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Leading the Charge by Dr. Rahul Ravilla: The Newer Immune-Related Side-Effects Impacts Continuity of Care in Individuals with Cancer on Immune Checkpoint Inhibitors

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Immunotherapy agents for treatment of cancer have been explored for several decades, but effective drugs have only recently been identified and are increasingly being used in multiple cancer types. In parallel, there is growing recognition of adverse side effects in multiple organ systems mediated by dysregulation of the immune system, which can be exacerbated by co-morbidities often found in cancer patients such as diabetes, chronic lung diseases, and hypertension. These often results after several months of initiation of the immunotherapy. As a result, internists and other non-oncology clinicians are routinely encountering immunotherapy patients in the continuity clinics, who present with a varied range of symptoms. These information and enhancement of health literacy is being facilitated with novel contributions of Dr. Rahul Ravilla, a consultant hemato-oncologist with deep passion in high-value chronic care of cancer patients.

An accurate diagnosis is critical in these often complex clinical settings in which the consequences of the underlying cancer and other comorbidities must be distinguished from the variable manifestations of treatment toxicity. Dr. Rahul Ravilla is pioneering in his roles in helping the medical community identify these stochastically appearing symptoms. Dr. Ravilla started his pioneering clinical contributions while serving his Fellowship at the world renowned Winthrop Rockefeller Cancer Institute, an affiliate of the University of Arkansas for Medical Sciences. In a first of its kind study, Dr. Ravilla and his group reported three cases of immunotherapy-related sarcoidosis-like syndrome/lymphadenopathy; two cases occurred during adjuvant ipilimumab for stage III surgically resected melanoma and one case during pembrolizumab for stage IV metastatic melanoma (1). Immunotherapy with checkpoint inhibitors has revolutionized the management of metastatic melanoma. These checkpoints, namely the cytotoxic T lymphocyte antigen 4 and the programmed T cell death 1 receptor, possess an inhibitory effect on the T cell function. Pharmacologic inhibition of cytotoxic T lymphocyte antigen 4 with ipilimumab and programmed T cell death 1 with either pembrolizumab or nivolumab has resulted in long-term sustained responses among patients with metastatic melanoma. The adverse events of these medications are predominantly immune related, as elaborated by Dr. Ravilla for the first time and validated by numerous clinical investigators across the globe. Sarcoidosis-like syndrome/lymphadenopathy represents a challenging adverse event to the oncologist as it can be mistaken for progressive disease. Hence, awareness of such adverse event and obtaining a biopsy of the enlarged lymph nodes will confirm the diagnosis and avoid the unnecessary change of current therapies for those with stage IV disease or adding new ones for those with stage III disease. These studies led by Dr. Ravilla and his team are truly original and novel in its scope.

Over the last two decades, molecular-targeted agents have become mainstream treatment for many types of malignancies and have improved the overall survival of patients. However, most patients eventually develop resistance to these targeted therapies. Recently, immunotherapies such as immune checkpoint inhibitors have revolutionized the treatment paradigm for many types of malignancies. Immune checkpoint inhibitors have been approved for treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck squamous cell carcinoma, Hodgkin's lymphoma, bladder cancer and gastric cancer. However, oncologists have been faced with immune-related adverse events caused by immune checkpoint inhibitors; these are generally mild but can be fatal in some cases. Dr. Ravilla has established his accomplishments as a clinician extraordinaire by identifying and reporting these advanced complaints (1-3). Because immune checkpoint inhibitors have distinct toxicity profiles from those of chemotherapy or targeted therapy, many oncologists are not familiar with the principles for optimal management of immune-related adverse events, which require early recognition and appropriate treatment without delay. To achieve this, oncologists like Dr. Ravilla has taken key steps in educating patients and health-care workers, develop checklists of appropriate tests for immune-related adverse events and collaborate closely with organ specialists. Clinical questions that remain include whether immune checkpoint inhibitors should be administered to patients with autoimmune disease and whether patients for whom immune-related adverse events lead to delays in immunotherapy should be

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retreated. Dr. Ravilla has also demonstrated that these newer agents have the ability to cause pancytopenia and bone marrow suppression similar to the more traditional cytotoxic therapies (2). The predicted use of combination immunotherapies in the near future means that oncologists will face a higher incidence and severity of immune-related adverse events.

