New Paradigm in Gastrointestinal Cancer Treatment

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The first Kindai International Symposium on Gastrointestinal Cancer (KISGIC) was held on July 8, 2017 in Osaka, Japan. The main theme of this symposium was: “New paradigm in gastrointestinal cancer treatment.” This symposium focused on recent progress on upper gastrointestinal cancer, lower intestinal cancer, pancreatobiliary cancer, and liver cancer.

Endoscopic submucosal dissection (ESD) has been widely used in the resection of superficial esophageal cancers. Since its use has been extended to cases involving large esophageal tumors occupying nearly the whole lumen or the whole circumference of the lumen, the occurrence of esophageal stricture has increased. Although endoscopic injection of triamcinolone (TA) is widely used for the prevention of postoperative stricture, a significant number of patients still develop stricture after TA injection therapy. Okamoto et al. [1] performed a retrospective review of the data from 57 patients treated with near- or whole-circumferential ESD and with TA injection. They found that an extensive circumferential mucosal defect (covering more than 75% of the circumference) was associated with a high risk of developing postoperative esophageal stricture, even after preventive injection of TA. Authors concluded that endoscopic TA injection is not sufficient for the prevention of esophageal stricture in patients bearing a mucosal defect covering more than seven-eighths of the circumference after ESD. In such cases, alternative strategies, including the application of

polyglycolic acid sheets with fibrin glue with or without TA injection, may be useful to avoid postoperative stricture.

Gastric cancer is the third leading cause of cancer-related deaths worldwide. Geographically, gastric cancer is very common in East Asia, where the prevalence rate of *Helicobacter pylori* infection is high. Chronic gastric infection due to *H. pylori* initially causes chronic active gastritis, which can then lead to the development of peptic ulcers, atrophic gastritis, and gastric cancer. A protective effect against gastric cancer has been reported to persist for more than 10 years after *H. pylori* eradication. Therefore, *H. pylori* can be considered one of the most important causes of gastric cancer. *H. pylori*-associated gastric cancer is one of the best examples of inflammation-related cancer. Therefore, it is clear that eradication of *H. pylori* reduces the risk for gastric cancer even in the presence of severe gastric atrophy and intestinal metaplasia. Thus, *H. pylori* eradication is the most effective strategy for the prevention of gastric cancer. Adachi et al. [2] attempted to determine whether metronidazole (MNZ)-based triple therapy is superior to clarithromycin (CAM)-based triple therapy as a first-line eradication treatment for *H. pylori*. They found that MNZ-based triple therapy containing esomeprazole and amoxicillin (AMPC) is superior to clarithromycin (CAM)-based triple therapy containing esomeprazole and AMPC as a first-line eradication treatment against *H. pylori*.

Colorectal cancer is one of the most common fatal malignancies worldwide. Inflammatory bowel disease (IBD), comprising ulcerative colitis and Crohn's disease, is thought to result from aberrant activation of the intestinal immune system and is a major risk factor for colorectal cancer, so-called colitis-associated cancer. Cancer stem cells, the microenvironment, and the immune system interact with each other through cytokines. In the context of chronic inflammation, immune responses would affect proliferation of stem cells and increase the expression of stem cell markers. The expression of stress response proteins and gankyrin that functionally link chronic inflammation and tumorigenesis in IBD is significantly correlated with that of a stem cell marker Bmi1. In mice, Bmi1 is required for intestinal tumorigenesis. Yamada et al. [3] found a significant association between Bmi1 expression and chronic inflammation in IBD patients. Their study represents the first report of the expression of Bmi1 in inflammation-associated colorectal cancer that is associated with refractory clinical course. Therefore, Bmi1 might be involved in the mechanistic connection between chronic inflammation and tumorigenesis in IBD.

Sakurai et al. [4] reported prophylactic suturing closure of mucosal defects after endoscopic resection of colorectal tumors in patients at a high risk of bleeding after ESD, who receive anti-thrombotics or anti-platelet agents.

Computer-aided diagnosis (CAD) is becoming a next-generation tool for the diagnosis of human disease. The CAD of colon polyps has been reported previously. Previous studies have reported the usefulness of CAD for colon polyps. The higher rate of correct diagnoses using a CAD system suggests the potential for this diagnostic tool to improve the quality of colonoscopic examinations. In addition to conventional CAD, a convolutional neural network (CNN) system utilizing artificial intelligence has been developing rapidly over the past 5 years. Komeda et al. [5] attempted to generate a unique CNN-CAD system with an amoxicillin (AMPC) function that studied endoscopic images extracted from movies obtained with colonoscopes used in routine examinations. They found that the accuracy of the 10-fold cross-validation is 0.751, where the accuracy is the ratio of the number of correct answers over the number of all the answers produced by the CNN and the decisions by the CNN were correct in 7 of 10 cases. Therefore, they concluded that a CNN-CAD system using routine colonoscopy might be useful for the rapid diagnosis of colorectal polyp classification.

