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Short Communication

New Therapies for GI Cancer "Under the Track" Gastrointestinal Oncology

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New treatments are emerging in field of gastroentrogy oncology and it includes advancements in gastroesophageal colorectal, pancreatic and anal canal carcinomas.

FDA has approved angiogenesis inhibitor ramuciromab in unresectable, advanced or metastatic gastric and gastroesophageal junction tumors after therapy with flouropyrimidines and platinum drugs. Trastuzumab is approved for locally advanced and metastatic HER-2neu positive gastroesopheageal ca only and PD-1 inhibitor, pembrolizumab, in heavily pre-treated patients with metastatic gastric cancer. The major findings were that it is feasible. In terms of toxicity it is feasible. pembrolizumab achieved a decrease in tumour size. Adjuvant imatinib has become a standard treatment in all patients with significant risk for recurrence after resection of primary GISTs. FDA also approved erlotinib hydrochloride in combination with gemcitabine for the treatment of patients with locally advanced, unresectable or metastatic pancreatic carcinoma. "In colon cancer, the antiangiogenic agent's bevacizumab is approved in combination with other agents. EGFR-1 (epidermal growth factor receptor 1) signaling pathway is thought to play a pivotal role in tumor growth and progress of colorectal cancer. **Cetuximab targets an epidermal growth factor receptor (EGFR), which is found in about 80 percent of colorectal cancers. Its effective in patients with NO K-ras mutation. Erbitux is effective even if EGFR is not found in an individual tumor. In treatment of anal canal ca traditionally treated** *with abdominoperineal resection, resulting in high rates of morbidity and local recurrence. Pioneering work led to the finding that radiation therapy (RT) combined with 5-fluorouracil (5-FU) and mitomycin results in high rates of local control and disease-free and colostomy-free survival without surgery.*

Introduction

GI cancer are the most common form of cancer. This includes cancers of the oesophagus, gallbladder, liver, pancreas, stomach, small intestine, bowel (large intestine or colon and rectum), and anus. GI cancers do not discriminate between men and women. survival rates of gi cancers is lower than breast and prostate carcinoma. Screening, early detection and diagnosis, treating the disease early can improve the survival. There is also advancement in treatment of these cancers. Newer targeted therapy is also developed in gastrointestinal oncology.

Esophageal and Gastric Tumors

Esophagus is a hollow muscular tube. Its carcinoma is more prevalent in persons having barretts esophagus which occurs due to reflux induced changes in lower esophageal mucosa.esophageal tumors could be adenocarcinoma or squamous cell carcinoma. Stomach is muscular organ that receives and stores food. Most stomach cancers are adenocarcinoma, few are gastrointestinal stromal tumours (GIST) and neuroendocrine tumours (NET. the addition of trastuzumab to standard chemotherapy in locally advanced gastic and esophageal tumor patients with human epidermal growth factor receptor-2 (HER-2)-positive tumors has dramatically changed the management algorithm in this subset of patients. This has been established after achieving statistically significant increase in OS in the Trastuzumab for Gastric Cancer (ToGA) study (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.51–0.83), corresponding to median survival of 16 months versus 11.8 months. ToGA study was a randomized controlled trial that compared cisplatin and a fluoropyrimidine combination with the same combination in addition to trastuzumab [1]. cardiotoxicity was noted with trastuzumab.

Ramucirumab is a monoclonal antibody for vascular endothelial growth factor receptor-2, with demonstrated activity both as a monotherapy and as a part of combination strategy in the management of advanced Gasric/Gastroesophageal junction (GEJ) cancer. The efficacy of ramucirumab in the second-line treatment of advanced gastric/gastroesophageal carcinomas has been proved by two randomized controlled studies. The toxicity profile of ramucirumab in these studies includes risks of hypertension, gastrointestinal perforation, proteinuria, and neutropenia.

The first study is the ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD) study, which was conducted to evaluate whether ramucirumab may improve survival in patients with advanced Gastric carcinoma [2]. Patients with advanced gastric/GEJ adenocarcinoma after progressing on first-line chemotherapy (n=355) were randomized (2:1) to receive either ramucirumab 8 mg/kg (n=238) or a placebo (n=117), IV once every 2 weeks. In patients in the ramucirumab group, median OS was 5.2 months, while in patients in the placebo was 3.8 months. The second study is the ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW) trial in which patients (n=665) with advanced gastric/GEJ adenocarcinoma in the second-line setting were randomized to paclitaxel alone (80 mg/m^2 on days 1, 8, 15) or ramucirumab plus paclitaxel (8 mg/kg IV every 2 weeks) in 4-week cycles indefinitely. For patients receiving ramucirumab plus paclitaxel, median OS was 9.6 months, while it was 7.4 months for those receiving paclitaxel monotherapy (P=0.0169). Median PFS was 4.4 months in the combined treatment group and 2.9 months in the monotherapy group (P<0.0001) [3]. Thus, the REGARD and the RAINBOW studies have shown that ramucirumab (both alone and in

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combination with paclitaxel) is an effective new standard for second-line treatment of advanced gastric/GEJ adenocarcinoma.

