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Review Article

A Role of Therapy that Targets Immune Checkpoint Proteins for the Treatment of Melanoma Brain Metastasis, Liver, Breast, Pancreatic Cancer and Pancreatic Adenocarcinoma

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ABSTRACT

Checkpoint inhibitors are a type of immune therapy used to treat different types of cancers. These drugs block different checkpoint proteins, for example, CTLA-4, PD-1, and PD-L1 inhibitors.

They block proteins that stop the immune system from attacking the cancer cells. Checkpoints are also described as a type of monoclonal antibody that antagonizes binding between B7 to CTLA-4 and PD-L1 to PD-1.

Immune checkpoint inhibitors are used to treat BARCA mutated triple-negative breast cancer (TNBCS) in patients who do not respond to chemotherapy, and also in the treatment of highly mutated and solid tumors such as brain tumors, liver, and pancreatic cancers.

Immune checkpoint inhibitors exhibit an effect on solid tumors by suppressing CTLA-4, PD-1, and PDL-1. Anti-PD-1 is less toxic than anti-CTLA-4.

For melanoma Brain metastasis immune checkpoint therapy is more effective and Combination therapy has great efficacy and less toxicity which improves overall survival rather than individual therapy.

liver cancer as hepatocellular carcinoma and cholangiocarcinoma used treatment with Genetics based therapy while using alternative immune checkpoint ligands, co-inhibitory (eg. LAG-3) or decreased t-cell infiltration causing therapy failure.

Clinical studies for pancreatic cancer have not been completed yet and treating PDA needs more research as immune checkpoint inhibitors is a new treatment against PDA. A new potent class of nivolumab, pembrolizumab, and ipilimumab have been FDA approved.

For mutated tumors, Combination therapy between checkpoint inhibitors and chemotherapy has great efficacy and improves the city of life and overall survival, rather than individual therapy when using radiation or chemotherapy alone.

Introduction

The integral function of the immune system is its ability to differentiate between self and non-self-cells. For this purpose, the immune system depends on multiple"checkpoints", which are molecules on certain immune cells that need to be activated or inactivated to start an immune reaction. Tumor cells often take advantage of these checkpoints to avoid being detected and attacked by the immune stem. A novel mode of cancer treatment is checkpoint inhibitors. (1,2)

Immune checkpoint inhibitor has been along with the standing goal of cancer research as they activate the immune system to eliminate cancer cell and produce clinically relevant responses, they work by activating anti-tumor immunity. Immune checkpoint inhibitors activate the immune system to eliminate cancer cells and produce clinically relevant responses, they work by activating anti-tumor immunity. To provide immune checkpoint inhibitor, immune therapies enhance the cell-mediated immune response against tumor cells leading to the generation of a long- term memory lymphocyte population patrolling the body to rave growth of any cells, this leads to sustain the therapeutic effect. New clinical results suggest that Combination immunotherapies offer more potent anti-tumor activity. Cancer treatments are categorized into four different classes: one of them is immune therapies which are drugs that target the induction or augmentation of anticancer immune responses (3).

Preclinical data surrounding immune checkpoint proteins, including BTLA, VISTA, CD1 60, LAG3, TIM3, and CD244 exhibit that they are potential targets for inhibition. (4) .

The checkpoint acts as the brakes of the car, they help to prevent The immune system from getting out of control and attacking the body's cells. Checkpoints will suppress the activation of the immune system and activates T-cells into action.

In a normal physiological state, the body uses an immune checkpoint to organize the time and extent of the immune response in tissues to reduce their damage. Research suggested that the immune resistance's mechanism is that tumor cells take control of certain immune checkpoint pathways, ones against T cells that are specific for tumor antigens. Because many immune checkpoints are initiated by ligands- receptor interactions, they can be readily blocked by antibodies or modulated by recombinant forms of ligands. (5).

Immune therapy referred to as the immune checkpoints
exhibit positive outcomes in very advanced and metastatic cancers. These antibodies target specific molecules on immune cells to enhance the immune system to kill cancer cells. Two promising classes of antibodies, anti- CTLA- 4, and anti- PD- 1 are used as monotherapy and as a combination.

