely prescribed psychoactive drug class in the world[1]. Used in preoperative settings and prescribed for their sedative, anticonvulsant, and myorelaxant properties, BZDs are known to work quickly and effectively[1]. Recreationally, BZDs are widely accessible and illicit use is sensationalized throughout pop culture. Needless to say, this drug class is widely used among the population and is increasingly being prescribed to Canadians[2]. In a country with such an accessible supply and popular use of BZDs, how is proper and safe use ensured? If a BZD 'epidemic' emerges, how will Canada be able to combat it with the sole antidote being administered intravenously?

The BZD drug class works as a positive allosteric modulator at the benzodiazepine site of gamma aminobutyric acid (GABA)-A receptor, increasing GABA binding affinity and the frequency of chloride channel opening[3]. GABA-A receptor is a ligand-gated ion channel and an ionotropic receptor that plays a crucial role in mediating neuronal excitability4. Intended efficacy of BZDs requires the presence of GABA — the primary inhibitory neurotransmitter in the central nervous system— interacting at the receptor, and that the membrane potential allows for the efflux of chloride ions[5]. Through increasing the frequency of chloride efflux, the frequency of action potential propagation through cells is decreased, and thus results in an increase of the inhibitory effects of GABA on neuronal excitability[6]. An exception to this decrease in neuronal excitability is seen with embryonic cells, which have increased permeability to chloride ions upon positive modulation of GABA-A receptor and therefore exhibit excitatory effects[7].

Decreased neuronal excitability via BZDs thereby induces sedative, anxiolytic, and myorelaxant effects to name a few, and is consequently prescribed for an array of medical conditions. Commonly prescribed to manage insomnia, anxiety disorders, and at higher doses, epilepsy, BZDs are also used in surgery as a preoperative sedative. A similar class of CNS depressants, barbiturates, which are historically known to have a low therapeutic index, have been largely replaced by BZDs that possess a higher therapeutic index[8]. Barbiturates similarly act at the GABA-A receptor but have a different mechanism of action in which they directly open chloride channels that reputedly leads to higher potential of toxicity. In addition to the diverse uses of BZDs under medical supervision, the drug class is highly accessed by the public for illicit use. In the United States, the highest reported age group of BZD misuse is from 18-29 years of age[9], while in Canada, illicit use of sedatives among students in grades ten to twelve approximately doubled from 2014-2015 to 2016-2017[2]. Top Billboard music charts are frequently topped with songs that provoke the use of BZDs; especially the use of BZDs in an improper context and the concomitant use with other central nervous system (CNS) depressants. This promotion of illicit and concomitant drug use encourages negative behavioural habits, which can lead to significant health consequences.

Despite BZDs possessing a large therapeutic index — requiring substantially large doses to induce significant toxicity — the concomitant use of BZDs with other CNS depressants can quickly increase the chances of morbidity and mortality through synergistic depressant effects[2]. Barbiturates are stringently controlled due to their low therapeutic index relative to BZDs, resulting in frequent prescribing of BZDs from perceived safety versus other drug classes. Occasional or short-term use of BZDs has a low addiction risk, but as the medication is used longer, the risk of addiction increases[10].

Chronic BZD use (>4 weeks) can result in dependence; as outlined in the DSM-V criteria for sedative, hypnotic, and anxiolytic use disorder[11]. In some cases, BZDs are abused concomitantly with other CNS depressants to enhance sedative effects; for example, BZDs and alcohol[12]. Alcohol interacts at the same receptor as BZDs — the GABA-A receptor — and acts in an agonist-like fashion. With the concomitant use causing a synergistic increase in CNS depression, there is an increased likelihood of BZD overdose[12]. BZD overdose displays symptoms including cyanosis, moderate to severe respiratory depression, stupor, disorientation, tremors, and coma13. These symptoms can lead to complications, such as muscle damage, brain damage, pneumonia, and death in the most severe cases. Although BZD overdose is rare when the medication is solely used, death from concomitant use with other CNS depressants is prevalent in Canada[13].

Statistics in Canada are not collected for deaths exclusively related to BZDs, but rather in a grouping of CNS depressant-related deaths. It is known that CNS depressants played a role in 796 premature deaths in Canada in 2014, which is 13% higher than it was merely 7 years prior[2]. Focusing on the potential risk of sole BZD use could be a new interest area of statistical analysis in Canada. Looking at our neighbouring country, the United States, deaths involving BZDs and synthetic narcotics increased by 7.4 fold between 2012 and 20172. Albeit the opioid crisis being a prevalent issue in the United States, it is not to go unnoticed that approximately 20% of all opioid deaths and 35% of all overdose deaths from synthetic narcotics involved concomitant BZD use[2]. Relating this comparative data to Canada, specifically Ontario, BZDs were involved in approximately 50% of fatal opioid overdoses in 2015[2]. Needless to say, BZDs contribute to what is already a pharmaceutical opioid crisis in both countries and could very well be an independent issue that needs more attention and detailed statistical analysis in Canada.

Flumazenil is a BZD antagonist, used for several of BZD sedation, or in treating BZD overdose1[4] .

