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Unravelling the pharmacologic opportunities and future directions for targeted therapies in gastro-intestinal cancers part 2: Neuroendocrine tumours, hepatocellular carcinoma, and gastro-intestinal stromal tumours☆

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ABSTRACT

Until the 1990s, cytotoxic chemotherapy has been the cornerstone of medical therapy for gastrointestinal (GI) cancers. Better understanding of the cancer cell molecular biology has led to the therapeutic revolution of targeted therapies, i.e. monoclonal antibodies or small molecule inhibitors directed against proteins that are specifically overexpressed or mutated in cancer cells. These agents, being more specific to cancer cells, were expected to be less toxic than conventional cytotoxic agents.

However, their effects have sometimes been disappointing, due to intrinsic or acquired resistance mechanisms, or to an activity restricted to some tumour settings, illustrating the importance of patient selection and early identification of predictive biomarkers of response to these therapies.

Targeted agents have provided clinical benefit in many GI cancer types. Particularly, some GI tumours are considered chemoresistant and targeted therapies have offered a new therapeutic base for their management. Hence, somatostatin receptor-directed strategies, sorafenib, and imatinib have revolutioned the management of neuroendocrine tumours (NET), hepatocellular carcinoma (HCC), and gastrointestinal stromal tumours (GIST), respectively, and are now used as first-line treatment in many patients affected by these tumours. However, these agents face problems of resistances and identification of predictive biomarkers from imaging and/or biology.

Abbreviations: 5FU, 5-fluorouracil; 95%CI, 95% confidence interval; AA, amino acid; AFP, alpha fetoprotein; AML, actue myeloid leukemia; Ang2, angiopoietin 2; ATP, adenosine triphosphate; BCLC, Barcelona-Clinic Liver Cancer classification; BSC, best supportive care; CAPOX, capecitabine plus oxaliplatin; CML, chronic myeloid leukemia; CT-scan, computed-tomography scan; CTLA-4, cytotoxic T lymphocyte antigen-4; DCR, disease control rate; DFS, disease free survival; DOPA, diethylene triamine penta-acetic acid; DTPA, 1,4,7,10-tetraazacyclododecane-1,4,7,20-tetra-acetic acid; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; FOLFOX, 5-fluorouraci, leucovorin, and oxaliplatin; G1/G2/G3, grade 1/grade 2/grade 3; GEMOX, gemcitabine plus oxaliplatin; GH, growth hormone; GI, gastrointestinal; GIST, gastrointestinal stroma tumour; GM-CSF, granulocyte-macrophage colony stimulating factor; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HBV, hepatitis B virus; HCV, hepatitis C virus; HPF, high-power field; HR, hazard ratio; HSP90, heat shock protein 90; IGF, insulin-like growth factor; IFN, interferon; IL, interleukin; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MDS, myelodysplastic syndrome; MKI, multikinase inhibitor; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NAFLD, non-alcoholic fatty liver disease; NK, natural killer; NET, neuroendocrine tumour; ORR, overall response rate; OS, overall survival; PD-1, Programmed Death 1; PD-L1, Programmed Death Ligand 1; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PET, positon-emission tomography; PFS, progression-free survival; PlGF, placental growth factor; pNET, pancreatic neuroendocrine tumour; PRRT, peptide-receptor radiation therapy; PS, performance status; PTEN, phosphatase and tensin homolog; QoL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumours; RFS, recurrence-free survival; SDF, stromal cell-derived factor; SDH, succinate dehydrogenase; siNET, small-intestinal neuroendocrine tumour; SST, somatostatin; SSTA, somatostatin analogue; SSTR, somatostatin receptor; TACE, transarterial chemoembolization; TCR, T-cell receptor; TGF, transforming growth factor; TKR, tyrosine kinase receptor; Treg, T regulatory lymphocyte; TSC2, tuberous sclerosis complex 2; TTF, time to failure; TTP, time to progression; TTR, time to recurrence; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VIP, vasointestinal peptide; WHO, World Health Organization; WT, wild type.

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We propose a comprehensive two-part review providing a panoramic approach of the successes and failures of targeted agents in GI cancers to unravel the pharmacologic opportunities and future directions for these agents in GI oncology. In this second part, we will focus on NET, HCC, and GIST, whose treatment relies primarily on targeted therapies.

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1. Introduction

Until the 1990s, cytotoxic chemotherapy has been the cornerstone of medical therapy for gastrointestinal (GI) cancers. Better understanding of the molecular biology of cancer cell has led to the therapeutic revolution of targeted therapies, i.e. monoclonal antibodies (mAb) or small molecule inhibitors (multikinase inhibitors [MKI]) directed against proteins that are specifically either overexpressed or mutated in cancer cells. These drugs were expected to be more specific to cancer cells and less toxic than conventional cytotoxic agents. However, their anticipated effects have sometimes been disappointing, due to either intrinsic or acquired resistance mechanisms, or to an activity restricted to some tumour settings or molecular subgroups (Holohan, Van Schaeybroeck, Longley, & Johnston, 2013). The identification of predictive biomarkers of response to these therapies, through deeper knowledge of GI tumour biology and phenotypic and molecular subtypes, has therefore become a major issue.

