EDITORIAL

New Urologic Oncology Drugs and The New Toxicities

We are in a time that some might call the "golden age" in the treatment of malignant diseases. In the treatment of advanced stages of cancers such as prostate, bladder, and kidney cancer we have moved beyond the traditional approaches to these diseases. The rapid development and FDA approval of many new targeted cancer therapies are benefiting patients in terms of improved survival. Along with these significant advances, new and unique toxicities are also being increasingly recognized. These toxicities can impact diverse organ systems that are not normally encountered in urologic practice.

Posterior reversible encephalopathy syndrome (PRES) is a syndrome that can include seizure, headache, impaired vision and increased blood pressure that is diagnosed by brain MRI. There are many traditional oncologic medications such as chemotherapy that can cause PRES. However, on this list are medications commonly used in urologic oncology such as therapies for kidney cancer (such as sunitinib, pazopanib). Although extremely rare, due to PRES reports in men treated with enzalutamide the drug's package insert adverse event section now includes PRES.

The immune check point inhibitors have assumed a prominent role in urologic oncology. These new agents take advantage of interactions between cancer cells and their host's immune system. Five programmed cell death receptor-1 (PD-1) and programmed cell death receptor-1 ligand (PD-L1) check point inhibitors (atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab) have been approved in advanced renal cell carcinoma and bladder carcinoma.

PD-1 or PD-L1 antibodies block either the PD-1 receptor or its ligand. These check point inhibitors interfere with the normal inhibition of the T-cell immune responses against tumors allowing a more robust immune response against the tumor. This enhanced immune responsiveness can also induce unique immune-related adverse events. These adverse events can involve many different organ systems including the gastrointestinal tract, liver, lungs, nervous system, skin, endocrine system and others. In addition to impacting quality of life, these side effects can be life-threatening and sometimes fatal.

Pneumonitis is a life-threatening complication associated with the use of check point inhibitor therapy. Patients with renal cell carcinoma appear to be particularly sensitive to this side effect compared with other check point inhibitor treated cancers such as melanoma. Inflammatory arthritis and other cases of rheumatic immune related adverse events have been reported with checkpoint inhibitors. Although rare (< 5%), immune-related neurologic toxicities are diverse and may include: necrotizing myopathy, neuropathy, cerebellar ataxia, retinopathy, and simple headache.

There is a current lack of understanding of the specific mechanisms behind these significant immunotherapy-related adverse events that can impact any organ system. A common theme is that after recognition of a drug related adverse event, prompt discontinuation of the check point inhibitor as an example, can be life saving. Concern about the toxicity of agents such as check point inhibitors has led to the development of programs to increase awareness across all medical specialties. The Association of Community Cancer Centers is sponsoring The Institute of Clinical Immuno-Oncology to promote awareness of side effects that may be associated with newer immunotherapies. Knowledge of these unique side effects is the first step towards effective management.

The expanding use of these newer targeted anti-cancer agents requires that all clinicians become skilled in the recognition and treatment of these adverse events. As more urologists engage in administering therapy in advanced cancers, familiarity of these potential toxicities is essential. While systemic side effects are typically associated with treating these advanced cancers, many of these new agents are being studied in earlier disease states. As an example, the systemic administration of check point inhibitors is being evaluated in non-muscle invasive bladder cancer. This suggests that in the future, these treatment related toxicities may also be associated with non-metastatic disease.

Heightened awareness of these potential adverse events will allow prompt diagnosis and management. This can result in decreased morbidity and mortality of these new agents that otherwise should extend the quality and quantity of life for many patients with advanced prostate, bladder and kidney cancer.

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