A Review on Biomarkers for Prediction of Treatment Outcome in Gastric Cancer

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Abstract. *Currently, therapeutic management of gastric cancer is mainly based on clinical data and histological features. Although several new treatment options have recently been introduced, inter-individual variability of response and drug resistance are still a challenge. Many promising markers have been identified to predict prognosis and likelihood of response to therapy, in order to tailor treatment regimens on the basis of patients' individual features. However, despite recent developments in gene sequencing and molecular diagnostics, many biomarkers still have a controversial role. Published data are often contradictory and at the moment, no molecular marker, other than Human epidermal growth factor receptor-2 (HER2) status for trastuzumab-based treatment, has entered the mainstream of clinical practice. The primary obstacle to the identification of reliable markers lies in technical difficulties in quantitatively assessing molecular alterations; genome-wide analyses are also often misleading due to the complexity of biological processes. Nevertheless, many biomarkers are being evaluated in clinical trials in order to identify criteria for stratifying patients and establish customized therapeutic approaches. In this review, we provide an update on promising biological prognostic and predictive markers, with a focus on growth factor signalling molecules, DNA repair systems, fluoropyrimidine metabolism and apoptotic pathways.*

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Gastric cancer (GC) is the second leading cause of cancer mortality in the world (1). Surgical resection remains the only potentially curative treatment, but many patients eventually die due to recurrence even with the addition of perioperative chemotherapy or adjuvant chemoradiation (2, 3). Outcome of unresectable or metastatic GC is still extremely poor, although palliative chemotherapy has been demonstrated to confer a benefit of survival and quality of life (4). There is no consensus regarding the standard regimen for advanced GC, although cisplatin and 5-fluorouracil (5-FU) combinations showed satisfactory efficacy and represent the most utilized regimens, with or without other agents such as epirubicin or docetaxel (5). Cisplatin and 5-FU have recently been replaced by oxaliplatin and capecitabine, in light of equivalent efficacy and significantly less toxic effects (6).

The pathological stage is the most important tool used to assess prognosis and predict the need for adjuvant systemic treatment in resectable GC; moreover, only clinical prognostic factors are available to drive the treatment decision-making in the metastatic setting (7). However, GC is a heterogeneous disease, both biologically and genetically. Although the role of many genetic alterations seems unclear, they represent a promising tool for stratifying patients according to tumour biological behaviour and likelihood of response to systemic therapy. Nevertheless, the independent validation of the most promising prognostic and predictive biomarkers is required before they can be routinely employed in clinical practice. Active research is gaining insight into the molecular characterization of the various genetic pathways involved in GC. This represents the first step towards the personalization of treatment, avoiding potentially harmful treatments for patients who are not likely to gain a benefit, and developing newer targeted therapies towards established molecular drivers of the neoplastic progression.

Biomarkers can be investigated at various levels: genetic analyses including polymorphism evaluation, gene expression profiling or DNA sequencing; transcriptional

assays such as reverse transcriptional-polymerase chain reaction (RT-PCR) for mRNA level detection; and transductional tests, such as immunohistochemistry for protein expression. However, such a variety of available methods is not free of threats; not only does it present dvantages towards a wider comprehension of biomarkers, but it can also be misleading due to discrepancies obtained with different techniques.

The aim of this review is to provide an update on the most recent data on biological prognostic and predictive markers in patients with GC, with a view to their possible future relevance in clinical practice.

Literature Search Methodology

The evidence regarding tissue biomarkers in GC derives from two different sources: retrospective series, and prospective studies designed to investigate a biomarker's prognostic or predictive value. For this review, the PubMed database was searched for articles concerning biomarkers in GC before December 2012; early release publications were also included. The search terms were 'gastric cancer' AND 'biomarker' AND 'prognosis' AND 'carcinogenesis'.

Studies were eligible if they evaluated the association of biomarker expression with survival or tumour response in GC; the outcomes of interest were overall survival (OS), event-free survival (EFS) and radiological response.

Growth Factor Signalling Pathways

Constitutive activation of growth factor signalling pathways through receptor mutations or enhanced expression has a key role in GC progression and may be involved in prognosis or response to targeted therapies.