The antagonist has a mechanism of action that competitively inhibits the activity of BZD and non-BZD substances that act at the benzodiazepine site of the GABA-A receptor14. The sole administration of flumazenil is via intravenous (IV) infusion, with 80% of reversal responses occurring within the first three minutes[14]. In hospitals or settings in which IV infusion can be administered, flumazenil is a dependable antidote with the exception of its use in patients who rely on a BZD for seizure management14. It becomes hard to see a practical public treatment of BZD overdose with the inability of flumazenil to be accessibly administered by the public. High BZD accessibility and low antidote accessibility, despite BZDs being increasingly prescribed and contributing to drug-related deaths in Canada, is becoming a concerning dilemma[2]. Researching alternative modes of flumazenil administration, or designing a new BZD antagonist should be taken to interest to help reduce the threat of increasing fatalities. Although naloxone has become integrated into pharmacies across Canada to help combat the opioid crisis, BZDs are notedly prevalent in opioid-related deaths. Thus, a dual-drug with an opioid antidote and BZD antidote could help reduce CNS depressant related deaths when responding to a suspected opioid or BZD overdose[2].

BZDs are increasingly prescribed in Canada, with many synthetic narcotics-related deaths involving BZD use. Through high misuse in middle-aged demographic and sensationalized BZD misuse in pop-culture, it is unassured that BZDs will not further contribute to CNS depressant related deaths. This is especially true as the current BZD antidote is only available for IV administration. Whether the solution is a novel and accessible BZD antagonist or an alternative flumazenil administration method, this area of research is assured to have useful applications for the health of Canadians.

References

1. Marin H, Escobar JI. Clinical Psychopharmacology: A Practical Approach. WORLD SCIENTIFIC; 2013. doi:10.1142/8120

2. Canadian Centre on Substance Use and Addiction. Prescription Sedatives.; 2019. https://www.ccsa.ca/sites/default/files/2019-06/CCSA-Canadian-Drug-Summary-Sedatives-2019-en.pdf

3. Paronis CA. Modulating GABA modulators. Br J Pharmacol. 2006;147(3):237-238. doi:10.1038/sj.bjp.0706552

4. Sigel E, Steinmann ME. Structure, function, and modulation of GABA(A) receptors. J Biol Chem. 2012;287(48):40224-40231. doi:10.1074/jbc.R112.386664

5. Jewett BE, Sharma S. Physiology, GABA. In: StatPearls. StatPearls Publishing; 2020. Accessed October 31, 2020. http://www.ncbi.nlm.nih.gov/books/NBK513311/

6. Tulane University School of Medicine. BZD Pharmacology Overview. Published online 2013. tmedweb.tulane.edu/pharmwiki/doku.php/BZD_pharmacology

7. Olsen RW, DeLorey TM. GABA Receptor Physiology and Pharmacology. Basic Neurochemistry: Molecular, Cellular and Medical Aspects 6th edition. Published online 1999. Accessed October 31, 2020. https://www.ncbi.nlm.nih.gov/books/NBK28090/

8. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects. Ochsner J. 2013;13(2):214-223.

9. Kurtz SP, Buttram ME, Surratt HL. Benzodiazepine dependence among young adult participants in the club scene who use drugs. J Psychoactive Drugs. 2017;49(1):39-46. doi:10.1080/02791072.2016.1269978

10. Anti-Anxiety Medications (Benzodiazepines). CAMH. Accessed October 31, 2020. https://www.camh.ca/en/health-info/mental-illness-and-addiction-index/anti-anxiety-medications-benzodiazepines

11. Substance Use Disorders. Substance Abuse and Mental Health Services Administration (US); 2016. Accessed October 31, 2020. https://www.ncbi.nlm.nih.gov/books/NBK519702/

12. Linnoila MI. Benzodiazepines and alcohol. Journal of Psychiatric Research. 1990;24:121-127. doi:10.1016/0022-3956(90)90043-P

13. BZD Overdose: Risks, Signs, Symptoms & Side Effects. Published 2018. www.drugabuse.com/BZDs/overdose/

14. Sharbaf Shoar N, Bistas KG, Saadabadi A. Flumazenil. In: StatPearls. StatPearls Publishing; 2020. Accessed October 31, 2020. http://www.ncbi.nlm.nih.gov/books/NBK470180/

Quality of Life After Chemotherapy

By: Danlin Zeng

Cancer, one of the most dreaded diseases of the 21st century due to its inability to be cured unless detected early, is a leading cause of death worldwide. In 2012 there were 8.2 million[1]. As the global population grows, the rate of cancer incidence continues to increase as well. Based on statistics from previous years, an estimated 83,000 cancer deaths will occur in Canada in 20202. On average, 617 Canadians are diagnosed, and 228 Canadians die from cancer every day[2]. The most common ways to eradicate cancer include radiation therapy, surgery, and chemotherapy. This article discusses the use of chemotherapy, the administration of drugs to cure cancer, and its effects on a patient's quality of life.

A multitude of chemotherapy drugs are available, yet all of them essentially serve the same purpose: to kill rapidly dividing cells in the body, which includes cancer cells that proliferate at an uncontrollable rate. However, apart from prolonging the lives of many cancer patients, chemotherapy also has devastating effects on what may be their last stages of life. The fundamental flaw of chemotherapy is that it cannot distinguish between rapidly proliferating cancer cells and normal cells. Normal cells that divide rapidly, including hair follicles and epithelial cells, are also targets of chemotherapy. This explains why many patients undergoing chemotherapy suffer from hair loss and nausea. Chemotherapy-induced toxicities are disabling and distressing to say the least. Cognitive deficiencies such as problems with attention, memory, and logical reasoning, as well as other symptoms including motivational deficit, fatigue, and neuropathy can remain for many years even after discontinuation of treatment[3,4]. As many as 80% of cancer survivors experience cognitive impairment due to chemotherapy, and up to 60% of patients have their daily activities impacted by symptoms of fatigue[5].

