Review Paper

Practice changing updates In Gastro-intestinal oncology 2018

Abstract

In this article the pivotal presentations at major conferences for gastro-intestinal cancers have been discussed. This year the presentations on Colon, pancreas and hepatocellular cancers have practice changing potential. The following selected presentations highlights the conference updates in gastrointestinal malignancies.

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First-line FOLFOX plus panitumumab (Pan) followed by 5FU/LV plus Pan or single-agent Pan as maintenance therapy in patients with RAS wild-type metastatic colorectal cancer: The VALENTINO study[1]

The optimal approach to maintenance treatment is less clear for patients with mCRC who achieve stability or deeper response with induction chemotherapy with anti-endothelial growth factor receptor (anti-EGFR) agents such as cetuximab or panitumumab. In this phase II VALENTINO trial, 229 patients with previously untreated, RAS wild type advanced mCRC were enrolled to evaluate whether maintenance with panitumumab monotherapy was non-inferior 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 10 month PFS rate at 62.8% compared to 52.8% with monotherapy. The median PFS was significant with combination strategy at 13 months vs 10.2 months. (HR 1.55 (95%CI 1.09-2.02, p=0.011). However, the trial failed to meet the criteria for non-inferiority of panitumumab monotherapy, which was set at a threshold of HR <1.515. Therefore fluoropyramidine plus panitumumab should be the preferred maintenance option for patients who have stopped oxaliplatin.

A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7[2]

Approximately one-fifth of the patients with mCRC will develop peritoneal carcinomatosis (PC) and is associated with worse survival outcomes compared to metastasis elsewhere[3]. The phase III PRODIGE 7 is the first prospective French randomized trial to evaluate HIPEC in mCRC patients with PC. In this study 265 patients, who were required to achieve macroscopically complete surgical resection (R0/R1) or resection with ≤1 mm residual tumor tissue, were randomly assigned in the operating room to the HIPEC or non-HIPEC groups. Patients in the HIPEC arm received intraperitoneal oxaliplatin 460 mg/m2 heated

to 43°C over 30 minutes following cyto-reduction surgery. Majority of the patients (96%) were also treated with systemic chemotherapy for 6 months, peri-operatively. At the median follow-up of 64 months no significant difference in terms of recurrence free ((13.1 vs 11.1months; HR, 0.91; 95%, 0.69–1.19; p = .486) and overall survival between the HIPEC and non-HIPEC groups. The median OS with and without HIPEC(41.7 vs 41.2 months; HR 1.00; 95% CI, 0.73–1.37; p = .995). Post-operatively, the long term morbidity ((24.1% vs 13.6% ;p = .030).) and mortality was high in HIPEC arm. The 30 and 60-day mortality rates in HIPEC arm were 1.5% and 2.6%, respectively. Therefore the authors concluded that given the lack of survival benefit and the increased risk of postoperative complications the HIPEC has limited role for PC patients undergoing debulking surgery. The cytoreductive surgery alone showed satisfactory survival outcomes.

Role of Oxaliplatin in neoadjuvant and adjuvant setting in localized rectal cancer:

The current guidelines suggests preoperative fluoropyramidine based chemo radiation for 2/3 stage rectal cancer. Despite low local regional relapse of 5% to 6% with pre-op chemoradiation, 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 chemoradiation and adjuvant therapy were presented at ASCO this year.

Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Final results of PETACC-6[4]

PETACC-6 study compared preoperative chemoradiation plus capecitabine followed by adjuvant capecitabine with or without oxaliplatin (CAPOX vs Capecitabine) in 1090 patients with T3/4 or node-positive rectal cancer. The primary endpoint was disease free survival (DFS). At median follow-up of 68 months, there was no difference between CAPOX and capecitabine arms in 5 year DFS 70.5 m vs 71.3 m (HR 1.02; p=0.84 95%CI (0.82, 1.28)) respectively. Irrespective of stage 2 or 3, the 5-year OS was similar with or without oxaliplatin (80.1% and 83.1%, respectively), as were loco regional relapse (6.0% and 8.7%) and distant relapse (19.2% and 21.4%).

Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial[5].