Checkpoint inhibitors have been approved for use in different malignancies including metastatic melanoma, advanced non-small cell lung cancer, metastatic renal cell carcinoma, refractory Hodgkin's lymphoma, advanced bladder cancer, and advanced head and neck cancer, and the list continues to grow. In general, these agents seem to be well tolerated in most patients and apparently less toxic compared to conventional chemotherapy. However, the toxicities here, termed immune-related adverse events (irAEs), are unique and different from the traditional complexities arising out of conventional chemotherapy. There is no prospective data on these toxicities and clinical adversities, and guidelines or recommendations are only based on symptomatic management from the ongoing clinical trials. Treating oncologists need to be aware and alert themselves to the subtleties in presentation and the differences in the way the irAEs needs to be managed. Although most irAEs are low-grade and manageable, they have the potential to emerge as life-threatening and turn out a rapid downhill course if not promptly treated. Additionally, irAEs could even lead to death, if managed incorrectly. Dr. Ravilla is showing the beacon for the clinicians and the oncologists in this regard. Many of these patients have to follow-up with their primary care physicians during routine segments of their therapies. As a result, it is very important that primary care physicians are made aware about these complications as well.

The pioneering work of Dr. Ravilla is highly significant in terms of treating elderly individuals with these immunotherapy agents. Monoclonal antibodies targeting immune checkpoint molecules CTLA-4, PD-1 or PD-L1 are emerging as promising anticancer therapeutics in multiple cancer subtypes resulting in remarkable and long-lasting clinical responses. These immune checkpoint blockers (ICBs) have already obtained approval for the treatment of patients with metastatic melanoma, advanced/refractory non-small cell lung cancer and kidney cancer. ICBs enhance immune responses against cancer cells but can also lead to inflammatory side effects called immune-related adverse events (irAEs). Such toxicities are distinct from those associated with traditional chemotherapeutic agents or molecularly targeted therapies. Although severe irAEs remain rare (~10% of cases under monotherapy), they can become life-threatening if not anticipated and managed appropriately. As malignancies are frequently diagnosed in older patients, ICB treatment of elderly presents a unique challenge. However, the knowledge about efficacy and toxicity of these molecules in this specific population is limited, as most of the studies have involved a low number of older patients. With his long and intense clinical experience, both as an internist and a hemato-oncologist, Dr. Ravilla is at the forefront of showcasing the path for the chronic care of these newer agents and bringing hope both for the elderly patients and their caregivers alike. With an aging America, the influence of these findings are apparent!

The increased understanding of the human immune system and emergence of immune modulation techniques have led to a new era in cancer therapy, and the idea of using our own biology to treat cancer is a revolutionary segment of oncology. To ensure the immune system does not cause harm the human host when reacting to a foreign antigen, humans have evolved immune checkpoint proteins and mechanisms to quickly halt an immune response. However, in the case of cancer, malignant cells have developed several mechanisms to evade the human immune system, including the ability to limit immune responses through such immune checkpoints. New cancer therapies have made use of the accumulating knowledge regarding immune regulation and immune system checkpoints; for example, cytotoxic T-lymphocyte antigen 4 (CTLA4) and the programmed cell death 1 (PD1) pathway. Interestingly, a correlation seems to exist between overall patient survival and the incidence and severity of IRAEs. This trend might be due to the monitoring of patients for longer time and the bias resulting from extended duration of symptomatic observation. However, the correlation could also be the effect of autoimmunity being indicative of a nonspecifically hyperactive immune system resulting in increased antitumor efficacy. This notion is supported by a decrease in cancer-specific mortality in patients who also experience IRAEs, including endocrine IRAEs. With the increased clinical application of immunotherapeutics, understanding the occurrence, detection and management of IRAEs in the patient population is important. Major advances in the understanding of the immune response in cancer have led to rapid progress in clinical immunotherapy trials in the past decade, some of which are being led by Dr. Ravilla himself. Although immunotherapies lack the traditional profile of chemotherapy-related adverse effects, a rare, yet major set of IRAEs has emerged. In clinical trials, an increased susceptibility to hypophysitis in those treated with CTLA4-targeted immunotherapy has been revealed. PD-1-targeted treatments have been predominately linked with primary thyroid dysfunction, along with a few cases of type 1 diabetes mellitus.

