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PD-1 VS PD-L1 Inhibitors in Metastatic Cancers

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ABSTRACT

Immunotherapy is a new and developing field with the potential to change the way medical professionals approach diseases with high mortality rates such as metastatic cancers. However, due to the little time immunotherapy has been around, there has been little testing to evaluate the effectiveness of immunotherapeutic devices in metastatic cancers. This study in particular will compare the efficacy of immunotherapeutic devices that block PD-1 inhibitors and PD-L1 inhibitors based on research available on the subject. The goal of this study is to see which immunotherapeutic drug group has the most potential as a treatment for metastatic cancers as of now and to introduce more awareness to this sort of treatment in the oncological field.

Introduction

Diseases and ailments are issues that we as humans have faced ever since our first days. As we evolved, they adapted with us, taking more of our lives. However, humanity has learned to fight back. Beginning with simple herbal remedies, we have built a medical system that has been able to brave the toughest of diseases. These advancements have taken us all the way to perhaps the pinnacle medicine - Immunotherapy.

In order to dive into the world of immunotherapy, one must understand the overarching issue that requires such drastic measures to be taken in the first place - Cancer. Cancer is an ailment that arises from genetic mishaps, where changes in genes result in incorrect information being sent to cells in how they must divide. This creates abnormal cells which continue to grow, becoming a mass or tumor. These lecherous tumors hijack resources that the body needs to function, leading to organs not getting adequate oxygen supply. As the abnormal cells continue to grow, they lead to the actual cells and organs obtaining less and less resources, eventually leading them to failure (National Cancer Institute, 2021). Metastatic Cancers specifically are the final stages of cancer. Generally classified as Stage IV Cancer, although occasionally Stage III Cancers fit this description, a Metastatic Cancer occurs when the cancerous cells spread from the original area of infection to a distant area. If a cancer spreads to another part of the body, it keeps the name of the area which it initially affected. For example, breast cancer that goes to the lungs is called metastatic breast cancer (National Cancer Institute, 2021). Metastatic Cancers can arise as they spread through the blood streams, blood vessels, and tissues of the body, which makes them especially dangerous as from these new locations, there are more vantage points for the cancer to spread. This makes immunotherapy an extremely useful asset in this scenario. Depending on where the cancer originates, it is possible to identify where the cancer can spread, which is how metastatic cancers are being treated currently. However, it is very difficult to cure cancers that reach metastasis, and often doctors are forced to just manage cancers at this level for as long as possible. By altering the way the body responds to cancers throughout itself, it is far easier to manage dreadful cancers such as metastatic cancers rather than localizing treatment to specific areas. For these reasons, this paper will aim to identify which kind of checkpoint immunotherapy is more viable for use when inhibiting the PD-1 and PD-L1 pathway of Metastatic Cancers — PD-1 inhibitor drugs or PD-L1 inhibitor drugs. The significance of this research is that a comparative analysis has not yet been done on Immunotherapy on the PD-1/PD-L1 pathways specifically in Metastatic Cancers.

Literature Review

Pathways and Proteins/Ligands

There are several different pathways within the human body which are used to regulate the production and usage of different cells and hormones. When it comes to the body's immune response to cancers, arguably, the biggest regulatory pathway is the PD-1 and PD-L1 pathway. PD-1 (Programmed Cell Death Protein 1) is a protein that is located on the surface of T-Cells, which are a special kind of lymphocyte (white blood cell), that cause the body's immune response to foreign bodies. PD-L1 (Programmed Death Ligand 1) is a protein that is located all across the body in myeloid cells, B cells, and much more. The purpose of PD-L1 is to link with PD-1 in order to prevent T-Cells from over proliferation and harming the helpful cells and proteins in the body. However, metastatic cancers generally have extremely high levels of PD-L1 on their surfaces, meaning that they react with PD-1 of T-Cells and prevent them from effectively fighting off the cancer (Han et. al, 2020). What this means is that the body is unable to produce an effective immune response to the cancer. The purpose of checkpoint inhibitors is to block or disable either PD-1 or PD-L1 so the pathway cannot be completed and the T-Cell regulation never occurs, leading to a greater response from the body's own immune system rather than using harmful chemicals that can affect non-invasive cells such as what happens in practices like radiation therapy and chemotherapy.

