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Review Article

Recent Advances in the Systemic Treatment of Gastrointestinal Malignancy

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Abstract

In the following article, practice changing updates on gastrointestinal cancers management have been discussed. For metastatic colorectal cancer with RAS wild-type, fluoropyrimidine plus panitumumab combination has been the preferred maintenance option for patients who have stopped oxaliplatin. The cytoreductive surgery alone showed satisfactory survival outcomes in colorectal cancer patients with peritoneal carcinomatosis. Dose escalation of regorafenib showed better clinical outcomes than the standard dosing regimen. Adjuvant FOLFIRINOX is the new treatment option for selected resected pancreatic cancer patients. Neoadjuvant treatment is the new paradigm for borderline and resectable pancreatic cancer patients. Several options for advanced hepatocellular cancers now available and more clinical studies are required for optimal treatment sequencing. Trifluridine/tipiracil showed improved overall survival in esophageal cancers beyond the second line.

Keywords: *Gastric, gastrointestinal malignancy, pancreatic*

Colorectal

The optimal approach to maintenance treatment is less clear for patients with metastatic colorectal cancer (mCRC) who achieve stability or deeper response with induction chemotherapy with anti-endothelial growth factor receptor agents such as cetuximab or panitumumab. In this Phase II VALENTINO trial,[1] 229 patients with previously untreated, RAS wild-type advanced mCRC were enrolled to evaluate whether maintenance with panitumumab monotherapy was noninferior to maintenance with 5-fluorouracil/leucovorin (5-FU/LV) plus panitumumab. After a median follow-up of 13.8 months, the combination maintenance regimen showed a 10-month progression-free survival (PFS) rate at 62.8% compared to 52.8% with monotherapy. The median PFS was significant with the combination strategy at 13 months versus 10.2 months (Hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.09–2.02, P = 0.011). However, the trial failed to meet the criteria for noninferiority of panitumumab monotherapy, which was set at a threshold of HR <1.515. Therefore, fluoropyrimidine plus panitumumab should be the preferred maintenance option for patients who have stopped oxaliplatin.

The current guidelines suggest preoperative fluoropyrimidine-based chemoradiation for Stage 2 and 3 rectal cancer. Despite low local-regional relapse of 5%–6% with preoperative chemoradiation (CRT), 30% of patients still develop distant metastasis. The long-term survival is only 65% and needs improvement. Three randomized trials evaluating the role of oxaliplatin to preoperative CRT and adjuvant therapy were presented at a major conference recently.[2-4] Irrespective of Stage 2 or 3, the 5-year overall survival (OS) was similar with or without oxaliplatin as radiation sensitizer. There was no improvement in the outcome in terms of locoregional relapse and distant relapse. For locally-advanced rectal cancer patients, neoadjuvant mFOLFOX6 ± radiation did not improve disease-free survival compared to 5-FU CRT. However, mFOLFOX + RT improved the rate of pathologic complete response (pCR), potentially enabling patients for a "watch and wait" options to avoid or delay surgery.

For mCRCs with a molecular print of microsatellite-high, nivolumab has been approved for the patients progressed on oxaliplatin and irinotecan-based regimen.

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Checkmate-142 is a multicenter, nonrandomized Phase 2 trial evaluated single-agent nivolumab or in combination with other immune therapies in patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) progressed on fluoropyrimidine, irinotecan, and oxaliplatin.[5] The combination cohort received four doses of nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg every 3 weeks, followed by nivolumab at 3 mg/kg every 2 weeks. At a median follow-up of 13.3 months, the overall response rate (ORR) was 55% in combination cohort as compared to 31% in nivolumab monotherapy cohort. This needs to be interpreted cautiously, as this is not a randomized trial and this is a cross-cohort comparison. Twelve-month PFS was 71%, and 12-month OS was 85% in the combination cohort. Grade — adverse events (AEs) were relatively common in combination cohort (32% vs. 20%). This combination has now been incorporated in the National Comprehensive Cancer Network guidelines.

