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ASCO 2015 Update on Gastrointestinal Cancer: Checkpoint Inhibition, Multimodality Strategies and Secondary Prevention

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Each spring, thousands of oncology professionals gather in Chicago for the American Society of Clinical Oncology (ASCO) Annual Meeting. This year's meeting may be most remembered for the presentation of multiple striking abstracts employing a new class of drug treatments that seek to reawaken the immune system's response to cancer. Indeed, several of the studies presented on immune checkpoint inhibitors will be reviewed here, as they are potential new strategies for the treatment of various gastrointestinal (GI) malignancies. Additionally, a powerful feature of the management of GI malignancies is the opportunity to harness multiple modalities of treatment and integrate the expertise of numerous specialists. As such, a second major theme highlighted at the meeting was the advancement of integrated components of multimodality GI care. In an age of rapid expansion in the cost of cancer care, a third theme of the GI sessions was the potential to develop simple and high value secondary prevention interventions. In this commentary, I will highlight several abstracts presented on the themes of immune checkpoint inhibition, optimal multimodality treatment, and secondary prevention with the goal of placing the results in the context of wider efforts to improve outcomes for patients with GI malignancies.

Immune Checkpoint Inhibition in GI Cancer

The application of an improved understanding of cancer's ability to evade the immune system and its reversal through immune checkpoint inhibitors has already revolutionized the treatment of multiple malignancies. Early data were perhaps strongest in the traditionally immune therapy sensitive diseases such as melanoma and renal cell carcinoma, but increasingly diseases with a high mutation burden such as non-small cell lung cancer have also become targets for this strategy. A developing paradigm is that higher mutation rates result in multiple neo-antigens, which provide a synergistic stimulus for the immune response that is unleashed with blockade of an immune checkpoint, especially the

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programmed death-1 (PD-1) receptor-ligand interaction. While the application of PD-1 or PD-L1 inhibitors to the majority of patients with colorectal cancer (CRC) has not demonstrated significant promise, Le et al. tested the hypothesis that tumors deficient in DNA mismatch repair (MMR), which have amongst the highest mutation rates of all malignancies, may be a subset sensitive to these agents [1]. They studied 13 patients with MMR deficient colorectal cancer, 25 patients with MMR proficient colorectal cancer, and 10 patients with MMR deficient cancers other than CRC, including 4 ampullary/biliary, 2 small bowel, and 1 gastric. Deficiency of MMR was established using standard PCR-based (microsatellite instability) or immunohistochemical testing. The PD-1 inhibitor pembrolizumab 10 mg/kg was administered every 2 weeks and the co-primary endpoints of the study were 20-week immune related progression free survival (PFS) and overall response rate. Objective response was observed in 62% of patients with MMR deficient CRC, and 60% of MMR deficient non-CRC, while none of the 25 patients with MMR proficient CRC responded. The co-primary endpoint of 20-week immune-related PFS was not reported, although at time of early analysis median PFS was 2.3 months in the MMR proficient CRC cohort and not yet reached in the MMR deficient groups. With confirmation in follow up studies, these early results imply that treatment may differ for MMR deficient versus proficient CRC in the near future. Moreover, with abstracts also highlighting potential new treatment options for BRAF mutated CRC [2, 3] and HER2 amplified CRC [4], these are important new steps in defining precision treatment options for patients with advanced CRC that go beyond EGFR inhibitors and assessment of RAS mutation status.