Despite the current clinical understanding of IRAEs, which has led to effective treatment strategies with hormonal replacement and other appropriate therapies, additional studies are needed to further understand the clinical characteristics and chronology of these adverse effects and clarify the mechanism by which immunotherapy results in endocrinopathies and other multiorgan dysfunctions. Dr. Ravilla's clinical accomplishments merits unrestricted applaud in this aspect. Several other clinician investigators are building upon this work and evaluating the newer avenues for management of these emergent clinical conditions. Dr Ravilla is a leader in cancer immunotherapy research as a clinician-scientist. As a principal investigator of several important clinical trials, his studies have contributed to the approval of ipilimumab for use in advanced melanoma. The clinical use of immune checkpoint inhibitors is expanding rapidly. Oncology

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practitioners will therefore be required to recognize and manage irAEs in a growing patient population. Early recognition and treatment are essential to prevent patient morbidity and mortality, and adherence to established algorithms is highly recommended. Immune checkpoint inhibitors are already part of oncologists' therapeutic arsenal as effective therapies for otherwise untreatable neoplasia, such as metastatic melanoma or lung cancer. Their use is expected to increase exponentially in the near future as additional agents become available and their approval is extended to different tumor types. Adverse events affecting the endocrine system are among the most frequent and complex toxicities oncologists may face, and some may be life-threatening if not recognized. Dr. Ravilla has identified areas of uncertainty and unmet requirements in administering these novel therapies, including promoting essential interaction between diverse physicians like endocrinologists, internists and oncologists. In fact, Dr. Ravilla is deeply vested in primary care of diabetes and have authored state-of-the-art reviews on diabetes (4). Cancer immunotherapies are gradually emerging as an important source of iatrogenic type I diabetes in individuals with cancer and undergoing immunotherapy (5-7). Prospective registry studies based on structured documentation of side effects in routine clinical practice are currently lacking and urgently needed. These studies are being stimulated by Dr. Ravilla. Dr. Ravilla's scholastic contributions in these management protocols are practice changing, as he leads in identifying the complex challenges related to these frontline therapies. Dr. Ravilla's approaches involves the treatment of aggressive forms of cancer and the preservation of an acceptable quality of life for his patients. In all these cumulative roles, Dr. Ravilla is currently leading the charge at New York Oncology-Hematology based in Albany, New York, helping the nononcologists to continue to care for these patients in the community.

REFERENCES

[1] Firwana B, Ravilla R, Raval M, Hutchins L, Mahmoud F. Sarcoidosis-like syndrome and lymphadenopathy due to checkpoint inhibitors. J Oncol Pharm Pract. 2017 Dec;23(8):620-624.
[2] Atwal D, Joshi KP, Ravilla R, Mahmoud F. Pembrolizumab-Induced Pancytopenia: A Case Report. Perm J. 2017;21:17-004.
[3] Abdallah AO, Herlopian A, Ravilla R, Bansal M, Chandra-Reddy S, Mahmoud F, Ong S, Gokden M, Hutchins L. Ipilimumab-induced necrotic myelopathy in a patient with metastatic melanoma: A case report and review of literature. J Oncol Pharm Pract. 2016 Jun;22(3):537-42.
[4] Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, Marco A, Shekhawat NS, Montales MT, Kuriakose K, Sasapu A, Beebe A, Patil N, Musham CK, Lohani GP, Mirza W. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front Endocrinol (Lausanne). 2017 Jan 24;8:6.
[5] http://packageinserts.bms.com/pi/pi_yervoy.pdf.
[6] http://packageinserts.bms.com/pi/pi_opdivo.pdf
[7] Joshi M. N., Whitelaw B. C., Palomar M. T., Wu Y., and Carroll P. V.. 2016. Immune checkpoint inhibitor related hypophysitis and endocrine dysfunction: clinical review. Clin. Endocrinol. (Oxf) 85:331–339.

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