

Biologic therapies in gastrointestinal cancer: Is there any light at the end of the tunnel?

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The prognosis of patients with advanced gastrointestinal (GI) malignancies has not changed significantly in the last decade, despite concerted efforts to optimize treatment using conventional modalities such as surgery, chemotherapy and radiotherapy, with chemotherapy continuing to constitute the mainstay of treatment for patients with metastatic GI malignancies. However, even with the introduction of new antineoplastic agents (irinotecan, oxaliplatin, raltitrexed, gemcitabine, taxanes), their prognosis remains dismal. Recently, our knowledge of molecular oncology has significantly increased, endorsing recognition of the main signaling pathways that promote malignant cell transformation. This in turn has raised hopes for the development of a novel therapeutic strategy that would target neoplastic cells, whilst minimizing both damage to noncancerous cells and any side effects resulting from the given therapy. These so-called targeted therapies require two main requisites: A molecule-target that would be abundant, stable, specific and easily accessible through the bloodstream and a molecule-ligand with a high affinity for the target and easily tumor diffusible. With regard to GI malignancies, agents acting on growth, transcription, apoptosis-promotion and DNA-repair factors are being investigated in phase I/II clinical trials, with a few having entered phase III studies and even fewer being introduced into clinical practice.^{1,2}

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The EGFR pathway

The EGFR family autocrine pathway plays a critical role in the malignant and metastatic development potential of GI tumors. Ligands binding to their extracellular domain initiate a molecular cascade that promotes cellular proliferation and differentiation, while its overexpression has been correlated with a more aggressive tumor phenotype (colorectal 25-70%, gastric 33%, pancreatic 30-50%) and, hence, a worse prognosis for GI cancer patients. EGFR targeting can be achieved through two principal mechanisms: Either through monoclonal antibodies that prevent ligand binding or by means of small-molecule tyrosine-kinase inhibitors (TKIs) that inhibit the adenosine triphosphate binding site of the growth factor receptor.

Cetuximab (IMC-C225, Erbitux) is a recombinant human/mouse chimeric IgG1 monoclonal antibody that targets the extra-cellular domain of the human EGFR (ErbB-1). Its efficacy has been demonstrated in colorectal cancer (CRC) patients previously treated with chemotherapy, as a single agent, or in combination with irinotecan: The median response duration was 5.7 and 4.2 months in the combination and mono-therapy arm, respectively. Further studies in CRC patients refractory to oxaliplatin and irinotecan demonstrated an overall response rate of 9-14% and a median duration of response of 6.5 months. Toxicities attributed to Cetuximab include infusion allergic reactions (3%) and an acne-like rash (61%), while its administration does not seem to aggravate chemotherapy toxicities. With regard to other GI malignancies, Cetuximab is currently under investigation in a large phase III clinical trial in combination with gemcitabine for advanced EGFR positive pancreatic cancer (SWOG 0205), though EGFR expression in pancreatic adenocarcinoma is not as high as in CRC.^{3,4}

Trastuzumab (Herceptin) is a recombinant human-

ized anti-HER2 monoclonal antibody with proven activity in breast cancer. However, its therapeutic role in advanced CRC is still unclear, and several phase I/II clinical trials are currently in progress. Gefinitib (ZD1839, Iressa) is an orally selective quinazoline EGFR tyrosine kinase inhibitor with documented activity in CRC cell lines. Several feasibility and pharmacokinetic studies have been performed in CRC patients. However, a large-scale clinical trial to evaluate its clinical efficacy is not expected in the near future, especially following the encouraging results with gefinitib in lung cancer.⁵ Erlotinib (OSI-774), another EGFR tyrosine kinase inhibitor has been shown to offer a marginal survival benefit, when added to gemcitabine, in pancreatic cancer patients, while clinical trials are in progress to evaluate its role in gastric and esophageal cancer.^{6,7,8}

Imatinib (ST571, Glivec) is an oral tyrosine kinase inhibitor that blocks several trans-membrane receptors, such as c-KIT, c-abl, PDGF-R and BCR-ABL. Several studies have demonstrated a spectacular clinical and radiological response in patients with gastrointestinal stromal tumors (GIST), with only marginal toxicity (haematological, nausea, periorbital and ankle edema). A prerequisite for Imatinib activity is over expression of c-KIT.⁹

