Title

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Cancer is uncontrollable growth of harmful cells that spread throughout the body.The immune system consists of a set of cells, tissues and proteins that work together to fight off any invading pathogens or diseases in the body. The immune system is divided into two subsystems which is the innate and adaptive immune system. The innate immune system works to immediately provide defense against any invasive disease while the adaptive immune system holds memory of the specific antigens needed to fight off any diseases for future references. One of the ways that cancer manages to evade the immune system's defense mechanisms is through the programmed death ligand 1 (PD-L1) pathway where cancer manages to send repressive signals to the T cell causing it to fail to recognize or attack cancer. Immunotherapy is a form of treatment where it aid's the body's immune system to fight off any diseases present in your body. Immunotherapy enhances the body's current immune system to help fight against any diseases. Immunotherapy is attractive to individuals because it helps fight against cancer's evading mechanisms allowing to produce promising outcomes for the patient. In this review we will explore Classic Hodgkin's lymphoma disease and talk about how it can be used to treat Classic Hodgkin's lymphoma as well as other techniques to increase the survival of patients.

Classic Hodgkin's lymphoma is a cancerous disease that occurs in the lymphatic system and is known as one of the most curable cancers with 95% of the Hodgkin's lymphoma disease falling under Classic Hodgkin's lymphoma (CHL) while the other 5% falls under Nodular lymphocyte predominant Hodgkin lymphoma. The lymphatic system is made of a series of organs, tissues and cells such as B and T cells that carry nutrients and proteins to other cells and tissues. CHL occurs when there is a genetic mutation in the cell hindering the cell from undergoing normal apoptosis causing the lymphocytes to divide uncontrollably and create more cancer cells. CHL also occurs through the birth of abnormal type B cells which are called Reed-Sternberg cells that multiply and attract inflammatory cells that cause the creation of tumors . Currently there are 4 subtypes of Hodgins lymphoma which are nodular sclerosis classical Hodgkins lymphoma (NSCHL), mixed cellularity classical Hodgkins lymphoma (MCCHL), Lymphocyte-rich Hodgkin lymphoma(LRHL) and Lymphocyte-depleted Hodgkin lymphoma(LDHL). These subtypes occur because of the appearance in the cells and who they occur in. NSCHL occurs commonly for teens starting in their neck or chest. MCCHL occurs for people infected with HIV disease, mostly children and elderly. Lymphocyte-depleted Hodgkin lymphoma is a rare subtype found in elderly and people with HIV and happens in the liver or spleen. Lymphocyte-rich Hodgkin lymphoma occurs in the upper body. Demographic statistics for Hoddgkins lymphoma vary around the world but in the United states it occurs commonly in early adulthood until late adulthood. Estimated number of appearances for this disease is 4,350 males in the US and 3,940 females with a total of 910 deaths in 2024. It is mostly prevalent in early adulthood- ages 15-19 and late adulthood-50 and above with the average diagnostic age being 39.Classical Hodgkin's lymphoma has 4 stages. Stage 1 is the cancer in one of your lymph nodes, Stage 2 is the cancer in multiple lymph nodes on one side of the body, Stage 3 is the cancer on both sides of the body and Stage 4 is the cancer can be found in both above and below your body. CHL is diagnosed through a procedure called biopsy where a small amount of

cells are removed from a swollen node and if diagnosed have to go through MRI scan or PET/CT scan to find which areas of the body is affected by the disease. Most people when diagnosed with classic Hodgkin's lymphoma have about a 5 year survival rate of 80% of the people being diagnosed with it live 5 years after. People with CHL can more or less live a normal life but face symptoms such as swelling near the neck, itching, fevers and unexplained weight loss. Treatment for this disease can be chemotherapy followed by radiation or even immunotherapy. Classic Hodgkin lymphoma cells usually have the CD30 in them. Immunotherapy drug Brentuximab vedotin is an anti-CD30 antibody attached to a chemotherapy drug. The antibody acts like a homing signal, bringing the chemo drug to the lymphoma cells with CD30 on them. The drug enters the cells and kills them when they divide into new cells.

Classical Hodgkin's lymphoma copes up with the defense mechanisms of the immune system by utilizing its reed sternberg cells which are abnormal lymphocyte cells created from B cells that attach themselves onto PD-L1 and PD-L2 receptors allowing the cancer to send repressive signals to the T cell causing the immune system to fail to recognize or attack cancer. This allows the disease to escape the defense mechanism and infect other parts of the body.The Reed sternberg cells also release cytokine and chemokine secretion which attract T cells and NK cells and inhibits their cytotoxic ability allowing the cancer cells to thrive in sustainable tumor growth environment. Immunotherapy has shown promising outcomes in treating classical Hodgkin's lymphoma. In order to fight back against the Reed sternberg cells that attach themselves onto PD-L1 and PD-L2 receptors a drug called nivolumab blocks the interaction between the Reed sterberg cells and the receptors to allow T cells to to identify and fight back against cancer cells. Additionally these drugs would also help in slowing tumor growth associated with this cancer. This drug is administered as an IV where patients received 3 mg/kg every 2 weeks and led to a very high success rate of 95%. Another drug called pembrolizumab works in the same way as nivolumab with the only difference being that it has a bigger binding site on the PD-L1 receptors as compared to nivolumab. Pembrolizumab is also administered as an IV where patients receive 10 mg/kg every 2 weeks for up to 2 years until the disease is eradicated. Though both these drugs come with a high success rate for eradication for disease it comes with side effects such as diarrhea, constipation, skin rash, and fatigue. Currently both these drugs are FDA approved drugs and are well in play as treatment options for people suffering with Classical Hodgkin's lymphoma . Despite having a high success rate with these drugs there have been cases of relapses for about 10-20% of people depending on their risk factors and stage. In order to combat against the relapsed cells a new developed drug approved by the FDA is used specially for relapsed cells of CHL called brentuximab vedotin(BV). It works by attaching itself to the contaminated lymphoma cell and delivers vedotin to it to kill it. BV was also combined with the use of other methods for the best way to fight against relapsed CHL. In a study done from 2011-2020 55 patients were given BV + DHAP(dexamethasone, cytarabine, cisplatin;) which had a CR rate of 81% showcasing the use of the combination of these two methods allowed for the eradication for 81% of the disease.It was also combined with nivolumab and was given to 93 patients which resulted in a CR rate of 67%.