The Human Epidermal Growth Factor Receptor 2 (HER2) pathway. The HER2 protein is a transmembrane tyrosine kinase receptor, which belongs to the epidermal growth factor receptor (EGFR) family. The protein, encoded by the *HER2* oncogene, is the first successfully-exploited molecule in targeted therapies for GC. HER2 does not bind to any known ligand, but represents a heterodimerization partner for other EGRF receptors. At the biomolecular level, the HER2 pathway is responsible for the repair of DNA damage (particularly, inter-strand cross-links induced by platinum analogues), so that HER2-targeted inhibition may synergize with chemotherapy and increase apoptotic stress (8).

Trastuzumab is a fully-humanized monoclonal antibody targeting the HER2 protein by directly binding to its extracellular domain. Trastuzumab added to a platinum-plus-fluoro-pyrimidine doublet chemotherapy is a new standard-of-care for patients with HER2-positive metastatic GC. HER2 expression has become the biomarker for identifying patients who are likely to show a survival benefit with trastuzumab (9).

Besides being a predictive factor for targeted therapies, HER2 expression has been correlated with some important clinicopathological features, including depth of tumour invasion, involved lymph nodes, intestinal-like subtype and tumour stage (10, 11). The clinical significance of HER2 overexpression remains to be defined. A recent systematic review investigating the prognostic value of HER-2 overexpression found that 20 studies (57%) reported no difference in OS, two (6%) showed significantly longer OS, and 13 (37%) significantly worse OS (12). In addition, a recent retrospective analysis provided strong evidence that HER2 status does not influence outcomes after D2 dissection for GC cancer in East Asian patients, in contrast to breast cancer studies (13). Moreover, discordant results have been reported regarding the prevalence of immunohistochemical HER2 overexpression accounting for 12-18% of cases (10, 14).

The Mesenchymal Epithelial Transition (MET) pathway. MET is a transmembrane tyrosine kinase receptor with high affinity for hepatocyte growth factor/scatter factor (HGF/SF). Autophosphorylation of MET activates several signalling transduction cascades, leading to cancer cell proliferation, angiogenesis, invasion and metastasis. Qualitative assays, such as immunohistochemistry show overexpression of MET in 18-68% of GC tissues. *In situ* hybridization demonstrated a gain of gene copy number in fewer than 20% of the cases (15).

MET-positive tumours were more frequently associated with serosal invasion and other unfavourable features (15). In fact, c-MET overexpression was significantly associated with more advanced disease stage and poor prognosis in some studies (16). Although MET amplification may play a central role in determining GC prognosis, future studies should focus on the possible negative predictive role for response to chemotherapy or targeted therapies. Recently, gene amplification has been correlated with responsiveness to MET inhibitors such as crizotinib (17).

The ongoing development of MET inhibitors requires the selection of a target patient population. Promising results were recently reported in a randomized phase II trial investigating chemotherapy-plus-placebo or two different dose levels of rilotumumab, an experimental fully-humanized monoclonal antibody targeting MET (18). Furthermore, an analytically validated biomarker assay is being explored to predict clinical responses (19).

DNA Repair Systems

Chemotherapy resistance is a multifactorial process. DNA repair systems allow cells to identify and correct damage to DNA molecules, including chemotherapy-induced ones. Activation of repair mechanisms is often involved in acquired drug resistance and the identification of biomarkers

Table I. *Main results of translational studies investigating DNA repair-related biomarkers in terms of chemotherapy outcome in GC.*

