Gastric Carcinoma: The Role Of PI3K/Akt/Mtor Signaling

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ABSTRACT

Gastric cancer is the fourth most common malignant disease and the second leading cause of cancer mortality worldwide. In 2008, an estimated 989,000 new cases were reported according to the International Agency for Research on Cancer. Unfortunately, due to the vague and unspecific symptoms of this malignancy, many patients do not present for evaluation in its early stages.

INTRODUCTION

Gastric tumor is the second driving reason for death from harmful infection overall and most much of the time found in cutting edge stages. Since corrective surgery is viewed as the main alternative for cure, early location of resectable gastric growth is to a great degree critical for good patient results. In this way, noninvasive demonstrative modalities, for example, transformative endoscopy and positron discharge tomography are used as screening apparatuses for gastric disease.

To date, early gastric growth is being dealt with utilizing insignificantly obtrusive techniques, for example, endoscopic treatment and laparoscopic surgery, while in cutting edge malignancy it is important to consider multimodality treatment including chemotherapy, radiotherapy, and surgery. Due to the consequences of expansive clinical trials, surgery with broadened lymphadenectomy couldn't be suggested as a standard treatment for cutting edge gastric disease. Late clinical trials had demonstrated survival advantages of adjuvant chemotherapy after healing resection contrasted and surgery alone.

What's more, late advances of atomic focused on specialists would assume a critical part as one of the modalities for cutting edge gastric tumor. In this survey, we outline the present status of symptomatic innovation and treatment for gastric growth.

Gastric growth death rates have remained generally unaltered in the course of recent years, and gastric disease keeps on being one of the main sources of malignancy related passing. All around directed studies have fortified changes to surgical choice making and method. Microarray studies connected to prescient result models are ready to propel our comprehension of the biologic conduct of gastric disease and enhance surgical administration and result.

Regardless of the diminishing overall occurrence, gastric tumor represents 3% to 10% of all disease related deaths. Although the survival rate for gastric growth has consistently enhanced in nations, for example, Japan, it has not in North America. The significant mortality connected with gastric malignancy has won notwithstanding specialized advances in surgery and the utilization of adjuvant treatment.

Ninety percent of all tumors of the stomach are harmful, and gastric adenocarcinoma contains 95% of the aggregate number of malignancies. Curative treatment includes surgical resection, most usually an aggregate or subtotal gastrectomy, with a going with lymphadenectomy. The general 5-year survival rate of patients with resectable gastric tumor ranges from 10% to 30%.
Key Insights

Current Treatments for Advanced GC

In January of 2010, trastuzumab was approved as the first targeted therapy for the treatment of patients with HER2-positive GC. The HER family consists of four members: HER-1 (epidermal growth factor receptor (EGFR), HER-2, HER-3, and HER-4. HER-1, HER-3, and HER-4 are all activated via ligand binding, whereas HER-2 does not require a ligand for activation \[12,13\]. The activation of these receptors triggers phosphorylation cascades and the subsequent activation of a number of signaling transducers, thus activating both the PI3K/AKT and Ras/Raf pathways, which are important in cancer cell proliferation and survival. Trastuzumab is a humanized recombinant monoclonal antibody that selectively binds to the extracellular domain of HER-2, thereby blocking its downstream signaling. HER-2 amplification or over-expression is observed in about 15% to 25% of GC cases \[14\]. HER-2 over-expression is more common in intestinal-type and gastroesophageal junction (GEJ) tumors than in diffuse-type and gastric tumors \[15\].

The PI3K/AKT Pathway

PI3K is a family of intracellular lipid kinases involved in the signaling network that regulates cell survival, proliferation, differentiation, migration, and metabolism \[16\]. PI3Ks can be categorized into three classes (I–III) according to their substrate preferences and sequence homologies. The activation of receptor tyrosine kinases (RTKs), such as EGFR, IGFR, and HER2, activates class IA PI3Ks. The binding of PIP3 to AKT leads to the membrane recruitment of AKT and its subsequent phosphorylation by PDK1 (3-phosphoinositide-dependent kinase) and PDK2 \[17,18\]. Activated AKT translocates to the cytoplasm and nucleus and activates the downstream targets involved in cell survival, proliferation, cell cycle progression, growth, migration, and angiogenesis \[19\]. PIP3 levels are tightly controlled by stringent PI3K regulation and via PTEN PIP3 phosphatase and SHIP (SH2-containing inositol5-phosphatase), which converts PIP3 back to phosphatidylinositol 4, 5-bisphosphate.

Everolimus is a mTORC1 selective inhibitor and has been tested in GC patients in phase II and phase III trials. In the recent phase II trial, everolimus demonstrated anti-tumor activity with a response rate of 3.7% (2/44) and a disease control rate (DCR) of 38.9% (17/44 \[20\]). However, aeverolimus phase III study failed to achieve a survival benefit in comparison with the best supportive care (BSC) in previously treated advanced GC cases \[21\].

There are two types of PI3K inhibitors targeting the p110 catalytic subunit that are currently under clinical development: pan-PI3K inhibitors and isoform-specific PI3K inhibitors. Pan-PI3K inhibitors are active against all family members of PI3K, whereas isoform specific inhibitors selectively inhibit p110α, β, or δ \[22\]. These include the panPI3K inhibitors BKM120 (Novartis), PX-886 (Oncothyreon), XL147 (SAR245408; Sanofi) and the p110a selective inhibitors BYL719, GDC0032, and INK1117 \[22\]. Some of the dual PI3K/mTOR inhibitors currently being investigated in clinical trials include BEZ235, XL765, GDC-0980, GDC0084, SF1126, and PF-46915 etc \[23\]. The clinical anti-tumor activity of some of these inhibitors has been reported \[24\].

AKT plays a central role in the activation of the PI3K/AKT pathway to facilitate cellular survival and suppress cell apoptosis. A number of AKT inhibitors have entered clinical trials. These include the allosteric inhibitors perifosine (Keryx Biopharmaceuticals) and MK-2206 (Merck) and the ATP competitive inhibitors AZD5363, GSK690693 and GDC0068 etc \[25\].

CONCLUSION

It is critical to validate and implement biomarkers and assays for the selection of patients with a predictive response to the therapy. Another approach for improving efficacy is to combine the inhibitors of the PI3K/AKT pathway with chemo or other targeted agents. Preclinical translational studies based on rational design and the safety profiles of the inhibitors will help in choosing the right agents and combinations.
REFERENCES