Cancer immunotherapies in clinical development can typically be categorized into 3 major types: nonspecific or adjuvant therapies, targeted therapies, and vaccines.

First, nonspecific immunotherapies include drugs that may stimulate an immune response or drive the growth and proliferation of immune cells which target and kill cancer cells. Second, immunotherapies which are called targeted therapies like (monoclonal antibodies, mAbs, and small molecule inhibitors), and third, the vaccines that are antigens made from cancer cells designed to stimulate the immune system to attack the tumor.

ICIs described in this publication are cancer immunotherapies that are categorized under mAbs. (6,7)

T-cells in tumors do not functionally work in all cases so the strategy for the therapeutic target that acts to boost the immune system to modulate either the costimulatory or check into proteins that express is ended on the T-cell surface. (8,9)

Agents that turn on costimulatory proteins could directly activate T cells. In contrast, agents that block checkpoint proteins could enhance the immune system to activate T cells. Anti- CTLA- 4 and anti- PD- 1 are checkpoint proteins that enhance T cell function by preventing inhibitory signals.

They regulate immune responses at different levels (early and late, respectively) and by different mechanisms. (10,11)

The new appearance of immune checkpoint inhibitors eg. T-Lymphocyte antigen4 and PD-1 (programmed cell death) have a role in the treatment of solid tumors, The combination therapy between different immune checkpoint inhibitors therapies has reduced toxicity and improved the response, We make potential synergistic combinations between checkpoint Blockade and newer immune therapies.

The checkpoint Blockade (radiation, chemotherapy, and targeted therapies) and newer immune therapies (cancer vaccine, oncolytic virusea).

There are reliable biomarkers that are necessary to define patients who achieve clinical benefit with minimal toxicity in combination therapy. (12,13)

Immune checkpoints such as CTLA-4 and PD-1 play a role in T cell activation or apoptosis, subsequent Preclinical research showed their important role in the maintenance of peripheral immune tolerance and development of cancer immune therapy.

Mice deficient in immune checkpoints CTLA-4 or PD-1 develop an autoimmune-like disease. Therefore, it was surprising that single-agents-CTLA-4 and anti-PD-1 are so effective anticancer treatments in humans.

These therapies have revolutionized cancer immunotherapy as they showed for the first time in many years of research their effect on metastatic melanoma (14)

Finally, immune inhibitors have had a significant ant role in treatment treating the last two decades the US Food and Drug Administration (FDA) approvals of two different antibodies, (1) against cytotoxic T- lymphocytes antigen-4 (CTLA-4) and (2) against programmed death-1 (PD-1) for treating different types of cancer. (4).

Review

The role of an immune checkpoint inhibitor in the treatment of:

Melanoma Brain Metastasis:

Brain tumors are very rare and most of them are malignant. Glioblastoma is the most common brain tumor and the most common source of metastatic brain tumors that come from lungs, breasts, and skin. (15).

Studies reported that melanoma Brain metastasis is treated with both SRS and anti-CTLA-4 therapy as well as SRS and anti-PD-1 therapy.(16,17,18)

Tumors utilize immune checkpoints as major mechanisms of immunity. The best- characterized immune checkpoints are cytotoxic T- lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (D-1). Ipilimumab(a monoclonal antibody targeting CTLA-4), was the first immune checkpoint approved by the FDA for the treatment of advanced melanoma. (19,20)

Later, nivolumab and pembrolizumab which both are anti-PD-1 (monoclonal antibodies) also was approved by FDA for treating different types of cancer including melanoma.(14,21)

The data suggest that the combination therapy of anti -PD-1and SRS may result in greater and more rapid lesion shrinkage in the initial months after SRS than a combination between anti-CTLA-4 and SRS(22).

Preclinical studies suggest that combination therapy is more effective than individual therapies. Synergism between checkpoint blockade and radiation therapy has been shown in preclinical trials. (23).

The results suggest that immunotherapy with radiotherapy in the treatment of brain metastasis and early lesional has a synergistic effect response that is greater and more rapid. (22).

