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Focused update on Gastrointestinal (GI) Oncology from ASCO 2016

The 52nd annual meeting of American Society of Clinical Oncology was held in Chicago, Illinois, on June 3-7, 2016, gathering 30,000 oncology professionals giving the attendees the opportunity to discuss and view ground-breaking research. In this article the pivotal presentations at American Society of Clinical Oncology (ASCO) 2016 related to colorectal cancer (CRC) and other gastrointestinal malignancies have been discussed. The presentations on pancreatic cancer and Neuroendocrine tumors have practice changing potential. The provocative retrospective study on Sidedness in KRAS wild type in patients with metastatic colorectal cancer (CRC) receiving biologics such as epidermal growth factor receptor (EGFR) targeted antibody and vascular endothelial receptor targeted antibody (VEGF) treatment could be a change in the paradigm of management of these patients. The addition of Doxorubicin to sorafenib was not superior to sorafenib alone for advanced hepatocellular carcinoma. For resectable gastric cancer patients, Post-operative chemoradiation resulted in similar survival when compared with post-operative chemotherapy. The novel Peptide Receptor nuclide therapy has significantly increased progression free survival in low grade metastatic midgut neuroendocrine tumors (NETTER-1). The Immunotherapy in colorectal and non-colorectal malignancies continuous to evolve as noted in several presentations. Microsatellite Instability has again been confirmed to be an important predictor in patients with stage IV colon cancer receiving immunotherapy. As expected, the immunotherapy and precision medicine was featured heavily in ASCO 2016. The selected presentations from 2016 annual meeting of American Society of Clinical Oncology (ASCO) related to GI Oncology have been reviewed here.

COLORECTAL CANCER

Epidermal growth factor receptor (EGFR) targeted antibodies approved for clinical use in patients with metastatic CRC. Several retrospective studies in CRC patients receiving anti-EGFR antibody treatment have shown that patients with mutated KRAS did not benefit from anti-EGFR therapy. The KRAS data has changed the paradigm of anti-EGFR antibody treatment in CRC. The retrospective analyses of KRAS data from CRYSTAL,[1] OPUS[2] and EVEREST[3] have further demonstrated patients with K-RAS mutant CRC do not benefit from anti-EGFR antibody treatment. The addition of cetuximab to FOLF-IRI or FOLFOX as first-line treatment only benefits patients with wild-type KRAS tumors. National Cancer Institute (NCI) has suspended all ongoing U.S. cooperative group studies involving anti-EGFR antibody in CRC since June 2008[4] and led to the amendment of protocols as appropriate.

Dr. Venook presented the retrospective data (Abstract 3504) on impact of the primary tumor location on survival in colorectal cancer in K-ras Wild type patients. Based on the CALGB/SWOG 8405 trial.[5] This was originally a randomized trial looking at either cetuximab or bevacizumab in the first line setting patients, initially all Ras patients, to first line chemotherapy per oncologist's choice. In the current study the investigators assessed the impact of primary tumor location on survival in kras-wt metastatic CRC. Among 1137 patients reviewed retrospectively, about 1/4 patient had right-sided tumors; two thirds had left-sided tumors. There have been some interesting findings, that majority of all left-sided tumors tended to be younger and more males, less synchronous tumors and were more likely to have prior adjuvant chemotherapy. Additionally primary tumors were more likely to be in the left side and more patients had liver only metastases. The overall survival there was a 14 month median survival difference between the left side and the right sided tumors (33.2m (Left) vs 19.4 m (Right)). In terms of the biologics they received, subjects who received bevacizumab did better on the left side than the right with about a seven month difference in survival (31.4 m (left) vs 24.2 m (Right)), but this was even significantly greater when cetuximab was the biologic used in the first line with 19.3 months difference in survival (36.0m (Left) vs 16.7m (Right)), in other words, about 19 months inferior when it was on the right side of the bowel. The overall survival in patients with stage four cancers is 14 months greater with left-sided tumors than right-sided tumors. Cetuximab appears to be more effective than bevacizumab in k-ras wild type in left side where as bevacizumab appears to be more effective on the on the right side. This data is in agreement with previous results from FIRE 3 study that was presented a few years ago. This was a randomized trial between Cetuximab versus bevacizumab the first line setting with FOLFIRI as the chemotherapeutic backbone. A twenty months difference in survival was demonstrated with cetuximab in right versus left same with bevacizumab.

