Novel targeted therapies in the treatment of gastric and esophageal cancer

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Esophageal cancer (EC) and gastric cancer (GC) constitute a major cause of cancer deaths worldwide. Recent improvements in both surgical techniques and adjuvant/neoadjuvant radiotherapy and chemotherapy approaches have increased the survival of patients with loco-regional disease. However, most of the patients with GC or EC have advanced disease either at diagnosis or at follow-up. Despite recent advances in the treatment of advanced disease, these patients still do poorly. An emerging understanding of the molecular pathways that characterize cell growth, cell cycle, apoptosis, angiogenesis and invasion has provided novel targets in cancer therapy. In this review we describe the current status of targeted therapies in the treatment of EC and GC. These therapeutic strategies include EGFR inhibitors, antiangiogenic agents, cell cycle inhibitors, apoptosis promoters and matrix metalloproteinases inhibitors. The emerging data from the clinical development of these compounds has provided novel opportunities in the treatment of EC and GC that will probably translate into efficacy advantage in the treatment of these common malignancies.

Key words: targeted therapies, EGFR inhibitors, angiogenesis inhibitors, gastric cancer, esophageal cancer

Introduction

Esophageal cancer (EC) and gastric cancer (GC) are highly frequent, being the eighth and the second leading causes of cancer-related deaths worldwide, respectively [1]. Whereas globally, squamous-cell EC continues to be the most common histology, as it is clearly related to tobacco and alcohol consumption, the incidence of adenocarcinomas of the distal esophagus and gastroesophageal junction is continuously increasing both in the United States and in north and western Europe [2]. Despite recent advances in the treatment, patients with EC and GC still do poorly. Recent advances in the field of oncology have resulted in increased survival of patients with advanced GC. However, median survival beyond 1 year has not yet been achieved in any randomized study with combination chemotherapy [3, 4] despite an increase in percentages of response rates in the range of 40%–50% with the introduction of more recent regimens including taxanes and/or camptothecin analogues [5–8]. Most of these series reproduce median survival results of approximately 10 months, which compares poorly with the results achieved in advanced colorectal cancer (CRC; 20 months), with similar percentages of response rate [9, 10]. This difference in median survival raises the hypothesis of rapidly acquired pharmacological resistance through specific molecular pathways in GC. Therefore, new strategies are warranted in order to improve these results. New biological therapies aim to inhibit or modulate different targets of signal transduction pathways that are thought to be functionally selective or over-expressed in certain tumor types. GC and EC belong to these tumor models with overexpressed signal transduction pathways that are potential targets of a number of new drugs that are currently being developed. In addition, no active second-line therapy has demonstrated definitive clinical benefit for patients with advanced GC or EC that have progressed after first-line chemotherapy, which renders this clinical setting an orphan-drug situation, suitable for regulatory rapid approval track applications with new active drugs even at an early stage of development. Unfortunately, until now this opportunity has not translated into rapid clinical investigations in this patient population and clinical data are limited in GC and EC with the new biological agents that are being evaluated in gastrointestinal cancer treatment.

For the purpose of this review, these novel agents will be divided into five different categories according to the pattern of acquired capabilities of the malignant cells, elegantly described by Hanahan and Weinberg [11]: (1) agents directed to interfere with the self-sufficiency in growth signals, such as epidermal growth factor receptor (EGFR) inhibitors; (2) agents directed to inhibit the angiogenesis process; (3) agents directed to interfere with the limitless replicative potential, such as cell cycle inhibitors; (4) agents directed to promote apoptosis, such as proteasome inhibitors; and (5) agents directed to inhibit the...
tissue invasion and the metastasis processes, such as matrix metalloproteinases inhibitors.

**Epidermal growth factor receptor inhibitors**

Biological agents that target the EGFR are at the forefront of novel anticancer therapies [12]. The EGFR is a tyrosine kinase receptor that belongs to the ErbB family and is abnormally expressed and activated in cancer cells in many tumor types. EGFR is highly expressed in patients with advanced GC and EC [13]. Following stimulation by its natural ligands, the EGFR initiates signal transduction cascades, which promote cell division, migration and angiogenesis, and inhibit apoptosis (Figure 1).

