Chapter 6

Clinical Implications of Molecular Heterogeneity of Gastric Cancer

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Additional information is available at the end of the chapter

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Abstract

Gastric cancer incidence has been steadily declining in countries with low frequencies of gastric carcinoma since early 1930s. In areas with higher incidences, the decline has been less obvious and slower. Nevertheless, gastric adenocarcinoma remains one of the most common causes of cancer-related death worldwide. The poor outcome has been attributed to late detection of the condition, particularly in Americas and Europe, aggressive pathogenesis and lack of symptoms during early stages of the tumor development. In addition, sporadic stomach cancer mostly affects elderly individuals. In the majority of countries with low incidence, the average age at the disease presentation is above 65. Therefore, gastric adenocarcinoma, among other diseases associated with old age, raises health concerns in countries with changing demographic age profiles that show a trend of an increase in the proportion of the population aged over 60. The low 5-year survival rate of patients underscores the critical need for the development of more accurate diagnostic tools and safe targeted chemotherapeutics. However, the heterogeneity of molecular changes represents one of the most pressing issues in the current research of gastric cancer, impeding the translation of genetic aberrations into novel applications for medical practice.

Keywords: antineoplastic agent, cancer, chemotherapy, clinical trials, gastric adenocarcinoma, gastroesophageal junction adenocarcinoma, molecular heterogeneity, monoclonal antibodies, small-molecule inhibitor, targeted therapy

1. Introduction

The incidence of gastric cancer (GC) has been declining globally in the last decades. This slow, yet steady decrease in incidence and mortality rates has been attributed to improved medical treatment of peptic ulcers and chronic gastritis, development of protocols for *Helicobacter pylori* eradication, lifestyle changes, and introduction of safer food preservation methods [1, 2]. However,

it is also important to note that the total incidence of most common gastric malignancy, adenocarcinoma, varies by geographic areas up to 20-fold between the highest and the lowest risk populations. The high risk areas are in certain Asian regions, such as Japan, China and Korea, followed by Eastern Europe and some countries in South America [3]. Low-risk populations are located in North America, India, the Philippines, most countries in Africa, some Western European countries and Australia [4]. Up to 10% of GCs arise as a consequence of inherited cancer predisposition syndromes, such as Li-Fraumeni syndrome, Lynch syndrome, Peutz-Jeghers syndrome, hereditary breast and ovarian cancer, MUTYH-associated adenomatous polyposis (MAP), familial adenomatous polyposis (FAP), juvenile polyposis syndrome and PTEN hamartoma tumor syndrome (Cowden syndrome) [5, 6]. Genetic counselling and mutation analyses, regular endoscopic surveillance and screening of the at-risk family members and risk-reduction surgery of stomach have greatly improved management of patients with hereditary mutations predisposing to the development of hereditary GC [5, 7]. However, approximately 90% of GCs are sporadic and typically occur in elderly population [6, 8]. Despite improvements in the diagnostic procedures, most cases of sporadic GCs are still detected at advanced stages due to the lack of specific symptoms associated with the early phases of tumor development. Consequently, high mortality rates attributable to advanced GC contribute significantly to the public health burden worldwide. The estimated overall 5-year relative survival rates of patients with advanced GC in developed countries are still low, around 30% [9]. An additional reason for concern is the demographic transition to the older population accounting for the significant proportion of population in developed countries [10]. This demographic shift will have an impact on health services, as the number of people over the age of 65, who comprise the highest risk group for the development of sporadic GC, has been steadily increasing in these countries. The challenge most countries are facing at the present time is how to improve the healthy life expectancy with regard to early detection of chronic and degenerative diseases, including cancers.

2. From basic research to clinical needs

Research efforts have identified several risk factors, including environmental factors as well as epigenetic and genetic aberrations, which could be implicated in the initiation and progression of gastric malignancies. Advances in high-throughput technologies and bioinformatic systematic analyses have been complementing our knowledge of an intricate network of genetic and epigenetic changes associated with stomach carcinogenesis. Unfortunately, only a few of common mutations could be associated with the development of sporadic gastric adenocarcinomas, which is the most common type of GC in the non-Asian world regions. In addition, breakthroughs in next-generation sequencing and SNP profiling microarrays have revealed another dimension, contributing to the heterogeneity of cancers. Genetic background, which affects the susceptibility for developing GC, could also be responsible for differences in responses to drugs and outcome measures evaluating survival, efficacy and safety of novel biological therapeutics in distinct populations.