Liver cancer:

Checkpoint blocking approved its role in the management of the prognosis of liver cancer PD-1, PDL-1, CTLA-4, and B7-1 inhibition seems to be clinically effective in tumor treatment.

PD-1 is found to suppress T cell activation in peripheral tissue in the late stage while CTLA-4 is found to regulate T-cell in lymph nodes at the priming stage. (24).

Genetics-based drugs were used with immune checkpoint blockers as a therapy for liver cancer. sing radiation or chemotherapy in combination with immune checkpoint inhibitors is reported to have a synergistic effect because of their multiple mechanisms. (25)

limitations:

1-Resistance is observed to immune checkpoint therapy.

2-Mutation of cancer immunogenicity is one of the reasons for therapy failure (eg. mutation in transporters B2 microglobulin for example)

3-Using alternative immune checkpoint ligands or alternative co-inhibitory immune checkpoints (eg. LAG-3) can also be a reason for therapy failure.

4-Decreased t-cell infiltration is one of the therapy failure reasons. (18, 26 ,27,28)

Clinical trials of using immune checkpoint inhibitors for HCC and cholangiocarcinoma are under observation. Encouraging clinical outcomes were reported from an ongoing phase I/II trial of the anti-PD-1antibody nivolumab at the 2015 American Society of Clinical Oncology(ASCO)showed that decreasing the tumor size to some extent in all cohorts including uninfected, HBV Infected, and hepatitis C virus-infected HCC patients.

It was proved that nivolumab in the treatment of HCC patients was effective and patients exhibit a response. In other trials, nivolumab showed a manageable safety profile, including acceptable tolerability.

The objective response rate was 20% in patients treated with nivolumab 3 mg/kg. (12,26,29,30,31,32)

Immunotherapy is promising for HCC and cholangiocarcinoma. Despite the ability of the patient's body is responding to only one immune therapeutic drug it is recommended to use combination immunotherapy for being more durable and potent.

In phase l experiment, it was exhibited that using of radiation frequently and cold cryo-ablation extremely for tumors enhancing immune response and anti-CTLA 4 treatment. Using this mixture is safe and results increase in intratumoral CD8+ T cells and activate T cells.

A combination of ablation treatment and immune checkpoint inhibitors was suggested to be used in advanced liver cancer. Using cisplatin as the chemotherapeutic drug can decrease PD-L2 production on tumor cells. Studies show that chemotherapy can enhance anti-tumor immunity so may combine and augment immune checkpoint therapy for the treatment of liver cancer. (29,33,34)

Epigenetic modulators increase immune checkpoints on the cell surface which enhance response to immune checkpoint inhibitors therapy.

A study on the use of histone methyltransferase and histone deacetylase inhibitors (HDACi) has been investigated in affecting immunity and cancer therapy. In vivo experiment showed that in mice with melanoma that HDACi increased expression of PD-1 and PD-2 through up-regulation of histone acetylation, the combination of HDACi and PD-1 blockade led to higher efficiency in tumor progression and improving survival rate than single-agent therapy.

3-Deazaneplanocin A and 5-aza- 2′deoxycytidine, two important DNMTi, enhanced the therapeutic efficacy of PD-L1 blockade in reducing tumor volume, increasing tumor-infiltrating CD8+ T cells, and Th1 -type chemokine expression in ovarian cancer in C57/BL6 mice.

Taking a 5-azacytidine drug makes the cancer cell more sensitive to anti-CTLA 4 and was observed to be more effective than using anti-CTLA 4 or 5-azacytidine alone in a mouse model having melanoma. (9,18, 35,36,37).

Immunotherapy with chemotherapy or radiation therapy when being used as a combination, they have synergistic action which may give hope to patients who have liver cancer with a dismal prognosis.

Breast cancer:

Breast cancer has a poor prognosis and is still facing the problem of tumor recurrence, resistance rate, and relapsing while the treatment has been prolonged. Triple-negative breast cancers' survival rate is worth than estrogen receptor-positive tumors due to a high relapse rate,(TNBC) is more diagnosed in people younger age>50 and people with BRCA mutations particularly(BRCA 1 and BRCA2), So it's Treated by chemotherapy alone but it recurrence again and may cause death, the combination of therapy that achieves an effective and durable treatment response is needed. (38,39).