Colonoscopic removal of adenomatous polyps or early cancer prevents death from colorectal cancer. ESD, which enables endoscopists to perform en bloc resection of flat or depressed colorectal tumors larger than 20 mm, has recently been introduced and become a standard procedure in Japan. Although postoperative bleeding (POB) is a major complication associated with ESD, risk factors for POB have not been fully identified. Okamoto et al. [6] found that anti-thrombotic therapy and rectal tumor location were strongly associated with POB in colorectal ESD. The incidence of POB was higher in patients who received heparin bridge therapy as a replacement of anti-thrombotic therapy than that in patients who did not receive heparin bridge therapy.

Colorectal cancer is one of the most common cancers, and 8–29% of patients with colorectal cancer have obstruction-related symptoms. Because obstructive colorectal cancer can be fatal, emergent management is needed. It was reported that the morbidity and mortality rates associated with emergent surgery were high. In the last few decades, there have been many reports about the usefulness of self-expanding metal stents (SEMS) for obstructive colorectal cancer. SEMS are used as a bridge to surgery (BTS) and for palliative therapy. A systematic review revealed that SEMS placement as a BTS has a lower stoma formation rate and complication rate than emergent surgery. However, concerns have been raised regarding the possibility for exacerbation of the oncological prognosis. A few RCTs and a cohort study have shown a significantly higher local disease recurrence rate with SEMS use than emergent surgery. The cancer recurrence rate has been shown to be higher in the subgroup of patients with stent-related perforations; thus, it is suggested that a lower perforation rate may improve the prognosis. Small diameter stents mitigate the mechanical impact of the stents on the tumor and the colonic wall, and can reduce the perforation rate. Ogawa et al. [7] found that the 18-mm diameter stents were effective similar to 22-mm diameter stents. Because 18-mm diameter stents are easy to handle and produce less mechanical stress, they have the potential to decrease the perforation rate and mitigate the stent's impact on the tumors. 18-mm diameter stents can be useful and safe, especially as a BTS.

Narrow band imaging (NBI), which visualizes vessel and surface patterns in detail, is generally considered to provide useful diagnostic information about gastrointestinal lesions identified via endoscopy. Several studies have indicated that NBI observations of colorectal polyps are very useful, accurate predictors of histology. The Japan NBI Expert Team (JNET) proposed a new NBI clas-

sification system for colorectal tumors in June 2014. In this classification system, types 1, 2A, 2B, and 3 correspond to hyperplastic polyps including sessile serrated polyps, low-grade dysplasia, high-grade dysplasia, shallow submucosal invasive carcinomas, and deep submucosal invasive carcinomas, respectively. To validate this system, Komeda et al. [8] performed a retrospective image evaluation study in which 199 colorectal tumors previously assessed by NBI magnifying endoscopy were classified by three blinded experienced colonoscopists using the JNET system. They concluded that JNET classification is useful for the diagnosis of hyperplastic polyps/sessile serrated polyps, low-grade dysplasia, and deep submucosal invasive, but not shallow submucosal invasive lesions. For low-confidence cases, magnified chromoendoscopy is recommended to ensure correct diagnoses.

The number of reports on the utility of contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) in the differential diagnosis of pancreatic masses has been increasing. CH-EUS depicted the hypoenhancement of pancreatic carcinomas with high sensitivity (89–96%) and specificity (64–94%). Nonetheless, the visual evaluation of CH-EUS scans may be influenced by the endosonographers' subjective impressions. Recent studies have described the quantitative perfusion analysis of pancreatic diseases using a time-intensity curve (TIC), which graphs the changes in signal intensity over time within a region of interest after infusion of an ultrasound contrast agent. Omoto et al. [9] attempted to clarify if quantitative perfusion analysis with CH-EUS characterizes pancreatic tumors and to find the most accurate hemodynamic parameter of TIC for differentiating pancreatic carcinoma from other pancreatic tumors. They found that pancreatic carcinomas exhibited markedly different TIC patterns from the other tumor types, with intensity at 60 s (I_{60}) being the most accurate diagnostic parameter. Quantitative perfusion analysis is useful for differentiating pancreatic carcinomas from other pancreatic tumors.