Discovery-oriented research performed in different world populations revealed that molecular aberrations found in sporadic GCs do not correlate well with macroscopic and microscopic

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classifications that are currently used in clinical practice for diagnosis and for rough assessment of the postoperative therapeutic management protocols [11]. For example, pathohistological Lauren classification, which is the most widely used diagnostic feature in clinical setting in Western countries, recognizes two main subtypes, intestinal and diffuse types of GC. Intestinal type of gastric adenocarcinoma is associated with intestinal metaplasia and tubular structures, whereas diffuse-type carcinomas mostly consist of discohesive cells and/or signet ring cells. Two additional subtypes fall into this classification, if the tumors do not fit into two major subtypes clearly. Approximately 14% of tumors, exhibiting characteristics of intestinal and diffuse morphology, are classified as mixed type, whereas roughly 10% of gastric tumors, which display uncommon features, are allocated into indeterminate category [11–16]. It should also be noted that all adenocarcinomas show heterogeneity at the histological level. For example, even if tumors were histologically classified as intestinal or diffuse type, they are in fact often a mixture of several coexisting tissue types, including more or less well-developed tubular structures, poorly cohesive cells and signet ring cells, though one of these cell types usually predominates [17]. In the past, researchers have been focused on determining distinct gene aberrations that could have been associated with these subtypes in order to constitute reliable biomarker panels, which would correlate with histological subtypes and indicate the likely course of disease progression. However, accumulating molecular data on GC aberrations revealed immense intertumor and intratumor heterogeneity of GCs [9, 18–21].

In recent years, molecular classifications, based on the results from high-throughput technologies, revealed the existence of different molecular subtypes regardless of pathohistological subtypes [17, 22–24]. The advantage of these novel classifications is that distinct aberrant molecular changes that characterize different subtypes could be exploited to develop novel treatment approaches. For example, the EBV subtype, recognized in the TCGA study, is defined by frequent amplification of *JAK2*, *CD274* (*PD-L1*) and *PDCD1LG2* (*PD-L2*) together with DNA hypermethylation and *PIK3CA* mutations [22]. Thus, patients with aberrations in PD-1 signaling pathways could benefit from addition of pembrolizumab or other antibodies targeting PD-1 axis [25]. Frequent occurrence of characteristic CpG island methylator phenotypes (CIMP) in GCs, particularly in association with *H. pylori* or Epstein-Barr virus infection, could lead to introduction of epigenetic modulators into standard treatment regimens used against early and advanced forms of adenocarcinomas [22]. Deciphering molecular heterogeneity of malignant gastric tumors and subsequent translation of this information into precision medicine or eventually into personalized medicine is the subject of several ongoing collaborative projects, such as The Cancer Genome Atlas (TCGA) based at the National Cancer Institute, the Cancer Genome Project at the Wellcome Trust Sanger Institute, and the International Cancer Genome Consortium, based at Ontario Institute for Cancer Research [22, 26–28].

However, the novelties of molecular classifications brought additional obstacles in translational research. It has become evident that there is a gap between real clinical needs and current genetic research. The resources being put into high-throughput identification of genetic and epigenetic changes accelerated the understanding of the molecular mechanisms underlying human diseases; however, the progression of this knowledge to patient benefit is lagging behind. In particular, surgical resection of stomach is still the main curative approach in the treatment of gastric cancer [29]. Although different types of nonsurgical treatment modalities,