Checkpoint Therapy

Checkpoint inhibitor immunotherapy is perhaps the most researched form of immunotherapy. Checkpoint inhibitor immunotherapy works by blocking certain proteins in the body from attacking the body itself while it tries to fight cancer (The University of Texas, 2022). When these proteins are blocked, or inhibited, it allows the body to focus on the actual cancer rather than attack itself. The therapy is mainly used against three proteins, the CTLA-4 protein, PD-1 protein, and PD-L1 protein. These proteins, or more specifically the over production of these proteins, are the cause of the tumor confusing the body into attacking itself. These inhibitors are administered through IV (Intravenous) fluids, which generally is not a hassle as patients are usually on an IV drip already. The issue with this type of treatment is that it does have side effects as the administered items are drugs, however, they are not nearly as serious as the side effects found in treatments like chemotherapy and radiotherapy. This is where drugs such as PD-1 and PD-L1 blockers take their place. In order to prevent the combination of proteins that will disrupt T-Cell production, these blockers stop one of the proteins from activating, putting T-Cell generation in overdrive and creating an immune response powerful enough to combat the invaders within the body (National Cancer Institute, 2022). This allows for the body to fight back against its ailment without external factors hurting the components that are beneficial to it.

Relative Infancy of Immunotherapy

Checkpoint inhibitors are extremely new in terms of the medical field. The idea of forcing the body to do the work itself rather than having external forces affect it was a novel plan that was deemed impossible due to the intricacies of the human anatomy and how unpredictable its components are. In fact, the first checkpoint inhibitors were not even seen as a possible use until 2010, when checkpoint blockade was shown to have clinical success within a controlled study. It took another two years, in 2012, for a checkpoint blocker to have a successful phase 1 test trial in study (Cancer Research Institute, 2022). Essentially, immunotherapy was not even an option until just over a decade ago, making it extremely new from a scientific standpoint. However, in the past few years, immunotherapy has boosted in popularity. It has become a primary treatment option within the medical field and several more drugs have been accepted as mainstream treatment. This means that its potential for growth is extremely high, as in such a short period of time it has become a valuable asset.

Findings

To conclude the literature review, there are several forms of immunotherapy, which each in their own way pose a valid solution to the problem that is Metastatic Cancer. In their own way, the therapies either manipulate, force, or completely rewire the immune system into performing actions that lead to different kinds of results. Finding a solution is a matter of weighing the risks to the rewards, the efficiency, proficiency, and sustainability of each of these immunotherapeutic outlets. Especially in a type of immunotherapy where the variables are the different drugs used, it is vital that a sustainable solution is found for individuals who cannot afford the more expensive treatments offered. The best manner in which to proceed is performing a meta-analysis that will take all these factors into consideration to see which kind of immunotherapy outlet is the most promising in becoming the mainstream treatment for Metastatic Cancers. Based on the literature review alone, it is my hypothesis that PD-1 inhibitors will be safer and more effective as they were the first to be researched and therefore have more knowledge surrounding them in the field (Cancer Research Institute, 2022)

Methodology

Overview

This study's focus, as mentioned earlier, is to identify if protein blockage or ligand blockage would be the most effective for the treatment of Metastatic Cancers through Checkpoint Therapy in the coming future through a holistic approach that aims to help the healthcare system. This will be accomplished by cross referencing several factors across several cancers for each kind of inhibitor such as safety and efficacy. These factors will then all be taken into consideration when choosing the most effective form of immunotherapy. Results will be taken cumulatively with PD-1 and PD-L1 inhibitors being the two overall groups being compared.

