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Original Research Paper

Medicine

TACKLING COLLATERAL DAMAGE: PIONEERING CARE OF DIABETES IN CANCER

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KEYWORDS :

Monoclonal antibodies (mAbs) that block immune inhibitory ligands CTLA-4 and PD-1, also called immune checkpoint inhibitors, have brought in revolution in the treatment of cancers that are resistant to conventional cancer therapies. As a result, life expectancy of patients with malignancies such as melanoma, lung cancer, renal cell carcinoma, and several other cancers has significantly improved.

Though immune checkpoint inhibitors-induced insulin-dependent diabetes is an uncommon but clinically significant event, several cases of such immune drug-induced diabetes has been reported in recent times. The visionary nature of Dr. Rahul Ravilla, a hemato-oncologist at New York Oncology and Hematology (NYOH) and Assistant Professor of Medicine at Albany Medical College, emerges from his critical contributions in promoting the management concepts of diabetes as a critical measure for excellence of care for patients with concomitant cancers. His co-first authored state of the art review on the clinical and pharmacological management of diabetes mellitus is highly laudable, as his commitment to primary and continued care is apparent (1). Not only some of these medications in diabetes management has an important role in cancer prevention, such as metformin, the efficient control of diabetes is critical in preservation of immune resistant to cancers. Dr. Ravilla has published an original study on how ATP, the energy coin of a cell, aids in packaging of insulin granules and renders a sophisticated mechanism of release kinetics of insulin (2). This paper (2) forms the foundation basis for providing deep insight of how immune activation with the use of checkpoint inhibitors alters the release mechanisms of insulin and the survival probability of the cellular constituents of the islets of Langerhans. Dr. Ravilla's intense commitment to both internal medicine and oncology has helped him create this kind of unique perspective in patient care.

Melanoma is the most frequently represented form of cancer that is currently treated with these innovative anticancer agents, and the most commonly used medications were either PD-1 or PD-L1 mAbs. Diabetic ketoacidosis has been seen as the presentation in a large cohort of the patients, indicating the severe nature of this adverse event. There are clinical and laboratory features of this iatrogenic form of diabetes induced by these agents that are similar to but also clearly different from spontaneous type 1 diabetes. Dr. Ravilla has kept a hawkish view of the complications arising out of the use of immune based cancer treatments (3-5). Most striking for the new onset diabetes is the difference in age of the time of onset, which was in the sixth decade. This late-onset diabetes is truly intriguing. The time between initial exposure to the immune checkpoint inhibitor and clinical presentation with diabetes may be variable but is usually rapid than thought for type 1 diabetes. This ranges between 1–52 weeks. The time to diabetes presentation is longer than for other irAEs (Immune Related Adverse Effects), such as thyroiditis, which on average occurs between 3 and 8 weeks after treatment. The loss of β-cells is acute, as demonstrated by the rapid progression from normoglycemia to hyperglycemia. Pancreatitis can also occur in these patients. Autoimmune, insulin-dependent diabetes occurs in close to 1% of patients treated with anti-PD-1 or -PD-L1 checkpoint inhibitors. This syndrome has similarities and differences compared with classic type 1 diabetes. The dominance of HLA-DR4 suggests an opportunity to identify those at highest risk of these complications and to discover insights into the mechanisms of this adverse event.

Diabetes and cancer are chronic conditions with tremendous impact on health worldwide. Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for many forms of cancer. Type 2 diabetes and cancer share several risk factors, but potential biologic links between the two diseases are not completely understood. Both diabetes and cancer are prevalent diseases whose incidence is enhancing globally. Worldwide, the prevalence of cancer has been difficult to establish because many areas do not have cancer registries, but in 2008 there were an estimated 12.4 million new cancer cases diagnosed. The most commonly diagnosed cancers are lung/bronchus, breast, and colorectal, whereas the most common causes of cancer deaths are lung, stomach, and liver cancer. In the U.S., the most commonly diagnosed cancers are prostate, lung/bronchus, and colon/rectum in men and breast, lung/bronchus, and colon/rectum in women. Of the world population between the ages of 20 and 79 years, an estimated 285 million people, or 6.6%, have diabetes. In 2007, diabetes prevalence in the U.S. was 10.7% of persons aged 20 years and older (23.6 million individuals), with an estimated 1.6 million new cases per year. Type 2 diabetes is the most common form, accounting for 95% of prevalent cases. Worldwide, cancer is the 2nd and diabetes is the 12th leading cause of death. In the U.S., cancer is the 2nd and diabetes is the 7th leading cause of death; the latter is likely an underestimate, since diabetes is underreported on the death certificates as both a cause and comorbid condition. Cancer and diabetes are diagnosed within the same individual more frequently than would be expected by chance, even after adjusting for age. Both diseases are complex with multiple subtypes. Diabetes is typically divided into two major subtypes, type 1 and type 2 diabetes, along with less common types, while cancer is typically classified by its anatomic origin (of which there are over 50, e.g., lymphoma, leukemia, lung, and breast cancer) and within which there may be multiple subtypes (e.g., leukemia).

Some cancers develop more commonly in patients with diabetes (predominantly type 2), while prostate cancer occurs less often in men with diabetes. The relative risks imparted by diabetes are greatest (about twofold or higher) for cancers of the liver, pancreas, and endometrium, and lesser (about 1.2–1.5 fold) for cancers of the colon and rectum, breast, and bladder. Other cancers (e.g., lung) do not appear to be associated with an increased risk in diabetes, and the evidence for others (e.g., kidney, non-Hodgkin lymphoma) is inconclusive. Few studies have explored links with type 1 diabetes. The use of immune inhibitors is providing an overview of the topic for the first time.