In this context, it appears crucial to gather updated clinical and translational data in a comprehensive review encompassing the lessons learned from the past as well as the yet unanswered questions regarding targeted therapies across the different GI cancer types. We propose a comprehensive two-part review providing a panoramic and chronological approach of the successes and failures of targeted agents that have reached phase III trials in GI cancers, to unravel the pharmacologic opportunities and future directions for these therapies in GI oncology. In the first part, we focused on adenocarcinomas and squamous cell carcinomas, for which targeted therapies are mostly used in combination with chemotherapy. We summarised the trajectories of targeted therapy development across these GI cancer types and highlighted how the clinical development of antiangiogenics, anti-EGFR, anti-HER2 agents, or, more recently, immune therapy, have followed strikingly different paths in terms of biological hypothesis, companion biomarkers, and refinement of their respective spectrum of sensitive tumours. In this second part, we focus on neuroendocrine tumours (NET), hepatocellular carcinoma (HCC), and gastrointestinal stromal tumours (GIST), whose treatment relies primarily on targeted therapies. For these selected GI tumours that were characterized by their poor sensitivity to chemotherapy, the advent of targeted therapies has been a complete shift of paradigm. These agents demonstrated their efficacy and offered a new therapeutic base for the management of these tumours. Hence, somatostatin receptor (SSTR)-directed strategies, sorafenib, and imatinib have revolutioned the management of NET, HCC, and GIST, respectively, and many patients affected by these tumours are now treated in first intent by targeted therapies only. However, these agents have to face problems of resistances and identification of predictive biomarkers from imaging and/or biology.

2. Neuroendocrine tumours (NET)

2.1. Epidemiology and therapeutic landscape

Digestive NET are a heterogeneous group of neoplasms arising from neuroendocrine cells that are organised as endocrine glands such as pancreas or scattered throughout the digestive tract. These rare tumours account for 1% of all digestive malignancies; nevertheless, NET are one of the most prevalent GI neoplasms after colorectal cancer, since they are usually slowly growing and associated with prolonged patient survival (Frilling et al., 2012, 2014; Yao, Hassan, et al., 2008). The most frequent malignant NET originate from small intestine (siNET) and pancreas (pNET). Of note, siNET and pNET exhibit differences regarding their biological and clinical features, thus their management must be considered separately.

The most important prognostic factors in neuroendocrine neoplasms are (i) tumour stage, (ii) differentiation, and (iii) grade, the latter being defined by the Ki67 proliferation index and mitotic index. In 2010, the World Health Organization (WHO) proposed a classification of neuroendocrine neoplasms into well-differentiated grade 1 (G1) (Ki67 <3% and mitotic index <2 per 10 high-power fields [HPF]) and grade 2 (G2) NET (Ki67 between 3%–20% and/or mitotic index between 2 and 20 per 10 HPF), and grade 3 (G3) neuroendocrine carcinomas (Ki67 >20% and/or mitotic index >20 per 10 HPF) (Perren et al., 2017). Noticeably, most, but not all, G3 neoplasms are poorly differentiated: about 20% of them are well-differentiated G3 NET, with Ki67 indexes ranging between 20% and 50%. These tumours will be regarded as a distinct entity in the upcoming 2017 WHO classification, and should rather be managed in the same way as well-differentiated G2 NET (Perren et al., 2017). Poorly differentiated neuroendocrine carcinoma differ drastically from well-differentiated NET for their natural history (i.e. much more aggressive behaviour) and management (i.e. central role of chemotherapy), and are beyond the scope of this review.

About 10%–20% of NET are functional, i.e. cause symptoms due to hypersecretion of hormones and peptides, the most frequent being gastrin and insulin in pNET, followed by glucagon and vasointestinal peptide (VIP), and mainly serotonin, causing carcinoid syndrome, in siNET. Importantly, these secretory syndromes are associated with increased morbidity and can be life-threatening; therefore, their control stands as a priority in the therapeutic management of functional NET, and relies on antisecretory treatments such as proton-pump inhibitors and somatostatin analogues (SSTA) (Frilling et al., 2014; Pavel et al., 2016).

The treatment strategy in patients with localised NET generally consists in surgical resection with curative intent. Therapeutic options for patients with advanced disease include: (i) local treatments, such as metastases surgical resection or percutaneous destruction, (ii) liver-

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