Research Method

The research method that will be used for this paper is meta-analysis, that will be conducted through a naive direct comparison. A meta-analysis is a research method where several related data sets of the same set are scrutinized and the combined data is used to draw conclusions (Haidich, 2010). I will be using various sources from several reputable databases and studies (PubMed, Clinical Trials.gov, National Library of Medicine, Journal of Clinical Oncology, etc.) in order to collect the data that will be used to compare and contrast the different groups of checkpoint inhibitors. A naive direct comparison is a way to analyze data that is often used in the medical field to compare different medications to see which is more efficient. Within a naive direct comparison, no adjustments are made for discrepancies in factors of data (Kim et. al, 2013). This process was implemented into this research's methodology to analyze the data collected through meta-analysis as there are simply not enough studies done on immunotherapies and immune blockers at this time to compare them under the exact same conditions and variables. Additionally, immunotherapies are personalized, and the dosages themselves depend on each individual patient, making an exact comparison virtually impossible. For these reasons, the best way at this moment, and most likely in the future of immunotherapy, is analyzing individual case studies rather than creating a situation where a patient has to take in several kinds of drugs. When used together, the meta-analysis will allow for a variety of sources and data to be utilized during the naive direct comparison to compare the factors being observed and draw efficient conclusions. This will then be used to draw conclusions while making an assessment of the success and safety of the PD-1 Inhibitors and PD-L1 inhibitors respectively to find the immunotherapeutic device that works best. This model is the perfect fit for this kind of research as it allows for exact replication of the method, the only changes that would need to be made are the variables themselves. Additionally, the method allows for a step-by-step analysis of each factor that goes into this project, allowing for the audience to

discern for themselves what factors play the largest role within the overall success of a checkpoint inhibitor drug group. A source that inspired this study's process was "The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis", where a step-by-step approach to a meta-analysis for medical research is provided (Shirfani et. al, 2010). However, this model only analyzes one variable, while I will be analyzing 3 different cancers. This limitation will be overcome by finding the average overall safety and efficiency of each drug within one cancer and averaging out the statistics between different cancers. Finally, the statistics per drug for all cancers will be averaged with other drugs in its respective group (PD-1 or PD-L1) and then compared. Essentially, all variables will be taken into consideration, and there may be different answers for different cases of patients, such as a patient's duration under treatment or the severity of their cancer. Through sifting through the data in this manner, I will be able to analyze each drug individually, each cancer individually, as well as the holistic results between drug groups and cancers.

Selected Factors

For this paper, the observed checkpoint inhibitor groups will be focused upon drugs that block the PD-1 pathways and PD-L1 pathways. For PD-1 pathways, the drugs pembrolizumab and nivolumab will be observed. For PD-L1 pathways, Atelizolumab, Avelumab, and Durvalumab will be observed. The manner in which these types of immunotherapies were selected was that they were all the most highly researched and published drugs and pathways as they are the only immuno blockers that are currently FDA approved (Ai et. al, 2020).

The primary reason for PD-1 and PD-L1 being selected over all other pathways involved with TNBC and immune checkpoint blocking is because these are the primary pathways involved in the release of T-Cells used to kill the cancer within the body. As mentioned in the literature review, when bound to a sister protein (CTLA-4 to B7-1 or B7-2 and PD-1 and PD-L1 to each other), the body's ability to regulate T-Cells is significantly diminished, meaning there is a result of amelioration of the patient's condition. The primary reason that B7 and CTLA-4 will not be observed is because there is a lack of research on the B7 proteins and a drug has not yet been developed to counter it. Therefore, it would be impossible to juxtapose the effect the ligand has against the protein. Even with the PD-L1 and PD-1 proteins, there are several drugs within these pathways that have little to no research on them, so it is important for the right kinds of drugs to be observed in a paper such as this.

A limitation to the observation is that many of these drugs interact differently with different people as immunotherapy is personalized medicine and everybody's bodies are different, so it is vital to choose studies where the subjects of the study are kept constant.