There are several potential strategies to target the EGFR. However, monoclonal antibodies (mAbs) and the low molecular weight tyrosine kinase inhibitors (TKIs) are the most developed ones and have reached the clinical scenario. mAbs bind to the extracellular domain of the receptor and compete with the natural ligands (TGF-α and EGF) binding to the receptor, therefore blocking activation of the receptor. On the contrary, TKIs compete with ATP binding to the tyrosine kinase portion of the endodomain of the receptor and, thereby, abrogate the receptor’s catalytic activity (Figure 2). Both strategies appear to be equally effective at blocking the downstream receptor-dependant signaling pathways, including the MAPK, the PI3K/Akt and the Jak/Stat pathways.

In 1983, John Mendelsohn and coworkers created a murine mAb, M225, which could block the proliferation of tumor cells both in vitro and in xenograft models. Among all the available anti-EGFR mAbs (Table 1), the chimeric IgG1 cetuximab (‘Erbitux’, C225) is the one furthest ahead in clinical development [14]. In fact, cetuximab has been approved for the treatment of advanced CRC refractory to irinotecan-based chemotherapy [15–17]. However, no clinical trial has yet been performed in an EC or GC population. Cetuximab has been demonstrated to enhance the antitumour effect of both topotecan and irinotecan in CRC cell lines in vitro and in mice xenograft models [18, 19]. This property is interesting because irinotecan is one of the most active single agents in advanced GC. Other anti-EGFR mAbs that have a similar mechanism of action to cetuximab are in clinical development. Matuzumab (EMD72000) is a humanized IgG1 mAb with high affinity currently in phase I and II development. This mAb has a prolonged half-life that may allow for a less frequent administration schedule. In an ongoing trial, pharmacokinetic, pharmacodynamic and efficacy data indicate that a more convenient schedule with matuzumab every 2 or every 3 weeks is feasible [20]. The limited efficacy information from the phase I studies shows a similar efficacy to cetuximab in patients with refractory CRC [20, 21] and one of two patients with EC included in the initial phase I trial responded to the treatment [21]. A phase II trial in the second-line setting in patients with advanced GC is being performed in Germany and a phase I/II study is being conducted at the Royal Marsden in EGFR-positive lower EC and GC combining matuzumab with epirubicin/cisplatin/capecitabine chemotherapy. Panitumumab (ABX-EGF) is a fully human IgG2 mAb with high affinity for the EGFR. In a phase I/II study of panitumumab in patients with advanced refractory CRC, this mAb showed a similar efficacy to cetuximab in this population, but no data on either GC or EC is available [22].

![Figure 1. Epidermal growth factor receptor (EGFR) signal transduction pathways.](image-url)
There are a large number of TKIs directed to the EGFR family in clinical development (Table 2). Gefitinib (‘Iressa’, ZD1839) has been evaluated in GC and EC in two different studies. In the first study, gefitinib was administered at 250 or 500 mg in Japanese and non-Japanese patients with advanced GC that had failed one or two previous chemotherapy regimens. The safety profile was optimal but clinical activity was modest, with only one patient achieving a partial response (PR) and 12 out of 71 evaluable patients presenting stabilization of the disease (SD) [23]. Furthermore, pharmacodynamic data from this study have shown that gefitinib was biologically active in these gastric tumors [24]. All the patients involved in this trial had late-stage, metastatic disease, with approximately 50% of patients receiving gefitinib as a third-line therapy. It is possible that the disease was too advanced for this biological activity to translate into clinical benefit. In the second study, 27 patients with advanced EC (adenocarcinoma) were treated with gefitinib 250 mg daily. Almost 70% of the patients had previously received chemotherapy. Thirteen per cent of the patients achieved a PR and a total of 42% of patients obtained disease control. Interestingly, a gene-profiling analysis in paired tumor biopsies was done within this study to demonstrate changes in tumor gene expression after gefitinib exposure [25].

