The coming of age: immunotherapy in gastrointestinal malignancies

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Gastrointestinal (GI) cancers, including colorectal cancer (CRC), gastric-esophageal cancer (GEC), pancreatic adenocarcinoma (PAC), hepatocellular cancer (HCC) and cholangiocarcinoma (CCA), remain a major health problem worldwide. If detected early, given advancements in diagnostic strategies and multimodality therapeutic approaches with surgical resection, chemotherapy and/or radiation therapy, improvement in long term survival has been observed. Despite progress, 1 in 4 patients still present with advanced metastatic disease at diagnosis and many of these patients have reported median survivals less than a year. Over the last decade novel targeted agents when incorporated with chemotherapy help extend survival of patients with metastatic GI cancers. These agents include EGFR/HER-2 and VEGFR targeted agents (cetuximab, panitumumab, bevacizumab, aflibercept, and regorafenib for CRC; trastuzumab and ramucirumab for GEC; and sorafenib for HCC). Despite these advances, many patients with advanced GI cancers, succumb to their disease thus, it is imperative to develop novel therapeutic approaches for patients affected by those cancers.

In recent years, we have witnessed immunotherapy-based agents transform how we manage patient's malignant melanoma, non-small cell lung cancer, genitourinary cancers, head and neck cancers and Hodgkin's lymphoma to list a few. Unfortunately, the progress of immunotherapy-based agents in GI cancers has been slow, although in 2017 we have seen approval of (I) Nivolumab/Pembrolizumab for patients with metastatic CRC with high microsatellite instability (MSI-H) or DNA mismatch repair deficiency (dMMR), (II) Pembrolizumab for patients with advanced gastric and GE junction tumors, who have failed at least two lines of chemotherapy and express PD-L1 protein, (III) Nivolumab for the treatment of patients with *HCC* following prior sorafenib, regardless of PD-L1 status.

Immunotherapy in GI cancers has made its most impact among patients with tumors that have MSI-H or DNA dMMR, which make up approximately 15% of patients CRC, albeit a smaller percentage of this subgroup have advanced tumors (1,2). The high burden of somatic mutations demonstrated in MSI-H or dMMR tumors can be recognized by the patient's immune system and is often characterized by a dense immune infiltration and a cytokine-rich environment. Despite this high level of immunogenicity, MSI-H tumors are not spontaneously eradicated by the immune system, indicating that there are a number of escape mechanisms employed by the tumor. One such mechanism is the upregulation of check point inhibitory molecules. The clinical efficacy and responses noted with checkpoint inhibitors, have been impressive and usually independent of tumor or immune cell PD-L1 expression, BRAF or KRAS mutation status (3). Conversely, the clinical impact of checkpoint inhibitors has not been observed amongst microsatellite stable (MSS) mCRC patients. Further, many GI tumors are known for their poor immunogenicity, lack of effector T-cell responses and an immunosuppressive tumor microenvironment (TME) (4). In this report, Kalyan *et al*. and Aurora *et al*. provide insight into the mechanism of immune resistance and ongoing pre-clinical and clinical research utilizing novel immunomodulatory agents, to enhance clinical efficacy of both MSI-H and MSS colorectal tumors.

HCC is currently the fastest growing cause of cancer specific mortality in the United States. In the last decade, sorafenib was the only systemic therapy approved for patients with advanced HCC. Unlike other GI tumors, HCC often develops in the setting of patients with underlying liver cirrhosis as a result of chronic hepatitis and inflammation. This is supported by pathological reports of inflammatory infiltrates often observed in resected HCC tumors. Growth of HCC tumors however, relies on a complex immunosuppressive network to modify the host immune system and to evade destruction (5). Further, native hepatic and immune cells produce many inhibitory cytokines that promote tolerogenicity and limit immune response (6). The approval of the checkpoint inhibitor, Nivolumab in September 2017, highlights that reversing the immune suppressive environment surrounding these tumors can result in durable tumor responses at least in a subgroup of patients with advanced HCC. In this special edition Lee *et al*. and Kamil *et al*., describe the key signaling pathways and immunosuppressive network in HCC, role of its extracellular matrix, report results of recent immunotherapy based studies and highlight future combinatorial approaches to treat advanced HCC.