Mechanisms underlying chemotherapy resistance include increased efflux of chemotherapeutic agents from cells, increased biotransformation and detoxification of such agents in the liver, and anti-apoptotic mechanisms[2] To avoid the onset of resistance, patients may be required to undergo combination treatment, which further exacerbates any adverse effects experienced by patients. Although studies have suggested that neuroinflammation may play an important role in chemotherapy-induced toxicities, the possibility of other mechanisms such as oxidative stress or mitochondrial dysfunction have also been suggested[4,5]. For instance, one of the most well-known potent chemotherapeutic agents, cisplatin, has shown to be effective against various cancers including that of the bladder, lung, and ovaries[7]. Cisplatin interferes with DNA repair, thus resulting in extensive DNA damage and prompts cancer cells to undergo apoptosis, also known as programmed cell death[3]. Toxicity from cisplatin can cause debilitating organ damage, which often results in dose reduction or cessation of chemotherapy[8]. To date, there are no FDA-approved treatments to treat or prevent many of these symptoms that shape how cancer patients' experience the world, because the underlying mechanism causing such symptoms have not yet been elucidated[4,6]. The burden of suffering can be alleviated through palliative care, but not completely eliminated for most cancer patients whose cancer has progressed past the point of reversal.

Psychologists have termed the process of experiencing a disease and coping with the psychological and social effects of that disease the illness experience. Chronic illnesses can change an individual's self-identity as well as how others perceive them. For instance, upon being diagnosed with a chronic illness such as cancer, every decision in an individual's life will start to revolve around the disease. In the case of toxicities resulting from chemotherapy becoming permanent, the patient is constantly reminded of their previous struggle with a devastating disease and this may impede the patient from reverting to a normal life. Fatigue resulting from chemotherapy decreases a patient's capacity for physical and mental work due to exhaustion, which cannot be simply relieved by rest.4 However, society may perceive such an individual as idle, failing to empathize with the patients' circumstances. A patient's experience with chemotherapy treatment becomes inevitably intertwined to their social identity and perceived merit. Changes to a patient's self-identity are an inevitable part of the illness experience.

Despite all the negative effects of chemotherapy, these treatments are undeniably easier to tolerate than it was decades ago. Recent medical advances have developed advanced combination drug delivery strategies using nanotechnology[9]. Nano-carriers allow different drugs to be administered simultaneously and unifies each drug's pharmacokinetics, which provides a solution to the concern of many cancer patients involving the possibility of relapse due to the development of chemotherapy-resistance cancer. Combination chemo-therapy regimens may also reduce the aforementioned toxicities while providing synergistic effects[10]. Furthermore, with extensive research focusing on the improvement of early detection, cancer survival rates have been significantly improved while minimizing the use of chemotherapy regimens that inevitably result in a multitude of adverse effects[8].

References

1. World Health Organization, Department of Information, Evidence and Research, mortality database (accessed on 04/07/2020).

2. Brenner DR, Weir HK, Demers AA, Ellison LF, Louzado C, Shaw A, Turner D, Woods RR, Smith LM. Projected estimates of cancer in Canada in 2020, CMAJ. 2020;192:E199-205.

3. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014;740:364-378.

4. Bock PR, Hanisch J, Matthes H, Zänker KS. Targeting inflammation in cancer-related-fatigue: a rationale for mistletoe therapy as supportive care in colorectal cancer patients. Inflamm Allergy Drug Targets. 2014;13(2):105-111.

5. Vichaya EG, Chiu GS, Krukowski K, et al. Mechanisms of chemotherapy-induced behavioral toxicities. Front Neurosci. 2015;9:131. Published 2015 Apr 21.

6. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain. 2014;155(12):2461-2470.

7. Florea AM, Büsselberg D. Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. Cancers (Basel). 2011;3(1):1351-1371.

8. Giurgiovich A. J., Diwan B. A., Olivero O. A., Anderson L. M., Rice J. M., Poirier M. C. (1997). Elevated mitochondrial cisplatin-DNA adduct levels in rat tissues after transplacental cisplatin exposure. Carcinogenesis 18, 93–96.

9. Garcia G, Odaimi M. Systemic Combination Chemotherapy in Elderly Pancreatic Cancer: a Review. J Gastrointest Cancer. 2017;48(2):121-128.

Usage of Medical Cannabis for the treatment of Parkinson's symptoms

By: Neeki Alavi

Parkinson's disease is a progressive neurodegenerative disease that affects 1 in every 500 Canadians[1]. This disease impacts patients in a wide variety of symptoms that occur in different orders and different intensities [2]. Given its complex symptomatic nature, it is a challenging disease to control and cure. At the molecular level in the brain, neurons are the cells in your brain that control your movement. In Parkinson's those neurons become impaired or die1. When particular neurons in the brain become negatively affected, less dopamine is produced, which causes movement problems. Despite knowing what causes the decreased dopamine in the brain, current research is unsure of why those cells that produce dopamine die[1].

There are currently no laboratory tests that are able to diagnose Parkinson's[1]. The current diagnosis is made by observable symptoms that develop gradually, as levels of dopamine fall. The main symptoms that can be observed include tremors, rigidity, bradykinesia, and postural instability[3]. There are multiple other symptoms that patients with Parkinson's can undergo, for example, tiredness, depression, and difficulties eating and swallowing[3].