Erlotinib (‘Tarceva’, OSI-774) has been also evaluated in patients with advanced EC. In a phase II study performed at MSKCC, 20 patients with either adenocarcinomas or squamous carcinomas were treated with erlotinib. Three patients presented a PR (all with squamous carcinoma histology) and eight patients presented SD, for a PR rate of 15% and a disease control rate of 55% [26]. In a second study, 70 patients with either GC or gastroesophageal junction cancer (GEJC) were treated with erlotinib. No patient in the GC cohort (26 patients) presented an objective response, but five patients in the GEJC cohort presented an objective response [including one complete response (CR)] for an overall response rate (RR) of 11%. The median overall survival (OS) was 3.5 months and 6.7 months in the GC and GEJC cohorts, respectively [27]. These preliminary efficacy results with TKIs, especially in the GEJC and EC population, merit further clinical evaluation. In addition, there is preclinical evidence of a synergistic antitumor effect combining cytotoxics with TKIs in several tumor types, including GC [28]. In one preclinical study SN-38, the active metabolite of irinotecan, was shown to enhance EGFR-pathway signaling in GC cells, this effect being abrogated by gefitinib [29].

The area of research continues to expand and a number of issues are of particular interest for the future development of EGFR inhibitors in GC and EC. First, it is not known what level of EGFR expression is required to obtain clinical benefit. While a relationship appears to exist between the levels of the erbB-2 receptor and response to trastuzumab (Herceptin®), no clear association has emerged between the levels of EGFR and response to EGFR inhibitors. Secondly, it remains to be established which patients will show the greatest response to these therapies. There is a clear need to identify predictor factors of response (e.g. gene and proteomic profile) in order to select the patients who have a fair chance of responding to EGFR inhibitors. Several studies in patients with advanced CRC treated with anti-EGFR mAbs have incorporated transcriptional profiling end points and the preliminary results have been presented [30]. In patients with advanced non-small-cell lung cancer (NSCLC), the presence of mutations in the tyrosine kinase domain of the EGFR has been shown to play an instrumental role in the clinical activity of the TKIs, gefitinib and erlotinib [31–33]. By contrast, patients with advanced CRC rarely show mutations in the catalytic domain of the EGFR and no correlation
Table 2. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)

<table>
<thead>
<tr>
<th>Type of inhibition</th>
<th>Agent</th>
<th>EGFR IC₅₀</th>
<th>HER2 IC₅₀</th>
<th>Irreversible</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR specific &amp; reversible</td>
<td>ZD1839 – Gefitinib</td>
<td>0.02</td>
<td>3.7</td>
<td>No</td>
<td>Phase II &amp; III</td>
</tr>
<tr>
<td></td>
<td>OSI-774 – Erlotinib</td>
<td>0.02</td>
<td>3.5</td>
<td>No</td>
<td>Phase II &amp; III</td>
</tr>
<tr>
<td></td>
<td>PKI-166</td>
<td></td>
<td></td>
<td>No</td>
<td>Phase I</td>
</tr>
<tr>
<td>EGFR specific &amp; irreversible</td>
<td>EKB-569</td>
<td>0.038</td>
<td>1.2</td>
<td>Yes</td>
<td>Phase I &amp; II</td>
</tr>
<tr>
<td>Pan-HER reversible</td>
<td>GW-2016 – Lapatinib</td>
<td>0.011</td>
<td>0.009</td>
<td>No</td>
<td>Phase I &amp; II</td>
</tr>
<tr>
<td>Pan-HER irreversible</td>
<td>CI-1033</td>
<td>0.0008</td>
<td>0.019</td>
<td>Yes</td>
<td>Phase I</td>
</tr>
<tr>
<td>Pan-HER &amp; KDR reversible</td>
<td>AEE788</td>
<td>0.002</td>
<td>0.006</td>
<td>No</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

has been observed between these mutations and clinical activity in this population [34]. To date, there is no information on whether these mutations play any role in patients with EC and GC. Therefore, in the same way as in the field of NSCLC and CRC, studies in patients with GC and EC should incorporate these transcriptional profiling endpoints.

