Her-2 in Gastrointestinal Tumours

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Gastrointestinal (GI) tumors account for a quarter of all the cancer burden and a third of the global cancer-related mortality. Among them, some cancers retain a dismal prognosis; therefore, newer and innovative therapies are urgently needed in priority disease areas of high-unmet medical need. In this context, HER2 could be a relevant prognostic and predictive biomarker acting as a target for specific drugs. However, if the role of HER2 has been object of investigation for several years in gastric cancer, it is not well established in other GI malignancies. The aim of this narrative review was to portray the current landscape of the potential role of HER2 as a predictive biomarker for GI tumors beyond gastric cancer. In colon cancer, the benefit from anti-HER2 therapies is less clear than in gastric neoplasms for the lack of controlled studies. Pancreatic, biliary tract adenocarcinomas and hepatocarcinoma may derive a less clear clinical benefit by using anti-HER2 agents in HER2 positive tumors. Overall, the results are promising and seem to suggest that the integration of multiple modalities of therapies can optimize the cancer care. However, further prospective trials are needed to validate the use of personalized targeted therapies in this field.

Keywords: biliary cancer ; colorectal cancer ; cholangiocarcinoma ; prognostic factor ; predictive ; GIST ; precision medicine ; target therapy ; metastatic cancer

1. Introduction

Tumors arising from the gastrointestinal (GI) tract account for a quarter of all the cancer burden and a third of the global cancer- related mortality [1][2]. In 2018, an estimated 4.8 million new cases and 3.4 million related deaths occurred. The Surveillance, Epidemiology, and End Results population-based (SEER) data estimated that 1- and 3-year cancer specific survival rates for GI tumors are approximately 29% and 6.2% in patients <60 years, and 22.8% and 4.8% in patients ≥60 years old, respectively [3]. However, some GI tumors still retain a dismal prognosis: the 5-year overall survival (OS) rate for advanced gastric cancer is still below 30% and less than 3% for patients with metastatic pancreatic cancer [4][5]. Given the poor survival rates, newer and innovative therapies are urgently needed in priority disease areas of high-unmet medical need.

In the last decade, significant advances have taken place in the diagnosis, treatment, and prognosis of GI tumors, and the progresses in molecular biology have resulted in the introduction of target therapies, positioned as cornerstones of treatment, thus transforming the characterization of tumors and the consideration of therapeutic combinations [6][7][8].

Gastric and colon cancers spearhead the incidence and mortality of GI cancers, and account for the most data regarding the benefits reached with the incorporation of molecular diagnosis and target therapy in recent years [9][10]. One of the most intensively studied pathways is RAS-RAF- mitogen-activated protein kinase (MAPK), linked to the epidermal growth factor receptor (EGFR) signaling. There are several other transmembrane proteins functioning as receptors that might play a significant role in the GI tumorigenesis, including the human epidermal growth factor receptor 2 (HER2). A growing number of studies consolidated HER2 as a relevant driver of cancerogenesis with a reproducible value as a prognostic and predictive biomarker in upper GI cancers, linking it to a more aggressive biological behavior, actively involved in tumor progression, serosa involvement, local and distant metastases, higher disease stage, and higher frequency of recurrence.

In gastric and esophago-gastric junctional adenocarcinoma (EGJ), HER2 is a known oncogenic driver, with important implications for treatment. Overexpression or amplification, determined by immunohistochemistry (IHC), occurs in a range between 9% and 27% of all the tumors [11]. The relevance of anti-HER2 drugs in GI cancers was established with Trastuzumab in the ToGA trial for patients with advanced and metastatic EGJ and gastric adenocarcinomas. In the HER2 positive tumours, the addition of trastuzumab was associated with a median OS improvement of 2.7 months if compared to chemotherapy alone, with a predictable safety profile. These results established Trastuzumab as the standard of care in the first-line treatment for HER2 positive gastric cancer in combination with platinum-based chemotherapy [12].

Moving from its evidence in gastric cancer treatment, the evaluation of HER2 status is becoming important also in other GI tumor types. Colorectal cancer is one of the most investigated in this field, reporting the strongest evidences existing in the literature beyond gastric cancer regarding the role of HER2 as predictive biomarker [13]. However, in colon cancer the benefit from anti-HER2 therapies is less clear than in gastric neoplasms, for the lack of controlled studies. In fact, although the breakthrough for target therapies came after the discovery of anti-EGFR treatments for RAS-RAF wild type tumors, anti-HER2 therapies have not been found to have the same impact on response or survival in colorectal cancer if compared to the gastric one [14][15].