In advanced hepatocellular cancer (HCC), Dr. El-Khoueiry presented interim results of a phase I study of the PD-1 inhibitor nivolumab in 3 cohorts, including a cohort of patients infected with hepatitis B, a cohort of patients infected with hepatitis C, and a cohort without evidence of hepatitis B or C infection [5]. Although not directly tested in the study, the underlying hypothesis was that both the safety and efficacy of immune checkpoint inhibition may differ amongst these cohorts due to the presence or absence of specific viral infection. Importantly, all patients with hepatitis B were required to be on antiviral therapy. The primary endpoints of this phase I study included safety and tolerability, dose limiting toxicity, and establishment of the maximum tolerated dose. Interim analysis of 47 patients demonstrated that nivolumab could be administered to this population without unexpected toxicity, although the hepatitis B cohort had not yet completed dose escalation. Serious toxicity was reassuringly rare, with the most common grade 3 event of AST or ALT elevation occurring in about 10% of the patients studied. Objective responses were observed in 19% of 42 evaluable patients, including 2 complete responses. Interestingly, the responses were distributed across the cohorts, although perhaps numerically highest in the hepatitis C cohort. However, establishing a difference in response by etiology of liver disease in HCC will require more study. In those who responded, the duration of response was long and response was maintained for over 1 year despite stopping the drug in several patients. These are early data, but could represent a paradigm shift for a disease that has not had a new treatment since sorafenib's approval.

Finally, investigators in the KEYNOTE-012 program evaluated the efficacy of pembrolizumab in the approximately 40% of gastric of gastroesophageal junction adenocarcinoma patients whose tumors contained stromal or 1% tumor nest cell PD-L1

staining using a prototype assay [6]. In 39 treated patients, the overall response rate was 22% by central review with a median time to response of 8 weeks (range, 7–16) and a median response duration of 40 weeks, although response is ongoing in 4 patients. Toxicity was mild as has now come to be expected with this class of agents. Similar findings were observed in 23 PD-L1+ esophageal cancer patients in KEYNOTE-028 [7]. Further study in esophagogastric cancer is clearly warranted, a phase II study (NCT02335411) of pembrolizumab monotherapy or in combination with chemotherapy and a phase III study (NCT02370498) comparing pembrolizumab to paclitaxel in the second line treatment of advanced esophagogastric cancer are ongoing. Thus, the application of immune checkpoint inhibition is coming of age in GI cancers with early evidence of promise gastric cancer, HCC and in MMR deficient cancers such as a subset of CRC. Larger studies are being conducted to confirm these findings, and the results of these studies may revolutionize treatment of these malignancies in the near future.

Optimizing Multimodality Treatment

Integration of chemotherapy, radiation therapy, surgery, and other forms of local therapy is a feature of the treatment of many GI malignancies. Two major studies presented at the colorectal cancer session examined the role of multi-modality treatment of colorectal cancer liver metastases (CRCLM). The CLOCC study was a randomized study of 119 patients with up to 10 smaller than 4 cm unresectable CRCLM as determined at a multidisciplinary tumor board [8]. Patients were randomized to chemotherapy alone, or to chemotherapy plus radiofrequency ablation (RFA). The study was originally designed as a phase III study, but was modified to a phase II due to low accrual, and subsequently didn't reach the target enrollment of 152 patients. Twenty-seven of the 57 patients in the combined modality arm had the addition of surgery to the liver RFA treatment procedure. Additionally, seven patients in the chemotherapy alone arm underwent a liver-directed surgery. After a median follow up of 9.7 years, median PFS was improved from 9.7 months (chemotherapy) to 16.8 months (chemotherapy + RFA; HR 0.57, 95% CI 0.38–0.85, $p = 0.005$). Overall survival was also improved from 40.5 to 45.6 months (HR 0.58, 95% CI 0.38–0.88, $p = 0.010$). For a study that did not even reach a modified accrual target, this study has a powerful message. There is a clear role for the involvement of local ablative techniques in CRCLM and these patients should be discussed at multidisciplinary tumor boards whenever possible.

The second study in multidisciplinary treatment of CRCLM was the much anticipated SIFLOX study [9]. This multi-national study was a randomized 530 patient phase III study of mFOLFOX6 +/- bevacizumab alone or with selective internal radiotherapy (SIRT). The majority of patients enrolled on the study had synchronous disease, 40% had extrahepatic disease, and the primary was still in place in nearly half. Adding SIRT to chemotherapy resulted in modest increases in hematologic toxicity, and a few percentage of gastric ulceration, ascites, and hepatic failure related to the procedure. The primary endpoint of overall progression free survival (PFS) was not improved in the combined therapy arm (10.2 vs. 10.7 months; HR 0.93, 95% CI 0.77–1.12, $p = 0.43$). However, PFS in the liver was prolonged from 12.6 to 20.5 months (HR 0.69, 95% CI: 0.55–0.90, $p = 0.002$). These data suggest that adding SIRT to first line chemotherapy may have a role in some patients with advanced CRC; however, the optimal patient selection strategy remains to be defined.