There is also no complete treatment for Parkinson's. Drugs and medication therapies are used to reduce its symptoms. Many of the medications taken by Parkinson's patients focus on temporarily replenishing or imitating dopamine since many of the motor symptoms of Parkinson's are the results from a lack of dopamine[4]. Some common medications used in Canada include: levodopa which converts into dopamine in the brain to replace depleted dopamine, dopamine agonists which mimic the action of dopamine, and COMT inhibitors, which block the enzyme that breaks down levodopa before reaching the brain[4].

Despite the dozens of drugs already in the market for the treatment of Parkinson's symptoms, some of the drugs are only effective during certain stages of the disease, for example, levodopa is only valid during the early and intermediate stages[5] (Patel, 2019). Therefore, other treatment types such as the use of cannabis have been tested with those patients with developed symptoms.

Cannabis contains chemical substances called cannabinoids6. Cannabis itself contains over 400 identified compounds, including over 100 cannabinoids[7]. These cannabinoid compounds have a pharmacologic effect on cannabinoid receptors in the human body. The most active cannabinoid is called tetrahydrocannabinol (THC). This compound is able to have an effect on the brain due to its physical similarity to the endogenous cannabinoid neurotransmitter produced by the brain called Anandamide[7]. In terms of the specific role of THC, it is a partial agonist for those cannabinoid receptors (CB1 and CB2) in the brain. This means that THC binds and activates the given receptor, however, only has partial efficacy in comparison to a full agonist's ability. This causes a disinhibition of dopaminergic neurons, resulting in the decreased dopamine release. Since dopamine plays several roles in the body, its depletion has several negative effects on the body.

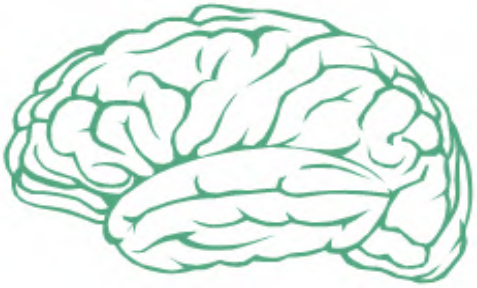
On October 17th 2018, the Cannabis Act was instated in Canada that allows for each province and territory to determine how cannabis is distributed and sold within their areas [8]. All of Canada has allowed for the legal purchasing of cannabis, each jurisdiction having different legal age limits and where to legally purchase it8. This sparked the start of cannabis research for positive therapeutic effects in a variety of diseases, including Parkinson's Disease.

In the past, a 2004 survey on Cannabis use in Parkinson's disease studied 339 patients in Czech Republic[9]. After cannabis use, 45.9% of the patients described to have a substantial alleviation of their symptoms, 30.6% had felt in improvement of rest tremor, 44.7% felt an improvement in bradykinesia, 37.7% felt an improvement of muscle rigidity, and 14.1% had an improvement in L-dopa-induced dyskinesias[9]. Out of the 339 patients, only 4 of them reported that cannabis worsened their symptoms[9]. Despite this study being done almost 20 years ago, it shows promising effects as to the future that cannabis can have on these patients.

More recently, a research article on the self-reported efficacy of Cannabis and other complementary medicines were able to classify all of the alternative medicine methods for the improvement of Parkinson's symptoms, cannabis use being one of them[10]. Despite only a small number of participants in the study had reported cannabis use for the improvement of their symptoms, 78% of those who did reported any improvement, more specifically they reported benefits in mood (56%), sleep (56%), motor symptoms (22%), and quality of life (22%)[6].

Despite the positive feedback, according to Parkinson Society British Columbia, there is currently no conclusive evidence that demonstrates cannabis being beneficial for people with Parkinson's[6]. Therefore, those patients in Canada who do undergo Cannabis treatment are done on a case by case basis.

To date, the usage of cannabis for Parkinson's symptoms have given promising results but there is conflicting evidence suggesting it not being beneficial [11]. Cannabis treatment may be a future option for Parkinson's, however, there is still more research to be conducted regarding the correct dosing and formulation. Next steps in the research process include studies that provide clear data on the safety and efficacy of Cannabis in Parkinson's patients. Until further studies are conducted, cannabis use for Parkinson's should be proceeded with caution.



References

1.Parkinson's Disease | UCB. Accessed June 30, 2020. https://www.ucb-canada.ca/en/Patients/Conditions/Parkinson-s-Disease

2. Stages of Parkinson's. Parkinson's Foundation. Accessed November 2, 2020. https://www.parkinson.org/Understanding-Parkinsons/What-is-Parkinsons/Stages-of-Parkinsons

3. Parkinson's Disease. National Institute on Aging. Accessed November 2, 2020. http://www.nia.nih.gov/health/parkinsons-disease

4. Treatments. Parkinson Canada. Accessed November 2, 2020. https://www.parkinson.ca/about-parkinsons/treatments/

5. Patel R, Kamil S, Shah M, Bhimanadham N, Imran S. Pros and Cons of Marijuana in Treatment of Parkinson's Disease. PMID: 31403009. 2019;11. doi:10.7759/cureus.4813

6. Medical and Recreational Cannabis and Parkinson's Disease. Published online 2019. https://www.parkinson.bc.ca/media/171860/cannabis-and-parkinsons.pdf

7. Marijuana, Cannabis & Δ9-tetrahydrocannabinol (THC). Published online 2019. http://tmedweb.tulane.edu/pharmwiki/doku.php/marijuana_thc

8. Canada H. Cannabis sales and distribution in the provinces and territories. aem. Published June 20, 2018. Accessed November 2, 2020. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/laws-regulations/provinces-territories.html