The use of anti-HER2 in other GI malignancies and non-adenocarcinoma histology variants are recent fields of investigation. Pancreatic, biliary tract adenocarcinomas, and hepatocarcinoma may derive a less clear clinical benefit by using anti-HER2 agents in HER2 positive tumors [8][14][15].

2. HER2 pathway and Its Alterations in GI Tumors

The first molecular pathway studied in GI tumors was the EGFR family pathway, which includes EGFR/HER1, HER2/neu, HER3, and HER4 receptors. Each receptor consists of an extracellular ligand-binding domain, an intracellular domain with tyrosine kinases activity, and a short, lipophilic, transmembrane component. The selective binding of ligands to the receptors leads to homo- or hetero-dimerization with other members of the EGFR family, the phosphorylation of intracellular domain, and the activation of downstream pathways including the RAS/RAF/MAPK and phosphatidylinositol-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways. Stimulation of these pathways influences many aspects of tumor cell biology, such as proliferation, differentiation, migration, and apoptosis [16].

Among these receptors, HER2 plays a key role in GI tumors. HER2 alterations were historically investigated in breast cancer [17]. However, over the last decades the research has focused also on the role of HER2 in GI tumors. *HER2/neu* gene, located on chromosome 17q21, encodes the HER2 protein; when the oncogene is amplified, it can lead to HER2 receptor overexpression, resulting in a prolongation of trasductional signal with uncontrolled cell growth and tumorigenesis. To date, the specific ligand of this receptor has not been identified yet and it is considered a ligand-independent orphan receptor. Additionally, HER2 mostly acts as the suitable partner for the other EGFR receptors to create heterodimers, especially HER3.

The other most frequent alterations of HER2 pathway beyond amplifications are somatic mutations. These are variable according to the cancer type and can lead to pathological uncontrolled signal transduction [18].

An interesting field of research in this regard has focused on the role of HER2 as mechanism of acquired resistance to anti-EGFR agents. In particular, in colorectal cancer the presence of HER2 amplification or overexpression could lead to resistance to those drugs in patients with RAS-RAF wild type tumors [13]. Likewise, the presence of alterations in other EGFRs as well as the loss of HER2 expression after treatment with anti-HER2 drugs could be responsible for the primary and/or acquired resistance to anti HER2 agents, respectively [19][20][21].

3. Role of HER2 across Gastrointestinal Cancer Types

3.1. Colorectal Cancer

Colorectal cancer (CRC) has benefited from anti-HER2 targeted therapy [22][23]. HER2 overexpression in CRC is an emerging biomarker and accounts for around 5% of all cases [24][25]. Patients with HER2-positive CRC have been enrolled in several early phase I-II trials in order to investigate various combinations encompassing HER2 targeted drugs. Previously, a phase II trial (NCT00003995) tested the addition of trastuzumab to irinotecan in the first and second lines for advanced CRC [26]. HER2 status was assessed by IHC and verified by fluorescent in situ hybridization (FISH). Despite the discordant findings between these techniques, patients harboring HER2 amplification had partial response to this combination. Unfortunately, the trial was closed earlier because of poor accrual [26]. Similarly, another phase II trial (NCT00006015) that combined trastuzumab to FOLFOX regimen as a second line treatment in the metastatic disease was also terminated because of the lack of sufficient accrual [27]. Trastuzumab was also combined to a farnesyl protein transferase inhibitor (tipifarnib) in a phase I trial in molecularly unselected patients; it proved to have an acceptable safety profile (NCT00005842). However, this new agent failed to show improved survival for this indication in a phase III trial [28]. Since then, most clinical studies showed some signs of early efficacy but without further development [29][30]. Later, the combination of pertuzumab, the EGFR inhibitor cetuximab, and irinotecan has been evaluated in the second line by a phase I trial (NCT00551421) in a molecularly unselected group of patients, refractory to first-line chemotherapy plus cetuximab [31]. The trial terminated early due to the safety issues of the combination. The reported objective response rate was 14% [31]. Recently, the phase II HERACLES-A trial evaluated the objective response rate of dual trastuzumab and