Future subset analyses, especially focusing on the subset with liver only metastases, may be helpful. Until then, the selection of patients for SIRT will be heavily individualized, focusing on attempts to identify those with the greatest chance of benefit from control of liver disease.

In rectal cancer, a number of ongoing studies are evaluating the concepts of selective radiation therapy and administering all chemotherapy before surgery. The FOWARC study [10], presented by Dr. Deng on behalf of the Chinese Society of Colorectal Surgery, was a randomized study investigating the role of modified FOLFOX6 alone or with radiation as a neoadjuvant treatment for MRI or endorectal ultrasound staged T3/T4 or node positive rectal cancer. The study included three arms; a) deGramont 5-FU with radiation followed by total mesorectal excision (TME) and adjuvant deGramont 5-FU, b) modified FOLFOX6 with radiation followed by TME and adjuvant mFOLFOX6 and c) mFOLFOX6 alone with TME and subsequent adjuvant mFOLFOX6. The primary endpoint of the study is 3-year disease free survival, although the data presented were for the secondary endpoints of pathologic complete response (pCR) and toxicity. As has been observed in prior studies, mFOLFOX6 with radiation is associated with increased grade 3/4 leukopenia, diarrhea, and nausea/vomiting. R0 resection was completed in roughly 90% of patients, well balanced between the arms. However, pCR was 6% in the mFOLFOX6 alone arm, 14.3% in the deGramont arm, and 28.0% in the mFOLFOX6 with radiation arm. These data add to the growing list of studies using 5-FU and oxaliplatin with radiation in locally advanced rectal cancer including the ACCORD 12/0405, STAR-01, CAO/ARO/AIO-04, and NSABP R-04 trials. The message from these studies is that adding oxaliplatin to chemoradiation has the potential for higher rates of pCR at the expense of certain increased toxicity. As no convincing data exists for improvement in disease free or overall survival with this approach, it cannot currently be recommended.

In locally advanced esophagogastric cancers, the optimal intensity and integration of chemotherapy, radiation therapy, and extent of surgery remain somewhat controversial. The UK Medical Research Council OEO5 is an important negative study for the intensity of chemotherapy [11]. This study was conducted to evaluate the role of increased intensity chemotherapy prior to surgery for resectable esophageal and gastroesophageal junction (Siewert I and II) cancers. Eight hundred ninety-seven patients were randomized to 2 cycles of cisplatin and 5-fluorouracil (CF) versus 4 cycles of epirubicin, cisplatin, and capecitabine (ECX). The ECX regimen was associated with increased rates of grade 3 or higher neutropenia, febrile neutropenia, and palmar plantar erythrodysesthesia syndrome as expected. It also improved tumor regression grade by the Mandard criteria (e.g. 11% grade 1 [pathologic CR] vs 3% in the CF arm) and trended towards improvement in R0 resection rate (67% vs 60%, $p = 0.059$). Additionally, there was a minor trend towards improvement in PFS (HR 0.86, 95% C.I. 0.74 – 1.01). However, there was no improvement in overall survival with ECX treatment (HR 0.92, 95% C.I. 0.79–1.08). The survival outcomes for both arms of this study were better than expected. These data argue that 6 weeks of neoadjuvant doublet chemotherapy is sufficient and by indirect comparison, argue against continuation of the same chemotherapy in the post-operative setting.

