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SNI: Neuro-Oncology

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Editor: **Ekkehard Kasper,** M.D., Harvard Medical School, Boston, MA, USA

Editorial

Immune checkpoint inhibitors: Advances and impact in neuro-oncology

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Received: 21 October 18 Accepted: 27 November 18 Published: 25 January 19

Key Words: Immune checkpoint inhibitors, immunotherapy, T-cells, Nobel prize, James P. Allison, Tasuko Honjo, neuro-oncology

INTRODUCTION

The Nobel Assembly, consisting of 50 professors at the Karolinska Institutet, in Sweden, awarded the 2018 Nobel Prize in Physiology or Medicine jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation.[29]

Dr. James Allison is an American immunologist who holds the position of professor and chair of immunology at the University of Texas M.D. Anderson Cancer Center. Dr. Tasuku Honjo is a Japanese immunologist who is a professor of immunology at Kyoto University.[29] Allison and Honjo explored different mechanisms that halt the immune system and can be used in the treatment of cancer. They studied two different proteins, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), respectively.[28] When these proteins were inhibited using checkpoint inhibitors, the immune system was unleashed to attack tumors [Figure 1]. Therapies based on these discoveries proved to be highly efficient against certain forms of cancer.

Clinical studies exploring the effects of CTLA-4 and PD-1 blockades have been dramatic. The treatment agents that are referred to as "immune checkpoint inhibitors," have completely altered the outcome for certain groups of patients with advanced cancer. In tumors of the central nervous system (CNS) though, their effects remain to be seen. In this paper, we explore the impact of immune checkpoint inhibitors on CNS-related neoplasms and discuss the latest advances targeting CTLA-4 and PD-1 in neuro-oncology.

CTLA-4 TARGETTED IMMUNOTHERAPY

In 1996, James Allison, lead investigator in his laboratory at University of California, Berkeley, published in *Science* his observation that CTLA-4, a protein known as a target in the treatment of autoimmune diseases, is a negative regulator of T-cell activation.[17] His *in vivo* studies in mice showed that administering antibodies to CTLA-4 resulted in the rejection of tumors, including pre-established tumors.

Access this article online	
Quick Response Code:	Website: www.surgicalneurologyint.com
	DOI: 10.4103/sni.sni_366_18

How to cite this article: Fares J, Fares MY, Fares Y. Immune checkpoint inhibitors: Advances and impact in neuro-oncology. Surg Neurol Int 2019;10:9. http://surgicalneurologyint.com/Immune-checkpoint-inhibitors:-Advances-and-impact-in-neuro-oncology/

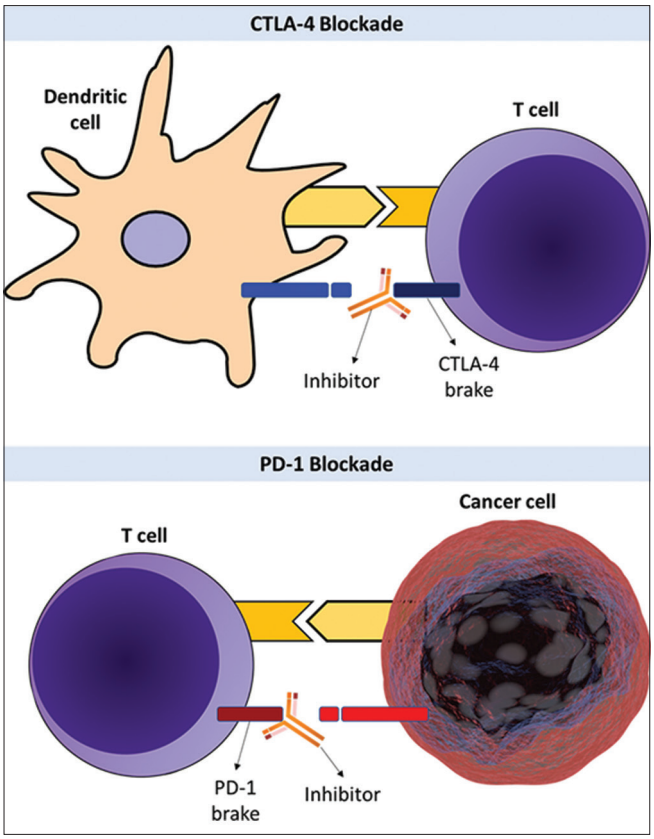

Figure 1: ***Upper half*****: cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) checkpoint protein functions as a brake on T-cells that inhibits T-cell activation. CTLA-4 inhibitors block the function of the brake leading to activation of T-cells and attack on cancer cells.** ***Lower half*****: programmed cell death protein 1 (PD-1) is another checkpoint protein that functions as a brake that inhibits T-cell activation. PD-1 blockade inhibits the function of the brake leading to activation of T-cells and highly efficient attack on cancer cells**

Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. He concluded that the blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells. One year after, another paper was published by his group in the *Proceedings of the National Academy of Sciences*,[15] whereby they demonstrated that *in vivo* antibody-mediated blockade of CTLA-4 enhances antiprostate cancer immune responses in murine models. The therapeutic response raised by anti-CTLA-4 administration ranges from marked reductions in growth to complete rejection of the tumor cells. These experiments suggested that appropriate manipulation of T-cell inhibitory signals may provide a fundamental and highly adaptable basis for prostate cancer immunotherapy. Further clinical studies in other cancer groups continued to show that CTLA-4 antibody blockade increases tumor immunity in some previously vaccinated patients who had advanced ovarian cancer or metastatic melanoma.[10] In 2010, exciting results from an important clinical study showed that ipilimumab, which is a drug based on the CTLA-4 antibody, cleared advanced late-stage melanoma in 22% of patients in clinical trials, for 3 years or longer.[11] In 2011, the Food and Drug Administration (FDA) approved ipilimumab as a treatment for metastatic melanoma.

DISCOVERY OF PD-1

In 1992, 4 years before Allison's observations on CTLA-4 were published, Tasuko Honjo discovered PD-1 as a novel member of the immunoglobulin gene superfamily. His new observation published in *The EMBO Journal* suggested that the PD-1 protein may be involved in the classical type of programmed cell death.[12] In 1999, Honjo *et al.* published another study in *Immunity*,[23] which showed that inducing a mutation in the PD-1 gene, and thus inhibiting its activity, augmented T-cell proliferation and activity. This suggested that PD-1 serves as a negative regulator of immune responses. One year later in the *Journal of Experimental Medicine*,[7] Honjo *et al.* described that the ligand of PD-1 (PD-L1) plays a central role in the inhibition of T-cell receptor-mediated lymphocyte proliferation and cytokine secretion. PD-1 and PD-L1 engagement may subsequently determine the extent of immune responses at sites of inflammation. In 2005, Honjo's laboratory published another study in *International Immunology* that reported that PD-1 blockade not only augments the antitumor activity of T-cells but can also inhibit the hematogenous dissemination of cancer cells.[13] As metastasis is the major cause of death in cancer patients, PD-1 blockade was effective in inhibiting melanoma metastasis to the liver, and colon cancer metastasis to the lungs. These results cemented PD-1 blockade as a powerful tool for the treatment of hematogenous spread of various tumor cells. Further studies showed that anti-PD-1 antibodies enhance human natural killer cell function through trafficking, immune complex formation, and cytotoxicity toward cancer-specific cells.[3] Clinical progress followed and, in 2012, trials demonstrated that experimental drugs that block PD-1 and its activating ligand, PD-L1, have clear efficacy in the treatment of patients with different types of metastatic cancers.[30]

IMPACT IN NEURO-ONCOLOGY

The development of immune checkpoint inhibitors targeting CTLA-4 and PD-1 has significantly improved the treatment of a variety of cancers, such as metastatic melanoma, non-small cell lung cancer, and renal cell carcinoma. Nevertheless, little has been said about the effect of these inhibitors on CNS-related neoplasms.

Glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor (46%), as well as

the deadliest.[20] Its 5-year survival rate is ≤5% and it maintains the status of being incurable. Current therapeutic approaches comprise surgical resection, radiation, and chemotherapy.[27] Still, despite aggressive treatments, GBM recurs. Recent advancements and the introduction of new therapeutic drugs, such as temozolomide, modestly improved survival. Therefore, new and innovative approaches for GBM treatment are needed.