Gastric cancer stage	No of patients	Biomarker	Result	First author (Reference)
Advanced	76	ERCC1 mRNA	In patients treated with FOLFOX regimen, ERCC1 expression is related to worse OS ($p<0.0001$)	Metzger, 1998 (20)
Advanced	64	ERCC1 protein IHC	In patients treated with FOLFOX regimen, ERCC1 expression is not related to response but to OS in multivariate analysis ($p=0.003$)	Kwon, 2007 (26)
Locally advanced	61	ERCC1 mRNA	In patients treated with neoadjuvant cisplatin and 5-fluorouracil regimen, ERCC1 expression is not related to response and OS	Napieralski, 2005 (21)
Advanced	76	ERCC1 mRNA	In patients treated with FOLFOX regimen, ERCC1 expression is related to worse OS ($p<0.0001$)	Wei, 2008 (21)
Advanced	140	ERCC1 mRNA	In all patients, ERCC1 expression is related to worse OS in multivariate analysis ($p<0.001$); in 43 cisplatin-treated patients, ERCC1 expression is related to worse response ($p=0.008$)	Matsubara, 2008 (22)
Advanced	32	ERCC1 protein IHC	In patients treated with cisplatin regimen, ERCC1 expression is not related to response and OS	Yun, 2010 (23)
Advanced	59	BRCA1 mRNA	In patients treated with second-line docetaxel, BRCA1 expression is related to better OS ($p=0.0062$)	Wei, 2011 (28)

BRCA1: Breast cancer-1; ERCC1: excision repair cross-complementing group-1; FOLFOX: folinic acid, fluorouracil and oxaliplatin; IHC: immunohistochemistry; OS: overall survival.

involved in repair pathways might be useful in stratifying patients according to prognosis and likelihood of chemotherapy response. Table I summarizes the main results of translational studies investigating DNA repair-related biomarkers in terms of chemotherapy outcome in GC.

The nucleotide excision repair (NER) pathway. DNA repair mechanisms are involved in biological response to several drugs, especially platinum analogues. Platinum–DNA adducts are mainly repaired by the NER pathway, including the excision repair cross-complementing-1 (ERCC1) group, xeroderma pigmentosum group-D (XPD, also known as ERCC2) and X-ray repair cross-complementing group (XRCC). The ERCC1 enzyme plays a central role through removal of platinum–DNA adducts and repair of interstrand DNA cross-links. High levels of DNA repair proteins, such as breast cancer-1 (BRCA1) and ERCC1, were correlated with worse outcome of platinum-based treatments in a variety of malignancies including GC.

Many studies addressing the role of ERCC1 have been performed in a retrospective fashion with different cut-off levels. Consequently, results are often conflicting. It is unclear whether ERCC1 expression by immunohistochemistry (IHC) and mRNA levels by RT-PCR stratify patients into homogeneous groups; moreover, there is no proven correlation between these two methods and their sensitivity and specificity. IHC is readily-available and easier to standardize across laboratories; on the other hand, RT-PCR requires fresh tumour samples, but is a highly sensitive semiquantitative assay. Some older studies reported survival advantage in patients with low *ERCC1* mRNA levels treated with cisplatin and 5-fluorouracil (20). These results were later confirmed by RT-PCR studies showing that *ERCC1* mRNA was a negative predictor of response to Folinic Acid, 5-FU and Oxaliplatin (FOLFOX) treatment (21) and other regimens (22). Conversely, other analyses based on RT-PCR did not find any significant difference in survival nor in response to cisplatin-containing regimens (23); neither did IHC studies (24, 25).

The shorter survival in FOLFOX-treated patients with elevated ERCC1 protein (26) or overexpression of *ERCC1* mRNA (22) suggests that alternative regimens (irinotecan or taxane-based) could be a better option. However, due to conflicting results on ERCC1 as biomarker in GC, international consensus is needed to mandate a homogeneous ERCC1 assessment methodology, as are prospective trials sufficiently powered to detect an interaction between platinum chemotherapy and ERCC1 expression.

BRCA1. BRCA1 and BRCA2 are two frequently mutated genes in familiar breast and ovarian cancers. They are key components of the homologous recombination system, a machinery involved in the repair of cisplatin-induced double-strand breaks recognized in the S phase of the cell cycle. Although BRCA1 may mediate platinum resistance, high expression could be positively associated with docetaxel sensitivity (27). In a retrospective series of patients with advanced GC treated with second-line docetaxel, mortality was higher in patients with low BRCA1 levels by RT-PCR ($p=0.037$) (28). Moreover, the mutant TT homozygous polymorphism of BRCA1 was a positive predictor of progression-free ($p=0.05$) and overall survival ($p=0.03$) in a series of 207 patients with GC treated with cisplatin and a taxane (29).