9. Venderová K, Růzicka E, Vorísek V, Visnovský P. Survey on cannabis use in Parkinson's disease: subjective improvement of motor symptoms. Mov Disord. 2004;19(9):1102-1106. doi:10.1002/mds.20111

10. Finseth TA, Hedeman JL, Brown RP, Johnson KI, Binder MS, Kluger BM. Self-reported efficacy of cannabis and other complementary medicine modalities by Parkinson's disease patients in colorado. Evid Based Complement Alternat Med. 2015;2015:874849. doi:10.1155/2015/874849

11. Rachel Dolhun MVPMC. Ask the MD: Medical Marijuana and Parkinson's Disease | Parkinson's Disease. Accessed November 2, 2020. https://www.michaeljfox.org/news/ask-md-medical-marijuana-and-parkinsons-disease

The Ethics of a COVID-19 Vaccine*

By: Maya MacNeil Soltysiak

To date, COVID-19 has claimed over 1 million lives worldwide. Researchers are scrambling to develop a vaccine to hinder its destruction. Vaccines function by allowing one's immune system to develop immunity to a virus[1]. "Herd Immunity" is when 70 – 90% of a population is immune to an illness, preventing the virus from spreading through the population and infecting those who are not immune[2]. While this desired state can be reached by the natural progression of a virus through a population over time, the introduction of a vaccine aims to help reach this point faster and, therefore, helps to save lives.

Vaccine development is a multi-phase process, generally completed over a period of 10 years[3], but currently researchers are trying to complete this process in one year. Many companies and research institutions are working on RNA-based COVID-19 vaccine candidates, as RNA-based vaccine development can be easier and quicker than traditional vaccine development[4]. However, an RNA-based vaccine has never been licensed for humans[5]. While the science involved in the current crisis is in itself challenging due to the novelty of the virus, this unprecedented, expedited process faces another barrier - ethics.

There are general ethical considerations applicable to vaccine development and dissemination – such as safety of the vaccine, social and scientific benefit, collaborative partnership, autonomy – however, a COVID-19 vaccine also presents unique challenges. This is because some populations are more vulnerable to getting infected with COVID-19 and to developing serious complications than others; proposed trials to quicken the development process may not be effective or ethical; and decisions must be made on resource distribution, if and when a COVID-19 vaccine is successfully developed.

COVID-19 has been found to devastate older populations and those with underlying health conditions, and has left young, healthy individuals the least affected. However, in terms of vaccine candidate testing, it is generally safest to test vaccines on young, healthy individuals – the people who have the greatest chance of recovery if adversely affected. It seems that there has been no shortage of individuals of this demographic volunteering to be participants in COVID-19 vaccine trials, through initiatives like 1DaySooner. While we must thank these courageous volunteers, their sacrifice might not be as effective as hoped. The reactions of young, healthy bodies to COVID-19 are different than older, compromised bodies, and so their reactions to a COVID-19 vaccine candidate's effects are unlikely to be fully applicable or synonymous with that of other populations[6]. This means that the data collected from these trials might not be very useful to helping those suffering the most from COVID-19. International ethical guidelines for health-related human research, however, requires that studies produce information of social and scientific value[7]. So, is the participation of these well-intentioned volunteers worth the risk? Would the data collected be truly valuable?

Another ethical aspect of vaccine development is trial design. The conventional, 'gold-standard' clinical trial design is the randomized controlled trial (RCT). This method includes injecting participants with either the experimental vaccine or the placebo or standard of care, and then monitoring to see which participants are more likely to contract the disease in daily life6. The RCT is considered to be the most ethical and reliable trial design for producing useful information and data on vaccine efficacy[8].

COVID-19 presents challenges to the RCT, however, primarily because of the urgency of the crisis at hand and the fact that it generally takes time for people to become exposed to infection in daily life. Indeed, with physical distancing, isolation and masking measures put in place by many jurisdictions to curtail the spread of COVID-19, some participants may never come into contact with the disease in order to be exposed. This has some researchers suggesting alternative trial designs, one of which is a Human Challenge Study whereby participants would be injected with either the experimental vaccine or placebo and then deliberately infected with the virus6. Because of the increased risk of disease, this method is generally only used to test alternative treatments for conditions that already have an available remedy. It is thus problematic to consider using this method to research COVID-19 since much is still unknown about the disease and there is no known cure. Can informed consent be validly given then by a participant6? Some would argue that these risks are outweighed by the benefit of decreased trial timing produced by Human Challenge Studies. However, an article in STAT News argues that a conventional trial for COVID-19 vaccine candidates would likely take just as long as a Human Challenge Study for COVID-19 because of the lack of safety data, the need for multiple doses, and the gradual expansion of the study required to obtain sufficient data6. If true, a Human Challenge Study would not provide speedier results but would arguably only carry greater risk and pose serious ethical issues.

A final matter for consideration is, if an effective COVID-19 vaccine is developed, who will receive the first doses? Frontline workers? The most susceptible? Individuals chosen by lottery? Some preliminary discussions give priority to frontline workers, vulnerable individuals, and those living and working in high-transmission settings[9,10]. Others have suggested a possible tiered system for vaccine distribution[11].