A breakthrough in cancer immunotherapy was the discovery of an Immune checkpoint inhibitor for the treatment of cancer in combination with chemotherapy-like platinum agents such as cisplatin. (40,41)

Combining chemotherapy with anti-CTLA-4 and anti(PD-1 /PD-L1) causes deficiency in BRCA-1 mutation of breast cancer and improvement of survival. (42)

Due to increasing in activated tumor-infiltrating cytotoxic CD8+ T cells and CD4+ T cells was accompanied by the induction of polyfunctional effector CD4+ T cells, causing a turn up from suppressive to a cytotoxic immune phenotype in TILs.

Toxicity with anti-CTLA4 is higher than with anti(PD-1 /PD-L1) due to the different distribution of ligands due to PD-1 preventing binding between PD-L1 and PD-L2 ligand (, where they found that combination may cause lots of side effects. The combination between Checkpoint inhibitor and chemotherapy shows a great result n TNBC with patient BRCA1 -mutated tumor in the clinical trial, and possibly other hypermutated breast tumors. (43,44)

Results of the animal test suggest that: No increase in toxicity was observed in mice treated with the combination compared to chemotherapy alone,

chemotherapy can act as an immunological adjuvant in the tumor microenvironment by promoting the release of tumor antigens via immunogenic cell death, thus priming DE Novo T cell responses and improving the efficacy of checkpoint blockade. (45)

Mechanism of an immune checkpoint inhibitor for the treatment of breast cancer targeting(CTLA-4)and(PD-1 /PD-L1), ICI used with patients have no response for chemotherapy alone, checkpoint protein such as PD-L1 on tumor cells and PD-1 on T cells help keep immune response in check (when PD-L1 bind with PD-1 send signal off that prevent T-cell to kill tumor cell) by blocking this binding between PD-L1 and PD-1 by using(anti-PD-L1)and(anti-PD-1) send a signal on that enable T cell to kill tumor cell, Immune checkpoint inhibitor blocking the binding of B7 to CTLA-4 by (anti-CTLA-4) activate T cell to kill the tumor.

Pancreatic cancer:

FDA approved the role of immune checkpoint inhibitors in the treatment of solid pancreatic tumors by suppressing CTLA-4, PD-1, and PDL-1 (which were forming protein-expressing tumors and weakened immune response), so by inhibiting them T-cells and immune response increased .(1,46)

Le et al observed the stable disease in five patients (two Arm A, three

Arm B), four according to RECIST (two Arm A, two Arm B) and one according to irRC (Arm B), when treated with 1 0 mg/kg Ipilimumab alone (Arm A) or in combination with GVAX-vaccine (Arm B).

Royal et al, noted delayed progression in one patient when treated with 3 mg/kg Ipilimumab.

Furthermore greater overall survival of 5.7 mo in patients treated with Ipilimumab and GVAX-vaccine, compared to 3.6 mo of Ipilimumab monotherapy was in this study noted.

Aglietta et al demonstrated a partial response in two patients with advanced pancreatic ductal adenocarcinoma, receiving 1 5 mg/kg Tremelimumab.

Among patients with pancreatic ductal adenocarcinoma, immune checkpoint therapies also appear to be effective.(5,47,48,49)

These studies are limited, these results of treatment with immune checkpoint inhibitors in PDA indicatthatat further research is needed. pancreatic adenocarcinoma (PDAC) is an exocrine pancreatic cancer that begins in the cells that line the ducts of the pancreas.PDAC is the most common type of pancreatic cancer, accounting for more than 90% of pancreatic cancer diagnoses. It has been reported that up to 10% of PDAC have a hereditary component. (50).

The extent of mutational changes in pancreatic tumors generates gene instability that appears to play an essential role in PDAC tumor growth and resistance to treatments. PDAC is the fourth most common cause of cancer-related deaths in the United States and a major health issue.