FOWARC is a Chinese multicenter, randomized trial (involving 495 patients with stage II or III rectal cancer to compare the efficacy of preoperative treatment with modified FOLFOX6 with or without radiation (RT) vs 5-FU plus radiotherapy. Therefore it has a study arm with no radiation. The primary endpoint was DFS at 3 years defined as the interval from randomization to incomplete surgical resection, locregional or metastatic recurrence or death, whichever occurred first. Folfox with or with out radiation did not improve local recurrence (10.3% in RT-- FU-RT group, 8% in FOLFOX-RT group, 8.7% in FOLFOX group.). A higher pathologic complete response rate observed with FOLFOX -RT (29.1%), compared with either 5-FU plus RT (13.1%) or FOLOX alone (6.9%). The incidence of liver metastasis was lower in FOLFOX-RT compared to FOLFOX or 5FU-RT (3.5% vs 8.3% vs 11.5%). No significant difference in terms of 3 year OS was noted in either of the study arms. Therefore the investigators concluded that n locally advanced rectal cancer patients, neoadjuvant mFOLFOX6 ± RT did not improve DFS compared to 5FU CRT. mFOLFOX + RT , Improved the rate of pCR, potentially enabling patients for a ‘watch and wait’ options to avoid or delay surgery. mFOLFOX alone did not significantly compromise 3-year DFS or local control compared to other treatments

Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142[7]

This multicenter, non-randomized phase 2 trial evaluated single agent nivolumab or in combination with other immune therapies in patients with microsatellite high (MSI-H) or deficient mismatch repair (dMMR) progressed on fluoropyramidine, irinotecan and oxaliplatin. One cohort of this study investigated the combination of two checkpoint inhibitors nivolumab and ipilimumab as the synergism was shown previously in other tumor types1. The combination cohort (n=119) received 4 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 median follow up of 13.3 month the overall response rate (ORR) was 55% in combination cohort compared to 31% in nivolumab monotherapy cohort. Twelve-month PFS was 71% (95% CI, 61.4%-78.7%), and 12-month OS was 85% (95% CI, 77.0%-90.2%) in combination cohort. Grade ¾ AE's were relatively common in combination cohort (32% vs 20%) but were manageable.

Regorafenib Dose Optimization Study (ReDOS): Randomized Phase II Trial to Evaluate Dosing Strategies for regorafenib in Refractory Metastatic Colorectal Cancer—An ACCRU Network Study[8].

Regorafenib is an oral multikinase inhibitor that showed improved overall survival in previously treated metastatic colorectal cancers in the CORRECT study[9]. 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. The randomized ReDOS study in 123 patients, compared fixed dose of regorafenib (160mg) to dose- escalated regimen (80mg/day with weekly dose escalation up to 160 mg) as tolerated for 21 days during 28-day cycle. The primary endpoint was the patient proportion who completed two treatment cycles and this was met with 43% in escalated dose arm vs 24% in standard arm (p=(0.028). There was no change in median PFS (2.5month vs 2 months). Treatment discontinuation rate was higher in escalated arm due to adverse effects(18.5% vs 9.7 %) however, the incidence of grade ¾ toxicity was lower in escalation arm (fatigue 13% vs 17.%; hand-foot rash 14.8 vs 16%). Thus, this study supports the dose escalation strategy for treatment of advanced colorectal cancers with regorafinib.

NON-COLORECTAL

Pancreas

It is estimated by 2020 pancreatic cancer would be the second most leading cause of cancer related death in the United States. Hence this is an area of need to improve our treatment strategies in metastatic and non-metastatic disease. There were few key trials presented ASCO 2018 that may change treatment landscape for early stage pancreatic cancer.

Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas[10].

PRODIGE 24/CCTG PA is a randomized adjuvant trial of modified FOLFIRINOX versus gemcitabine for 6 months after surgery in 493 patients with resectable cancers. Adjuvant therapy was initiated 3-12 weeks following surgery. Modified FOLFIRINOX yielded an unprecedented median overall survival of 54 months versus 35 months with gemcitabine. The median disease-free survival was 22 months versus 13 months. Patient receiving modified FOLFIRINOX had severe adverse effects, but are manageable. This

included diarrhea, nausea, vomiting and fatigue. Also 66% of patients were able to complete 6 months of modified FOLFIRINOX. It is also interesting to note that gemcitabine alone yielded median overall survival of 35 months. However, in ESAPC-4 trial we observed a median OS of 25 months with gemcitabine. This may be due to the difference in either tumor biology or patient tolerance to treatment in the French and Canadian population in the current study. Modified FOLFIRINOX has the potential to b standard of care for adjuvant management in good performance status patents.

Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1) : A randomized, controlled, multicenter phase III trial[11].

