Clinical characteristics, biomarkers and treatment outcome of GEP-NENs in China

Neuroendocrine neoplasms (NENs) are a rare group of tumors with high heterogeneity. Gastroenteropancreatic NENs (GEP-NENs) consist of the largest proportion of NENs. Chinese doctors did not pay much attention to this group of tumors until the nomenclature and classification of neuroendocrine tumors of digestive system were updated by the World Health Organization (WHO) in 2010. Since then, more and more studies of GEP-NENs have been carried out, and the clinical characteristics, biomarkers and treatment outcome of GEP-NENs in Chinese patients have gradually been explored.

Clinical characteristics of GEP-NENs in China

There are still no epidemiological data of NENs based on the population in mainland China. Our previous study showed that the most common primary sites for GEP-NENs were pancreas (34.8%) and rectum (20.2%), followed by stomach (14.0%). Neuroendocrine tumor (NET) accounts for the largest proportion (69.8%). Neuroendocrine carcinoma (NEC) and mixed adenoneuroendocrine carcinoma (MANEC) account for 27.2% and 3.0%, respectively. A multicenter retrospective study of GEP-NENs in China also showed that pancreas and rectum were the most common primary locations.

In recent years, several multicenter studies were conducted to investigate the clinicopathological features of NENs in different tumor locations. For example, we recently summarized the clinicopathological characteristics of colorectal NENs including 41 patients with colonic NENs and 288 patients with rectal NENs. Colonic NENs had a more aggressive nature than that of rectal NENs. In these 41 colonic NENs patients, 61.0% and 17.1% patients were NEC and MANEC, respectively. 48.8% of the patients manifested distant metastases when diagnosed. The most common endoscopic appearance of colonic NENs was ulcerative or cauliflower-like tumors. The prognosis of colonic NENs was not favorable with a 3-year survival rate of only 46.1%. In contrast, most of the rectal NENs (92.7%) were well differentiated NET. Only 7.0% and 0.3% of patients were NEC and MANEC, respectively. In addition, rectal NENs tended to be a local-regional disease with only 8.3% having advanced diseases when diagnosed. Submucosal tumor was the most common appearance under endoscopy. The 3-year survival rate of rectal NENs was 94.0%, which was much better than that of colonic NENs.

Another multicenter study with a large sample (977 patients included) compared the clinicopathological features of pancreatic NENs between Chinese patients and American patients. This study showed that Chinese patients with pancreatic NENs were inclined to be younger, have less non-functional tumors larger in size than American patients. In Chinese patients, insulinoma was the most common pancreatic NENs subtype (52.2%), followed by non-functional tumor (39.7%). Most of the tumors (49.6%) were located in the head/neck region of pancreas. 57.7%, 38.3% and 3.8% of patients had grade 1, grade 2 and grade 3 diseases, respectively. Metastatic rate of lymph node and distant location were 5.4% and 22.7%, respectively. Recently, a multicenter study supported by ten medical centers, including eight Chinese centers and two American centers, proposed a modified staging classification for pancreatic NENs. This multicenter study found the deficiencies of current staging classifications and proposed a modified one which had a higher prognostic validity for pancreatic NENs in both Chinese patients and American patients.

Stomach is also a common location of NENs in Chinese patients. In the recent consensus guideline proposed by the European Neuroendocrine Tumor Society (ENETS), gastric NENs is divided into three types according to the serum gastrin levels and gastric pH. Type 1 and type 2 are respectively caused by atrophic gastritis-associated and Zollinger-Ellison syndrome-associated hypergastrinemia. Type 3 gastric NENs are not associated with hypergastrinemia, which is mostly thought as a high grade (often grade 3 NEC) tumor. However, in China, some experts suggest to further divide type 3 gastric NENs into two more types (new type 3 and type 4). New type 3 is considered as well or moderately differentiated tumor, which is not associated with hypergastrinemia, while type 4 G-NENs are grade 3 NEC. A study including 241 gastric NENs based on this novel classification was published recently. Survival analysis showed patients with new type 3 and type 4 had significantly different overall survival. Whether dividing gastric NENs into 4 types helps improving the management of patients or not needs further study.
Biomarkers study of GEP-NECs in China

Currently circulating biomarker studies in China focus on investigating the value of serum chromogranin A (CgA) in GEP-NECs. However, in China, only several large medical centers provide serum CgA measurement. Our previous study showed a serum CgA cutoff value of 95 ng/mL could help discriminate between healthy subjects or disease-free patients, and patients with active disease with sensitivity of 51.2% and specificity of 87.5%. Furthermore, serum CgA could be used to evaluate tumor burden and therapeutic response, and predict the survival outcomes in GEP-NECs patients. Other studies from China also showed similar results. Additionally, a multicenter study revealed that serum CgA was not significantly elevated in patients with insulinoma. Therefore, serum CgA had limited value in patients with insulinoma.