including chemotherapy, radiation therapy, chemoradiation, as well as targeted therapies, have been evaluated in clinical studies and have been subsequently integrated in clinical setting, these regimens have not been internationally standardized and remain in the form of guidelines and recommendations [30]. In recent years, several roadmaps and initiatives have been established, with the aim to advance the knowledge transfer, promote collaborations between different scientific disciplines and medical environment, and determine the main obstacles, which hinder the progression and implementation of effective health care solutions [31–33]. The main recognized barriers have been associated with (i) the explosion of molecular research conducted by highly specialized scientists, (ii) the fragmented fields of biomedical research, (iii) the dynamics of basic research with regard to promotion, obtaining funding and grants, which resulted in separation of basic and clinically relevant research, (iv) differences in education and training, (v) lack of communication between clinicians and researchers and (vi) the separation of methodologies and infrastructure available in clinical environment and specialized molecular research laboratories [32, 33]. In addition, complex regulatory issues, associated with research ethical procedures and approvals and clearances of innovative biomedical devices or approaches, have been recognized as limiting factors in translational research [34]. One of the most pressing medical research problems in heterogeneous diseases, such as GC, issuing from the accumulating research data, is the biological elucidation of molecular changes and how they affect processes and metabolic pathways in malignant cells. Although several molecular targets have been identified in complex diseases, only a few targeted therapies and other novel treatment approaches have been found to be effective in the management of malignant diseases. Another concern, which also has roots in underlying molecular changes driving the malignant phenotype, is the development of drug resistance, which results in therapeutic failure. Although multidisciplinary research efforts have identified main pathways as well as some specific genetic determinants implicated in this phenomenon, innate or acquired resistance of cancer cells remains a significant challenge of translational medicine [33, 34].

3. Targeted management of gastric cancer

Gastrointestinal malignancies are highly aggressive and currently used standard therapies showed only a modest effect on improving survival and preventing recurrence [35]. Targeted therapies, based on antibodies or small molecule compounds, targeting specific molecular aberrations associated with gastric tumors, could offer improved outcomes and potentially fewer adverse effects. In general, antibody-based therapies are aimed against specific targets on the cell surface, whereas the design of small molecules is focused on their capacity to penetrate the cell membranes and target molecules inside cells.

3.1. Monoclonal antibodies

A number of monoclonal antibodies targeting different proteins, including EGFR, PD-1 (CD279), VEGF growth factor family, MET, and IGF-1R, are currently being tested and evaluated in clinical trials (**Table 1**) [36–39].

Target	Anticancer agent	Approval status in EU or USA
EGFR	Cetuximab	Advanced colorectal cancers with wild-type *KRAS*, EGFR-expressing
		Squamous cell carcinoma of the head and neck
	Matuzumab	Discontinued, no benefits
	Nimotuzumab	High-grade glioma[b] (orphan status withdrawn in 2008)
		Pancreatic cancer[b]
	Panitumumab	Metastatic colorectal cancer with wild-type *KRAS*
CD3, EpCAM	Catumaxomab	Gastric cancer[b]
HER2	Ado-Trastuzumab emtansine (T-DM1)[a]	Advanced or metastatic breast cancer, HER2-positive
	Pertuzumab	Breast cancer, HER2-positive
	Trastuzumab	Breast cancer, HER2-positive
		Gastric cancer, HER2-positive
		Gastroesophageal junction adenocarcinoma, HER2-positive
IGF1R/IGF1/IGF2	Robatumumab	Terminated due to business reasons
HGF/MET	Margetuximab	Clinical trial (NCT02689284), recruiting participants, promising preliminary results
	Onartuzumab	Clinical trial (NCT01662869), MET-positive gastric cancer
	Rilotumumab	Gastric cancer (orphan status)[b], (HGF-positive)
PD-1	Atezolizumab	Locally advanced or metastatic urothelial carcinoma[c]
		Metastatic nonsmall cell lung cancer[c]
	Durvalumab	Bladder cancer (in review for approval)[c]
	Nivolumab	Nonsmall cell lung cancer
		Renal cell carcinoma
		Hodgkin disease
		Melanoma, BRAF V600 wild-type or BRAFV600 mutation-positive
		Recurrent or metastatic squamous cell carcinoma of the head and neck[c]
	Pembrolizumab	Unresectable or metastatic melanoma
		Metastatic squamous cell carcinoma of the head and neck[c]
		Metastatic nonsmall cell lung cancer
VEGFR/VEGF	Bevacizumab	Metastatic colorectal cancer
		Nonsquamous nonsmall cell lung cancer
		Glioblastoma[c]
		Metastatic renal cell carcinoma with interferon alfa[c]
		Cervical cancer
		Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer
		Metastatic breast cancer[b]
		Metastatic kidney cancer[b]

Target	Anticancer agent	Approval status in EU or USA
	Ramucirumab	Advanced gastric cancer
		Nonsmall cell lung cancer
		Metastatic colorectal cancer

[a]Antibody-drug conjugate (ADC) of stably linked trastuzumab and potent microtubule inhibitor emtansine.
[b]Only in Europe.
[c]Only in USA.