Inhibiting neoangiogenesis

VEGF (vascular endothelial growth factor), a neoangiogenesis growth factor, has been shown to be a negative prognostic factor for CRC patients. Bevacizumab is a humanized anti-VEGF antibody that is currently under investigation in CRC. The ECOG Second-line Trial E3200 enrolled 828 pts with advanced colorectal cancer, who had failed first line chemotherapy, into three arms: a) FOLFOX (5-FU+Oxaliplatin+LV), b) FOLFOX+Bevacizumab and c) bevacizumab. The mono-therapy arm was closed prematurely because of its inferiority to the control arm (FOLFOX), while the addition of Bevacizumab to chemotherapy resulted in a prolonged overall median survival that ranged from 10.7 to 12.5 months.¹⁰⁻¹² Bevacizumab is currently under first-line chemotherapy investigation against hepatocellular carcinoma as a mono-therapy, CRC in combination with Oxaliplatin and advanced gastric and gastro-esophageal carcinomas in combination with cisplatin and irinotecan.^{13,14} With regard to toxicity, allergic reactions, hypertension and gastrointestinal hemorrhages have been reported after its administration.^{12,13} Another antiangiogenic factor with some antineoplastic activity is thalidomide, widely used in multiple myeloma and AIDS-related Kaposi sarcomas. When administered to metastatic CRC,

gastric, esophageal and hepatocellular cancer patients, progression free survival increased somewhat, while an overall improvement of symptoms also resulted. The main toxicities observed included fatigue, constipation, peripheral neuropathy and neutropenia.⁵

The farnesyl transferase pathway

Ras proteins constitute a fundamental intermediate in signal transduction pathways, mainly activated by farnesylation, a lipid modification catalyzed by farnesyl transferase, an enzyme localized on the inner cell membrane surface. The accumulative activation of K-RAS oncogenes has been observed in 90% of pancreatic cancer and 50% of CRC. Zarnestra (R115777) is a farnesyl transferase inhibitor with significant antiproliferative activity *in vitro*, in human GI malignant cell lines (LoVo, CAPAN-2). However, in clinical pancreatic cancer trials, the results were rather disappointing.⁵

Matrix metalloproteinase inhibitors

The MMPs (matrix metalloproteinase proteins) constitute a family of zinc dependent endopeptidases responsible for extra-cellular matrix degradation. They are over expressed in several neoplastic diseases and, it is believed that they promote both cancer cell invasion and motility by penetrating the basement membranes. Marimastat (BB2516) is an oral MMP inhibitor that has been used with gemcitabine in pancreatic cancer patients. Although no additional benefit in overall survival was observed, it appears to have a palliation advantage, while the patient subgroup with operable disease had an increased disease-free survival. Palliative improvement was also observed in patients with CRC and liver metastasis, as well as in patients with inoperable gastric cancer.¹⁵

COX-2 inhibitors

Recently, it has been shown that the COX-2 enzyme that converts arachidonic acid to prostaglandins is over expressed in a variety of tumors, including CRC. Several epidemiological studies have suggested the potential chemopreventive role of celecoxib, a selective COX-2 inhibitor. Its effectiveness in familial adenomatous polyposis has been demonstrated without any doubt, while it is currently being evaluated in advanced CRC.

In conclusion, targeted therapies have already gained their place in the armamentarium against GI malignancies. Imatinib and cetuximab are already part of everyday clinical practice for GIST tumors and CRC, respectively, while other agents have not yet produced concrete evidence of clinical benefit, despite the encouraging *in*

in vitro and animal results. Although current data provide some answers, they generate many more questions, each seeking a reply. The interpretation of preclinical data in the clinical setting, the application of targeted therapies concurrently with conventional chemotherapy, or sequentially, as maintenance treatment and the optimal dosing are merely some of the issues addressed by ongoing studies. Despite all of the above-mentioned uncertainties, we should be optimistic that biologic therapies constitute a significant step forward in cancer treatment. As they develop along with our understanding of molecular oncology and malignant progression, they encourage us to approach neoplasms from a new perspective, abandoning our "cytotoxic" cancer therapy model in favor of a "cytostatic" one. In fact, targeted therapies have already achieved their first major victory by modifying cancer research from disease-oriented to patient-oriented therapies. It seems there is indeed light at the end of the tunnel and this may very well be the adoption of drugs tailored in accordance to the tumor's molecular profile. This novel strategy would certainly be more effective and less toxic than the current therapeutic modalities.

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