Regorafenib is an oral multikinase inhibitor that showed improved OS in previously treated mCRCs in the CORRECT study.[6] The recommended dose was 160 mg oral daily once for 3 weeks in a 28-day cycle. However, it is associated with significant toxicities such as hand-foot skin rash and fatigue and almost every patient requires dose reductions or dose delays. The randomized Regorafenib dose optimization study in 123 patients, compared fixed dose of regorafenib (160 mg) to a dose-escalated regimen (80 mg/day with weekly dose escalation up to 160 mg) as tolerated for 21 days during a 28-day cycle.[7] The primary endpoint was the patient proportion who completed two treatment cycles, and this was met with 43% in escalated dose arm versus 24% in standard arm (P = 0.028). The incidence of Grade 3 or 4 toxicity was lower in escalation arm, thus, considered as a reasonable strategy for treatment with regorafenib.

Approximately, one-fifth of the patients with mCRC will develop peritoneal carcinomatosis (PC) and is associated with worse survival outcomes.[8] The phase III PRODIGE 7[9] was the first prospective French randomized trial to evaluate hyperthermic intraperitoneal chemotherapy (HIPEC) in mCRC patients with PC. In this study, 265 patients were randomly assigned in the operating room to the HIPEC or non-HIPEC group. Patients in the HIPEC arm received intraperitoneal oxaliplatin 460 mg/m^2 heated to 43°C over 30 min following cytoreduction surgery. At the median follow-up of 64 months, no significant difference was reported in terms of recurrence free (13.1 vs. 11.1 months; P = 0.486) and OS (41.7 vs. 41.2 months; P = 0.995) between HIPEC and nonHIPEC groups. The perioperative mortality was high in the HIPEC arm. Therefore, the authors concluded that given the lack of survival benefit and the increased risk of postoperative complications, the HIPEC has a limited role for PC patients undergoing optimal debulking surgery.

Noncolorectal

Pancreas

It is estimated that by the year 2020, pancreatic cancer would be the second-most leading cause of cancer-related deaths in the United States. Hence, there is a need to improve treatment strategies in metastatic and nonmetastatic diseases.

PRODIGE 24/CCTGPA is a randomized adjuvant trial of modified FOLFIRINOX versus gemcitabine for 6 months after surgery in 493 patients with resectable cancers.[10] Adjuvant therapy was initiated 3–12 weeks following surgery. Modified FOLFIRINOX yielded an improved median OS of 54 months versus 35 months with gemcitabine. The median disease-free survival was 22 months versus 13 months. However, as expected, modified FOLFIRINOX was associated with severe treatment-related AEs. Modified FOLFIRINOX is now been considered as one of the standards of care for adjuvant management in good performance status patients.

PREOPANC–1 demonstrated neoadjuvant CRT followed by surgery is superior to upfront surgery for localized and borderline resectable pancreatic cancers.[11] Two hundred and forty-six patients with resectable cancers were randomly assigned to surgery upfront versus gemcitabine-based chemotherapy plus radiation for 10 weeks before surgery. Median OS was 17.1 months with preoperative CRT compared to 13.7 months with upfront surgery. Furthermore, the 2-year survival rate was 42% in the preoperative CRT arm compared to surgery alone arm. The radial surgical resection in the neoadjuvant therapy group was significantly improved to 63% (R0 resection) compared to 31% in the group that did not receive neoadjuvant therapy. This trial emphasizes the importance of neoadjuvant therapy even in resectable cancers, and several high volume institutions do reflect this change of pursuing neoadjuvant therapy before surgery for resectable cancers.

The maintenance strategy for metastatic pancreatic cancer patients who achieved a maximal response or long-term stability on FOLFIRINOX is unknown. PRODIGE 35-PANOPTIMOX is a randomized Phase II trial, evaluated oxaliplatin "stop-and-go" strategy and an alternative sequential strategy in metastatic pancreatic cancers.[12] Two hundred and seventy-three patients were randomized to receive 6 months of FOLFIRINOX (Arm A) or 4 months of FOLFIRINOX followed by LV5FU2 (fluoropyrimidine/LV) maintenance (Arm B) or alternating gemcitabine and FOLFIRI (Arm C). The median PFS was 6.3, 5.7, and 4.5 months, with a median OS of 10.1, 11.2, and 7.3 months, respectively. The trial failed to show the benefit of stop-and-go as PFS/OS was similar and neuropathy was worse in arm B. Therefore, an induction-maintenance strategy with discontinuing oxaliplatin and irinotecan after

4 months of FOLFIRINOX is a reasonable strategy in metastatic pancreatic cancer.