PREOPANC–1, demonstrated neoadjuvant chemoradiation (CRT) followed by surgery is superior to surgery without neoadjuvant therapy for localized pancreatic cancers. 246 patients with resectable cancers were randomly assigned to surgery upfront versus gemcitabine based chemotherapy plus radiation for 10 weeks prior to surgery. Both arms received chemotherapy after surgery. Median overall survival was 17.1 months with preoperative CRT compared to 13.7 months with upfront surgery. Also, the 2 year survivial rate was 42% in pre-operative CRT arm compared to surgery alone arm. The radial surgical resection in the neoadjuvant therapy group was 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 prior to surgery for resectable cancers

FOLFIRINOX until progression, FOLFIRINOX with maintenance treatment, or sequential treatment with gemcitabine and FOLFIRI.3 for first-line treatment of metastatic pancreatic cancer: A randomized phase II trial (PRODIGE 35-PANOPTIMOX) [12].

In 2011 PRODIGE4-ACCORD11 study had shown the superiority of 6-months FOLFIRINOX over gemcitabine in metastatic pancreatic cancers with PFS (6.4 vs. 3.3 m; HR: 0.47; 95%CI: 0.37-0.59; p<0.001) and OS (11.1 vs. 6.8 m; HR: 0.57; 95%CI: 0.45-0.73; p<0.001), at the cost of higher toxicity, especially peripheral neuropathy. In this randomized Phase II trial, the investigators aimed to assess an oxaliplatin ‘stop-and-go’ strategy and an alternative sequential strategy in metastatic pancreatic cancers. 273 patients were randomized to receive 6 months of FOLFIRINOX (arm A; n = 91), 4 months of FOLFIRINOX followed by LV5FU2 maintenance (arm B; n = 92), or alternating gemcitabine and FOLFIRI.3 every 2 months (arm C; n = 90). Grade 3/4 neurotoxicity was 10% and 19% of patients in arm A and B, respectively. The 6-month PFS rate was 47% in arm A, 44% in arm B, and 34% in arm C, with median PFS of 6.3, 5.7, and 4.5 months, respectively. The 4-month ORR was 35% in arm A, 41% in arm B, and 17% in arm C, with median overall survival of 10.1, 11.2, and 7.3 months, respectively. Based on the results we can conclude that alternating Gemcitabine/FOLFIRI strategy is inferior. The trial failed to show that a stop-and-go strategy was any better than limiting exposure to FOLFIRINOX to 6 months as PFS/OS was similar and neuropathy was worse in arm B. Therefore OPTIMOX-like induction-maintenance strategy with discontinuing oxaliplatin and irinotecan after 4 months is a feasible strategy in metastatic pancreatic cancer.

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) [13].

Temozolomide is a newer alkylating agent that is better than streptozocin. MGMT deficiency is associated with higher response rates to temozolomide and is more commonly seen in pancreatic NETs. Capecitabine can deplete MGMT, and hence the synergistic action with temozolomide. This is the first prospective RCT with these agents. Total of 144 patients with progressive, grade 1/2, metastatic pancreatic NETs were randomized to either temozolomide alone or temozolomide/capecitabine (CAPTEM). All patients had progressive disease within the past 12 months. There was a longer time from diagnosis in the CAPTEM arm (34.0 vs. 24.4 months; p = 0.11) though it did not reach statistical significance. Median PFS was 14.4 months with temozolomide alone, versus with 22.7 months with CAPTEM (HR 0.58, 95% CI [0.36, 0.93]; p = 0.023). Median OS was 38 months with temozolomide alone, and it had not yet been reached with CAPTEM (HR 0.41, 95% CI [0.21, 0.82]; p = 0.012). More patients in the temozolomide single agent arm had WHO intermediate grade (grade 2) disease, at 54.9% compared with 31.9% in the CAPTEM arm (p = 0.013). Sensitivity analysis revealed that grade was not significantly associated with either PFS (p = 0.41) or OS (p = 0.28). HR were unchanged after adjusting for grade. Response rates were similar between the arms. No CR with CATPEM, 2.8% CR rate with temozolomide alone; the PR were 25.0% with monotherapy and 33.3% with the CAPTEM, and the ORR were 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. Hence CAPTEM regimen will be used more often. Now that PRRT is approved in the US we will need to figure out sequencing of various treatment (CAPTEM, everolimus, sutent and PRRT) for neuroendocrine tumors.

Hepatocellular Cancer

Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: Results from the randomized phase III CELESTIAL trial[14].

