Growth factor receptor-related therapy for gastric cancer

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Our understanding of gastric cancer is moving very rapidly. Many epidemiological, clinical and molecular features are contributing significantly to our current view of this disease. Gastric cancer has been considered a single heterogeneous disease with several epidemiological and histopathological characteristics; for the purposes of medical management, gastric cancer is treated in a uniform fashion, without regard to subtype. The trend nowadays is to split any neoplastic disease into several groups with the aim of having more homogeneous groups in which a more rational therapeutic approach according to sound biological factors could be applicable. A recent review proposes a molecular classification of gastric cancer into three different groups: proximal non-diffuse, diffuse and distal non-diffuse gastric cancer [1]. By examining the gene expression of individual gastric cancers, the authors found that individual tumours according to location and diffuse or non-diffuse subtypes had in fact distinct gene expression and support the hypothesis that gastric cancer subtypes may be distinguished molecularly. The presence of different biomarkers and therapeutic targets for each disease subtype is also likely. If we could distinguish new molecular gastric cancer subtypes, such a distinction will allow us to begin to manage each of these diseases differently and uniquely. As we improve our understanding of gastric cancer heterogeneity and its clinical consequences, our hope is to improve patient outcomes with improved prevention, screening, and treatment options, using distinct biological subtypes for improved application of targeted therapies.

However, the amount of information on the value of targeted drugs in gastric cancer is limited. Trastuzumab in combination with chemotherapy is so far the only targeted agent approved for the treatment of advanced gastric cancer. When studied in a large randomised controlled trial in HER2-positive patients, trastuzumab significantly prolonged survival as well as response rate and progression-free survival without excessive toxicity [2]. The trastuzumab effect was quantitatively more important in those individuals whose tumours had HER2+++ or were detected by FISH, supporting the hypothesis of oncogenic dependence on HER2 to maximise the effect of the drug. Lapatinib, an oral tyrosine kinase inhibitor (TKI) against HER2, is also being studied in phase III trials in advanced gastric cancer. Some retrospective analyses have hypothesised on the prognostic value of the overexpression of HER3. Overexpression of HER3 is claimed to be one of the commonest mechanisms of resistance to trastuzumab. Some monoclonal antibodies are being therapeutically developed to dually target EGFR and HER3 simultaneously to circumvent these potential mechanisms of resistance. The anti-EGFR antibodies cetuximab and panitumumab are also being studied in advanced gastric cancer in phase III designed trials. However, the results of those trials are still pending at the moment of writing.

Bevacizumab, a targeted agent directed against the vascular epithelial growth factor (VEGF), known to be effective against colorectal cancer, was also studied in a randomised trial. However, despite being able to increase response rate and progression-free survival, the addition of bevacizumab to combination chemotherapy did not show any increase in overall survival [3]. Some other anti-angiogenic compounds, like VEGF trapping agents or some TKI inhibitors against VEGF receptors are also under development.

Many other signalling pathways, apart from the epidermal growth factor receptor (EGFR) family or anti-angiogenics, are potentially involved in gastric cancer growth and progression. The insulin-like receptor type I pathway could be also involved, as well as the c-MET receptor pathway. Several agents, not only antibodies, but also TKIs blocking these receptors at different levels are also under clinical development. The hepatocyte growth factor and its receptor c-MET are highly expressed in more than 75% of gastric cancer samples. The amplification of the c-Met gene was observed in about 15% of gastric cancer samples, but its prevalence could be higher in individuals with metastatic lesions. Another fact of potential therapeutic interest is the frequent

coexpression of c-MET and HER3. Agents targeting those two membrane receptors are shown to be synergistic in vitro.

Not only membrane-related receptors can be potential targets for therapy in advanced gastric cancer. The downstream signalling pathways depending on them could also be very relevant. Among them we should underline the potential role of PI3K, AKT and m-TOR. Signalling through the PI3K/PTEN/AKT/mTOR pathway is responsible for balancing cell survival and apoptosis. The signal is initiated by growth factors and hormones that bind receptor tyrosine kinases such as EGFR, VEGFR and platelet-derived growth factor receptor (PDGFR). These receptors then activate PI3Ks resulting in a kinase cascade through AKT and mTOR, generating cell survival, growth, and angiogenesis signals. PTEN negatively regulates this pathway by dephosphorylating phosphatidylinositol trisphosphate (PIP3) and negating the signal generated by PI3K. This pathway has been shown to be commonly activated in cancer, including gastric cancer, and in the progression of Barrett's neoplasm to oesophagogastric tumours. Furthermore, studies in several cancer types have demonstrated that this pathway plays a key role in the development of resistance to several conventional cytotoxic agents such as platinum compounds, taxanes, and fluoropyrimidines. In an extensive analysis, investigators from MD Anderson determined whether genetic variations in the genes for PI3K, PTEN, AKT1, AKT2, and mTOR were associated with variation in recurrence, survival, and pathological response [4]. Significant associations were observed between several single nucleotide polymorphisms (SNPs) and clinical outcomes. In individual SNP analyses, they identified seven SNPs associated with recurrence risk and recurrence-free survival rates. Although this information should be further validated in prospective trials, it helps us in addressing the question of a personalised therapeutic approach for our patients.

mTOR is frequently activated in gastric cancer [5]. Although both mTOR and phosphorylated-mTOR overexpression was associated with tumour progression, only p-mTOR overexpression was an independent predictor of survival after resection of primary gastric cancer. Moreover, p-mTOR directly correlated with nodal metastasis and vascular endothelial growth factor expression and microvessel density, suggesting a novel molecular basis for the critical role of mTOR activation in gastric cancer development and progression and the deregulated mTOR/vascular endothelial growth factor signalling could be a promising new molecular target for designing novel preventive/therapeutic strategies to control this tumour. Some m-TOR inhibitors, such as everolimus, are currently undergoing development in phase III trials in gastric cancer.

Conflict of interest statement

A. Cervantes received honoraria for participating in advisory board meetings and for giving lectures in promotional activities by Roche, Merck Serono and Amgem.

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