There are also a number of studies from China investigating tissue biomarkers for evaluating the biologic behavior of GEP-NECs. Here, we reviewed several representative studies. In gastrinoma and insulinoma of pancreas, loss of heterozygosity (LOH) of chromosome 1q was successively found, which was associated with tumor aggressive growth. The presence of LOH of chromosome 1q was found to be correlated with aggressive growth, presence of liver metastases and postoperative development of hepatic metastases. Han X, et al. found the role of expression of CK19 and KIT in resectable pancreatic NECs. Their study showed that KIT-positive tumor was associated with higher Ki-67 index and advanced tumor node metastasis (TNM) stage compared with KIT-negative tumor. Meanwhile positive CK19 expression was correlated with non-functioning tumors, regional lymph nodes metastases, and advanced stage. Also in pancreatic NECs, another biomarker, alpha-internexin was tested. This study showed that reduced expression of alpha-internexin was correlated with advanced stage, metastases, and recurrence. Furthermore, reduced expression of alpha-internexin indicated shorter overall survival in patients with pancreatic NECs.

Our previous study investigated the expression of O(6)-methylguanine-DNA methyltransferase (MGMT) and its clinical significance in GEP-NECs. MGMT expression deficiency was thought to be associated with better response to temozolomide-based chemotherapy. In this study, we found that the MGMT deficiency rate was similar in pancreatic NECs and in gastrointestinal NECs. This result indicated that temozolomide-based chemotherapy might have comparable efficacy on pancreatic NECs and gastrointestinal NECs in Chinese patients. Recently, we also investigated the prognostic significance of somatostatin receptors (SSTR) in advanced GEP-NET patients. We found expression of SSTR2/SSTR5 were prognostic factors indicating favorable survival.

Treatment outcome of GEP-NECs in China

In China, GEP-NECs patients were treated by operation (by endoscopy or surgery), interventional therapy, chemotherapy, biotherapy and molecular target therapy. Peptide receptor radionuclide therapy (PRRT) is not available yet. Still, there are few publications related with the treatment outcomes of GEP-NECs in China. Recently, two multicenter retrospective studies of octreotide long-acting repeatable (LAR) and sunitinib in the treatment of advanced GEP-NET were conducted. In the first study, 54 patients with advanced GEP-NET who received octreotide LAR treatment in four centers across China were included to investigate the efficacy and safety of octreotide LAR in Chinese GEP-NET patients. The median time to progression was 20.2 months with the objective response rate being 5.6% and the stable disease rate being 79.6%. 25.9% of the patients experienced adverse drug reactions. No one experienced a serious adverse event.

In the second study, a total of 50 patients with unresectable or metastatic GEP-NET who were treated with sunitinib were evaluated retrospectively. The median time to progression (TTP) was 15.1 months. This study demonstrated that sunitinib had similar treatment efficacy in Chinese patients compared to western patients. A 25 mg/day dosage was better tolerated than 37.5 mg/day in Chinese patients. Sunitinib-related hypertension might be a predictor of a better treatment effect.

More recently, a phase II study evaluated the activity and safety of irinotecan plus cisplatin (IP) followed by maintenance treatment of octreotide long-acting release (LAR) in advanced GEP-NEC. To date, this is the sole prospective study assessing treatment response of GEP-NEC in China. In this study, patients were further classified into two groups: high proliferation neuroendocrine tumor (NET) group with well differentiation and Ki-67 index between 20-60% and poorly differentiated NEC (PDNEC) group. This study revealed that the patients in high proliferation NET group had a lower response rate compared to the PDNEC group. Hence, IP might not be an effective treatment strategy in patients with high proliferation NET.

Discussion

The clinicopathological features of GEP-NECs in Chinese patients and the value of different biomarkers are gradually gaining understanding in the recent years. There are several differences of clinical characteristics between Chinese patients and western patients with GEP-NECs. On the one hand, the tumor locations of GEP-NECs are different. The most common tumor locations of GEP-NECs in Chinese patients are rectum and pancreas, followed by stomach. Small intestine is not a common site of GEP-NECs. While in western patients, small intestine and rectum are two predominant tumor sites of GEP-NECs. On the other hand, at the same tumor site, Chinese patients share different clinicopathological features from western patients. For instance, Chinese patients with pancreatic NEENs tended to be younger, have less non-functional tumors and larger tumor size than those of American patients. These heterogeneities may have derived from ethnic differences.
Biomarkers including circulating biomarkers and tissue biomarkers are crucial in the management of patients with GEP-NENs. In China, the most widely used circulating biomarker is serum CgA. However, this biomarker is limited by its relatively low specificity. As for the tissue biomarker, a group of biomarkers were studied and have shown certain significance in evaluating the biologic nature of GEP-NENs. However, most of these studies focused on pancreatic NENs. The role of these biomarkers in gastrointestinal NENs is less understood.

Data of the treatment outcome of GEP-NENs in China is still limited. Our present two studies are limited by their retrospective nature. In the future, more well-designed prospective studies are required to help Chinese doctors to better understand the treatment outcome of GEP-NENs in Chinese patients.

REFERENCES


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