These propositions imply a mixed bioethical resource distribution model - administering the first doses of the vaccine to those who are essential to keeping society functioning and to those who need it the most. But where do developing countries stand in such a vaccine allocation plan? The resources and money at the disposal of developed countries have put many of them at the forefront of the race to develop a COVID-19 vaccine, and this may secure them the first doses of any successful vaccine. Governments are investing millions of dollars into their national research institutions and universities, hoping their scientists will be the first to succeed[11]. Further, many countries are securing orders with companies showing promising vaccine candidates - the United States and British governments, for example, have already placed orders with AstraZeneca, a global biopharmaceutical company, for their vaccine candidate[11]. This inequality in access is compounded by the unwillingness of some companies to contribute to the international sharing of COVID-19 research and information due to patent and intellectual property concerns [10]. Nevertheless, there are initiatives of solidarity being made by organizations such as GAVI - a global Vaccine Alliance working on creating equal access to vaccines for the poorest countries, and other groups pledging not-for-profit pricing for their future vaccines to help developing countries, such as Johnson and Johnson and AstraZeneca[11].

Amidst the global frenzy to develop a COVID-19 vaccine in record time, the above issues must not be ignored. The impressive consideration much of the world has shown throughout this pandemic crisis must continue, with everyone working towards a solution in an effective, ethical manner that is safe and beneficial to all.

***This article was written in June 2020 and all statistics were accurate at the time of writing**

References

1. CDC. Understanding How Vaccines Work. Published online 2018:2.

2. D'Souza G, Dowdy D. What is Herd Immunity and How Can We Achieve It With COVID-19? Johns Hopkins Bloomberg School of Public Health. Accessed October 19, 2020. https://www.jhsph.edu/covid-19/articles/achieving-herd-immunity-with-covid19.html

3. Kirkley S. It can take 10 years to develop a vaccine. How do you do it in one? Inside Canada's race for a COVID-19 vaccine | National Post. Accessed October 19, 2020. https://nationalpost.com/news/canada/it-can-take-10-years-to-develop-a-vaccine-how-do-you-do-it-in-one-inside-canadas-race-for-a-covid-19-vaccine

4. Blackburn L. RNA Vaccines: An Introduction. PHG Foundation

5. King A. RNA vaccines are coronavirus frontrunners. Chemistry World. Accessed October 19, 2020. https://www.chemistryworld.com/news/rna-vaccines-are-coronavirus-frontrunners/4011326.article

6. Rosenblatt M. Challenge trials aren't the answer to a speedy Covid-19 vaccine. STAT. Published June 23, 2020. Accessed October 19, 2020. https://www.statnews.com/2020/06/23/challenge-trials-live-coronavirus-speedy-covid-19-vaccine/

7. World Health Organization, Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-Related Research Involving Humans. CIOMS; 2017.

8. Joseph A. The response to Covid-19 is critical. It's also making clinical trials harder. STAT. Published May 5, 2020. Accessed October 19, 2020. https://www.statnews.com/2020/05/05/efforts-to-beat-back-the-coronavirus-are-critical-theyre-also-making-clinical-trials-harder/

9. Staff-Reuters. WHO hoping for coronavirus vaccine this year - National | Globalnews.ca. Accessed October 19, 2020. https://globalnews.ca/news/7084419/who-coronavirus-vaccine-hope/

10. Staff-Reuters. 37 countries pledge to share coronavirus research, vaccines and treatments - National | Globalnews.ca. Accessed October 19, 2020. https://globalnews.ca/news/7002536/coronavirus-research-share-access/

11. Cheng M, Larson C. As rich nations prepare for coronavirus vaccine, others could be left behind: experts. Global News. Accessed October 19, 2020. https://globalnews.ca/news/7079365/coronavirus-vaccines-countries/

Viability of treating HIV-associated lymphomas with autologous stem cell transplantation

By: Rachel Kuah

Autologous hematopoietic stem cell transplantation (AHCT) has been a standard treatment for lymphoma cancer patients for many years. Up until recent studies and clinical trials, however, patients infected with human immunodeficiency virus (HIV) were considered ineligible for this treatment. AHCT was widely considered unsafe for HIV-positive patients due to their immunocompromised states which contribute to an increased risk of complications such as opportunistic infections, or chemotherapy-related issues1. Fortunately, improvements to anti-HIV treatments have emerged via combined antiretroviral therapy (cART). This has allowed many HIV-related lymphoma (HRL) patients to not only become eligible candidates for AHCT, but also acquire outcomes comparable to HIV-negative lymphoma patients[1].

Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) are two major types of hematological cancers in which malignant tumors develop in the lymphatic system. Despite their differences, the link between infectious agents and increased NHL and HL incidence has been recognized for decades[2,3]. HIV infection has been noted as a primary risk factor for lymphoma cancer, with the relative risk of HIV patients developing NHL being sixty to two hundred times more than uninfected patients. Furthermore, HL is considered one of the most common malignancies developed by HIV patients[4].

A decrease in function of the immune system is a common cause of lymphoma development in HIV patients. Immunosuppression due to HIV makes the body prone to opportunistic infections such as Epstein-Barr virus, and human herpesvirus 8[4]. These viral infections can significantly increase the risk of lymphoma because they initiate and promote malignant transformations of the body's immune system through genetic mutation or dysregulation[4].

Another risk factor for lymphoma due to immunosuppression is exaggerated cytokine release that increases B-cell proliferation and thus escalates the frequency of potential cancer-causing mutations[4]. The combination of HIV having a delayed disease onset with its ability to transform when incorporated in host DNA can turn an initially non-cancerous HIV infection into the primary cause for lymphoma onset[4].