Dr. Shragg and her colleagues (Abstract 3505) attempted to further address this issue by assessing SEER database of the 18 registries they had over 60,000 patients. Basic drawbacks of this study were that, they didn't have any information on K-ras and secondly the only information they had about chemotherapy was from those patients who had Medicare (above 65 years of age). Once again It was demonstrated that patients on the left side to be younger and there were more males on the on that side as

well and once again they showed that there was indeed a difference in stage 4 disease between the left side and the right with the hazard ratio of 1.25 for stage three disease there was a difference but not quite as striking a stage IV with the hazard ratio of 1.12 and no difference noted in in stage II disease.

So why the difference between right and left side tumors in terms of clinical outcomes? To address this Dr. Michael Lee (Abstract 3601) and colleagues from the MD Anderson try to look at this and look at molecular features associated with survival and with anti-EGFR therapy. Colon cancer is biologically heterogeneous, with mutation profiles that are different, microsatellite instability, with consensus molecular subtyping (CMS) classification that was reported two years ago. Molecular analyses suggest that these right sided tumors are impacted by high BRAF, hypermethylation and so distinct gene expression patterns.

From clinical point of view right-sided tumors patients tended to be older, more females, often occur late presentation, histologically mucinous tumors or Signet cell tumors and finally peritoneal metastases are more common with right than left sided. It seems the side of cancer really is a surrogate marker for the tumor biology with differential BRAF and hypermethylation status. As this is a retrospective ad hoc analysis; it has its own strengths and limitations. This study may generalizable to the way these patients are being treated now with multimodality treatment strategies. Comprehensive molecular analysis of specimens and precise biomarkers are needed from phase 2 and 3 prospective clinical trial cohorts, in order to individualize patient care.

PANCREATIC DUCTAL CANCER

Surgical resection remains the only potential curative strategy for pancreatic ductal carcinoma (PDC) patients. However, 5-year survival for surgically resected patients is less than 30% and most patients die of distant and local progression. Therefore, effective adjuvant strategies have been sought to enhance clinical outcomes. The Gastrointestinal Tumor Study Group (GITSG) 9173 trial indicated that post-operative 5-FU and radiotherapy extended the median overall survival to 20 months, as compared with 12 months with observation alone. The European Study Group for Pancreatic Cancer (ESPAC-1) had indicated for the first time that adjuvant systemic chemotherapy led to a superior survival as compared with the either the no chemotherapy or the chemo-radiotherapy, thus, setting the stage for adjuvant treatment for resectable PDC.[6] There was an advantage to taking chemotherapy with the five-year survival at 21% and the no chemotherapy 8%. The Radiation Therapy Oncology Group (RTOG) 9704 indicated that adjuvant gemcitabine followed by chemo-radiation was superior to 5-FU for pancreatic head carcinomas.[7,8] The CONKO-1 study[9] was a multi-center, European trial which randomized 368 patients with surgically resected pancreatic cancer to post-operative gemcitabine for 6 months vs. observation. ESPAC-3[10] assessed over a thousand patients with resectable PDC comparing 5FU and Gemcitabine and found to be equal in terms of survival outcomes. 5FU was given as bolus and had relatively more toxicity compared to Gemcitabine. Gemcitabine thus became reference standard for adjuvant treatment for PDC.

ESPAC 4 is a randomized trial (Abstract 4006) presented by the UK group looking at gemcitabine alone versus combination of gemcitabine and capecitabine following the Whipple procedure. Over 700 patients with pancreatic ductal carcinoma, treated with curative intent in terms of the surgery, were randomized to adjuvant treatment of gem for six cycles (day 1,8,15) or combination of gemcitabine (1000 mg/m^2 d1,8,16 (6 cycles) and Capecitabine (830 mg/m^2 daily 21 days out of 28 days). The overall survival data has been presented and found at the two-year mark the survival curves started to separate with the HR.82 that was a statistically significant, with overall survival of 28 months when compared to Gemcitabine alone (25.5 months). The fiver year survival difference which is about 12% increasing from 16.3% with gemcitabine alone to 28.8% with combination, which is quite impressive. Slightly more toxicity was seen in the combination treatment Arm including hand-foot syndrome diarrhea and neutropenia, however, were manageable. The five years overall survival 29% for gemcitabine and capecitabine compared to the gemcitabine alone which is 16% now. Therefore it is likely be the standard of care and certainly an option to be discussed with our pts.