Table 1. Antineoplastic monoclonal antibodies, currently being evaluated in clinical trials for the treatment of gastric cancer.

The Phase III ToGA study (NCT01041404), which evaluated the addition of trastuzumab to chemotherapy for treatment of advanced gastric cancer and gastroesophageal junction (GEJ) cancer, was one of the first studies that clearly demonstrated the benefits of targeted therapy in a selected group of patients [40, 41]. Trastuzumab is a monoclonal antibody directed against HER2 (ERBB2, HER2/neu). Overexpression of HER2 was observed in approximately 10–20% of gastric and GEJ cancer patients in different populations [42]. In ToGA study, the patients, who were eligible for the treatment, were selected after evaluation of HER2 expression in tumor tissues using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). The median overall survival was significantly improved in patients who received trastuzumab and cisplatin-based chemotherapy in comparison with patients, who received only chemotherapy. In addition, further studies showed that the quality of life in HER2-positive patients, receiving trastuzumab in combination with chemotherapy, was improved and the toxicity burden was comparable to chemotherapy-alone arm [43]. It was also observed that the time to deterioration and quality-adjusted time without symptoms of disease or toxicity were prolonged in the trastuzumab-chemotherapy arm. Additional post hoc exploratory analyses investigated the correlations between HER2 overexpression and clinical and epidemiological features of patients [44]. Interestingly, HER2 overexpression levels were similar in patients from Europe and Asia, whereas they were lower in patients from Central/South America. Overexpression or amplification of HER2 was more common in intestinal GCs than diffuse or mixed types of GC, which was in concordance with other studies [45, 46]. In addition, GEJ tumors showed higher rate of HER2 overexpression or amplification than stomach tumors, indicating that GEJ adenocarcinoma differs in etiology and pathogenesis from distal stomach tumors. Evaluation of HER2 staining performance indicated great variability and the researchers concluded that ideally six to eight specimens should be collected in order to obtain accurate estimation of HER2-positivity. HER2 testing and trastuzumab treatment have been integrated in clinical settings in several developed countries.

Ramucirumab is a monoclonal antibody, targeting angiogenesis-related protein VEGFR2. It has been or is being evaluated in more than 20 clinical trials (NCT01246960, NCT01170663, NCT01983878, NCT02661971, NCT02314117, NCT00917384, NCT02934464 and so on) [47]. First published results demonstrated promising results for this biological drug, indicating that combination of ramucirumab with paclitaxel or platinum-containing or fluoropyrimidine-containing chemotherapy increases overall survival, progression-free survival as well

as quality of life when compared to chemotherapy-only arm [48–50]. In 2014, FDA approved the addition of ramucirumab to paclitaxel as the treatment for patients with advanced GC or GEJ adenocarcinoma as well as its use as monotherapy for patients who did not respond to the first-line therapy with platinum- or fluoropyrimidine-containing chemotherapy [51]. However, another Phase II study (NCT01246960), evaluating addition of ramucirumab to combined leucovorin, 5-fluorouracil and oxaliplatin chemotherapy (FOLFOX), did not show an improvement of outcome measures, progression-free survival and overall survival, in participants with gastric, esophageal and GEJ cancers [52].

