Immune Checkpoint Inhibitor Therapy

- Gamma Knife stereotactic radiotherapy combined with tislelizumab as later-line therapy in pMMR/MSS/MSI-L metastatic colorectal cancer: a phase II trial analysis
- Immunotherapy for High-Grade Gliomas
- Targeting tumor metabolism to augment CD8⁺ T cell anti-tumor immunity
- BRAF/MEK inhibition induces cell state transitions boosting immune checkpoint sensitivity in BRAF(V600E)-mutant glioma
- Revised European Society of Endocrinology Clinical Practice Guideline for the management of aggressive pituitary tumours and pituitary carcinomas
- Theranostic Role of Advanced Nanotechnological Tools in Early Brain Metastases in Lung Cancer: An Updated Review
- Loss of LAPTM4A inhibits M2 polarization of tumor-associated macrophages in glioblastoma, promoting immune activation and enhancing anti-PD1 therapy
- Correlation of Peripheral Blood CD4/CD8 Ratio with Efficacy and Prognosis in Patients with Non-Small Cell Lung Cancer Receiving PD-1/PD-L1 Inhibitors

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The most well-known immune checkpoint inhibitors target molecules such as PD-1 (programmed cell death protein 1), PD-L1 (programmed death-ligand 1), and CTLA4 (cytotoxic T-lymphocyte-associated protein 4). PD-1/PD-L1 Inhibitors:

CTLA-4 Inhibitors:

CTLA-4 (Cytotoxic T-Lymphocyte-Associated Protein 4): CTLA-4 is another checkpoint protein that regulates the early stages of T cell activation. It competes with the co-stimulatory molecule CD28 to bind to B7 molecules on antigen-presenting cells. CTLA-4 Inhibitors (e.g., Ipilimumab): By blocking CTLA-4, these inhibitors enhance the activation of T cells, promoting an anti-tumor immune response. These checkpoint inhibitors have shown remarkable success in the treatment of various cancers, leading to long-lasting responses in some patients. However, not all patients respond equally to these therapies, and there can be side effects related to immune system hyperactivity.

Key points about immune checkpoint inhibitors:

Response Rates: While some patients experience significant and durable responses, not all patients respond to checkpoint inhibitors. Biomarkers such as PD-L1 expression are often used to predict responses in certain cancers.

Combination Therapies: Researchers are exploring combinations of checkpoint inhibitors or combining them with other treatment modalities, such as chemotherapy or targeted therapies, to improve efficacy.

Side Effects: Immune-related adverse events (irAEs) can occur, affecting various organs. Common side effects include skin rash, colitis, hepatitis, and endocrine abnormalities. Prompt recognition and management of these side effects are crucial.

Approved Indications: Checkpoint inhibitors have been approved for various cancers, including melanoma, lung cancer, kidney cancer, bladder cancer, and more. Ongoing research aims to expand their use to other cancer types.

Immunotherapies targeting immune checkpoints represent a paradigm shift in cancer treatment, providing new hope for patients with certain types of cancer. Ongoing research continues to refine and expand the use of these therapies.

Immune checkpoint inhibitor therapy is a revolutionary form of cancer treatment that enhances the body's immune response against cancer cells. It works by blocking certain inhibitory signals that cancer cells use to evade the immune system. Immune checkpoints are molecules on immune cells that, when activated, regulate the immune response to prevent excessive immune activity and maintain immune homeostasis. However, cancer cells can exploit these checkpoints to avoid immune attacks, allowing them to grow and spread unchecked.

Mechanism of Action: Immune checkpoint inhibitors work by targeting specific checkpoint proteins on immune cells or cancer cells. The two most well-known immune checkpoint proteins targeted by these inhibitors are:

PD-1 (Programmed Cell Death Protein 1): Found on T cells, PD-1 helps regulate immune responses. When PD-1 binds to its ligand PD-L1 (Programmed Death-Ligand 1), which is often expressed on cancer cells, it downregulates the immune response and allows cancer cells to escape detection. Checkpoint inhibitors targeting PD-1 or PD-L1 prevent this interaction, leading to enhanced T cell activity against cancer cells. CTLA-4 (Cytotoxic T-Lymphocyte-Associated Protein 4): CTLA-4 is another checkpoint protein expressed on T cells. It competes with a co-stimulatory molecule (CD28) for binding to antigen-presenting cells, thereby suppressing T cell activation. Inhibiting CTLA-4 with checkpoint inhibitors promotes T cell activation and tumor cell destruction.