GEC remains a difficult cancer to treat. Cytotoxic chemotherapy and radiation therapy is active but it provides only modest benefit. Recently, the Cancer Genome Atlas (TCGA) Network performed a comprehensive molecular characterization of gastric cancer (GC), leading to classification of GC into four subclasses—those associated with (I) Epstein-Barr virus (EBV) infection, (II) microsatellite instability (MSI), (IIII) chromosomal instability (CIN) and (IV) low rates of gene mutation and amplification, thus genomic stability (GS) (7). EBV-associated GCs exhibit recurrent amplifications of 9p24.1 locus which contains PD-L1 and PD-L2. The MSI subtype and the upregulation of PD-L1 and PD-L2 in the EBV-associated GC make these subtypes an attractive option for evaluation for immunotherapeutic agents. This was further supported by the recent approval of pembrolizumab for patients with advanced gastric and GE junction tumors, who have failed at least two lines of chemotherapy and express PD-L1 protein. Ammannagari and Atasoy, review the emerging data on the activity of checkpoint inhibitors in GEC, discuss the need for new therapeutic approaches and the role of biomarkers in this setting.

PAC remains the most lethal of all GI malignancies. Harnessing the immune system to attack cancer has made progress in other GI tumors described above, yet these strategies have yet to make significant strides in PAC. A number of barriers to immune therapy in PAC have been reported and include low levels of neoantigens, the unique immunosuppressive TME, and limited intra-tumoral infiltrating T-lymphocytes (8,9). Despite this, a number of pre-clinical and early clinical data suggests that PAC may be more immunogenic than initially thought, however these strategies have yet to make significant strides in terms of clinical benefit. In this edition, Kamil *et al*. again highlights the heterogeneous milieu of cellular elements and tumor cells in the TME of PAC and the signaling pathways that lead to barriers to therap. Rosenberg *et al*. discuss some of the strategies of overcoming barriers to response to immune therapies in PAC, as well as ongoing strategies currently being evaluated in the clinical trial setting.

With promising data emerging on the single agent immunotherapy use in a subset of patients with GI malignancies, we are still left with a large subset of patients with GI cancers showing no clinical efficacy to immunotherapeutic agents. To address this, current clinical research is evaluating novel approaches to enhance immunotherapy as a treatment strategy. In this edition, Shalaan and Meyer, present their perspective of reported synergistic antitumor activity of radiation therapy combined with immune checkpoint inhibitors, the opportunities it possesses to and discuss unique considerations to develop this combination in GI cancers.

Finally, despite the current excitement fueled by the clinical efficacy observed with single agent immunotherapeutic agents, we must be cautious and consider the toxicity profile of these novel class of drugs. In most cases the adverse event profile associated with immunotherapy agents have been mild and manageable, often much more acceptable to patients compared to the traditional chemotherapy. However, physicians need to be educated on the management of clinical significant immune-related toxicities. This may be of particular concern especially among patients who are known to have underlying organ abnormalities from their underlying cancer or as complications from prior treatments. To focus into this topic, Sanjeevaiah and colleagues review the recognition, workup and management of suspected checkpoint inhibitor related immune-hepatitis.

In conclusion, there has been a paradigm shift on how we approach the management of patients with GI malignancies. Physicians are now in the era of precision oncology and will use these resources to help identify patients that would be best suited to be treated with novel therapeutic

approaches. Further, a large body of literature is evaluating response to immunotherapy via novel mechanisms of the gut microbiota, including assessing if certain microbiota composition may reduce tumor growth. Pre-clinical evidence has shown oral administration of Bifidobacterium species are associated with profound anti-tumor effect when combined with anti-PDL1 therapy (10,11). Promising clinical trials have also been initiated to assess combination treatments using PD-1 or PD-L1 blockade in combination with (I) anti-CTLA4, (II) anti-TIM-3, anti-LAG3 and IDO inhibitors, (III) TLRs agonists, (IV) Oncolytic viruses, (V) agents that increase antigen presentation such as the COX-2, JAK1/2 or MEK inhibitors and (VI) targeted therapy (anti-HER2, anti-VEGFR). Where possible patients should be strongly encouraged to participate in these clinical trials to establish the efficacy of these combinatory approaches, identify predictive and prognostic biomarkers, and build further on our current understanding of the immunotherapy treatment landscape.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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