Sorafenib is the only TKI approved by FDA for the first-line treatment of unresectable or advanced hepatocellular carcinoma (HCC). Several TKI drugs are being studied in second line setting including Cabozantinib which inhibits VEGFR, MET and AXL. In the past, tivantinib (selective MET inhibitor) failed as a second line therapy in MET upregulated HCC. This may be due to other escaping signaling pathways. In addition to inhibiting MET, cabozantanib also inhibits VEGFR and AXL.

This is a phase III trial with 707 patients with Child Pugh A cirrhosis that had progressed on at least 1 prior systemic therapy, were randomized in a 2:1 ratio to treatment with cabozantinib at 60 mg daily (n = 470) or placebo (n = 237). 70% patients had received prior sorafenib. The objective response rate (ORR) was 4% with cabozantinib versus 0.4% with placebo (p = .0086). And disease control rate was 64% with cabozantanib versus 33% with placebo. 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) ; 95% CI, 0.63-0.92; P = .0049). The median PFS with cabozantinib was 5.2 months versus 1.9 months with placebo (HR, 0.44, 95% CI, 0.36-0.52; P <.0001). As expected, patients that received cabozantanib had relatively more adverse effects versus placebo such as palmar-plantar erythrodysesthesia (17% vs 0%), hypertension (16% vs 2%), increased aspartate aminotransferase (12% vs 7%), fatigue (10% vs 4%), and diarrhea (10% vs 2%). In patients with advanced HCC, cabozantinib significantly improved OS, PFS and ORR after prior systemic anticancer therapy. The safety profile of cabozantinib was acceptable and rate of discontinuation due to treatment related adverse effects was low. Based on this study, cabozantanib is being reviewed by FDA, if approved, could be one of the viable options for patients with advanced HCC

after prior systemic anticancer therapy in unresectable or advanced HCC. This study was recently published in an esteemed peer-review journal[15].

REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib[16].

Advanced HCC that has failed first line of therapy is associated with poor prognosis due to aggressive nature of the disease, and the prognosis is dismal (in the range of few months) for patients with elevated AFP levels, which constitutes about half of the cases. Hence second line therapy is an area of need for HCC. Typically, biomarker driven trials (e.g. MET upregulation) has failed in HCC. REACH-2 is the very first Phase 3 trial in biomarker-selected HCCs with positive findings. This is a follow-up to the phase III REACH trial. In June 2014, the REACH study reported that single agent ramucirumab did not show OS improvement compared with placebo in the in second-line setting for with advanced HCC. Subgroup analysis in AFP high patients did show an OS improvement with ramucirumab. This led to the phase III REACH-2 study, a multicenter, randomized, double-blind study in advanced HCC who failed Sorafenib (intolerance or progressed), and had elevated AFP ≥400 ng/mL. 565 patients were randomized to to Ramucirumab 8mg/kg at every 2 weeks (n = 283) versus placebo (n = 282). In HCC patients with elevated AFP, the median OS for patients with a baseline AFP >400 ng/mL was 7.8 months with ramucirumab vs 4.2 months with placebo (HR, 0.674; 95% CI, 0.51-0.90; P = .0059). In contrast, for HCC patients with a baseline AFP <400 ng/mL, OS was 10.1 months with ramucirumab compared to 11.8 months with placebo. With the positive findings of REACH2 study the hypothesis generated by the REACH trial results was confirmed with a prespecified subgroup analysis of advanced HCC patients with high AFP levels. Ramucirumab improved PFS and OS in second-line treatment of advanced HCC with elevated AFP levels. It is unclear where ramucirumab will fit in given the recent positive outcomes with regorafenib, nivolumab, and cabozantinib.

Randomized, open label, multicenter, phase II trial comparing transarterial chemoembolization (TACE) plus sorafenib with TACE alone in patients with hepatocellular carcinoma (HCC): TACTICS trial[17].