The variables that will be looked at for this study are the Objective Response Rate (ORR), Progression Free Survival (PFS), the Overall Survival (OS), and Adverse Effects (AE) that are grade 3 or above. The ORR is the measure of patients that have any kind of positive reaction to the treatment that slightly or greatly ameliorates their case. The PFS is the amount of time the disease still exists within a patient but does not get any worse. The OS is the timeframe in which the patient stays alive from the onset of treatment. A grade 3+ AE is a side-effect of treatment that requires immediate medical treatment. Through these variables, the safety and the efficiency of the different treatments can be observed (National Cancer Institute, 2022).

The metastatic cancers that will be observed for the purposes of this study will be Breast Cancer, Colorectal Cancers, and Prostate Cancers. The reason for this is that these are the most common and deadly cancers. Breast Cancer has up to 283,000 new cases and 44,000 deaths annually, Colorectal Cancers have around 149,000 new cases and 53,000 deaths annually, and Prostate Cancers have around 249,000 new cases and 34,000 deaths annually (National Cancer Institute, 2021). Because these cancers are so widespread, it is best for a study to be done on them as they have a lot of corresponding data as the scale at which they are present allows for several studies to be done on them.

Instruments

The instruments will be rather simple, as most of the experiment will occur electronically. For communication purposes, Gmail will be used, whether it be with administrators or researchers I wish to obtain materials/resources from. For the majority of my documentation, I will be making use of either Office 360 or Google's resources, however the final document will be written on Word. For data collection, reputable databases like EBSCO and PubMed will used.

Procedure

The first step to be taken is data collection. This will be done through contacting an expert advisor and other researchers, but mainly through analysis of papers found on databases. Then context behind each pathway and drug behind checkpoint inhibition therapy in metastatic cancers explored will be collected in order to explain them within the paper before documenting data sets. Data on several aspects of the topic will then be collected, and the variables which will be observed specifically are long term and short-term success as well as safety. These data points will then be put in a table for each cancer. Then, each drug will be sorted into its own drug group, and the average of the scores for each drug will be taken, giving statistics for each type of pathway inhibitor as a whole. Finally, these statistics will be used individually as well as cumulatively to draw conclusions about which group of pathway blocker drugs are better, PD-1 or PD-L1. Some notes that need to be accounted for before observing the data are the differences in which papers report certain statistics and group-based studies. In certain studies, a paper may report the PFS or OS in terms of median months, while others may report them as percentages after a certain amount of time. A hypothetical of this could be one study reporting a PFS of 12 months while another reports the PFS as 40% at 2 months. How this difference was overcome was through a simple thought process. If the median, or middle, value of data is around 40%, when compared to a study where at a lower amount of time has passed only 40% of the group observed meets the standard, the study with the 12-month median will have been more effective as a whole. The data displayed below also displays group-based studies. In these studies, the same set of criteria was used for two separate groups, and when results were reported, some values (for example ORR) were reported individually and other values (for example PFS, OS) were reported as a mean of both groups. This was acknowledged in the data tables by shared values having superscripts with the same number attached to them (Ex: 3%[1]).

Data Analysis

Table 1. Results of ORR, PFS, OS, and AE on metastatic breast cancer when checkpoint therapy is induced.

Breast Cancer	ORR	PFS	OS	Grade 3+ AE
Pembrolizumab	37%	2.4 months	7.0 months	17.9%
Pembrolizumab	47%	8.3 months	---	4%
Nivolumab	17%	1.4 months	8.8 months	No Grade 4+
Nivolumab	6%	---	---	---
Atezolizumab	56%	7.2 months	21.3 months	22%
Avelumab	23%	25% at 5.5 months	33.3% at 15 months	14%

Within this table, for the ORR, both of Pembrolizumab's studies had relatively high values (37% and 47%), however Atezolizumab had the highest value with the singular study reporting a 56% ORR. For all the studies in the table, the PFS had similar values and there were none that particularly stood out. However, in the OS, Atezolizumab had extremely impressive results, with an OS of 21.3 months far exceeding any of the other studies present. As far as Grade 3+ AE went, all the drug groups had relatively similar levels, so no notable values were found.