Intraductal papillary mucinous neoplasms (IPMNs) are a well-characterized group of intraductal mucin-producing cystic neoplasms of the pancreas with malignant potential. In the 2012 international consensus guidelines, high-risk IPMN included 2 clinical categories with “high-risk stigmata” and “worrisome features,” and different therapeutic strategies were recommended for both groups. It is recommended that patients with “high-risk stigmata” should be treated by surgical resection. Patients who have “worrisome features” and additional high-risk signs should also undergo resection, while patients with

“worrisome features” alone should receive careful follow-up. The “high-risk stigmata” of IPMNs that can be detected by EUS are an enhancing solid component inside the cyst and dilatation of the main pancreatic duct (>10 mm). Additional high-risk signs among the “worrisome features” are a definite mural nodule and suspected main duct involvement. Thus, the current guidelines focus on the morphological features of IPMN as revealed by EUS. On the other hand, although not described in previous reports, clinical experience suggests that evidence of chronic pancreatitis (CP) is frequently identified in the background pancreatic parenchyma of IPMN patients by EUS (EUS-CP findings). CP is a well-known risk factor for pancreatic malignancy, including pancreatic ductal adenocarcinoma (PDAC). However, the relationship remains unclear between malignant transformation of IPMN and pathological changes of the pancreatic parenchyma, such as atrophy, inflammation, and fibrosis. Moreover, changes of the background parenchyma are not considered to be a high-risk sign for malignant IPMN in the current guideline. Takenaka et al. [10] hypothesized that EUS-CP findings might be associated with malignant IPMN. To examine this hypothesis, they utilized a database of 69 consecutive patients with IPMNs who underwent preoperative EUS and surgical resection. They found that the detection of EUS-CP findings in the pancreatic parenchyma of IPMN patients was associated with invasive IPMC. They also stated that when EUS examination of IPMN is performed, the background parenchyma should be evaluated in addition to the morphological features of the tumor itself.

The gold standard procedure for biliary drainage (BD) is transpapillary drainage during endoscopic retrograde cholangiopancreatography (ERCP). However, ERCP may not be possible in patients with an inaccessible biliary orifice, such as patients with a surgically altered anatomy or duodenal involvement of the tumor. Alternative drainage options in these patients include surgical biliary bypass or percutaneous transhepatic BD; however, these procedures are associated with some adverse events. EUS-guided BD (EUS-BD) techniques such as EUS-guided choledochoduodenostomy (CDS), hepaticogastrostomy (HGS), antegrade stenting (AGS), and rendezvous stenting have recently been shown to be useful for BD after unsuccessful ERCP. Among these procedures, CDS and rendezvous stenting require the echoendoscope to reach the duodenum. Therefore, HGS or AGS is indicated in patients with an inaccessible duodenum. However, HGS is associated with a higher risk of adverse events compared with the other methods. When stent dysfunc-

tion occurs, re-intervention is more difficult after AGS alone than after HGS or CDS. Imai et al. [11] attempted to evaluate the technical success, functional success, adverse events, re-intervention rate, and stent patency before (HGS alone) and after (HGS with AGS) combining both methods and to compare these outcomes between the two groups. They found that although the technical success rate of HGS with AGS was lower than that of HGS, HGS with AGS was superior to HGS in terms of adverse events rate and stent patency in patients receiving chemotherapy. In other words, EUS-HGS both with and without AGS has equivalent short-term safety and efficacy when performed by experts. However, HGS plus AGS is preferred in patients undergoing chemotherapy because it allows for longer stent patency.

Risk factors for PDAC include diabetes mellitus, chronic pancreatitis, obesity, a family history of pancreatic cancer, and a history of smoking or alcohol consumption. Kamata et al. [12] attempted to evaluate the association between risk factors for PDAC and malignant IPMN. They found that there was no significant association between the risk factors for PDAC and malignant IPMN. The presence of several risk factors, especially a positive smoking history in addition to the presence of the mural nodules, is an indication for surgical resection in patients with IPMN.