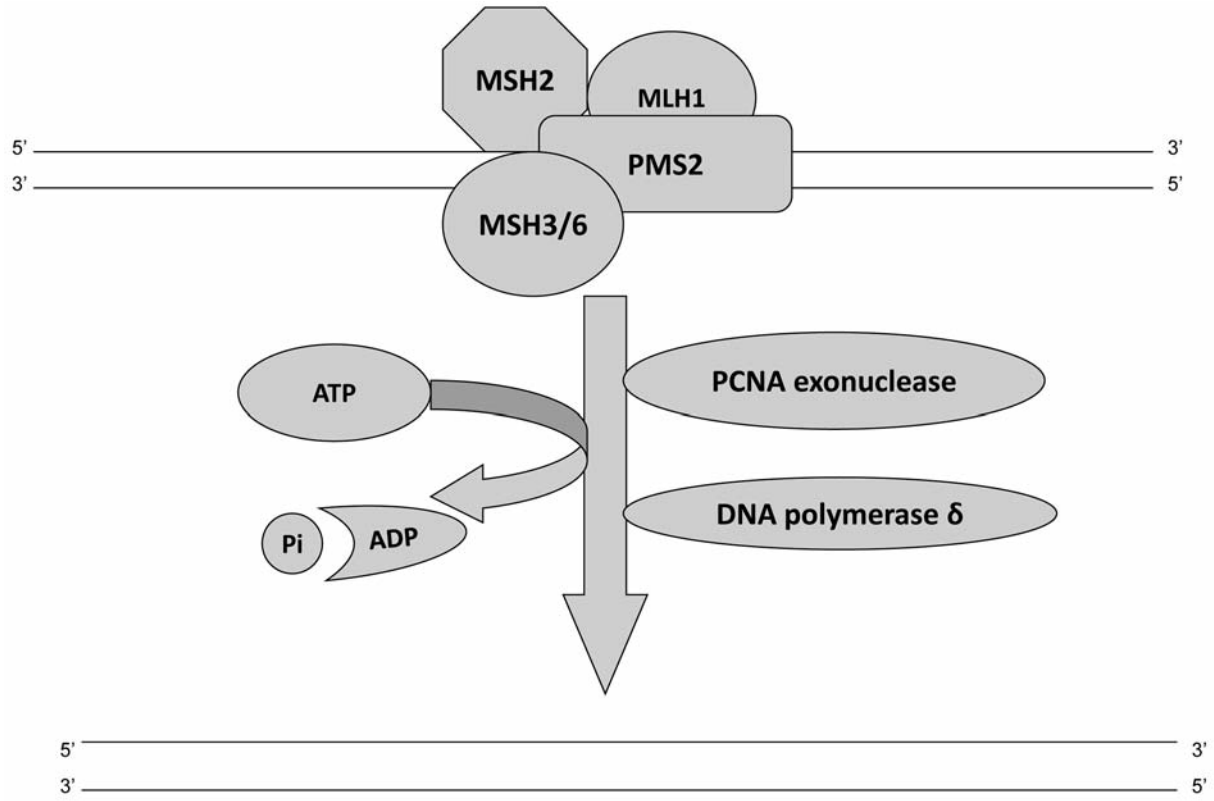

Figure 1. *DNA mismatch repair system pathways*.

Mismatch repair (MMR) genes. As highlighted in Figure 1, MMR plays a central role in post-replication DNA repair, mainly acting through the recognition of GpG interstrand adducts. Defective MMR genes lead to accumulation of spontaneous mutations through length variation of repeated oligonucleotide sequences, a condition named microsatellite instability (MSI), in fundamental genes such as Transforming growth factor beta receptor-2 (TGFβRII), Epidermal growth factor receptor (EGFR) and BCL2-associated X protein (BAX); thus the MMR system has a fundamental pathogenic role. Loss of MMR function can be detected through PCR analysis of selected microsatellite markers, or by IHC study of MutL Homolog 1 (MLH1) and MutS Homolog 2 (MSH2). The former is to be preferred because of increased sensitivity, while the latter does not take into account the mutational status of other MMR genes like MutS Homolog-3 (MSH3), MutS Homolog 6 (MSH6) or Post-meiotic Segregation Increased (PMS) (30).