HEPATOCELLULAR CANCERS

Sorafenib is a multikinase inhibitor of Raf kinase, VEGF receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), and has been approved for the treatment of advanced hepatocellular cancer (HCC), based on the results of the SHARP trial[11] that demonstrated approximately three month survival benefit with sorafenib when compared to placebo in child Pugh A cirrhotics with HCC. In Asian countries, the incidence of HCC is higher than in the western nations and is more likely to be HBV-associated compared to HCV in Western population. Sorafenib significantly prolonged OS and PFS as compared with placebo in a randomized trial with 226 Asian HCC patients,[12] thus establishing this agent as a standard therapy for HCC. Since 2009 several chemotherapeutics and targeted agents have been investigated, however, none of them demonstrated superior survival than Sorafenib alone.

The combination of sorafenib and doxorubicin was found to be synergistic in phase 1 and 2 studies. Abou-Alfa

et al. presented the results of phase III ALLIANCE study (Abstract 4003), the combination of doxorubicin and sorafenib therapy in HCC patients with child's A cirrhosis. In a, 137 histologically proven HCC patients with child's A cirrhosis, no prior systemic therapy and good performance status and Child pugh score received the standard dose of 400 mg bid and doxorubicin 60 mg/m^2 IV q 3 weeks for 6 cycles. The median OS for child's B cases was 14 weeks and time to progression (TTP) was 13 weeks. There was some allowance for his patients high bilirubin allowed to dose reduce. This study was powered to detect 37% increase in median overall survival. Unfortunately a negative trial that did not demonstrate superiority with addition of cytotoxic chemotherapy. Indeed, the combination of chemotherapy with sorafenib appears harmful in terms of OS. Toxicity is also worse in combination arm. Therefore, it was concluded that chemotherapy is not recommended for advanced HCC.

GASTRIC CANCER

For clearly resectable gastric adenocarcinoma, two trials have been quoted as standard of care –"MAGIC"[13] with perioperative chemotherapy and "McDonald"[14] with post-operative chemo-radiation. One of the common scenarios that is encountered in clinical practice while treating resectable gastric cancer with perioperative chemotherapy is to weigh in the role of post-operative radiation or change in chemotherapy when there is low to modest treatment response of the tumor. The CRITICS trial (abstract 4000) attempted to readdress the role of radiation in adjuvant setting in a multicenter randomized phase III clinical trial of neoadjuvant chemotherapy followed by surgery and then continuing chemotherapy or switching to chemo-radiation. The study population received either ECC (Epirubicin, Cisplatin and Capecetabine) or EOC (Epirubicin, Oxaliplatin and Capecitabine), so basically platinum and fluoropyrimidine based chemotherapy. The radiation was delivered 45 Gray 25 fractions using IMRT techniques and they receive weekly cisplatin or capecitabine during the time of the radiation. Eligibility criteria included stage 1B to IVA resectable gastric cancers (83%) and Gastro-Esophageal junction (GEJ) tumors (17%). Primary endpoint was overall survival with secondary endpoint being progression free survival. This trial was powered to detect a 10% increase in the five year overall survival. Majority of study population had T3 or T4 disease and were node positive in about 50 percent. This trial did not demonstrate any overall survival with post-operative chemotherapy when compared to post-operative chemotherapy alone (40.9% vs 41.3% $P = 0.99$). It is important to note that this trial reflected the general clinical practice treating gastric cancer patients where only 46% of the planned patients could complete post-operative chemotherapy and about 50% could complete post-operative chemoradiation. This is the third trial, in addition to CALGB and ARTIST trials that have addressed the role of radiation in the adjuvant setting for gastric cancer and all of them have been failed to demonstrate positive clinical outcomes. Currently an ongoing trial called TOPGEAR is assessing the impact the radiation upfront so rather than in the adjuvant setting patients are randomized after two cycles of chemotherapy to third cycles of chemotherapy or to the radiation.