Efficacy and Side Effects: Checkpoint inhibitors have shown remarkable success in certain patients, leading to durable responses and improved overall survival. However, they can also cause immune-related adverse events (irAEs) due to the activation of the immune system against normal tissues. Common irAEs include rash, diarrhea, colitis, hepatitis, thyroid dysfunction, and pneumonitis. These side effects require prompt recognition and management, often with corticosteroids or immunosuppressive agents.

Combination Therapies: Researchers are exploring combination therapies with checkpoint inhibitors to enhance their efficacy. Combining checkpoint inhibitors with other immunotherapies, targeted therapies, or conventional treatments like chemotherapy may lead to improved responses and broader treatment applicability.

Conclusion: Immune checkpoint inhibitor therapy represents a significant advancement in cancer treatment, providing new hope for patients with various malignancies. By unleashing the immune system's potential to recognize and attack cancer cells, these inhibitors have transformed the landscape of cancer therapy. Ongoing research and clinical trials continue to refine these treatments, bringing us closer to the goal of personalized and effective cancer immunotherapy for a broader range of patients. However, as with any cancer treatment, careful patient selection, monitoring, and management of potential side effects are crucial to achieving the best possible outcomes.

Indications

Immune checkpoint inhibitor therapy has been approved for various types of cancer, including

melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, and many others. However, not all patients respond to these therapies, and the response rates can vary depending on the cancer type and the tumor's microenvironment.

These are the standard of care for urological cancers such as renal cell carcinoma and urothelial cancer. Several randomized phase III trials have shown that ICIs improve overall survival (OS) compared with the standard of care and provide durable antitumor activity, even for recurrent and/or metastatic disease

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The presence of tumor-antigen heterogeneity can present a challenge for the development of effective cancer immunotherapy, which aim to harness the immune system to attack cancer cells. This is because not all cancer cells may express the same antigens, and the immune system may not recognize all the tumor cells as foreign.

One approach to overcoming tumor-antigen heterogeneity is to target multiple antigens simultaneously. This can be done by developing combination therapies that target different antigens or by using personalized therapies that are tailored to the specific antigenic profile of an individual's tumor.

Another approach is to use strategies that enhance the immune system's ability to recognize and attack tumor cells. This can be achieved by using checkpoint inhibitors that block immune system suppression or by genetically modifying immune cells to express chimeric antigen receptors (CARs) that specifically recognize tumor antigens.

Immune checkpoints are molecules in the immune system that either turn up a signal (co-stimulatory molecules) or turn down a signal. Many cancers protect themselves from the immune system by inhibiting the T cell signal.

Since around 2010 inhibitory checkpoint molecules have been increasingly considered as new targets for cancer immunotherapy due to the effectiveness of two checkpoint inhibitor drugs that were initially indicated for advanced melanoma - Yervoy, from Bristol-Myers Squibb, and Keytruda, from Merck.

see Immune checkpoint inhibitor for melanoma.

An important part of the immune system is its ability to tell between normal cells in the body and those it sees as “foreign.” This lets the immune system attack the foreign cells while leaving the normal cells alone. To do this, it uses “checkpoints” – molecules on certain immune cells that need to be activated (or inactivated) to start an immune response.

Cancer cells sometimes find ways to use these checkpoints to avoid being attacked by the immune system. But drugs that target these checkpoints hold a lot of promise as cancer treatments.

Drugs that target PD-1 or PD-L1

PD-1 is a checkpoint protein on immune cells called T cells. It normally acts as a type of “off switch” that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-

L1, a protein on some normal (and cancer) cells. When PD-1 binds to PD-L1, it basically tells the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1, which helps them evade immune attack.

Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost the immune response against cancer cells. These drugs have shown a great deal of promise in treating certain cancers.

PD-1 inhibitors: Examples of drugs that target PD-1 include:

Pembrolizumab (Keytruda)

Nivolumab (Opdivo)

These drugs have been shown to be helpful in treating several types of cancer, including melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma. They are also being studied for use against many other types of cancer.

PD-L1 inhibitors: Examples of drugs that target PD-L1 include:

Atezolizumab (Tecentriq) Avelumab (Bavencio) Durvalumab (Imfinzi) These drugs have also been shown to be helpful in treating different types of cancer, including bladder cancer, non-small cell lung cancer, and Merkel cell skin cancer (Merkel cell carcinoma). They are also being studied for use against other types of cancer.

One concern with all of these drugs is that they can allow the immune system to attack some normal organs in the body, which can lead to serious side effects in some people. Common side effects of these drugs can include fatigue, cough, nausea, loss of appetite, skin rash, and itching. Less often they can cause more serious problems in the lungs, intestines, liver, kidneys, hormone-making glands, or other organs.

Many other drugs that target either PD-1 or PD-L1 are now being tested in clinical trials as well, both alone and combined with other drugs (see What’s new in cancer immunotherapy research?).

Drugs that target CTLA-4 CTLA-4 is another protein on some T cells that acts as a type of “off switch” to keep the immune system in check.

Ipilimumab (Yervoy) is a monoclonal antibody that attaches to CTLA-4 and stops it from working. This can boost the body’s immune response against cancer cells.

Because ipilimumab affects the immune system, it can sometimes cause serious or even life-threatening side effects. In fact, compared to drugs that target PD-1 or PD-L1, serious side effects seem to be more likely with ipilimumab.

Aggressive pituitary neuroendocrine tumors (APAs) are pituitary tumors that are refractory to standard treatments and carry a poor prognosis. Current treatment guidelines are not standardized but combines surgical resection, radiation therapy, and chemotherapy. Temozolomide is the only chemotherapeutic agent with documented effectiveness and is recommended for APA in European

Society of Endocrinology clinical guidelines.

A 57-year-old man presented with visual deterioration and bitemporal hemianopsia. MRI of the brain demonstrated a sellar mass suspected to be pituitary macroadenoma with a displacement of the stalk and optic nerve impingement. The patient underwent stereotactic endoscopic transsphenoidal resection of the mass. Postoperative MRI demonstrated gross total resection. Pathology revealed a sparsely granulated corticotroph adenoma with malignant transformation. Immunohistochemistry showed a loss of expression of MLH1 and PMS2 in the tumor cells. Proton therapy was recommended given an elevated Ki67 index and p53 positivity. Before radiotherapy, there was no radiographic evidence of residual tumor. Temozolomide therapy was initiated after surveillance MRI showed recurrence at 16 months postoperatively. However, MRI demonstrated marked progression after 3 cycles. Next-generation sequencing using the MSK-IMPACT platform identified somatic mutations in MLH1 Y548lfs*9 and TP53 R337C. Immunotherapy with ipilimumab/nivolumab was initiated, and MRI demonstrated no residual tumor burden 34 months postoperatively.

APA is a tumor with frequent recurrence and a short median expected length of survival. Shah et al. demonstrated the utility of immunotherapy in a single case report of APA, with complete resolution of recurrent APA and improved survival compared with a life expectancy [1)].

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Shah S, Manzoor S, Rothman Y, Hagen M, Pater L, Golnik K, Mahammedi A, Lin AL, Bhabhra R, Forbes JA, Sengupta S. Complete Response of a Patient With a Mismatch Repair Deficient Aggressive pituitary neuroendocrine tumor to Immune Checkpoint Inhibitor Therapy: A Case Report. Neurosurgery. 2022 May 13. doi: 10.1227/neu.0000000000002024. Epub ahead of print. PMID: 35544035.