The most extensively studied example of MMR defects is colorectal cancer, where MSI defines a subgroup of hereditary tumours including human non-poliposic colon cancer (HNPCC). Stomach is a preferential extracolonic cancer development site in patients with HNPCC, although MSI is found in 15-33% of sporadic primary GC (31).

Studies addressing the prognostic role of MMR in GC have involved a limited number of patients, obtaining conflicting results. Some studies demonstrated a survival advantage in patients carrying the MSI phenotype only for stage II disease (32). Others reported a better outcome in patients with multiple mutated microsatellite *loci* compared to patients with a single-mutated MSI marker (33), with a prevalence of older age, intestinal type, Borrmann's gross type II, distal location, lower rate of nodal metastases and lower pTNM stage (34, 35). However, another large study found that MSI tumours were associated with increased tumour size, and not with better outcome (31). Comparison with colorectal cancer, where MSI is a negative predictor of benefit to fluoropyrimidines, demanded the same evaluation for GC. A recent study did not detect any correlation of the MSI phenotype with response to 5-FU-based treatment (36). However, a larger study involving nearly 2,000 patients identified MMR dysfunction as a possible predictive biomarker for lack of benefit from adjuvant 5-FU chemotherapy after resection in stage II and III, but did not find any independent prognostic value for MSI in GC (37). Therefore, pre-treatment MSI evaluation in routine clinical practice for GC is considered premature, as the role of MSI as prognostic or predictive factor in GC has yet to be verified.