Based on previous more or less promising results in the treatment of glioblastoma, colon, breast and lung cancers targeting angiogenesis with monoclonal antibody bevacizumab directed against VEGFA, Avagast clinical study was launched with the aim to evaluate the benefit of bevacizumab for GC patients [53–61]. Bevacizumab was added to the first-line chemotherapy, consisting of cisplatin and capecitabine or fluorouracil (FU) [54]. The subsequent unadjusted analyses demonstrated improved overall response rate and progression-free survival in the bevacizumab-cisplatin-FU arm. Unadjusted overall survival rate did not reach statistical significance. The toxicity of the tested treatment was comparable with the placebo-cisplatin-FU chemotherapy as well as with previous findings in patients with colon cancer receiving similar treatment. Subgroup analyses demonstrated differences in the efficacy of bevacizumab addition to chemotherapy between examined populations. Efficacy was increased in Pan-American and possibly European populations (the results were not clear), whereas Asian patients appeared to have no benefit from treatment with bevacizumab. The research group also observed regional differences in median overall survival and progression-free survival, which could be attributed to different factors, such as different distributions of tumor histological types in the examined populations, differences in administering subsequent therapies and so on [54]. In a similar study, Avatar, which included patients from the China, the researchers also confirmed that patients receiving bevacizumab plus capecitabine-cisplatin did not show an improvement in overall survival and progression-free survival, when compared to placebo arm [62]. Although the response rate was higher in bevacizumab arm, the difference was not significant. Inconsistencies in overall survival of patients receiving bevacizumab in addition to chemotherapy, prompted further research, focused on evaluating plasma and tumor biomarkers and clinical outcomes [63]. High plasma VEGFA levels were associated with better overall survival, progression-free survival and overall response rate in the group of patients with high plasma VEGFA levels, receiving bevacizumab-cisplatin-FU therapy, in comparison with patients with low plasma VEGFA levels. Interestingly, the beneficial effect of bevacizumab in these patients with regard to two measured indicators, overall survival and progression-free response, was more prominent in non-Asian patients, whereas in Asian patients, the effect was not significant. In addition, a weak association between low levels of tumor neuropilin-1 expression and better overall survival, progression-free survival and overall response rate was observed in a group of patients, receiving bevacizumab, compared to patients who had high expression of neuropilin-1. In conclusion, both VEGFA and neuropilin-1 are promising predictive biomarkers for selection of patients who would benefit from addition of bevacizumab to standard chemotherapy, although, as researchers noted, more thorough investigations to further characterize these markers are needed [63].

A preliminary investigation Phase 1b KEYNOTE-012 (NCT01848834) of selected patients with GC or esophageal cancer who were PD-1L positive showed that this population of patients could benefit from treatment with pembrolizumab, a monoclonal IgG4 antibody designed to block the interaction between PD-1 (CD279) and its ligands PD-L1 (CD274) and PD-L2 [64]. PD-1L is one of two known ligands for PD-1 receptor that is implicated in downregulation of the immune system by terminating T cell activation [65]. PD-1L has been relatively frequently (from 25 to 65%) found overexpressed in gastric epithelial cells as well as in tumor infiltrating cells [66–69]. Activation of PD-1 axis is associated with tumor-induced immune suppression [70]. PD-1 overexpression has been less well characterized. Investigation of the expression of several immune checkpoint molecules, including PD-1 in peripheral blood mononuclear cells of patients with gastric adenocarcinoma prior to and after the surgery, showed that expression of PD-1 was upregulated on $CD4^+$ and $CD8^+$ T cells after surgery, reaching peaks on the days 1 and 7 after surgery, respectively [71]. The frequencies of $PD\text{-}1^+CD4^+$ and $PD\text{-}1^+CD8^+$ cells reached preoperative levels after approximately 30 days after the surgery, indicating that surgery stress suppresses immune activity and could promote immune evasion of tumor and metastatic cells [71]. In particular, this mechanism could affect the ability of circulating tumor cells, which are shed from primary tumor mass, to evade immune system and establish secondary tumor niches. Another study also confirmed significantly higher expression of PD-1 on T cells obtained from blood and tumor tissues in patients with GC, when compared to normal gastric tissues from controls [72]. In KEYNOTE-012 study, the overall response rate to treatment with pembrolizumab was 32% in Asian patients and 30% in non-Asian patients. The researchers also observed that significant associations existed between progression-free survival, overall response rate and PD-1L expression. Further analyses showed that overall response was 22% for all enrolled patients, although all responses were partial responses. It should be noted that this study was preliminary, the number of tested patients was small and the majority of patients had prior to enrolment in this study received two or more systemic or adjuvant therapies. The researchers also observed that although no treatment-related deaths occurred, four patients had to terminate the treatment due to immune-mediated toxic effects [25]. Further studies are currently being carried out in order to assess the safety, tolerability and antitumor activity of pembrolizumab in patients with GC (NCT02335411, NCT02370498, NCT02494583, and NCT02443324). In addition, the downregulation of activated T cells immediately after surgery through PD-1 signaling pathway, as demonstrated in one study [71], could be further explored to assess the benefit of administering PD-1 blocking antibodies prior to or immediately after surgery.