Pancreatic neuroendocrine tumors (pNETs) are treated with everolimus or sunitinib that have a minimal response. In the randomized cooperative group study of temozolomide or temozolomide and capecitabine in patients with advanced pNETs, a total of 144 patients with progressive, Grade 1/2, metastatic pancreatic NETs were randomized into either temozolomide alone or capecitabine/temzolomide (CAPTEM).[13] Median OS was 38 months with temozolomide alone, and it had not yet been reached at the time of presentation of this data with CAPTEM (HR 0.41, $P = 0.012$). ORR was 27.8% with monotherapy and 33.3% with CAPTEM ($P = 0.47$). Duration of response was longer with the CAPTEM, at 12.1 months versus 9.7 months. Temozolomide + capecitabine demonstrated improved PFS and OS versus temozolomide alone in patients with advanced pNETs. The ORR was high compared with most approved therapies, but there was no significant difference between the treatment arms.

Hepatocellular Cancer

Over the past years, major clinical trials on hepatocellular cancers have witnessed some promising results. However, numerous questions remain unanswered regarding the optimal incorporation of these advances into routine practice, and to complicate matters further, new findings are constantly being unveiled. Disease stage and treatment response were considered to be the most important prognostic indicators. With multiple viable therapeutic options, the treatment sequencing plays a critical role in management, especially for transitioning from locoregional to systemic therapy.

CELESTIAL is the Phase 3 study of cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib.[14] In this study, 707 patients with Child-Pugh A cirrhosis progressed on at least 1 prior systemic therapy were randomized in a 2:1 ratio to treatment with cabozantinib at 60 mg daily or placebo. The disease control rate was 64% with cabozantinib versus 33% with placebo and the median OS with cabozantinib was 10.2 months versus 8.0 months with placebo, resulting in a 24% reduction in the risk of death (HR, 0.76). The median PFS favored cabozantinib with 5.2 months versus 1.9 months with placebo (HR, 0.44, $P < 0.0001$). Common AEs with cabozantinib include hand-foot syndrome (17%), hypertension (16%), fatigue (10%), and diarrhea (10%). It is now considered the standard of care in the second-line setting for the management of advanced HCC.[15]

The phase III REACH-2 trial reported that ramucirumab improved overall and PFS versus placebo in patients with advanced HCC and increased α-fetoprotein levels in those who had previously received sorafenib.[16] Previous biomarker-driven trials such as upregulation of expression of MET had failed in HCC. REACH-2 is the very first Phase 3 trial in biomarker-selected HCCs with positive outcomes. Subgroup analysis in earlier REACH phase 3 study in AFP high patients showed an OS improvement with ramucirumab. This led to the phase III REACH-2, a multicenter, randomized, double-blind study in advanced HCC who were either progressed or intolerant to sorafenib and had elevated AFP ≥ 400 ng/mL. Patients were randomized to ramucirumab 8 mg/kg at every 2 weeks versus placebo. Ramucirumab significantly improved overall and PFS versus placebo with a median OS of 8.5 months versus 7.3 months (HR, 0.674; 95% CI, 0.51–0.90; $P = 0.0059$). The most common AEs in the ramucirumab group were fatigue (27%), peripheral edema (25%), hypertension (25%) with grade ≥3 AEs of hypertension (13%) in the ramucirumab arm.

In the phase II TACTICS trial,[17] 56 patients with unresectable HCC were randomized to receive transarterial chemoembolization (TACE) alone ($n = 76$) or sorafenib plus TACE ($n = 80$). The investigators introduced a new endpoint in this clinical trial, time to untreatable progression (TTUP) and/or progression to TACE refractoriness. Treatment with sorafenib following TACE was continued until TTUP, decline in liver function to the Child–Pugh class C, or the development of vascular invasion and/or extrahepatic spread. Development of new lesions while on sorafenib was not considered as a progressive disease in this study because this is attributable to the natural tumor biology of HCC and does not indicate treatment failure. It was reported that PFS was longer with sorafenib + TACE compared to TACE alone (26.7 vs. 20.6 months; $P = 0.02$). The TTUP endpoint needs validation and it is critical to await more mature survival outcomes of this study.