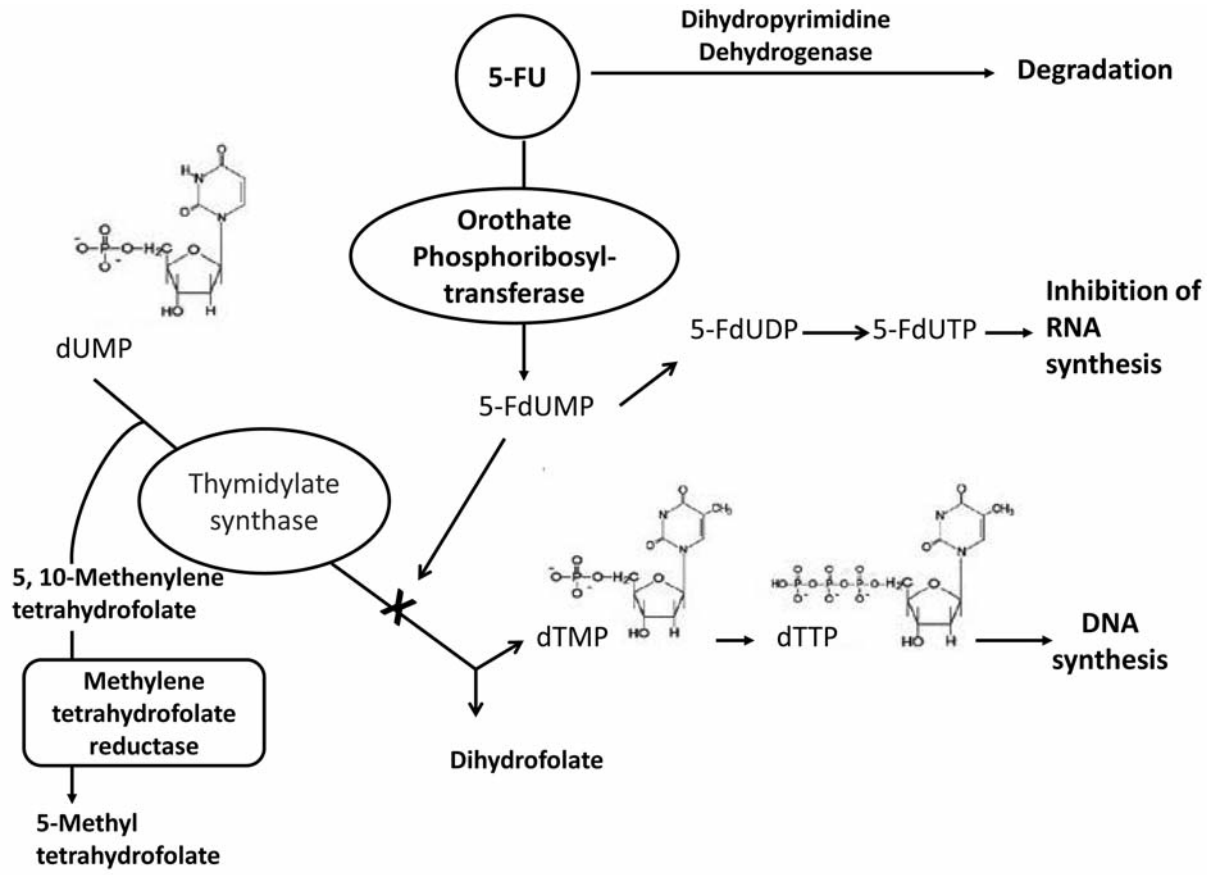

Figure 2. *Fluoropyrimidines methabolic pathways*.

Fluoropyrimidines Metabolism

5-FU is an S phase-specific agent which causes DNA double- and single-strand breaks and blocks RNA synthesis. As highlighted in Figure 2, thymidine phosphorylase (TYMP) is the enzyme responsible for conversion of 5-FU to fluorodeoxyuridine, which is then converted to the active metabolite fluorodeoxyuridine monophosphate (FdUMP). FdUMP has high affinity for thymidylate synthase (TYMS), the critical target for fluoropyrimidines. FdUMP forms a stable complex with the enzyme and 5,10-methylenetetrahydrofolate (CH2THF), thereby inhibiting DNA synthesis. Regulation of folate intracellular flow is mainly due to folate receptor methylenetetrahydrofolate reductase (MTHFR), which is strongly involved in fluoropyrimidine synthesis. 5-FU is also phosphorylated by orotate phosphoribosyl transferase, thereby inhibiting RNA synthesis. The rate-limiting enzyme in 5-FU catabolism is dihydropyrimidine dehydrogenase (DYPD), (38) which also converts the oral pro-drug capecitabine to 5-FU at the cellular level. TYMP activity in cancer cells has been correlated with intra-tumoural 5-FU concentration following the administration of capecitabine. There is much evidence in literature suggesting that alterations in pyrimidine metabolism affect response to fluoropyrimidines. According to their implication in metabolic pathways, a predictive role has been suspected for several gene products including TYMS, TYMP, MTHFR and DYPD.

TYMS is the most extensively studied enzyme, but its role as a predictive or prognostic biomarker in GC remains controversial. Many groups have recognized a negative predictive role for TYMS expression in response to fluoropyrimidines, both in the neoadjuvant setting (20, 39-41) and in advanced GC (42). Nevertheless, other studies have not identified any correlation between low TYMS expression and response to 5-FU in series of non-metastatic cases (24, 43-45). Several authors have underlined a possible prognostic role of TYMS, which may be involved in tumour progression rather than chemotherapy response (24, 39, 45, 46). Nevertheless, opposite results have been reported with regard to prognostic value of TYMS expression (20).

Table II. *Main results of translational studies investigating apoptosis-related biomarkers in terms of chemotherapy outcome in GC.*

Gastric cancer stage	No of patients	Biomarker	Result	First author (Reference)
Locally advanced	30	TP53	In patients treated with neoadjuvant cisplatin, epirubicin and 5-fluorouracil, TP53 expression is related to worse response (p=0.004)	Cascinu, 1998 (57)
Advanced	28	TP53 BCL-2	In patients treated with 5-fluorouracil, pirarubicin and cisplatin, TP53 and/or BCL-2 expression is not related to response but to worse OS (p=0.036)	Kikuyama, 2001 (48)
Advanced	23	BCL-2 BAX	BCL-2 expression is associated with worse survival (p=0.008) in BAX-positive tumours	Nakata, 1998 (60)
Advanced	23	TP53 BAX	TP53-positive/BAX-negative tumours are associated with no response to chemotherapy	Muguruma, 1998 (61)
Advanced	72	BAX	In patients treated with FOLFOX regimen, BAX expression is related to better OS in multivariate analysis (p=0.028)	Jeong, 2011 (25)
Advanced	23	BAX	In patients treated with COI regimen, BAX expression is related to better response (p=0.03), PFS (p=0.016) and OS (p=0.025)	Pietrantonio, 2012 (62)
Advanced	21	Survivin	In patients treated with cisplatin-based chemotherapy, survivin expression is related to worse OS (p<0.01)	Nakamura, 2004 (66)