In the phase II TACTICS trial, presented by Kudo et al, 56 patients with unresectable HCC were randomized to receive TACE alone (n = 76) or sorafenib plus TACE (n = 80). Of note, sorafenib was given for a longer period than in previous combination therapy studies. In previous trials, sorafenib was given for 17 to 21 weeks, but subgroup analysis indicated that a longer duration of therapy may improve outcome. Hence, patients received sorafenib for a median of 38.7 weeks in the TACTICS trial. Sorafenib 400 mg once daily was given for 2 to 3 weeks prior to TACE. During TACE sessions, patients received sorafenib 800 mg once daily. Notably, the investigators introduced a new endpoint in this clinical trial, time to untreatable progression (TTUP) and/or progression to TACE refractoriness. Treatment was continued until TTUP, decline in liver function to 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 progressive disease because this is attributable to the natural tumor biology of HCC and doesn't indicate treatment failure. Median PFS was longer with sorafenib plus TACE versus TACE alone (25.2 months vs 13.5 months; HR = 0.59; P = .006). In regard to TTUP endpoint, PFS was longer with sorafenib + TACE compared to TACE alone (26.7 months vs 20.6 months; HR = 0.57; P = .02). Though PFS results are favorable to sorafenib plus TACE, TTUP endpoint needs validation and it is critical to

await more mature survival outcomes of this study. Also, a study in the US with a larger sample size is warranted to confirm the findings.

Esophageal Cancer

The impact of the chemoradiation to surgery interval on pathological complete response: Short and long-term overall survival in esophageal cancer patients[18].

Optimal timing of esophagectomy following neoadjuvant trial is around 6-8 weeks. A consistent observation in several studies is that response to neoadjuvant therapy, particularly pathologic complete response (pathCR), is an indicator of better disease-free and overall survival. However, new data for esophageal cancer and other solid malignancies showed higher pCR rates if time intervals between CRT and surgery were longer, and this may translate to longer survival. Hence, Azab et al queried the National Cancer Database for answers. 5,181 patients with esophageal adenocarcinoma or squamous cell carcinoma who received neoadjuvant CRT followed 15 to 90 days later by definitive surgery during the period from 2004 to 2014. 81% had adenocarcinoma, and 73% and 35% had disease staged as cT3 and cN0, respectively, prior to surgery. The time intervals were divided into quintiles (Q1, 15 to 37 days; Q2, 38 to 45 days; Q3, 46 to 53 days; Q4, 54 to 64 days; and Q5, 65 to 90 days), and each quintile contained approximately 1,000 patients. pCR rates increased significantly across quintiles as the interval between neoadjuvant CRT and surgery increased (17.9%, 20.7%, 23.9%, 24.7%, 29.1% for Q1 through Q5, respectively; $p < 0.001$); however, the 90-day mortality rates also increased (5.8%, 6.3%, 6.8%, 8.6%, 8.4% for Q1 through Q5, respectively; $p = 0.04$). 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. Median overall survival (OS) also decreased significantly across quintiles (36.4, 35.1, 33.9, 33.2, 30.7 months for Q1 through Q5, respectively; $p = 0.008$. There was no difference in OS outcomes across quintiles in squamous cell carcinoma patients ($p = 0.8$), whereas adenocarcinoma patients demonstrated poorer OS if esophagectomy was delayed until 65 to 90 days after CRT versus sooner surgery ($p = 0.001$). Upon multivariate regression analysis, they observed that achieving pCR was independently associated with a reduced risk of mortality (HR 0.57, 95% CI [0.51, 0.64]; $p = 0.001$), whereas an interval of 65 to 90 days between CRT and surgery was associated with an increased risk (HR 1.16, 95% CI [1.02, 1.31]; $p = 0.027$). Though higher pCR rate is attained as CRT-S interval increases, esophagectomy is preferred to be performed within 65 days after CRT to evade worse 90-day mortality and reach improved OS. This data needs to be validated in a prospective randomized trial which would be challenging to conduct.

Conclusion

- Combination chemotherapy based maintenance remains treatment standard as the single-agent panitumumab failed to show progression-free survival benefits when compared with chemotherapy plus panitumumab in patients with RAS wild-type metastatic colorectal cancer (mCRC). Addition of oxaliplatin to either fluoropyramidine during radiation therapy did not improve clinical outcome. FOLFOX is reasonable adjuvant treatment option for rectal cancer particularly in pathologic stage III disease.
- Metastatic colorectal cancer patients with peritoneal carcinomatosis may not need HIPEC after thorough cytoreductive surgery. The combination of Nivolumab and Ipilimumab provided durable clinical benefit and emerged as one of the therapeutic options for the patients with metastatic

colorectal cancer with MSI-H or dMMR. The modification of the Regorafinib dosing made relatively more tolerable allowing for longer treatment duration leading to better clinical outcomes.

- Modified FOLFIRINOX is potentially new standard of care after pancreatic cancer resection in patients with good performance status . Neoadjuvant is an emerging therapeutic strategy in patients presented with resectable pancreatic cancer. More options now for advanced hepatocellular cancer, that may need further studies on optimal sequence.

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