TACE is often used to treat unresectable HCC; however, no consensus on the definition of TACE failure, hence, used in broader unselected populations.[18] Retrospective studies suggest that continuing TACE after refractoriness or failure may not be beneficial and may delay from receiving subsequent treatments because of the deterioration of liver function. With recent approvals of systemic therapy options, it is vital to reassess the risks of continuing TACE after failure. The OPTIMIS was an international, prospective, noninterventional study designed to assess the outcomes of patients with HCC treated with TACE, followed or not followed by sorafenib, in real-world clinical practice.[19] Evaluating patients with HCC for whom a decision to treat with TACE was made at study entry. This study enrolled patients with the Barcelona Clinic Liver Cancer stage B or higher. After propensity score matching to balance the cohorts, it was found that patients who were started on sorafenib immediately following TACE ineligibility had significantly increased median survival of 16.2 months compared to 12.1 months in those who did not receive

systemic treatment following TACE ineligibility. These data highlight the importance of the earlier start of systemic therapy.

Esophageal Cancer

The impact of the CRT to surgery interval on pathological complete response has been evaluated retrospectively in the National cancer database.[20] As pCR is an indicator of better disease-free and OS, previous data on esophageal cancer and other solid malignancies showed higher pCR rates if time intervals between CRT and surgery were longer. It was shown in this study that pCR rates increased as the interval between neoadjuvant CRT and surgery increased; however, the corresponding 90-day mortality rates also increased (P = 0.04). Overall, this translated into an 11% increase in the pCR rate and a 5% increase in the 90-day mortality rate for each additional week between CRT and surgery. The authors concluded that esophagectomy is preferred to be performed within 65 days after CRT to avoid worsened 90-day mortality risk.

Gastric and Esophageal Cancer

The standard chemotherapy for advanced gastric cancer includes fluoropyrimidines, platinum, taxanes, or irinotecan with biologics, including ramucirumab or trastuzumab (for Her2-Neu positive tumors). Immunotherapy has been recently considered as an option for MSI-H or PDL-1 >1 tumors. However, after the failure of the first- and second-line therapies, effective cytotoxic options are limited. The TAGS study is a pivotal phase III study that investigated the efficacy and safety of TAS-102 (trifluridine/tipiraci or Lonsurf) plus best supportive care (BSC) compared with placebo plus BSC in patients with metastatic gastric cancer that was refractory to standard treatments.[21] TAS-102 provided a 31% reduction in the risk of death compared with placebo with median OS of 5.7 months compared with 3.6 months for placebo (HR, 0.69; P = 0.0003). Based on this study, the Food and Drug Administration has granted a priority review for TAS-102 for use in previously treated patients with advanced or metastatic gastric adenocarcinoma, including cancer of the gastroesophageal junction.

Pembrolizumab has been approved for treatment of advanced gastric/gastroesophageal junctional (GEJ) tumors with MSI-H or positive expression of PDL-1. KEYNOTE-061 was a randomized clinical trial that assessed the efficacy and safety of pembrolizumab versus paclitaxel in previously treated patients with advanced gastric/GEJ cancer.[22] That study failed to show a survival improvement with pembrolizumab versus paclitaxel as the median OS was 9·1 months with pembrolizumab versus 8·3 months with paclitaxel (HR 0.82, P = 0.0421). In fact, what was disappointing was that the PFS was worse with pembrolizumab compared to paclitaxel (1.5 months vs. 4.1 months). It was concluded that the study did not meet the endpoint on OS. In a subset analysis, improvements in OS with pembrolizumab were noted in patients with ECOG PS 0, PD-L1 CPS ≥10 and MSI-high tumors.

Conclusion

Addition of oxaliplatin as a radiation sensitizer to fluoropyrimidine during radiation therapy did not improve clinical outcome in Stage 2/3 rectal cancer. FOLFOX is reasonable adjuvant treatment option for rectal cancer, particularly in pathologic Stage III disease. mCRC patients with PC could be managed with effective cytoreductive surgery alone. The combination of nivolumab and ipilimumab emerged as one of the therapeutic options for patients with mCRC with MSI-H or dMMR. The modification of the regorafenib dosing made relatively more leading to better clinical outcomes. Modified FOLFIRINOX is the potentially new adjuvant standard of care for resected pancreatic cancers. Neoadjuvant therapy is an emerging therapeutic strategy in patients presented with resectable or borderline pancreatic cancer. Combination of capecitabine and temozolomide showed the longest PFS reported for pNETs-directed therapy. Several therapeutic options are available for advanced or BCLC-C that draws attention on considering systemic therapy early in the treatment sequence than delaying it by multiple locoregional therapies. TAS 102 represents an effective therapeutic option for patients with heavily pretreated metastatic gastric cancer.

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Conflicts of interest

There are no conflicts of interest.

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