BAX: BCL-2-associated X protein; BCL-2: B-cell lymphoma-2; TP53: tumor protein-53; FOLFOX: folinic acid, fluorouracil and oxaliplatin; COI: capecitabine, oxaliplatin and irinotecan.

Several authors have identified TYMP expression as a positive predictive marker for response to fluoropyrimidines. Patients treated with 5'-deoxy-5-fluorouridine (5'-DFUR), a drug converted into 5-FU by TYMP, were more likely to respond to therapy if high TYMP levels were present in stromal perivascular cells (47). Tumoural TYMP expression was itself a possible predictive factor in several studies with adjuvant fluoropyrimidines (48-50); however, some authors report no correlation with outcome (24, 43, 45). Other authors have shown that TYMP/DYPD ratio was a reliable predictor of response to 5'-DFUR (51, 45). In fact, DYPD expression has been correlated to poor response to fluoropyrimidines (24, 40), although response to neoadjuvant 5-FU-based treatments was related to high MTHFR and not to DYPD in one series (43). Thus, the most promising approach consists in evaluating a combination of variables, which might have a more reliable predictive value than a single biomarker (52).

Apoptosis Regulation

A defective intrinsic apoptotic pathway is thought to mediate resistance to conventional chemotherapy, particularly DNA-damaging agents. Apoptosis is regulated by a genetic program involving both effectors and repressors. The up-regulation of anti-apoptotic factors (such as BCL-2, BCL-XL and survivin) or the down-regulation of pro-apoptotic mediators (such as BAX) may confer resistance to chemotherapy and radiotherapy. Table II summarizes the main results of translational studies investigating apoptosis-related biomarkers in terms of chemotherapy outcome in GC.

Tumour protein 53 (TP53). TP53 is a tumour-suppressor gene whose inactivation is involved in carcinogenesis of several malignancies, including GC. TP53 is known to be a cell-cycle checkpoint protein playing a regulatory role in cell proliferation and apoptosis. IHC nuclear staining of TP53 is considered as a surrogate marker for accumulation of a mutant protein, which is resistant to degradation. In GC, expression of TP53 by IHC ranges from 13 to 54% and seems to be greater in intestinal-type compared to diffuse-type GC, and in proximal compared to distal lesions (53). Abnormal staining for TP53 has been associated with high proliferative activity and increased metastatic potential (54), and with aggressive behaviour due to poor differentiation, serosal invasion, and lymph node metastasis (55). Studies addressing TP53 overexpression in GC led to controversial results in terms of disease relapse and survival (55, 56). TP53 expression was associated with reduced response to neoadjuvant cisplatin-based chemotherapy in a small series of samples (57). The discrepancies can be attributed to variations of IHC cut-off points, but also to the heterogeneity of the techniques used. Furthermore, the sample size of many retrospective studies may have been inadequate to find statistically significant differences.

BAX, BCL-2 and survivin. BAX is a BCL-2 family member induced by functional TP53. It plays a central role in cell-cycle regulation, countering the apoptosis repressor activity of both BCL-2 and BCL-XL. Moreover, it is involved in chemotherapy-induced cell death, with particular regard to

platinum-related cytotoxicity. The prognostic role of BAX was mainly studied in series of patients with GC who underwent curative surgery. It was correlated to unfavourable pathological features such as diffuse-type, poor differentiation or lymph node metastases, leading to a poor clinical outcome in terms of disease relapse and death (58, 59). At present, few data have been published about the prognostic or predictive role of BAX in advanced gastro-oesophageal cancer treated with chemotherapy. Differently from previous small series (60, 61), a recent retrospective study in patients with metastatic GC treated with FOLFOX regimen finally documented a significant association between low BAX expression and poor overall survival in both univariate and multivariate analysis; nevertheless, BAX expression failed to show a predictive role in terms of response rate in patients with measurable disease (25). We have recently shown that BAX expression evaluated by IHC was associated with a higher likelihood of clinical benefit with a first-line triplet combination regimen of capecitabine, oxaliplatin and irinotecan, in terms of response rate, progression-free survival and overall survival (62).