An ongoing phase 2 clinical trial that recruited 59 people is held in 9 locations throughout the United states and is looking to see the effectiveness of combining Nivolumab and Brentuximab vedotin in older patients with untreated CHL(NCT number 02758717). The study started on May 13, 2016 and is expected to be finished by September 9th, 2024. The trial is enrolling people over the age of 60 years and for people who have not received chemotherapy or any other checkpoint inhibitor such as Nivomulab and Brentuximab. Participants are also eligible if they currently have CHL and theiir Eastern Cooperative Oncology group(ECOG) status is either PS 0,1 or 2. The health officials will do a blood test upon registration for this study and are looking for specific scopes such as 100,000/mm^3 or greater number of Platelet counts, 3,000/mm^3 or greater number of Leukocytes, 9L or greater number of hemoglobin levels, 1500/mm^3 or greater number of Absolute neutrophil count (ANC) and, 2.0 mg or less number of Creatinine. The primary purpose of this trial is to treat the older people with nivolumab and BV drugs. Exclusion criteria for this trial includes men and women who have the potential to childbear, Co-morbid systemic illnesses such as heart disease, sensory impairment or diabetes, participants who use corticosteroid or any immunosuppressive drug and have a known history of pancreatitis. They will be given brentuximab vedotin IV over 30 minutes and nivolumab IV over 60 minutes on day 1 and will repeat every 21 days for 7 cycles and 6-8 weeks.The study's ultimate purpose is to see the effectiveness of the two drugs and also treat the current patients and after the treatment are looking for the Partial metabolic response(PMR) or Complete metabolic response(CMR) to see the effectiveness of the treatment. Another ongoing phase 2 clinical trial that has recruited 13 people is held in 5 locations across the United states. They are looking to see the effects of ipilimumab when it is given alone or in combination with Nivolumab to patients with relapsed or refractory classic Hodgkin's lymphoma(04938232). The study started on June 6th, 2021and is estimated to be completed by August 1st of 2026. Participants in this trial should have a document CHL with a tumor mass of 1.5cm or greater. These patients should have previously received systemic treatments such as autonomous stem cell transportation(ASCT) or HCT. They should have also received Nivolumab or pembrolizumab but there was still a relapse or progression of CHL after that . Patients should also be older than 18 years old and their ECOG performance status should be anywhere from PS 0-2. Patients will have a blood test and are eligible if their Absolute neutrophil count(ANC) is greater than 1.0x109/L, Platelets should be greater than75 x109/L. Finally the participants should willingly allow pre-treatment tumor samples by core needle or excisional surgical biopsy where the sample was acquired 90 days after PD1- therapy. The exclusion criteria for this study is patient is currently receiving anticancer therapy such as chemotherapy or radiation therapy, history of severe allergic or anaphylactic reactions to monoclonal antibody therapy, patients with autoimmune diseases such as asthma, patients who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, Patients with known HIV infection or hepatitis B or C infection, Patients who experienced grade 4 immune-related adverse events (irAEs) during treatment with a PD-1 immunotherapy. Patients will receive Ipilimumab alone and depending on response will receive either a maintenance course of Ipilimumab or a course of Nivolumab and Ipilimumab in combination followed by a maintenance course of Ipilimumab. Patients will receive Ipilimumab alone for 3 weeks for 4 study cycles and these patients who achieved an objective response will continue treatment with ipilimumab maintenance while the other patients will receive 4 cycles of nivolumab and ipilimumab followed by ipilimumab maintenance treatment. Patients who have progressive disease after fewer than 4 cycles of

ipilimumab are eligible to proceed to combination therapy with nivolumab and ipilimumab if they are clinically stable. Participants will receive up to 24 months of study treatment. Since both studies are still around phase 2 the treatments are relatively new and complete conclusive results are yet to be obtained.

CHL is a cancer in the lymphatic system because of the growth of Reed sternberg lymph nodes which produce harmful cells. Immunotherapy has been very successful in treating CHL with a success rate of 95% in most patients though there are cases for relapse. There are drugs being made currently to tackle them or drugs are combined in order to combat R/R(relapsed cells). Main immunotherapy drugs used to treat CHL are nivolumab and pembrolizumab which have improved outcomes and high success rates but sometimes for CHL R/R patients are given BV combined with nivolumab to eradicate the tumor. Currently researchers are mainly looking for efficient ways for treatment with lower side effects and trying to develop CAr-T therapies. Immunotherapy has the potential to revolutionize cHL treatment by offering more effective options for patients with relapsed or refractory disease and possibly improving long-term remission rates and overall survival.

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