EUS-guided fine-needle aspiration (EUS-FNA) has been widely used for the diagnosis of both inflammatory and tumor lesions located in and adjacent to the gastrointestinal tract. EUS-FNA has been considered to be a safe technique with few complications, as shown in recent review articles in which EUS-FNA-related morbidity and mortality rates were reported to be <1%. It should be noted, however, that needle tract seeding, although uncommon, can occur after diagnostic EUS-FNA and that this complication affects the prognosis of patients. Although an accurate value for the frequency of needle tract seeding caused by EUS-FNA has not been reported, the number of case reports on needle tract seeding have been rapidly increasing, especially in Japan. Minaga et al. [13] attempted to re-evaluate the safety of EUS-FNA because this complication may have a significant influence on patients' prognoses. They concluded that considering this serious complication, EUS-FNA should be performed only when the results obtained by this procedure are useful for therapeutic decision making. In addition, needle tract seeding following EUS-FNA might be avoided by setting the needle tract line within the surgical resection margins, if technically possible. Carefully planned endoscopic and imaging surveillance of the puncture sites

could lead to the early detection of needle tract seeding, which may improve the prognosis.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disorder characterized by multiple fibrotic strictures of the intra- and extrahepatic biliary tree. Previous studies have shown that >40% of deaths in patients with PSC are related to cholangiocarcinoma, gallbladder carcinoma, or colorectal carcinoma. Cholangiocarcinoma is the most relevant of these, with a lifetime risk in PSC patients of around 7–14% and a prognosis including a 5-year survival of <10%. Primary hepatic adenosquamous carcinoma (ASC) is defined as a rare subtype of cholangiocarcinoma, accounting for 2–3% of cholangiocarcinomas. ASC contains both adenocarcinoma and squamous cell carcinoma components, tends to present more aggressive clinicopathologic features, and has a poorer prognosis than other cholangiocarcinomas. Yamao et al. [14] first reported the first case of hepatic ASC in a patient with PSC. They concluded that patients with PSC should be recognized as being at risk of hepatic ASC, in addition to general cholangiocarcinoma, hepatocellular carcinoma (HCC), and metastatic liver tumor.

Pancreatic cancer has a poor prognosis, and early diagnosis is important for improved outcomes. Small pancreatic cancers have a better prognosis, although detection and diagnosis of noninvasive or small invasive lesions are often challenging. Pancreatic intraepithelial neoplasia (PanIN) is considered a precursor for invasive pancreatic cancer. PanIN is defined as a microscopic papillary or flat and noninvasive epithelial neoplasm arising from the pancreatic ductal epithelium. PanIN is divided into two subtypes: low-grade PanIN (previously reported as PanIN-1 and -2) and high-grade PanIN (previously reported as PanIN-3) involving a carcinoma in situ. As high-grade PanIN does not involve a mass-forming lesion, its diagnosis is challenging by imaging. Detection of high-grade PanIN involves the presence of an abnormal main pancreatic duct (MPD) form, including localized MPD stenosis with distal MPD dilation, focal ductal branch dilation, and cyst formation. Exacerbation of these findings with tumor progression is also a sign of high-grade PanIN. However, the natural history and time to progression of high-grade PanIN remain unclear. Yamao et al. [15] reported two cases of high-grade PanIN without morphological changes in the MPD over relatively long periods. They concluded that when findings of localized MPD stenosis and distal MPD dilation are detected, a definite diagnosis of high-grade PanINs should be considered by pancreatic juice cytology. Even if a definite diagnosis cannot be obtained, strict follow-up ob-

servation study should be performed. Re-examination should also be considered, particularly in cases with some risk factors for pancreatic cancer, even if there is no change in the MPD form.

EUS-guided pancreatic drainage has been described as a new drainage technique after an unsuccessful transpapillary approach for pancreatic duct strictures. Kamata et al. [16] reported a case who could not continue chemotherapy and was forced to stop chemotherapy due to repeated pancreatitis. Findings indicated that the pancreatic duct stone caused repeat pancreatitis, resulting in the discontinuation of chemotherapy. Although transpapillary pancreatic duct drainage was considerable, pancreatic duct drainage over the tumor and the pancreatic duct stricture was limited. The presence of the tumor in the head of the pancreas made stone removal more difficult. EUS-guided pancreatic drainage was successful in this patient; therefore, this technique may constitute salvage therapy when the transpapillary approach is difficult.

The early-stage pancreatic cancer (e-PC; stage I/II) detection rate is quite low at approximately 25%. Sakamoto et al. [17] conducted a study to evaluate the feasibility of a social program (the Kishiwada project) wherein their hospital, which specializes in PC and primary care medical offices (PMOs), used clinical findings to detect e-PC. They concluded that this social program with collaborations between medical centers that specialize in PC and PMOs used clinical findings, suggesting that not only general internal medicine offices (GIMs) but also other PMOs and indirect findings by US may play an important role in improving the e-PC detection rate.