AHCT following chemotherapy can now treat relapsed or refractory HRL patients given that cART is administered concomitantly to mitigate HIV progression[5]. Refractory lymphomas are those that have been unresponsive to an array of treatments and are thus undergoing salvage therapy as a last resort. Multiple studies have shown that successful AHCT can lead to remission, otherwise known as a temporary or permanent disappearance of lymphoma malignancies[6]. As was described by Snowden et al., treating HIV-associated lymphomas with AHCT generally begins with a mobilization phase where a stimulating factor is administered to enable the extraction of stem cells from the patient's bone marrow[6]. This stimulating factor allows for the stem cells to be harvested from the peripheral blood instead of directly from the bone marrow. Following this is the conditioning phase, where the patient receives high-dose chemotherapy to target lymphoma tumors and to suppress any autoimmune inflammatory effects. At this stage, cART is typically discontinued to prevent complications between drug regimens and can be resumed post-AHCT6–8. In the transplantation phase, the extracted autologous hematopoietic stem cells can now be re-infused into the patient. The goal of stem cell transplantation is to re-establish a properly functioning immune system that was previously compromised by HIV infection and high-dose chemotherapy.

In the subsequent aplastic phase, the body has not yet produced enough immune and blood cells to reconstitute a functioning immune system. For approximately two weeks after stem cell reinfusion the patient requires various supports in the form of antibodies, transfusions, and growth factors until enough stem cells have differentiated into non-cancerous blood cells.

Many studies have concluded that AHCT is a safe and efficacious treatment for HIV-associated NHL or HL. One study by Hubel et al., showed that the non-relapse mortality (NRM) for AHCT three years after the treatment was 10% amongst the HIV-positive cohort[5]. This percentage is only slighter higher than the NRM for HIV-negative patients of 6-9%. The study by Alvarnas et al. showed that improvements to anti-HIV treatments such as cART have allowed HRL patients to obtain outcomes with success rates comparable to those of HIV-negative patients1. Various other studies coming to a similar conclusion regarding the safety and efficacy of treating HRLs with a combination of AHCT and cART indicates that HIV infection should no longer be considered a significant risk factor preventing HRL patients from being treated with AHCT8[9]. This is not to say that AHCT is exempt from complications, infections, or adverse drug events. The Alvarnas et al. study reported that 55% of their HRL patients developed infections before reaching the one-year post-treatment mark, eleven of which were considered severe cases1. There were a total of sixteen readmissions for patients, with most of these being one-year post-AHCT. Despite these cases, the researchers concluded that AHCT can still be used to treat HRL patients since these outcomes do not statistically differ from those that are HIV-negative[1].

Drug interactions also have the potential to affect the prognosis of AHCT for HRLs. Anti-HIV medications used in cART can affect drug metabolism quite significantly. One of these medications is the protease inhibitor ritonavir. Ritonavir is a P-glycoprotein inhibitor, as well as a potent inducer of the CYP3A4 drug-metabolizing enzyme that approximately 50% of drugs are a substrate for[1,10]. Extensive consideration is thus required when administering antiretroviral drugs such as ritonavir, as many have the potential to alter the desired plasma concentrations of other administered drugs[11].

Alvarnas et al. identified that drug regimens such as those with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab yield progression-free survival (PFS) rates of 73-90% in patients with HIV-associated NHL1. The success of treatments is generally dependent on various patient factors such as treatment history, patient histology, and the efficacy of past treatments. Thus, whether a patient's disease state is relapsed, or refractory must also be considered in prognoses[1]. Multiple studies have seen that the PFS and overall survival (OS) rates were uninfluenced by patient HIV stage, CD4 cell count, or viral load [5,9]. This was likely due to cART controlling HIV progression[5].

Two other potentially problematic anti-HIV drugs used in cART are zidovudine and efavirenz. Zidovudine is noted for its myelosuppressive abilities that reduce bone marrow activity and thus affect the extraction of stem cells, while efavirenz is noted for its long half-life that increases the risk of developing antiretroviral resistance1. In many cases, the drug interactions that can occur due to the cART regimen and immunosuppressant drugs used on HRL patients can be prevented given that adjustments are made. For instance, replacing efavirenz with a similar anti-HIV drug at least two weeks prior to AHCT can greatly reduce the chance of complications[1,12].

The efficacy and safety of which AHCT can treat HIV-associated lymphoma patients is supported by various studies obtaining results that do not statistically differ from studies with HIV-negative cohorts. Without clinical trials to identify the various risk factors that can occur between cART regimens and AHCT, the number of favorable outcomes that can presently be accomplished in HIV patients would not be as high as they are now. Thus, trials that study new antiretroviral agents or different methods in stem cell transplantation should continue to include HIV patients, as they may have the potential to further improve survival and remission rates.

References

1. Alvarnas JC, Le Rademacher J, Wang Y, et al. Autologous hematopoietic cell transplantation for HIV-related lymphoma: results of the BMT CTN 0803/AMC 071 trial. Blood. 2016;128(8):1050-1058. doi:10.1182/blood-2015-08-664706

2. Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. Journal of Internal Medicine. 2008;264(6):537-548. doi:10.1111/j.1365-2796.2008.02031.x

3. Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. Lancet. 1991;337(8745):805-809. doi:10.1016/0140-6736(91)92513-2

4. Grogg KL, Miller RF, Dogan A. HIV infection and lymphoma. Journal of Clinical Pathology. 2007;60(12):1365-1372. doi:10.1136/jcp.2007.051953

5. Hübel K, Re A, Boumendil A, et al. Autologous stem cell transplantation for HIV-associated lymphoma in the antiretroviral and rituximab era: a retrospective study by the EBMT Lymphoma Working Party. Bone Marrow Transplantation. 2019;54(10):1625-1631. doi:10.1038/s41409-019-0480-x