Table 2. Results of ORR, PFS, OS, and AE on metastatic prostate cancer when checkpoint therapy is induced.

Prostate Cancer	ORR	PFS	OS	Grade 3+ AE
Pembrolizumab	5%	2.1 months	9.5 months	5%
Pembrolizumab	3%	2.1 months	7.9 months	5%
Nivolumab	25%	5.5 months	19 months	42.4%
Nivolumab	10%	3.8 months	15.2 months	52%
Atezolizumab	63%	6 months	22.1 months	5%
Atezolizumab	14%	3.4 months	15.2 months	11.5%
Avelumab	31%	8.4 months	14.4 months	16%
Avelumab	6%	3.6 months	11.6 months	14%

Above are the results for the data collected on Metastatic Prostate Cancer. For the ORR, Atezolizumab and Aveluab had the only notable values, with a respective 63% and 31%. The PFS was very similar between all studies and drugs, so no notable results can be concluded form that variable. The OS saw only Nivolumab and Atezolizumab with notable values (Nivolumab with 19 months and 15.2 months and Atezolizumab with 22.1 months and 15.2 months). For Grade 3+ Adverse Effects, Nivolumab and by far the highest number of cases, with both its studies having values of 42.4% and 52%.

Table 3. Results of ORR, PFS, OS, and AE on metastatic colorectal cancer when checkpoint therapy is induced.

Colorectal Cancer	ORR	PFS	OS	Grade 3+ AE
Pembrolizumab	45.1%	16.4 months	24 months	22%
Nivolumab	69%	74% at 24 months[1]	79% at 24 months[2]	22%[3]
Nivolumab	84%	74% at 24 months[1]	79% at 24 months[2]	22%[3]
Atezolizumab	2%	1.9 months	10 months	31%
Avelumab	24%	3.9 months	13.9 months	12.1%
Avelumab	81%	11.1 months	81% at 16.2 months	61%

In Metastatic Colorectal Cancer, the results were by far the most dramatic out of the three cancers observed. For the ORR the most notable results were Pembrolizumab (45.1%), Nivolumab (69% and 84%) and Avelumab (81%). For PFS, Nivolumab had the only real notable result, with 79% of patients having PFS at 24 months. For the OS, both Nivolumab and Avelumab had impressive yields, however Nivolumab edged Avelumab with 79% after 24 months versus 81% after just 16.2 months. For adverse effects, the only study that had a notably high percentage was one with Avelumab, at 61%.

Conclusions

Discussion

To understand how these results affect this study, they must be put in context in terms of the overarching research question: Due to the rise in prominence of immune checkpoint therapy as a treatment option for Metastatic Cancers, are PD-1 inhibitor drugs or PD-L1 inhibitor drugs more viable for use when inhibiting the PD-1 and PD-L1 pathway?

When observed in Metastatic Breast Cancer, the ORR of PD-1 Inhibitor Pembrolizumab and PD-L1 inhibitor Atezolizumab had very solid results, with Pemborlizumab being more consistent as the results were high in both studies, although Atezolizumab did have a higher ORR although it was only found in just one study. However, the PFS of Atezolizumab in comparison to all other drugs observed coupled with its high OR indicated that in Metastatic

Breast Cancer, PD-L1 inhibitors are more effective. Grade 3+ Adverse Effects had similar rates throughout all drug groups, so the results came out to be largely inconclusive for safety of PD-1 compared to PD-L1 Inhibitors in Metastatic Breast Cancer.