Repeated pancreatic juice cytology via endoscopic naso-pancreatic drainage (ENPD) is found to have high diagnostic yield and might be useful for the diagnosis of e-PC. EUS-FNA is also helpful for confirming the diagnosis of early pancreatic carcinoma, but its role is limited with respect to carcinoma in situ as no tumor has formed at this stage. Miyata et al. [18] reported that a case of repeated pancreatic juice cytology via ENPD was effective in the diagnosis of pancreatic carcinoma in situ. They speculated that a weak low echoic area around the MPD stricture on EUS might be related to the inflammatory changes accompanying carcinoma in situ of the pancreas.

HCC is the second leading cause of cancer mortality in the world. Sorafenib is an agent that has improved the time-to-progression (TTP) and overall survival (OS) in advanced stages of HCC with vascular invasion and/or extrahepatic spread [19]. Sorafenib is recommended by the consensus-based treatment algorithm for HCC pro-

posed by the Japan Society of Hepatology [20–22]. According to this algorithm, sorafenib is indicated in patients diagnosed with Child-Pugh stage A HCC with extrahepatic spread or vascular invasion. Sorafenib is also recommended in patients with Child-Pugh stage A HCC where transcatheter arterial chemoembolization (TACE) [23–26] and hepatic arterial infusion chemotherapy [26–28] are not indicated. Ogawa et al. [29] attempted to determine the relationship between treatment outcomes and hand-foot syndrome, and post-progression treatment after sorafenib therapy. They found that in sorafenib therapy, the patients with hand-foot syndrome and those who received postprogression treatment showed good OS. They also noted that the best results were observed when therapy was initiated at Child-Pugh grade A-5, which indicates that it is preferable to start sorafenib at the time when liver function is still well preserved. Starting sorafenib at a reduced dose in Japanese patients is also thought to lead to a better OS.

HCC is the fifth most common malignant tumor and the third cause of cancer death in the world. Advances of hepatic resection [27] and radiofrequency ablation [28, 30, 31] as curative treatments have improved the prognosis of HCC. However, it is well known that there is frequent recurrence after curative treatments for HCC. TACE has been performed as a palliative treatment against unresectable HCC in the patients with/without a past history of treatments, especially in BCLC-B (intermediate) stage HCC [32], and has been reported to be effective for improving prognosis of the patients with HCC. Recently, new criteria for predicting poor prognosis of HCC, time to TACE progression (TTTP), have been proposed [33]. TTTP showed a moderate correlation to OS after progression in the patients with BCLC-B HCC treated with TACE. Izumoto et al. [34] performed the validation study of the relationship between TTTP and OS after TACE. They concluded that TTTP showed a good correlation with OS. In the patients with the short TTTP, especially less than 5 months, it might be difficult to improve prognosis with repeated TACE procedure. In such cases, re-consideration of therapeutic strategy, switching treatment from TACE to tyrosine kinase inhibitors, might be needed [20, 35]. In addition, TTTP may be a good surrogate endpoint of OS in the TACE combination trial with molecular targeted agents or immune checkpoint inhibitors or both [26, 36].

Kudo and Arizumi [37] reviewed molecular targeted therapy in combination with TACE of negative trials such as post-TACE, BRISK-TA, SPACE, ORIENTAL, and TACE-2 trials. They state that TACE is the first-line treat-

ment for intermediate-stage HCC; however, repeated TACE sessions tend to impair liver function, resulting in shorter prognosis. Reducing the frequency of TACE, which is generally repeated upon tumor progression, is a challenging issue in the treatment of patients with intermediate-stage HCC. To address this issue, previous trials combined molecular targeted agents with TACE; however, the safety and efficacy of this combination could not be demonstrated, and none of the combination therapies is currently recommended. In such cases, post-trial treatment likely affects OS, making it difficult to evaluate treatment outcomes using OS. Instead of OS, TTP/progression-free survival is used as a primary endpoint in some trials; however, whether TTP/progression-free survival based on RECIST is an appropriate endpoint in clinical trials of TACE combination therapies remains unclear. In general, TTP corresponds to the period between randomization or the day of study initiation and disease progression. In their previous study, they proposed a novel endpoint, "time to TACE progression (TTTP)," as a progression-free period specific to patients treated with TACE and defined as the time from the initial TACE effect evaluation to progression [33]. They also verified that TTTP is correlated with OS, suggesting that TTTP could be a surrogate endpoint for OS and a better primary endpoint than OS for use in clinical studies of TACE in combination with molecular targeted agents or immunotherapy. They concluded that many clinical trials investigated the efficacy of TACE combined with molecular targeted agents; however, none of them demonstrated an OS benefit of the combination strategy or even improved TTP/progression-free survival. Nevertheless, these studies showed the antitumor effect of the molecular targeted agents as adjuvant therapy. It is important to consider the reasons for the negative outcomes of these trials and to carefully plan future clinical trials of combination therapy with TACE.