Survivin plays a key role in apoptosis suppression by binding caspase-3 and caspase-7, hence guiding the G_2/M phase of the cell cycle. Several studies have demonstrated a correlation between survivin expression and worse prognosis (63, 64). Survivin positivity was associated with increased tumour size, depth of invasion, lymph node metastasis and tumour stage; in addition, evidence exists that survivin may stimulate angiogenesis in cancer tissues (64). However, some authors have found that nuclear expression of survivin may be a positive prognostic factor, while cytoplasmic positivity is not correlated with survival (65). Survivin has also been investigated as a predictive factor for chemotherapy responsiveness. A study of patients with advanced GC treated with cisplatin demonstrated a significantly shorter survival to be associated with high survivin expression (66). Pre-clinical studies have identified an increased apoptotic rate and chemosensitivity when survivin was down-regulated (67).

BCL-2 is a negative regulator of apoptotic pathways by inhibition of essential adaptors for activation and cleavage of caspases. BCL-2 expression was associated with better prognosis in several malignancies, although the exact biological role and clinical implications of BCL-2 in GC are still unclear. Several studies have reported an inverse correlation between BCL-2 expression and tissue invasion or lymph node metastasis; moreover, BCL-2-positivity is more common in well- and moderately-differentiated intestinal-type cancers, whereas the more aggressive diffuse-type or signet ring cell carcinomas are usually negative (68). Nevertheless, broader series failed to demonstrate a significant association between BCL-2 expression and survival (69).

Conclusion and Future Directions

Prognosis of GC is dependent on the pathological stage, but many tumours with similar histopathological features confer significantly different prognoses and treatment outcomes. Prognostic or predictive biomarkers could stratify patients into homogeneous subgroups, orientating clinical decision making and allowing personalization of treatment. An accurate definition of the risk of recurrence may be crucial for choosing the most adequate surgical approach and for deciding whether to use adjuvant therapy.

A paradigm shift from a disease-specific new drug development to a biomarker-oriented investigation is becoming a priority in oncology research. Several biomarkers with a potential key role in cancer biology have been identified for their prognostic or predictive value in GC, but their clinical use remains controversial. They have been studied with different techniques, yet the majority of them need to be independently validated in broader clinical settings. In fact, despite the fact that several biomarkers have been studied over the past decades, results have often been conflicting and several drawbacks have affected the reliability of conclusions. Most published studies have used retrospective analyses of a single marker in a small series of patients; this design is unlikely to precisely predict disease outcome. Hence, clinicians are currently unable to use these data in clinical practice. Moreover, in practice, the distinction between prognostic and predictive factors is not straightforward, and many factors are both. Large prospective randomized trials have been advocated to reliably determine the role of various putative molecular markers: the ideal evaluation of a biomarker value comes from a prospective randomized trial, allowing for assessment of the prognostic importance of the marker in the control arm, and the predictive effect in the comparison of the experimental and control arms. Unfortunately, biomarker trials for chemotherapy often do not have the same economic appeal as those for new target agents. Furthermore, consensus is needed on the standards for what determines the validity of a biomarker before any marker can be used in clinical trials.

Despite these difficulties, some biomarkers have shown promising results. The introduction of new therapeutic agents and the validation of prognostic or predictive markers, along with new screening tools, might enable oncologists to tailor patient-specific chemotherapy by maximizing drug efficacy and minimizing adverse effects. Therefore, since there are many promising biomarkers available for study, a combinatorial approach to molecular prognostics, similar to the clinical prognostic profiles established for many malignancies, may represent an essential tool for future patient management.

Conflicts of Interest

All Authors declare no conflict of interests.

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