(PDAC) is a highly aggressive cancer with poor patient survival due to a lack of understanding of the etiology and tumor biology, early diagnostic markers, diverse genetics, rapid metastasis, screening, treatment of PDAC and delayed detection which is due to symptoms do not appear until the disease has progressed and metastasized to distinct sites.

Multiple studies have demonstrated that The poor prognosis and the difficulty in establishing efficacious therapeutic strategies for PDA come from the PDAC micro-environment. (51,52).

The Tumor micro-environment (TME) is characterized by dense desmoplasia and extensive immunosuppression which results in decreased stromal vascularization, altered immune cell infiltration, and hypoxia, inducing tumor growth and hindering drug activity. (53,54,55)

The surgical resection with chemotherapy provides the best treatment option for PDAC and is beneficial in patients whose cancer cells have not spread to critical abdominal vessels and adjacent organs.

Traditional treatments for PDAC are limited and ineffective such as radiation therapy or chemotherapy which despite recent advancements in systemic chemotherapeutic regimens, the median survival time of advanced pancreatic cancer patients remains 4-11 months.

During the last decades, Immunotherapy like immune checkpoint inhibitors offered encouraging results in preclinical models and several clinical trials have explored its therapeutic application in PDAC but in combination with other therapies which need more clinical research. (56,57).

clinical studies on treating PDA need more research as immune checkpoint therapy is a new treatment against PDA, A new potent class in treating different types of tumors like ipilimumab has been approved by FDA for different types of cancers and further information is needed about PDA to personalize combination treatment.

So in this research, we will study the effect of a combination between immune checkpoint inhibitors and stromal targeted therapy.

The clinical trials that are running now, describe that immune checkpoint therapy is a new and novel treatment perspective in the fight against PDA. A couple of trials are combining two of the checkpoints inhibitors, Durvalumab and Tremelimumab,

Other trials are testing checkpoint inhibitors in combination with cytostatics, in combination with a vaccine, or as monotherapy. Currently, no results from these trials are present.

Further knowledge is needed regarding the tumor of pancreatic ductal adenocarcinoma, to determine the activated immune suppressors within an individual patient's tumor to develop a personalized combination treatment. (58,59)

LAG-3(checkpoint molecule) is blocked by IMP321 (immune checkpoint blocker). There are other checkpoints TIM-3 and BTLA that can treat cancer. The combination therapy of ipilimumab and GVAX-vaccine improve survival more than monotherapy.

Cytostatic and radiation therapy leads to tumor cell death and antigen release that leads to t-cell activation in the tumor(60,61,62)

Conclusion

Immunotherapy by checkpoint inhibitor makes a breakthrough in In recent years that use immune checkpoint inhibitors to eliminate cancer cells of various types of solid tumors for example breast, pancreatic, liver, and brain tumors.

Nivolumab has been proved its efficacy and safety in hepatocellular carcinoma, on the other hand, Ipilimumab, Tremelimumab, and Durvalumab appear to be effective with pancreatic ductal adenocarcinoma. Also, Ipilimumab is approved by FDA to treat advanced melanoma.

FDA permitted the use of ipilimumab, pembrolizumab, and nivolumab which are immune checkpoint drugs for the treatment of non-small cell lung cancer and also for bladder cancer, and renal carcinoma, and lymphoma.

Combinations using immune-based therapy like vaccines, radiosurgery, chemotherapy or radiotherapy, and others with immune checkpoint inhibitors targeting CTLA-4, PD L1, and PD- 1 or a combination of multiple immune points inhibitors may be more effective in producing an anti-tumor immune response (Kyi and Postow,201 6), (Vaddepally RK, et al., 2020), like, checkpoint inhibition and SRS may be safe to administer, produce favorable survival outcomes and not increase the toxicity of therapy in the treatment of melanoma brain metastases .

Also in breast cancer, anti-PD1/PD L1 and anti-CTLA-4 can be used in different types of breast cancer, particularly in TNBC and it will increase the efficiency of treatment of breast cancer or advanced pancreatic cancer when a combination occurs between checkpoint inhibitor and chemotherapy or radiotherapy .

Finally, treatment with an immune checkpoint inhibitor shows that it needs more studies on a patient level to prove its true efficacy and it will be success.

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