Preclinical studies corroborate that CTLA-4 blockade has shown positive results in animal models of GBM. After blockade of CTLA-4, there was an increase in number of CD4 T cells with improved function.[6] Significant survival benefits have been shown in mouse models when combining a CTLA-4 inhibitor with other treatments, such as interleukin-12, tumor vaccine, and radiation therapy.[1,2,31] The benefits observed in these translational studies along with the successes seen in treating other non-CNS tumors in humans revealed the potential of targeting CTLA-4 in human glioma therapy. Ipilimumab, a CTLA-4 blocking monoclonal antibody, is currently in trial for malignant gliomas, after it has been FDA-approved for malignant melanomas.

PD-1 is highly expressed in GBM[4,32-34] and the tumor microenvironment.[5] Clinically, nivolumab, a fully human monoclonal antibody that inhibits PD-1 receptors, has provided benefit in multiple cancer types, including melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, ovarian cancer, gastric cancer, and head and neck cancers.[18] In GBM, nivolumab did not improve overall survival or overall response rate when compared with bevacizumab.[25] Nonetheless, responses with nivolumab were more durable. The limited effectiveness of immunotherapies in GBM is because these tumors have few T-cell infiltrates and low tumor mutation burden. This results in fewer cancer-specific neoantigens and poor tumor immunogenicity thus leading to poor responses to immunotherapy. Ongoing studies on GBM are currently evaluating the therapeutic effects of nivolumab in combination with other treatment regimens, such as radiation therapy and temozolomide.

Table 1: Immune-related adverse effects of immune checkpoint inhibitors

Adverse event	Incidence	Presentation/findings	Management
Rash and/or Pruritus	Most common: 50% with CTLA-4 inhibitors, 40% with PD-1 inhibitors and 60% with combination of inhibitors	Faintly erythematous, reticular, and maculopapular rash across the limbs and trunk Rare: Bullous pemphigoid, Stevens-Johnson syndrome and Sweet syndrome	Supportive care. Prednisone (in severe cases)
Diarrhea and/or Colitis	Common	Diarrhea Abdominal computed tomography: Mild diffuse bowel thickening or segmental colitis	Antidiarrheal agents, fluids and electrolytes
Hepatitis	Common	Elevations in levels of aspartate transaminase, alanine transaminase and, occasionally, bilirubin	Prednisone
Hypophysitis (pituitary inflammation)	Common: 10% with CTLA-4 inhibitors, 1%-7% with PD-1 inhibitors	Fatigue, headache, hypogonadism, hypotension, hypoglycemia Brain magnetic resonance imaging: Enhancement and enlargement of the pituitary Blood tests: low adrenocorticotropic hormone, thyrotropin, luteinizing hormone, follicle-stimulating hormone, growth hormone, and/or prolactin levels	Prednisone and hormone replacement
Pneumonitis	Rare (<10%)	Upper respiratory infection, new cough, shortness of breath or hypoxia Chest computed tomography: bilateral consolidative, ground glass opacities predominantly in peripheral distribution and interlobular septal thickening in basilar and peripheral distribution	Prednisone. Bronchoscopy and hospitalization (in moderate-severe cases)
Pancreatitis	Rare	Pain, radiographic findings of an inflamed pancreas, or elevated amylase and lipase levels	Prednisone
Hematologic toxicities	Rare	Anemia, neutropenia, and pure red cell aplasia	Discontinuation of therapy, prednisone, and blood transfusion (if needed)
Neurologic Toxicities	Rare (<5%)	Sensory neuropathies, aseptic meningitis, temporal arteritis, myasthenia gravis and Guillain-Barré syndrome Blood test: high white blood cell count (increased lymphocytes)	High-dose methylprednisolone and/or plasmapheresis. Discontinuation of therapy, intravenous immunoglobulin and/or supportive medications (in severe cases)

CTLA-4=cytotoxic T-lymphocyte-associated antigen 4, PD-1=programmed cell death protein 1

Metastatic brain tumors

Brain metastases outnumber primary malignant brain tumors with a ratio of 10 to 1.[22] The most common sources of metastatic brain tumors are malignancies originating in the lungs (39%), breast (17%), and skin (11%).[24] Prognosis following a diagnosis of metastatic brain disease is poor, with the average 2-year survival rate reported to be 8%.[9]

Studies have shown that immune checkpoint inhibitors are effective in the treatment of brain metastases from malignant melanoma and non-small cell lung cancer.[16] Nivolumab and the combination of nivolumab and ipilimumab improve response rates and progression-free survival in clinical trials of patients with metastatic melanoma.[19] Findings support the use of nivolumab plus ipilimumab as first-line therapy in patients with asymptomatic untreated brain metastases.