NEUROENDOCRINE NEOPLASMS

PROMID[15] and CLARINET[16] trials showed improvement in PFS with Somatostatin Analogues (SSA) in neuroendocrine tumors and therefore considered to be first line for treatment. Peptide receptor radionuclide therapy (PRRT) is an infusion administered by nuclear medicine physicians every 8 weeks for 4 times. This is essentially an SSA, an octreotide molecule s linked to a radioactive molecule called Lutesium^{177} that binds to octreotide receptor two and five. It is given systemically, intra vascular, for 30 minutes. To avoid radiation effects to kidneys, amino acids, lysine and arginine, will be infused for about 30 minutes followed by administration of these radiopharmaceutical simultaneously, with the amino acid infusion continued for 3 more hours for total of 4 hrs. PFS and OS advantage was demonstrated in a large case series previously suggesting that this compound is active in neuroendocrine malignancies. NETTER 1 (abstract 4005) is a randomized control trial in Europe and US. Patients who progressed on SSA randomized to receive 4 cycles of PRRT, The experimental group were still able to continue this medicine analog if they needed for symptom control. The comparative arm is a dose escalated group with 60 mg of SSA. The study compared the progression free survival in midgut tumors which is primary objective.

Tumors were well differentiated, low grade, KI 67 index of less than 20%, somatosensory receptor positive The median progression free survival was not reachable beyond 2 years with the hazard ratio 0.21 that is 79% risk reduction with a response rate of 18% compared to the SSA arm (3%). In fact the progression free survival of the SSA group was about eight months, thus evidence that increasing the dose of SSA has impact on PFS. Patients in experimental arm had short term GI toxicity including nausea vomiting and diarrhea and have been attributed to amino acid infusion that was given for renal protection. Therefore PRRT provides a major therapeutic benefit for patients progressing on SSAs, for whom few treatment options are available.

IMMUNOTHERAPY

There were two key takeaways regarding immune therapy in colon cancer. First, all colon patients in all stages must be tested for microsatellite status to learn if they

harbor inherited HNPCC syndrome and open a new therapeutic option with the checkpoint inhibitors that have demonstrated substantial clinical benefit in these patients with MSI-high metastatic disease. Even though these drugs are not formally approved in United States many sites gain access through company sponsored compassionate access programs. Second, based on a pre-clinical evidence, a small phase I trial (Abstract 3502) showed the combination of cobimetinib (MEK-1 Inhibitor) and atelzoliumab (PDL1 inhibitor) demonstrated interesting clinical benefit (response rate and prolonged stable disease) in MSS colon patients. MEK inhibition increased intra and peri-tumoral T cell accumulation by up regulation of MHC-1 on tumoral cells and therefore combined with PDL1 inhibitor it resulted in synergistic action. In this phase 1 trial, 23 KRAS mutant patients with metastatic colorectal cancer. The partial response was noted 17%, stable disease in 22% of enrolled patients. Based on these outcomes a larger randomized trial is in process of being initiated. This may be the most important observation presented. Before this, MSS colon patients who are at unmet need were considered to be unresponsive to immune therapies. These results have potential to open more opportunities for further exploration of combination trials of immune therapy for non MSI-high patients.

Last year Dr. Lee and colleagues demonstrated that patients who are MMR deficient either colon cancer or in fact non-CRC tumors have a significant benefit from pembrolizumab with no benefit if they were MMR proficient or MSI stable.[17] This year this group of investigators presented updated reports of MSI- H cohort of CRC with total of 28 patients that shower overall response of 57%. With this study as background Dr. Overman from the MD Anderson Cancer Center presented data (Checkmate 142 trial, Abstract 3501) on nivolimumab (PD1 inhibitor) with or without ipilimumab (CTLA4 inhibitor) in patients with microsatellite stable or high. The primary endpoint was the investigator assessment of the response rate. The study patients stopped monotherapy because of disease progression and the combination because of toxicity. The overall response rate was 25.5% for monotherapy and 33.3% to the combination. But the clinical benefit that includes both overall and stable response was significantly higher with the combination 81% compared to 56% for monotherapy.

In summary, this year at ASCO, ESPAC 4, adjuvant pancreatic cancer trial improved overall survival and five year overall survival and thus became reference standard. NETTER trial for metastatic midgut tumors is quite exciting with HR 0.21 and with very impressive progression free survival, response rate and early signs of overall survival it has high potential to become an excellent therapeutic option in future. CRITICS trial in resectable gastric cancers unfortunately does not advocate at this point using post-operative radiation treatment when you embark on a perioperative chemotherapy strategy. In Hepatocellular cancer chemotherapy does not tend to improve prove overall survival. Sorafenib alone continues to be the standard. For metastatic colon a cancer, side really does matter as it is not only prognostic but it is predictive of the treatment effect and clearly is a biologic surrogate marker. This may impact the paradigm of management in near future. Immune oncology space continues to expand in GI malignancy with new hope in MSS colorectal cancers.

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Conflicts of interest

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