**Angiogenesis inhibitors**

One novel approach in the treatment of solid tumors involves therapeutic agents that inhibit the neovascularization process of growing tumors. There is strong evidence that links tumor growth and metastasis with the angiogenesis process in most human tumors, including GC [35]. The formation of a vascular network in the tumor growth involves different complex pathways including angiogenic factors, membrane receptors and signaling transduction cascades, leading at the end to vessel formation [36]. The vascular endothelial growth factor (VEGF) is the most potent and specific angiogenic factor and its expression in pathology specimens in patients with GC and EC has been demonstrated to correlate with recurrence and prognosis. There is preclinical evidence showing cross-talk between angiogenic and tumor growth signaling pathways. One recent study suggests that the activation of the EGFR-pathway contributes to angiogenesis in GC by different mechanisms, including upregulation of VEGF and Neurepilin-1 expression [37]. Multiple strategies have been developed to inhibit the VEGF pathway but two different approaches have reached advanced clinical development. The first one is the generation of a humanized mAb, directed to the VEGF itself. Bevacizumab (‘Avastin’) is a recombinant humanized anti-VEGF mAb that is clinically being evaluated in many tumor types. The second strategy directed to the VEGF pathway comprises different small molecules TKIs that are directed to the receptors of the VEGF, Flt-1 and Flk-1/KDR. In this category there are several compounds, some of them specific to the VEGF receptors such as PTK787/ZK222584 (Vatalanib) and SU5416, and others that inhibit not only a VEGF receptor but also other tyrosine kinase receptors such as ZD6474, AEE788, SU6668 and SU11248.

Bevacizumab has demonstrated a survival advantage when added to irinotecan-, oxaliplatin- and 5-fluorouracil-based chemotherapy schedules in patients with advanced CRC [38–41], not only in the first-line setting but also in a refractory population. A vast development program including phase II and III studies with other irinotecan- and oxaliplatin-based schedules is ongoing in order to establish the role of bevacizumab and other anti-VEGF treatments, both in the first-line setting of patients with advanced CRC and in the adjuvant setting after radical surgery of locoregional colon cancer. Results of studies that address the efficacy of these compounds in pancreatic cancer and in GC are emerging. A phase II study in patients with advanced GC and GEJC with the combination of bevacizumab, cisplatin and irinotecan has been recently presented. Twelve out of 16 evaluable patients presented a PR (75%) [42]. Although these results are very encouraging, randomized phase II and phase III studies are needed to demonstrate the clinical benefit of bevacizumab in this setting.

The anti-angiogenesis effects of VEGF TR TKIs in GC have been demonstrated in different preclinical models. SU6668 has been shown to suppress peritoneal dissemination in an in vivo model with mice bearing TMK-1 human gastric tumors [43]. In another TMK-1 xenograft model, ZD6474 reduced tumor cell proliferation, increased tumor cell apoptosis and decreased microvessel density; these results show the capacity of some TKIs to target both angiogenesis and tumor growth signaling [44]. Despite the existence of preclinical rationale for clinically exploring the activity of VEGFR TKIs, to date, no clinical data with these compounds in GC and EC has been presented.