In pancreatic cancer, multidisciplinary cooperation within the intergroup has resulted in the establishment of a standardized definition for borderline resectable pancreatic cancer with the following criteria; 1) tumor-vessel interface (TVI) with superior mesenteric/portal vein (SMV) $\geq 180^\circ$, 2) TVI with superior mesenteric artery (SMA) or celiac trunk $< 180^\circ$, 3) reconstructable TVI with hepatic artery of any degree. Using this definition, they attempted a multi-institutional pilot study (A021101) of modified FOLFIRINOX followed by capecitabine and radiation followed by resection and adjuvant gemcitabine in 23 patients with borderline resectable pancreatic cancer [12]. Sixty-eight percent of patients did successfully undergo pancreatectomy, and 93% of these operations were R0. Impressively, 47% specimens had $< 5\%$ residual tumor cells following therapy. This study is important in that it demonstrates the ability to do multi-institutional clinical trials with multidisciplinary intervention in this increasingly defined patient population. Future studies based on this concept are expected to define standard treatment for this patient population.

Secondary Prevention in Colorectal Cancer

Two observational studies evaluated the association of vitamin D level and aspirin use on survival outcomes in patients with the diagnosis of advanced colorectal cancer. In the setting of an increased discussion of value in cancer care, demonstration that vitamin D supplementation or aspirin (or other COX inhibitor) use could improve survival would be a major breakthrough. Vitamin D has pleiotropic effects on cellular proliferation. In preclinical models, vitamin D levels are associated with increased proliferation of colorectal cancer cells and increased numbers of pre-neoplastic lesions. In population studies, lower vitamin D levels are associated with a higher risk of colorectal cancer. Using the extraordinarily rich database from CALGB/SWOG 80405, Dr. Ng and colleagues dissected the association of 25(OH) vitamin D levels and survival [13]. This randomized study ultimately accrued 2,334 patients with untreated advanced colorectal cancer, although the primary analysis that was presented at last years' ASCO meeting was conducted in the 1,140 patient subset of KRAS wild-type patients. In a cohort of 1,043 patients from the parent study, 25(OH) vitamin D was measured by radioimmunoassay post-diagnosis but pre-treatment and levels were associated with outcome. In multivariable models adjusting for age, sex, race/ethnicity, performance status, chemotherapy backbone, prior adjuvant therapy, assigned biologic, RAS mutation status, season of blood draw, geographic region, body mass index, and physical activity, higher vitamin D levels were associated with improved survival outcomes. In the highest quintile of patients with 25(OH) vitamin D levels above 24.0ng/mL there was a 35% reduction in the hazard of death (HR 0.65, 95% CI: 0.51 – 0.83). It remains to be determined whether this association is the result of more aggressive cancers that develop in a low vitamin D state or whether increasing vitamin D levels with supplementation can slow the growth of CRC and improve outcomes. The authors are appropriately following this data with a randomized phase II study of aggressive supplementation to begin the process of answering the intervention question.

Aspirin has established efficacy as a chemopreventive agent for colorectal cancer, although its use is limited due to the competing risks of adverse events from its use. Using a population based retrospective cohort design from comprehensive registries in Norway, Bains et al. asked the question of whether post-diagnosis aspirin use was associated with

survival in patients with colon cancer diagnosis [14]. A pharmacy prescription for aspirin after the diagnosis of colorectal cancer was associated with better both overall (HR 0.86) and colorectal cancer specific survival (HR 0.75) in this cohort of 25,644 Norwegian patients. As with any observational study, confounding cannot be completely excluded as the mediator of this result. Nonetheless, this study is consistent with other large studies and is based on clear biologic plausibility. It remains to be determined if aspirin use would have a greater benefit in certain tumors (e.g. PIK3CA mutated or COX-2 expressing) and if there is selective benefit in those not taking aspirin prior to colorectal cancer diagnosis as has been suggested by other studies. Nonetheless, these data provide further support to ongoing randomized trials of COX inhibitors as secondary prevention agents, including CALGB/Alliance 80702 (NCT01150045), which randomizes patients with resected stage III colon cancer to 3 years of celecoxib or placebo. The results of this and other therapeutic clinical trials in this arena are eagerly awaited, as these relatively low cost interventions would define potentially high value interventions to improve outcomes for patients with CRC. Along with the application of immune checkpoint inhibitors and refinement of multidisciplinary strategies, these abstracts highlight future promise for improved therapy to GI cancers.

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