Rilomet-1 (NCT01697072) study attempted to evaluate the addition of rilotumumab to standard cisplatin and capecitabine chemotherapy as a first-line therapy for patients with advanced MET-positive GC or GEJ adenocarcinoma [73, 74]. Rilotumumab is a human monoclonal antibody against c-MET (HGFR) factor. HGF is the only known ligand for HGFR or c-MET, a tyrosine kinase receptor, which has been found to be frequently overexpressed in tumor gastric tissues [75–80]. Although the first results were promising, showing trends toward improved survival of patients, all trials with this compound were later terminated, due to unexpected deaths of patients in the rilotumumab-chemotherapy arm compared with the chemotherapy-alone arm in one of the trials [81].

3.2. Small-molecule compounds

In 2010, FDA approved lapatinib, a small-molecule tyrosine kinase inhibitor of EGFR and HER2, for the treatment of HER2-positive breast cancer. Studies on gastric cell lines confirmed its antiproliferative activity [82]. Several clinical trials attempted to evaluate its effectivity and toxicity in patients with HER2-positive GC (NCT02015169, NCT00313599, NCT00447226, NCT00103324, NCT00680901, NCT00486954, NCT01123473 and so on). Currently, the results are still inconclusive, due to termination of some of these studies or negative results regarding the lapatinib efficacy. For example, in Phase II study (NCT01145404), which recruited HER2-positive patients with advanced GC, who have previously failed first-line platinum-based therapy, lapatinib addition to capecitabine or lapatinib monotherapy did not show improvements in overall survival and response rates and the study was prematurely terminated [83]. Nevertheless, interesting conclusions could be drawn from the observations from two larger studies involving lapatinib testing. A multinational randomized clinical trial, TRIAL-013/LOGiC (NCT00680901), investigated the benefit of the lapatinib addition to capecitabine-oxaliplatin (CapeOx) chemotherapy, administered to HER2-positive patients with locally advanced, unresectable, or metastatic gastric, esophageal, or GEJ cancer [45]. A total of 545 eligible patients were evaluated, and lapatinib efficacy analyses were performed in a group consisting of 454 patients with FISH confirmed amplification of HER2 (primary efficacy population, PEP). The underlying reason for this stratification was based on the results of previous studies performed on breast cancer patients, which showed that lapatinib administration benefits only a selected population of patients with HER2 amplification, regardless of the status of HER2 expression, determined with IHC [84]. Although the lapatinib addition to CapeOX did not improve overall survival in PEP and neither in the group of total eligible patients, there was significant improvement of progression-free survival in PEP. Additional analyses revealed that lapatinib was more effective in Asian patients and younger patients. In addition, lapatinib was less effective in patients, who had undergone gastrectomy with pylorus removed, than in patients with intact pylorus [45]. Based on these results, the authors did not recommend the use of lapatinib in combination with CapeOx in patients with HER2-positive GC [45]. In a TyTAN Phase III (NCT00486954) clinical trial, which included Asian patients, lapatinib addition to paclitaxel chemotherapy also did not significantly improve median overall survival and progression-free survival [85]. Lapatinib benefit was observed a small group of patients, whose gastric tumors were both FISH positive and had a score of 3+ in IHC evaluation. In addition, population stratification analyses showed that Chinese patients in the lapatinib arm had significantly improved overall survival and progression-free survival. Preliminary pharmacokinetic analyses performed as a part of trial revealed that lapatinib or lapatinib-paclitaxel administration could result in different plasma concentrations of the drugs. Furthermore, both $AUC_{0\text{-}24}$ (area under the concentration-time curve from time 0 to 24 h) and maximum plasma concentration of lapatinib were lower in patients with pylorus removed than in patients with intact pylorus [85].

The underlying causes of clinical outcomes associated with lapatinib administration and HER2 gene amplification levels were further thoroughly investigated in TRIAL-013/LOGiC cohort of patients [86]. Another group of upper gastrointestinal cancers, consisting of 419