Since insulin is produced by pancreatic β-cells and then transported via the portal vein to the liver, both the liver and the pancreas are exposed to high concentrations of endogenously produced insulin. Diabetes-related factors including steatosis, nonalcoholic fatty liver disease, and cirrhosis may also enhance susceptibility to liver cancer. With regard to pancreatic cancer, interpretation of the causal nature of the association is complicated by the fact that abnormal glucose metabolism may be a consequence of pancreatic cancer ("reverse causality"). However, a positive association between diabetes and pancreatic cancer risk has been found when restricted to diabetes that precedes the diagnosis of pancreatic cancer by at least 5 years, so reverse causation does not likely account for the entirety of the association.

Improved glucose control remains one of the central goals of effective diabetes management, which strives to minimize morbidity and mortality by reducing the risk of diabetes-associated complications. Several factors are considered by clinicians and patients when selecting pharmacologic diabetes therapies. These include the type of diabetes being treated, the glucose-lowering potential of a given agent, known acute and chronic adverse effects of treatment (such as weight gain, hypoglycemia, fluid retention, gastrointestinal intolerance), treatment costs, and patient comorbidities and characteristics. Only recently has the issue of cancer risk with diabetes treatments has been considered. The clinical efforts of Dr. Ravilla are pioneering from the stand point of the vigor that he has introduced for the tackling of comorbidities of cancer-diabetes syndemic.

Individuals with type 1 diabetes represent 5% of the diabetes population worldwide. The autoimmune destruction of the pancreatic β-cells results in the loss of insulin production and the need for immediate and lifelong insulin therapy. In contrast, type 2 diabetes is much more common and accounts for 95% of the diabetes population. Type 2 diabetes is generally associated with overweight and obesity (in an estimated 80% of cases), also increasing pre-disposition to cancer and commonly advances from a pre-diabetic state characterized by insulin resistance (hyperinsulinemia) to frank diabetes with sustained insulin resistance accompanied by a progressive reduction in insulin secretion. The resulting relative insulin deficiency gives rise to both fasting and postprandial hyperglycemia. Ongoing loss of insulin secretory capacity, along with a diminished incretin effect and several other pathophysiologic defects, makes the hyperglycemia of type 2 diabetes progressive, and transformation of a more type 1 phenotype temporally. This results in increasing use of pharmacologic agents over time and the eventual need for insulin therapy in approximately half of all patients. The selection of the most appropriate pharmacologic agent(s) for each patient involves clinical decision-making process that includes an ongoing risk/benefit analysis. Treatment with metformin is associated with reduced risk of cancer or cancer mortality. Metformin might improve cancer prognosis.

There are several important caveats in human studies of diabetes treatment and cancer risk that require careful consideration. First, most studies have limited power to detect modest associations, particularly for organ-specific cancers. Most diabetic patients are treated with one or more anti-hyperglycemic medications. Indeed, the progressive nature of type 2 diabetes, requiring changes in pharmacotherapy over time, adding complexity to studies of a long-term outcome such as cancer incidence. Therefore, it is extremely difficult to assess the independent association of a specific medication on cancer risk relative to no medication. For example, if some medications increase risk, while other decrease or have no effect on risk, different comparator drugs will likely lead to different associations and may explain some of the observed inconsistencies across studies. Dr. Ravilla has stimulated the conductance of these studies to gain a more succinct overview of the overlap between diabetes and cancer.

Because specific anti-hyperglycemic medications are associated with cancer risk factors, confounding by unmeasured or incompletely measured risk factors may at least in part explain the previously reported drug-cancer associations. Few studies examined risk associated with dose, duration, or recency of medication use, which might inform the biologic plausibility of observed associations. Many agents that affect carcinogenesis have long latencies or require a minimum exposure level, and risk associated with some agents may return to baseline after the exposure has been terminated for a period of time. Some diabetes medications have only recently come on the market (e.g., TZDs, insulin analogs, incretin-based therapies). Therefore, studies of these agents will only assess cancer risk associated with relatively short-term use. Diabetes and cancer are common diseases that are increasing rapidly in prevalence worldwide. The International Diabetes Federation (IDF) has projected that the number of people with diabetes in the world will increase from 382 million in 2013 to 592 million by 2035, with 80% of cases occurring in low-income and middle-income countries. In China alone, about 114 million adults have diabetes and most cases are undiagnosed. Meanwhile, WHO-projected global cancer incidence will increase from 14 million in 2012 to 22 million in 2032, with more than 60% of incident cancers and 70% of cancer deaths occurring in central and south America, Africa, and Asia. Incidence of cancer is rising rapidly in developing economies such as China, India, and Russia; alarmingly, cancer mortality rates in these countries are twice as high as those in the UK or USA.

Dr. Ravilla's approaches to the complex clinical care of patients with cancer and co-existent chronic medical conditions is truly remarkable and paradigm shifting. Diabetes alters properties of blood for example bio-chemical alterations in diabetes predisposes to clotting and thromboembolic events. Dr. Ravilla has been a keen advocate of the importance of routine primary care and regular PCP visits for early detection of potential cancers. For certain cancers, like the deadly pancreatic cancer, early thrombotic events are tell-tale signs. Dr. Ravilla has uniquely disseminated this information through his website *clotsense.com*. In another novel original study, Dr. Ravilla and his team has demonstrated that certain cancers like multiple myeloma increase the risk arterial thrombosis and predispose to stroke (6). This was a detailed study involving 1148 patients and complex analysis like multivariate logistic regression (6). This study was performed at the famous Winthrop P. Rockefeller Cancer Institute. Ace physician like Dr. Ravilla are at the helm of retaining the title for America as a top cancer care destination.

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