6. Snowden JA, Sharrack B, Akil M, et al. Autologous haematopoietic stem cell transplantation (aHSCT) for severe resistant autoimmune and inflammatory diseases - a guide for the generalist. Clinical Medicine (London, England). 2018;18(4):329-334. doi:10.7861/clinmedicine.18-4-329

7. Dunleavy K, Little RF, Pittaluga S, et al. The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. Blood. 2010;115(15):3017-3024. doi:10.1182/blood-2009-11-253039

8. Uldrick TS, Little RF. How I treat classical Hodgkin lymphoma in patients infected with human immunodeficiency virus. Blood. 2015;125(8):1226-1235; quiz 1355. doi:10.1182/blood-2014-08-551598

9. Schommers P, Gillor D, Hentrich M, et al. Incidence and risk factors for relapses in HIV-associated non-Hodgkin lymphoma as observed in the German HIV-related lymphoma cohort study. Haematologica. 2018;103(5):857-864. doi:10.3324/haematol.2017.180893

10. Haddad A, Davis M, Lagman R. The pharmacological importance of cytochrome CYP3A4 in the palliation of symptoms: review and recommendations for avoiding adverse drug interactions. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer. 2007;15(3):251-257. doi:10.1007/s00520-006-0127-5

11. Brown KC, Paul S, Kashuba ADM. Drug interactions with new and investigational antiretrovirals. Clinical Pharmacokinetics. 2009;48(4):211-241. doi:10.2165/00003088-200948040-00001

12. Krishnan A, Forman SJ. Hematopoietic stem cell transplantation for AIDS-related malignancies. Current Opinion in Oncology. 2010;22(5):456-460. doi:10.1097/CCO.0b013e32833d2cf0

The Drug Development Pipeline.....with some improvements

By: Nuha Maliath

The drug development pipeline is a lengthy and costly process. The discovery of a single new drug treatment, approved by the FDA, takes an average of twelve years and over 1 billion U.S dollars[1]. Additionally, there is a high degree of uncertainty surrounding the discovery of novel drug treatments. The purpose of this article is to briefly outline the drug development process and to detail some suggestions for making the pipeline more efficient.

The drug discovery pipeline starts with an extensive preclinical testing phase. Candidate small molecules (chemicals) are tested against a disease target within in-vitro models and animal species. Preclinical testing includes understanding the disease mechanism in order to find a target for a drug that can help improve the disease outcome. Target identification entails finding either a protein, DNA, or RNA that is contributing to the disease. The preclinical phase aims to study the potential therapeutic effects these molecules can have for these targets. While animal testing is required to ensure the safety of the drug. The target molecule needs to be optimized in order to be a proper fit for the disease target and be as safe as possible. Then, the results from preclinical trials of successful drug targets must be approved prior to the next phases of drug discovery.

The next three stages of drug discovery is Clinical Trials, where the drugs are tested in people. There are three parts to Clinical Trials: Phase I, Phase II and Phase III. Phase I starts with around 20-100 healthy volunteers and is performed to determine the safety and dosage of the new drug. Phase II increases recruitment with 100 to 500 volunteers, except these volunteers are patients who actually have the disease being targeted by the drug. Phase II also looks at safety but the focus now is the drug's efficacy. Finally, Phase III has 1,000 to 5,000 patient volunteers, allowing for further studies into efficacy, safety, and any unexpected reactions. Very few drugs will successfully make it out of clinical trials, but those that show promising results have to be reviewed and approved by the FDA or Health Canada.

In total the entire process, from preclinical testing to Phase II clinical trials, takes around 12-15 years. Finally, after approval the drug will enter the pharmaceutical market in what is known as Phase IV where additional surveillance is done to ensure adverse reactions are not occurring. Within all the stages of drug development, where is there room for improvement? There are many diseases in need of effective drugs, so how can the pharmaceutical industry get there more efficiently and effectively.

"The valley of death" refers to the gap between drugs that seem promising in preclinical testing but then fail to be effective in humans. Often animal models do not accurately mirror what the drug does in humans. Sometimes this means the predicted successful drug is not actually as effective or toxic to humans. Different strategies for rigorous preclinical testing must be explored that produce more predictable results in human studies. Genome wide association studies (GWAS) as a source to identify drug targets is believed to increase the probability of finding more successful drugs[2]. Studies of gene variants of a human disease can help successfully match drugs to the right target. However, the limitations to GWAS is that the sample size of human genetic data is very small and there is a limited number of diseases that have been genetically mapped.

More genetic data is required for studies to accurately translate into clinical trials. In addition to GWAS, other new technologies such as stem cells, organoids, and CRISPR can be used in preclinical studies rather than animal models. New developments in molecular biology have given a much better understanding of diseases which is especially advantageous when trying to identify more disease targets for drugs. Outside the pipeline itself, improvements in industry, academia, and governments involved with drug research should also be considered. An Open Science model with more collaborations within all industries would help with moving the drug discovery process farther along. Clinical trial information shared amongst each sector would help strengthen the reproducibility of trials and avoid resources being wasted.

Drug discovery is stretching resources while there is still so much uncertainty over the approval of new drugs. The structure of the pipeline explains why every stage is necessary, but with the discovery of new technologies, improvements to the pipeline should be prioritized.

References

1.Van Norman GA. Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs. JACC: Basic to Translational Science. 2016;1(3):170-179. doi:10.1016/j.jacbts.2016.03.002

2. Hingorani AD, Kuan V, Finan C, et al. Improving the odds of drug development success through human genomics: modelling study. Scientific Reports. 2019;9(1):18911. doi:10.1038/s41598-019-54849-w