Another scenario in the treatment of these malignancies is to combine drugs that target different pathways critical for the tumor growth. On this basis, a promising approach is the combination of drugs that target the EGFR pathway with drugs that target the angiogenesis process. There is some preclinical evidence that favors this approach: (a) the activation of EGFR by the ligands EGF or TGF-α can upregulate the production of VEGF in cancer cells; (b) EGFR inhibition reduces VEGF production; and (c) resistance to EGFR inhibitors is associated with VEGF overexpression. The synergistic effects of targeting both the EGFR pathway and the angiogenesis pathway have been shown in some preclinical models. In an in vivo model with xenografts bearing TMK-1 human gastric tumors, the combination of cetuximab and DC101 (an anti-VEGFR mAb) showed a synergistic effect in tumor control [45]. In a GEO human colon cancer xenograft model, the
combination of cetuximab and a human VEGF antisense oligonucleotide showed a clear synergistic effect in tumor control [46]. A randomized phase II combination study of either bevacizumab/cetuximab or bevacizumab/cetuximab/irinotecan was designed in patients with advanced CRC refractory to irinotecan-based chemotherapy. The preliminary results of this study (called BOND-2) were recently presented and, although there were no comparator arms with bevacizumab and cetuximab alone, the efficacy results in RR and median progression-free survival (PFS) were encouraging, suggesting a synergistic clinical effect targeting the two pathways [47]. The same clinical approach warrants further evaluation in patients with EC and GC.

**Cell cycle inhibitors**

Cyclin dependant kinases (CDKs) are regulators of the cell cycle that can be targeted directly with small molecules. These CDK inhibitors appear more active when combined with chemotherapy or radiotherapy in a time sequence dependent manner. Among all the CDK inhibitors, flavopiridol is the most tested agent and the one that has reached a vast clinical development, even in advanced GC. Flavopiridol is a pan CDK inhibitor (CDK 1, 3, 4 and 6) that binds to the ATP binding sites of all CDKs at nanomolar concentrations, and potentiates chemotherapy-induced apoptosis in GC cell lines when administered sequentially at some time-point after the chemotherapy treatment, although it may be antagonistic when administered concomitantly or before the chemotherapy treatment [48]. Flavopiridol was initially tested as a single agent in many different schedules. In a phase I study of flavopiridol administered in a 72-h infusion schedule, one patient with advanced GC achieved a CR [49]. However, a subsequent phase II study of flavopiridol with the same schedule in patients with advanced GC did not show any objective response in this population, flavopiridol being considered non-meaningly active as a single agent in this tumor population [50]. Flavopiridol has been evaluated in GC and EC in combination with active chemotherapy drugs. A phase I study has evaluated the combination of flavopiridol, irinotecan and cisplatin in patients with advanced refractory GC and EC, with clear signs of activity. In this limited study, five out of 11 patients with GC and two out of three with EC achieved a PR [51]. This encouraging PR rate is higher than that expected for patients treated with the combination of cisplatin and irinotecan in this refractory population. However, the definitive role of flavopiridol in this setting should be defined in the context of randomized studies. Two phase I/II studies have evaluated the combination of paclitaxel followed by flavopiridol. In the phase I study, one CR, one PR and one SD were seen in patients with EC—one of them previously treated with paclitaxel—and one SD in a patient with advanced GC [52]. However, a disease-oriented phase II study in patients with advanced refractory EC failed to demonstrate any clinical benefit in this population [53]. Another phase I study evaluated the combination of weekly docetaxel followed by flavopiridol, showing signs of activity in patients with advanced GC and EC. This study will be followed by a randomized phase II study at the recommended dose of docetaxel and flavopiridol versus docetaxel alone in taxane-naïve patients with advanced GC in the second-line setting [54].

