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Review

Targeted therapies in gastroesophageal cancer

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Abstract Gastroesophageal cancers comprising gastric cancer (GC), and cancers of the distal oesophagus and gastroesophageal junction (GEJ) are a global health threat. In Western populations the incidence of GC is declining which has been attributed to effective strategies of eradicating *Helicobacter pylori* infection. To the contrary, GEJ cancers are on the rise, with obesity and reflux disease being viewed as major risk factors. During the past decade perioperative chemotherapy, pre- or postoperative radio-chemotherapy, and, in Asian populations, adjuvant chemotherapy have been shown to improve the outcome of patients with advanced GC and GEJ cancers suited for surgery. Less progress has been made in the treatment of metastatic disease. The introduction of trastuzumab in combination with platinum/fluoropyrimidine-based chemotherapy for patients with HER2-positive disease has marked a turning point. Recently, several novel agents targeting growth factor receptors, angiogenic pathways, adhesion molecules and mediators of intracellular signal transduction have been clinically explored. Here we summarise the current status and future developments of molecularly targeted therapies in GC and GEJ cancer.

1. Introduction

Cancers of the stomach (GC), the gastroesophageal junction (GEJ) and the distal oesophagus are the second leading cause of cancer deaths worldwide [24]. Incidence rates and tumour localisation vary considerably between geographical regions thus implying genetic and environmental factors in disease pathophysiology. Adenocarcinomas of the distal stomach are dominant in Eastern Europe, Asia and South America. In contrast, cancers located in the proximal stomach or at the GEJ are more prevalent in Western Europe and North America [36]. This is attributed to the high association of *Helicobacter pylori* infection and additional nutritional and socioeconomic risk factors with distal GC in less-developed countries [54]. In contrast, risk factors for adenocarcinomas of the GEJ and distal oesoph-

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Abbreviations: ACCORD; Action Clinique COordonnées en cancérologie Digestive; AVAGAST; Avastin in Gastric Cancer trial; CLEOPATRA; Clinical Evaluation of Pertuzumab and

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Trastuzumab; DCR; Disease control rate; ERBB; Erythroblastic Leukemia Viral Oncogene; EXPAND; Erbitux in combination with Xeloda and cisPlatin in AdvaNceD esophagogastric cancer; FAST; First-Line Treatment of Patients with CLDN18.2-Positive adenocarcinomas of the stomach, the esophagus or the gastroesophageal junction; FOLFOX; Folinic acid, Fluorouracil, Oxaliplatin; FOLFIRI; folinic acid, fluorouracil, irinotecan; GRANITE; Gastric Anti-Tumor Trial with Everolimus; HER2; human epidermal growth factor receptor 2; Her-FLOT; herceptin-fluorouracil, leucovorin, oxaliplatin, taxol; JACOB; PERTUZUMAB, TRASTUZUMAB AND CHEMOTHERAPY IN HER2-POSITIVE METASTATIC GASTRIC OR GASTRO-OESOPHAGEAL JUNCTION CANCER; LOGIC; Lapatinib Optimization Study in ErbB2 (HER2) Positive Gastric Cancer; MAGIC; Medical Research Council Adjuvant Gastric Infusional Chemotherapy; MET; Mesenchymal Epithelial Transition Factor; NeoPECX; ECX+ Panitumumab vs. ECX Alone in Locally Advanced Gastric Cancer or Cancer of the Gastroesophageal Junction; RAD-PAC; rad001-paclitaxel; RAINBOW; Paclitaxel With or Without Ramucirumab in Metastatic Gastric Adenocarcinoma; REAL-3; Randomized EOC for Advanced and Locally Advanced Esophagogastric Cancer 3; REGARD; Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma; RILOMET; Rilotumumab with ECX as First-line Therapy in Advanced MET-Positive Gastric or Gastroesophageal Junction Adenocarcinoma; SAKK75/08; Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung; SCOPE; Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer; SWOG; Southwest Oncology Group; ToGA; Trastuzumab for Gastric Cancer; TORC; The mammalian Target of Rapamcin complex; TYTAN; http://www.discoverymedicine.com/category/medical-specialties/oncology/gynecological-cancer/breast-cancer/tykerb/

agus such as obesity and gastroesophageal reflux disease have become more prevalent in countries adopting a 'Western' life style. Accordingly, increased incidence rates have been observed in Western Europe and North Amercia [13].

2. Current treatment options for localised, locally advanced and metastatic disease

Surgical resection and, for very early stage cancers, endoscopic mucosal resection remains the standard of care for localised cancers of the upper gastrointestinal (GI) tract. However, the majority of patients are diagnosed with locally advanced tumours, regional lymph node involvement, or metastatic disease. Based on the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) and Action Clinique COordonnées en cancérologie Digestive (ACCORD) trials perioperative chemotherapy has been established as the standard of care for patients with locally advanced GEJ/GC scheduled for surgical resection including extensive (D2) lymphadenectomy in Western Europe [17,92]. Systemic treatments in the perioperative setting are largely based on platinum and fluoropyrimidine combinations, or in three-drug regimens including taxanes or anthracyclines. Preoperative radio-chemotherapy is another option for patients with advanced adenocarcinomas of the GEJ and the distal oesophagus. In particular, patients achieving a complete pathological response following induction therapy appear to benefit from this approach [83,71]. In contrast, based on the Southwest Oncology Group (SWOG)/Intergroup 0116 trial postoperative radio-chemotherapy has evolved as a standard of care in North American centres. This study mainly enroled patients with less extensive (D0 or D1) lymph node dissection [69]. Adjuvant chemotherapies following gastrectomy and D2 lymph node dissection have improved disease-specific and overall survival in Asian patient populations [63]. The fourth-generation oral fluoropyrimidine S1 combines the 5-fluorouracil prodrug tegafur with two biochemical modulators preventing degradation of 5-fluorouracil and reducing gastrointestinal toxicity. S1 is effective as monotherapy in the adjuvant setting and in combination with platinum agents in advanced cancer stages. It is widely used by Asian oncologists [1,63]. Despite these progresses more than 50% of patients undergoing potentially curative multimodal therapy for locally advanced GEJ/GC ultimately relapse. Palliative chemotherapy prolongs survival and improves cancer-related symptoms in these patients as well as in patients with primary metastatic disease [86]. Adding taxanes to platin- and fluoropyrimidine-based regimens enhances objective remission and disease control rates. However, the median survival time of patients with metastatic disease stagnates approximately at 12 months [17,79,92]. Combination chemotherapy can be more manageable without compromising on efficacy when using oxaliplatin, the oral fluoropyrimidine capecitabine and split-dose regimens instead of cisplatin, 5-fluorouracil and standard scheduling [2,18].

Recent insights into the biology of gastrointestinal cancers have nominated potential targets for novel therapies and biomarkers for stratification of patient populations. Here we review the current status and imminent developments of molecularly targeted therapies in GEJ/GC.

3. Growth factor receptors as therapeutic targets

Growth factor receptors are receptor tyrosine kinase proteins located in the plasma membrane. Their physiological function is to transduce signals derived from locally and systemically secreted ligands into the cell to promote proliferation and survival (Fig. 1). Ligand binding induces homo- or heterodimerisation of the receptor molecules, which facilitates autophosphorylation and activation of receptor tyrosine kinase. This leads to the recruitment of adaptor molecules to form signalling complexes at the inner cell membrane.