As seen in the tables above, Metastatic Prostate Cancer saw relatively high ORR levels in only Atezolizumab and Avelumab, the PD-L1 inhibitors being observed. The PD-1 inhibitors did not have notable ORR. While most of the OS was the same throughout, Nivolumab and Atezolizumab had higher results than the rest, with one study each where they shared an OS of 15.2 months and another set of studies where Atezolizumab had a slight advantage over Nivolumab (22.1 months vs 19 months). Due to the ORR being dominated by PD-L1 inhibitors and a slight advantage for Atezolizumab in the OS, the results were conclusive that PD-L1 inhibitors were more efficient in Metastatic Prostate Cancer when compared to their PD-1 counterparts. PD-L1 inhibitors were also indicated to be largely safer in Metastatic Prostate Cancer, as while all the other drugs shown had low levels of Grade 3+ Adverse Effects, Nivolumab, a PD-1 inhibitor, had two studies where close to half of the patients treated had experienced serious side effects. As such, it can be concluded that in Metastatic Prostate Cancers, PD-L1 inhibitor drugs are a safer and more effective form of treatment.

In Metastatic Colorectal Cancer, there were several high ORR yields for all drug groups, but there were 3 studies total that yielded high results for PD-1 inhibitors (Pembrolizumab and Nivolumab) in contrast to the one study yielding high results for PD-L1 results (Atezolizumab). In addition, Nivolumab's extremely high FPS overshadowed the results of all other drugs and studies for that variable. Although the OS for Atezolizumab was impressive, Nivolumab's ORR was slightly higher due to the longer duration the percentage was taken off. For these reasons, PD-1 inhibitors displayed a clear dominance for effectiveness within Metastatic Colorectal Cancer. As far as safety went, both Atezolizumab and Avelumab were the only drugs that had studies with notable Grade 3+ AE, with the PD-1 inhibitors AE staying moderate. For that reason, it can be concluded that In Metastatic Colorectal Cancer, PD-1 inhibitors not only are more effective but safer.

After analyzing the data, no conclusions can be drawn for Metastatic Cancers as a whole, disproving my initial hypothesis that PD-1 inhibitors would be safer and more efficient. The data is simply too diverse and the results within each of the cancers themselves are far too varied to reach a decisive conclusion encompassing all the cancers observed. This may be because each cancer is fundamentally different, and the way the drugs react to each cancer will differ as a consequence. Perhaps if there was more data sets available, I may have been able to go more in depth into a certain kind of cancer alone in order to reach a decisive conclusion rather than just a ground level one.

Limitations

The two main limitations of this paper are my student status as a researcher and the lack of data on this topic currently. As a high school student, it is extremely difficult to access data that is still ongoing on such a new field. The difficulty of collecting data may have been ameliorated by having more access to the databases and platforms that professionals in this field have access to. I attempted to get around this limitation by contacting a pathologist and requesting links and resources in order to search for studies done on the topic, and that was of great use for the data collection portion of this paper. The relative infancy of the topic was also a great hurdle when finding data for this paper. Research on Checkpoint inhibitors did not begin until 2000, and the first PD-1/PD-L1 inhibitor was not even approved for use until 2014 (Dobosz, 2019). Adding to this the limitation of the scope of this project being a specific kind of Cancer - Metastatic Cancers- There are very few studies to base the research upon at the moment. Perhaps if this study was redone in just a few years into the future where more ongoing studies on this topic had been completed and published, far more decisive results could be found, and it would be possible to come up with an overarching conclusion for metastatic cancers as a whole rather than just individual cancers.

Implications for Future Research

Immunotherapy, and more specifically checkpoint therapy, has a bright future in oncology. With just a couple decades of research and trials, it has grown to become one of our most formidable tools against cancer. The data presented in this study has all been from just the past decade, and though limited, it is clear that it has a major effect on patients' lives. By extending their lifespans by just a bit, it allows for patients to optimize that time with the people they love. If immunotherapy is further researched, this limited time can be transformed into a full and happy life. With more data, the method used in this may be able to be replicated and provide more effective results. This paper may serve as a first attempt at this kind of research within the topic of checkpoint therapy in metastatic cancers, and hopefully it can be used as a blueprint for future research. This kind of research may eventually be taken into consideration by doctors while deciding a treatment for their patients in the future. Overall, with the various strengths of immunotherapy as a treatment option for cancers, if the topic is looked into more, it is very possible diseases like metastatic cancers could be as treatable as the common cold.

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