Immune-related adverse events

Despite the effective antitumor immune response induced by these inhibitors, immune checkpoint blockade can result in inflammation of any organ. Inflammatory adverse effects that result from the treatment are known as immune-related adverse events. In general, PD-1 inhibitors have a lower incidence of immune-related adverse events compared with those that block CTLA-4. In addition, combination of nivolumab and ipilimumab has a higher rate of immune-related adverse events than either approach as monotherapy.[8] Adverse effects commonly include rash, colitis, hepatitis, endocrinopathies, and pneumonitis [Table 1].[8,26] Other studies have shown nephrotoxic side effects, such as acute interstitial nephritis and autoimmune kidney disease.[21] A multidisciplinary team approach is warranted to insure the right diagnosis and proper management of these side effects.

Cost of therapy

Therapies with immune checkpoint inhibitors are quite expensive. The average annual cost of treatment with each drug can surpass $100,000. Managing the immune-related adverse events will also add to the tally. This makes it much harder to make decisions on the sequence of treatments and the dosing schedule. Policymakers must be informed about the value of these treatments to develop cost-effective strategies for therapy. For example, Kohn *et al.*[14] developed a model that compared cost-effectiveness of different strategies for sequencing novel agents for the treatment of advanced melanoma. They found out that for patients with a specific subtype of advanced melanoma, first-line pembrolizumab every 3 weeks followed by second-line ipilimumab or first-line nivolumab followed by second-line ipilimumab are the most cost-effective, immune-based treatment strategies for metastatic melanoma.[14] Similar models in other cancers targeted with immune checkpoint inhibitors are necessary.

CONCLUSION

The discovery and evolution of immune checkpoint inhibitors is one of the most exciting advances in cancer immunotherapy. Non-CNS tumors, specifically, have experienced impressive responses with long-lasting survival benefits. Early preclinical work has demonstrated that immunotherapy may potentially hold similar promise for GBM and metastatic brain cancers; however, more studies on the patient level are required to validate its true efficacy. As CNS tumors can develop multiple mechanisms for immune-resistance, combinations using multiple checkpoint inhibitors targeting both CTLA-4 and PD-1, with or without other immune-based strategies may be the most effective means in generating an antitumor immune response. In addition, discovering new checkpoint proteins and targeting the immune active microenvironment of CNS tumors can be vital to overcome potential resistance mechanisms. Awareness and multidisciplinary management of immune-related adverse events and developing cost-effective strategies for treatment are also necessary to ensure the optimal clinical benefit from these therapeutic agents.

REFERENCES

1. Agarwalla P, Barnard Z, Fecci P, Dranoff G, Curry WT. Sequential immunotherapy by vaccination with GM-CSF-expressing glioma cells and CTLA-4 blockade effectively treats established murine intracranial tumors. J Immunother 2012;35:385-9.
2. Belcaid Z, Phallen JA, Zeng J, See AP, Mathios D, Gottschalk C, *et al.* Focal radiation therapy combined with 4-1BB activation and CTLA-4 blockade yields long-term survival and a protective antigen-specific memory response in a murine glioma model. PLoS One 2014;9:e101764.
3. Benson DM, Bakan CE, Mishra A, Hofmeister CC, Efebera Y, Becknell B, *et al.* The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: A therapeutic target for CT-011, a novel, monoclonal anti-PD-1 antibody. Blood 2010;116:2286-94.
4. Berghoff AS, Kiesel B, Widhalm G, Rajky O, Ricken G, Wöhrer A, *et al.* Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma. Neuro Oncol 2015;17:1064-75.
5. Bloch O, Crane CA, Kaur R, Safaee M, Rutkowski MJ, Parsa AT. Gliomas promote immunosuppression through induction of B7-H1 expression in tumor-associated macrophages. Clin Cancer Res 2013;19:3165-75.
6. Fecci PE, Ochiai H, Mitchell DA, Grossi PM, Sweeney AE, Archer GE, *et al.* Systemic CTLA-4 blockade ameliorates glioma-induced changes to the CD4+ T cell compartment without affecting regulatory T-cell function. Clin Cancer Res 2007;13:2158-67.
7. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, *et al.* Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027-34.
8. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: A review. JAMA Oncol 2016;2:1346-53.
9. Hall W, Djalilian H, Nussbaum E, Cho K, Wa H. Long-term survival with metastatic cancer to the brain. Med Ontol 2000;17:279-86.
10. Hodi FS, Mihm MC, Soiffer RJ, Haluska FG, Butler M, Seiden MV, *et al.* Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. Proc Natl Acad Sci U S A 2003;100:4712-7.
11. Hodi FS, O'day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, *et al.*

Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
12. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 1992;11:3887-95.
13. Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int Immunol 2004;17:133-44.
14. Kohn CG, Zeichner SB, Chen Q, Montero AJ, Goldstein DA, Flowers CR. Cost-effectiveness of immune checkpoint inhibition in BRAF wild-type advanced melanoma. J Clin Oncol 2017;35:1194.
15. Kwon ED, Hurwitz AA, Foster BA, Madias C, Feldhaus AL, Greenberg NM, *et al*. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. Proc Natl Acad Sci U S A 1997;94:8099-103.
16. Lauko A, Thapa B, Jia X, Ahluwalia MS. Efficacy of immune checkpoint inhibitors in patients with brain metastasis from NSCLC, RCC, and melanoma. J Clin Oncol 2018;36:214-214. doi: 10.1200/JCO.2018.36.5_suppl.214.
17. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734-6.
18. Lipson EJ, Forde PM, Hammers HJ, Emens LA, Taube JM, Topalian SL. Antagonists of PD-1 and PD-L1 in cancer treatment. Semin Oncol 2015;42:587-600.
19. Long GV, Atkinson V, Menzies AM, Lo S, Guminski AD, Brown MP, *et al.* A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mets): The Anti-PD1 Brain Collaboration (ABC). J Clin Oncol 2017;35 (15_suppl):9508-9508. doi: 10.1200/JCO.2017.35.15_suppl.9508.
20. Luksik AS, Maxwell R, Garzon-Muvdi T, Lim M. The role of immune checkpoint inhibition in the treatment of brain tumors. Neurotherapeutics 2017;14:1049-65.
21. Menke J, Lucas JA, Zeller GC, Keir ME, Huang XR, Tsuboi N, *et al.* Programmed death 1 ligand (PD-L) 1 and PD-L2 limit autoimmune kidney disease: Distinct roles. J Immunol 2007;179:7466-77.
22. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep 2012;14:48-54.
23. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 1999;11:141-51.
24. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases: Histology, multiplicity, surgery, and survival. Cancer 1996;78:1781-8.
25. Reardon DA, Omuro A, Brandes AA, Rieger J, Wick A, Sepulveda J, *et al.* OS10. 3 randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: CheckMate 143. Neuro Oncol 2017;19(Suppl 3):iii21.
26. Solinas C, Porcu M, De Silva P, Musi M, Aspeslagh S, Scartozzi M, *et al.* Cancer immunotherapy-associated hypophysitis. Semin Oncol 2018;45:181-6.
27. Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
28. Tang Prize. First Tang Prize for Biopharmaceutical Science Awarded to James P. Allison, PhD, and Tasuku Honjo, MD, PhD. Tang Prize 2014. Available from: http://www.tang-prize.org/en/media_detail.php?cat=24&id=396. [Last accessed on 2018 Oct 18].
29. The Nobel Prize in Physiology or Medicine 2018. NobelPrize.org. Nobel Media AB 2018. Available from: https://www.nobelprize.org/prizes/medicine/2018/summary/. Last accessed on 2018 Oct 18].
30. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, *et al.* Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
31. vom Berg J, Vrohlings M, Haller S, Haimovici A, Kulig P, Sledzinska A, *et al.* Intratumoral IL-12 combined with CTLA-4 blockade elicits T cell–mediated glioma rejection. J Exp Med 2013;210:2803-11.
32. Wilmotte R, Burkhardt K, Kindler V, Belkouch MC, Dussex G, Tribolet Nd, *et al.* B7-homolog 1 expression by human glioma: A new mechanism of immune evasion. Neuroreport 2005;16:1081-5.
33. Wintterle S, Schreiner B, Mitsdoerffer M, Schneider D, Chen L, Meyermann R, *et al.* Expression of the B7-related molecule B7-H1 by glioma cells: A potential mechanism of immune paralysis. Cancer Res 2003;63:7462-7.
34. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8:467-77.