**Apoptosis promoters**

The nuclear factor of κB (NF-κB) is involved in pro-survival and anti-apoptotic signals in response to stress and it has been shown to be implicated in the pathogenesis of several malignant tumors [55, 56], including GC. NF-κB is suggested to be the mediator of Helicobacter pylori associated gastritis and NF-κB expression is increased in gastric MALT lymphoma and GC [57]. Indeed, high expression of NF-κB has been associated with poor survival in patients with GC. Activation of the NF-κB signaling pathway can stimulate proliferation and/or reduce the effectiveness of chemotherapy or radiotherapy [58]. Transcription by NF-κB is prevented in quiescent cells through binding of a specific inhibitor protein, IκB, which sequesters the NF-κB p50/p65 heterodimer in the cytoplasm [59]. These observations of the consequences of NF-κB activation in tumor cells led several investigators to test the effect of preventing NF-κB activation in transformed cells, usually through inhibition of proteasome-mediated IκB degradation. Bortezomib (‘Velcade’, PS-341) is a small molecule and is a potent and selective inhibitor of the proteasome, which has received regulatory approval for the treatment of refractory myeloma. Bortezomib has shown antitumor activity in a variety of tumor types, including GC, in in vitro and mouse xenograft models. In a phase II study of bortezomib as a single agent, no objective responses were seen in patients with advanced GC or GEJC [60]. Patients with advanced GC were treated in another phase II study with bortezomib alone, if they had previously received chemotherapy treatment, or associated with irinotecan if they were chemo-naïve. The cohort of patients treated with the combination presented significant activity with a PR rate of 28% and a median PFS of 3.5 months, whereas in those patients treated with bortezomib alone, the RR was 0% and the median PFS 1.4 months [61]. Interestingly, a gene-profiling analysis in paired tumor biopsies was done within this study to demonstrate changes in tumor gene expression after bortezomib exposure. The preliminary results from eight paired tumor samples showed that the expression of 643 genes significantly changed after bortezomib treatment, and 42% of the genes changed by 2-fold between pre- and on-treatment. Significant upregulated and downregulated genes were related to apoptotic, phosphatidylinositol and MAPK signaling pathways [62].

**Matrix metalloproteinase inhibitors**

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes that are responsible for the breakdown of connective tissue proteins. These enzymes play an important role in normal processes of growth, differentiation and repair. There is now considerable evidence that aberrant MMP expression contributes to the invasive local growth and
spreads in different tumor types [63]. MMP-2, MMP-7, MMP-9 and MMP-14 are overexpressed in GC [64–66]. Indeed, expression of MMP-2 has been shown to be strongly associated with tumor progression and lymph node metastasis in GC [67]. A great effort was done in the last decade to develop several compounds with capacity to inhibit MMPs. Unfortunately, most clinical trials of MMP inhibitors (MMPIs) have yielded disappointing results, perhaps due to inappropriate study design or tumor staging, or to lack of selectivity. Marimastat (BB 2516, TA 2516) is an orally active MMPI. In a preclinical study, marimastat was shown to decrease the peritoneal spread of the human GC TMK-1 in a xenograft model [64]. In another in vivo model, marimastat decreased the growth in mice bearing MGLVA1 human gastric tumors [65]. A pilot clinical study demonstrated the safety profile of marimastat in patients with advanced GC or GEJC. In this study, 35 patients were treated with marimastat and, although no clear responses were reported, some patients presented clinical benefit. An endoscopic and pharmacodynamic evaluation with repetitive tumor biopsies was performed within the study and clear signs of activity were observed after the treatment: 32% of the patients showed an increased fibrotic cover of the tumor, 26% had decreased hemorrhagic appearance, and in at least two cases where comparative tumor histology was assessable, there was evidence of increased stromal fibrotic tissue compared with the basal specimens [66].

On the basis of these preclinical and clinical signs of activity, a phase III study was planned in patients with advanced GC and GEJC comparing marimastat versus placebo, with the primary objective being to demonstrate an advantage in the median OS for those patients allocated to receive marimastat [67]. A total of 369 patients were included in the study and they either had received previous 5-fluorouracil-based chemotherapy treatment (123 patients) or were chemo-naïve. The analysis of the population showed a median OS of 5.2 months and 4.5 months (hazard ratio 1.23, \( P = 0.07 \)) and a 2-year OS of 9% and 3% (hazard ratio 1.27, \( P = 0.024 \)) in the patients receiving marimastat and placebo, respectively. Although the primary objective of the study was not met, there was a clear trend for improvement of the median OS and a significant improvement of the 2-year OS figure in the patients treated with marimastat. When the analysis was limited to those patients that had previously received chemotherapy, there was a statistically significant improvement in the median OS (8.4 months versus 5.8 months, hazard ratio 1.53, \( P = 0.045 \)) and in the 2-year OS (18% versus 5%, hazard ratio 1.68, \( P = 0.006 \)) favoring the population that was treated with marimastat. There was also an advantage in the median and 2-year PFS in those patients treated with marimastat (hazard ratio 1.32, \( P = 0.009 \)). Although this was the first demonstration of a therapeutic benefit for a MMPI in cancer patients, no further development of marimastat has been done in this population.