(86%) gastric, 43 (8.8%) GEJ, and 26 (5.3%) esophageal cancers, obtained from commercial providers, was subsequently included for HER2 testing and analyses. This group was used to evaluate the concordance between different HER2 assay methods, which were performed in two central laboratories and local laboratory. The researchers observed high agreement rates between two different FISH methods, FDA-approved Dako HER2 IQFISH pharmDx FISH assay and PathVysion HER2 FISH assay (Abbott Molecular, Inc.), for detecting HER2 amplification. The concordance rate was also high (95%) between two central laboratories when evaluating results of FISH assays, whereas the concordance between local and central laboratories was 87%. Expression of HER2 was tested using the FDA-approved IHC test HercepTest (Dako Biotechnology). Comparison of local laboratory and central laboratory HER2 testing using IHC assay for the assessment of HER2 status in patients assigned to TRIO-013/LOGiC trial showed that the concordance rate was less than 50%. Comparison of agreement between IHC and FISH assays in central laboratories showed 88% overall agreement for cases from the commercially obtained upper gastrointestinal carcinomas and 91% for the TRIO-013/LOGiC cohort. Additional analyses confirmed the findings of Hecht and colleagues [45] that progression-free survival as well as overall survival was significantly higher in selected groups of patients, such as Asian patients and younger patients [45, 86]. These findings correlated well with the fact that these patients had higher levels of HER2 gene amplification. Interestingly, other studies also reported similar outcomes in GC patients with high HER2 amplification status when treated with monoclonal antibody trastuzumab [87, 88]. These findings pointed out clinically important aspect, which could underlie the discrepancy between studies and clinical trials, evaluating the benefit of anti-HER2 targeted chemotherapies. First, HER2 expression patterns differ between GC and breast cancer and furthermore, in GC the expression patterns are frequently heterogeneous [44, 46, 86, 88]. The optimal cutoff for selecting patients with GC who would benefit from addition of lapatinib to chemotherapy should be evaluated in further studies; however, at present, the results indicated that the cutoff value, based on FISH assays, could be the ratios 5.01–10.0 and >10.0 [86]. Second, it was also recognized that other alterations could affect the treatment with lapatinib. For example, it was established that in trastuzumab-resistant breast and esophagogastric cancers, MET amplification could contribute to intrinsic or treatment-acquired resistance to trastuzumab [89, 90]. Studies of breast and lung cancers have indicated that overexpression of other tyrosine kinases, including IGF-1R, other members of HER family, and EphA2, could lead to development of resistance mechanisms against anti-HER2 drugs, by bypassing anti-HER2 inhibition of MAPK and PI3K/Akt signaling pathways [91, 92]. Therefore, additional studies, focusing on molecular biomarkers for selection of eligible patients for anti-HER2 therapy, could improve the efficacy and safety of small molecular HER2 inhibitors as well as the safety of anti-HER2 antibodies.

Several other small molecule inhibitors, which have been approved for use in treatment of other cancers, are being tested in clinical studies. For example, sunitinib, which inhibits cellular signaling by targeting PDGFRs and VEGFRs, has been evaluated as safe for treatment of GC patients in a few Phase I studies; however, Phase II studies have not confirmed its efficacy and benefit [93–96]. The safety and benefit of apatinib, which selectively inhibits VEGFR2, have been shown in Phase II and Phase III clinical trials [97, 98]. However, recent reports from other studies have raised concerns regarding the toxicity of apatinib, since it has shown toxicity in previous studies on patients with metastatic triple-negative breast cancer [99].

4. Conclusion

In recent years, only two targeted therapeutics, trastuzumab and ramucirumab, have been approved in Western countries for treatment of advanced GC, which is less than the number of approved biological drugs for use in other common cancers. Several reasons could be responsible for that. First, although the explosion of knowledge on molecular mechanisms involved in human diseases has led to novel perspectives in medical treatment and diagnostic procedures, it appears that the enormous amount of molecular and biological information and the complexity of bioinformatic approaches, used to decipher the experimental data, in reality impede the transition from basic research to clinical applications. Second, clinical trials as well as basic research, utilizing novel high-throughput techniques, revealed great heterogeneity among populations. The consequences of interracial differences are particularly evident in the field of developing novel small-molecule drugs and antibodies. Genetic background in populations appears to account for unequal effectiveness and different safety profiles of targeted therapies in different population [100]. In addition, intratumor heterogeneity found within individuals further complicates the development of effective drugs. There is common consensus that novel molecular determinants should be investigated in order to establish genetic profiles, which would enable the identification of the patient subpopulations, in which the treatment with targeted anti-cancer agents would be most effective and beneficial. The first milestone in this process involves determination of different genetic landscapes of GCs across the world, followed by tight collaborations between researchers, healthcare practitioners and pharmaceutical companies. In addition, bioinformatic exploitation of biomedical data collected in databases and utilization and aggregation of already available research data from clinical studies and basic research could provide additional opportunities to identify disease-specific genetic profiles and establish suitable prognosis prediction models, which could guide personalized treatment management.

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