Expression of PD-L1 has been shown to be upregulated in some patients with gastric cancer. activity of the anti-PD-1 antibody pembrolizumab in patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction decreases tumor size and in term of toxicity its feasible [4].

Gastrointestinal stromal tumor (GIST) is a rare tumor, however, the commonest non-epithelial tumor of the gastrointestinal tract. these tumors had mutations in the KIT proto-oncogene [5]. The KIT protein is a transmembrane receptor for stem cell factor. The availability of the immunohistochemical marker, CD117, to the KIT protein, has revolutionized the diagnosis of GIST, by identifying a treatment target. Approximately 95% of GISTs stain positive for CD117, making it a very useful marker for diagnosis [6]. This has led to the development of the therapy with imatinib mesylate [7]. Treatment with this drug has led to significant improvements in survival, with overall response rates in excess of 80%. Toxicity was common but manageable. Oedema, anemia, rash, lethargy, nausea, bleeding, diarrhoea, and dyspnea.

Pancreatic Carcinoma

Pancreas is a glandular structure. Exocrine pancreas cells make enzymes. Neuroendocrine pancreas cells (such as islet cells) make hormones, including insulin and glucagon. Pancreatic cancer is an aggressive malignancy, presenting with advanced unresectable disease. Despite advances in the development of conventional chemotherapy, notably the establishment of gemcitabine as a standard of care, response rates to therapy are low and survival from the disease is still poor. Erlotinib (ERL) is a tyrosine kinase inhibitor of epidermal growth factor receptor [8,9]. Evidences suggest that over-expression of epidermal growth factor receptor relates to poor prognosis of pancreatic cancer [10,11] _erlotinib Mooreet al [12] firstly demonstrated significantly improved outcomes by GEM/ERL combination therapy as compared with GEM alone in their study in 2007. After that, Erlotinib was approved by US FDA for the treatment of advanced pancreatic cancer [13,14] having adverse events such as skin rash diarrhea.

Colorectal Carcinoma

Colorectal cancer is the third most common malignancy in men and the second most common in women worldwide. It is the fourth leading cause of cancer death. Approximately 35% of patients have metastatic disease at diagnosis. Newer therapies bevacizumab and cetuxima improved response rates in metastatic disease [15].

Bevacizumab *first anti-angiogenesis drug approved by the U.S. Food and Drug Administration (FDA with 5-fluorouracil (FU)-based chemotherapy for first-line treatment of metastatic carcinoma of the colon or rectum in February 2004, and for second-line treatment in June 2006.* Cetuximab has been shown to be effective in patients with KRAS wild-type mCRC. The CRYSTAL study showed that adding cetuximab to FOLFIRI (regimen of irinotecan, infusional fluorouracil and leucovorin) significantly improved results in the first-line treatment of KRAS wild-type mCRC [16,17].

Anal Canal Carcinoma

Squamous cell cancer (SCC) of the anus is a rare disease. The incidence of anal cancer in the general population has increased over the last 30 years. A higher incidence has been associated with female gender. The goal of treatment for patients with localized anal squamous-cell carcinoma is cure. Combined modality chemoradiation is recommended as first line treatment for all other cases, with salvage surgery reserved for those who fail on this regimen [18].

Conclusion

Gastrointestinal cancers are a global health problem with a relatively high mortality, particularly in the advanced stage. For metastatic gastric or gastroesophageal carcinoma, systemic chemotherapy is the backbone of treatment accompanied by trastuzumab anti-HER-2 therapy and Ramucirumab, a monoclonal antibody against VEGFR-2, has been shown to have a significant antitumor activity against Gastric and gastroesophageal cancer. Pembrolizumab has shown activity in PD-L1 positive recurrent or metastatic gastric or gastroesophageal carcinoma.

The introduction of imatinib mesylate has revolutionized the treatment of patients with locally advanced and metastatic GIST, leading to important gains in quality of life and survival.

Erlotinb in combination with gemcitabine has recently been shown to be superior to gemcitabine monotherapy with a very modest improvement in survival in pancreatic carcinoma. Bevacizumab, which is a recombinant humanized monoclonal antibody against VEGF activity, inhibits angiogenesis restricting the growth of malignant cells and thus prevents tumor spread in metastatic colorectal carcinoma

The benefit of cetuximab in combination with FOLFIRI as first-line treatment in patients with KRAS wild-type mCRC has been clearly demonstrated in the CRYSTAL study, so this combination could be considered. Radiation therapy combined with 5-fluorouracil (5-FU) and mitomycin results in high rates of local control and disease-free and colostomy-free survival without surgery in anal canal carcinoma.

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