Conclusions

In summary, advanced GC and EC offer clear opportunities for clinical research due to their poor prognosis. Their biology is well characterized but it lies behind other more prevalent tumors in the exploration of targeted therapies. However, their clinical and biological behavior make them a perfectly appropriate tumor population for targeted therapy, and efforts from the academic and pharmaceutical community should be implemented in the near future to emulate the impressive advances of targeted therapies recently achieved with their gastrointestinal counter part, CRC. In this review, we have described the current clinical development status of these targeted agents in GC and EC. Marimastat is the agent that has reached the most advanced clinical development showing clear survival benefit in patients with advanced GC. Other agents are still in initial clinical development, but their encouraging activity has prompted more

Other targeted therapies

Other cellular targets, including histone deacetylases, chaperone proteins and cell-cycle checkpoints, have been demonstrated to be critical in the balance of the tightly regulated pathways that promote either cell survival or cell death. New drugs are being developed against those specific targets and preliminary clinical and clinical evaluation of these compounds is expected in the near future.

The \( p53 \) gene constitutes a major genetic alteration in most patients with GC. The key role played by the \( p53 \) gene product in the regulation of the cell cycle, cell proliferation and cell apoptosis has been widely studied. The most precise analysis of this genetic alteration is gene sequencing. However, analyzing this gene in large numbers of patients is cumbersome due to the fact that \( p53 \) mutations are spread across the gene. As a result of this, various surrogate tests have been designed to assess whether the gene is mutated or not. Most of these tests are prompted to evaluate the presence of a mutated \( P53 \) protein, but unfortunately, they have contradictory results. This has led to the generation of data that are not consistent and, therefore, not comparable [72]. Recent sequencing studies have shown that up to 35% of GC have \( p53 \) mutations. Indeed, the \( p53 \) mutation status is related to the GC subsite and the histological subtype: mutations were more frequent in cancers of the cardia than in cancers of the antrum and body (54% versus 25%, \( P = 0.005 \)) and also more frequent in the intestinal type than in the diffuse type (42% versus 21%) [73]. It is well known that tumors with \( p53 \) mutations are particularly resistant to chemotherapy. The resistance of these tumors to agents, such as camptothecin analogues, is based on the activation of the cell cycle checkpoint protein called Chk1, which induces permanent G2 phase cell cycle arrest without cell death. Several compounds have been identified as Chk1 or Chk1-induced cascade inhibitors [74]. UCN-01, initially identified by the NCI drug screen panel as a CDK inhibitor, has recently been considered as a Chk1 inhibitor [75]. In preclinical models, UCN-01 has been demonstrated to enhance the induction of apoptosis by irinotecan. Unfortunately, the systemic clinical toxicity related to UCN-01 administration may prevent complete clinical development. Fortunately other Chk1 inhibitors are currently in clinical development, and it is anticipated that these compounds will be evaluated in \( p53 \)-mutated neoplasms such as CRC and GC.
extensive evaluation. In this category, EGFR inhibitors such as matuzumab, gefitinib and erlotinib, angiogenic inhibitors like bevacizumab, cell cycle inhibitors such as flavopiridol and apoptosis promoters such as bortezomib are at the forefront of current clinical development. Consequently, patients with advanced GC and EC should be considered for inclusion in clinical trials of targeted therapies in the search for more effective treatments.

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