Kudo reviewed the 2017 update of systemic therapy for HCC. The author pointed out that tumor reduction effect and toxicity of current standard of care (sorafenib) remain unsatisfactory. The development of novel molecular targeted agents, as alternatives to sorafenib, has been attempted up to now, although there are many difficulties unique to HCC to overcome. Nevertheless, the efficacy of 3 molecular targeted agents in succession has recently been proven. Two are the second-line agents, regorafenib and cabozantinib, which developed on sorafenib therapy. Another one is the first-line agent, lenvatinib, which was proven to be noninferior to sorafenib. Another group of agents that are attracting considerable interest are im-

mune checkpoint inhibitors, such as anti-programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies that kill cancer cells via a unique mechanism. The expected therapeutic effects of some of these agents are now being investigated in phase III studies. The most recent topics is the combination therapy of PD-1/PD-L1 with other immune checkpoint inhibitor, CTLA-4, or with tyrosine kinase inhibitor, or locoregional therapies, such as resection, ablation or TACE. He concluded that increased options for treatment using a molecular targeted agent and immune checkpoint inhibitors will benefit more HCC patients, but adequate selection of the treatment is important and should be actively explored.

Kudo reviewed the most updated topic, immuno-oncology in HCC. Clinical trials are currently ongoing to evaluate the utility of antibodies against PD-1, PD-L1, and CTLA-4 as monotherapy or combination therapy in patients with HCC. Results of combination treatment with the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab in HCC were presented at the 2017 annual meeting of ASCO. Response rates were 25% in all 40 patients and 40% in the 20 uninfected patients, both of which are encouraging. TACE and radiofrequency ablation can activate tumor immunogenicity by releasing tumor-associated antigen and by inducing the migration of cytotoxic T lymphocytes to small intrahepatic metastatic nodules. Subsequent administration of anti-PD-1 antibody could control these small intrahepatic metastatic nodules. In a nonclinical study, the combination of pembrolizumab and lenvatinib inhibited the cancer immunosuppressive environments induced by tumor-associated macrophages and Tregs. This, in turn, decreased the levels of TGF- β and IL-10, the expression of PD-1, and the inhibition of Tim-3, triggering anticancer immunity mediated by immunostimulatory cytokines such as IL-12. Studies such as these may provide insight into the appropriate molecular targeted agents to be used with immune checkpoint inhibitors.

Nishida and Kudo [38] described activation of oncogenic signaling and tumor immunosuppressive microenvironment in HCC. They stated that vascular endothelial growth factor (VEGF) induces myeloid-derived suppressor cell accumulation, inhibit maturation of dendritic cells, and induce Treg cells. VEGF also exerts immunosuppressive function through the expression of immune checkpoint molecules on CD8⁺ T cells, such as PD-1, T cell immunoglobulin and mucin domain 3 (TIM-3) and CTLA-4. Immunoregulatory enzyme, indoleamine 2,3-

dioxygenase, is overexpressed in HCC cell lines and human HCC tissues, which is an independent prognostic factor for HCC patients. Indoleamine 2,3-dioxygenase is upregulated by proinflammatory cytokines, such as interferon- γ , and inhibits T cell activation and promotes expansion of Treg cells. Similarly, lactic acid, which is generated through glycolysis in tumor cells, stimulates the expression of VEGF and M2-like polarization of tumor-associated macrophages. Activation of NF- κ B could also increase the expression of immunosuppressive cytokines, such as IL-2, IL-6, and IL-8 in cancer cells. They concluded that from this point of view, it is conceivable

that combination with inhibitors of oncogenic signaling improve the antitumor effect of anti-PD-1 and PD-L1 antibody.

Finally, I strongly believe this supplementary issue of *Oncology* focusing on “New paradigm in gastrointestinal cancer treatment” will be an invaluable one for all the readers of *Oncology*.

Disclosure Statement

The author has no conflicts of interest to declare.

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