lapatinib in metastatic CRC patients with HER2 overexpression and amplification and *KRAS* exon 2 wildtype [13][31]. At a median follow-up of 94 weeks, the combination resulted in 8/27 objective responses (30%, 95% confidence interval (CI): 14–50%) with one complete response (3%). The reported median progression-free survival (PFS) was 4.7 months (95% CI: 3.7–6.1), and the median OS was 10.0 months (95% CI: 7.9–15.8). Interestingly, intracranial progression was reported in 19% of the patients [32]. Grade 3 adverse events were reported in 22% of the patients. The second cohort (NCT03225937) of this trial evaluated the combination of pertuzumab and T-DM1, reporting an objective response of 10% (95% CI: 0–28); the proportion of patients with stable disease was 70% (95% CI: 50–85) [33]. However, this study did not meet its primary endpoint.

The efficacy of trastuzumab combined with tucatinib was explored in CRC patients with HER2 overexpression or amplification in the phase II open-label MOUNTAINEER trial in the second line setting [34]. A CLIA-certified HER2 IHC or next generation sequencing (NGS) test or an FDA-approved FISH test confirmed molecular status. Trastuzumab and tucatinib produced an overall response rate of 55% (12/22). After a median follow-up of 10.6 months, median PFS was 6.2 months (95% CI, 3.5-not reached (NR)), and median OS was 17.3 months (95% CI: 12.3-NR). The planned primary completion date of the trial will be in August 2021 [34]. Additionally, the phase II MyPathway basket trial has assessed the combination of trastuzumab and pertuzumab in 57 patients with HER2-amplified metastatic CRC [35]. Objective responses were observed in 32% of the patients (95% CI: 20–45); one patient had a complete response (2%). More recently, the TAPUR phase II study that enrolled 28 HER2-amplified CRC patients and treated with the pertuzumab/trastuzumab combination showed objective responses in 14% of the patients (14% (95% CI: 4–33) [36].

The ADC of trastuzumab was investigated in the phase II DESTINY-CRC01 trial that evaluated the efficacy of trastuzumab deruxtecan, focusing only on HER2 expressing CRC [37]. The confirmed objective response rate was 45.3% (95% CI: 19.8–70.1%), with a disease control rate of 83.0% and a median PFS of 6.9 months (95% CI: 4.1 months-NR). The authors emphasized recognizing and managing treatment-related interstitial lung disease, which occurred in 6.4% of the patients [37].

In conclusion, targeting HER2 amplified/overexpressed CRC is still under investigation and the current data are not mature yet to provide actionable findings for this group of tumors. There are currently more than 40 recorded clinical studies ongoing trials in this field [38]. This may potentially provide promising findings in the future for improving outcomes.

3.2. Small Bowel Cancers

Small bowel cancer is a rare subset of GI tumor (3% of all), whose genome profile is still under debate. Up to date, in fact, it is not very clear if these tumors might be more similar to the stomach, duodenum, or colon ones and, therefore, the systemic treatments in case of metastatic disease is mainly based on the chemotherapy schedules generally used in other GI malignancies (e.g., FOLFOX schedule) [2]. Therefore, there is a lack of target treatment for tumors, which arise from the small bowel. However, the small bowel cancers show deeply differences from CRC, with a poor prognosis (poorer than CRC), mostly due to a late diagnosis. Additionally, the knowledge available today seems to report a genetic profile more similar to the stomach cancer, but with some peculiarities. Schrock et al. analyzed 7559 samples from patients affected by gastric (*n*: 889), CRC (*n*: 6353) and small bowel cancer (*n*: 317) with the aim to compare the genomic profile of those tumors [39]. The genomic alterations in small bowel tumors were different from either CRC or gastric ones, confirming that those tumors represent a distinct entity. Additionally, they revealed to have HER2 mutations in 8.2% (versus 9.5% of gastric cancer and 5.1% of CRC) of samples, HER2 amplifications in 2.2% and both co-occurring alterations in three cases. The most important activating mutations were S310F/Y, V777L, V842I, D769Y and L755S. These alterations could represent possible targets for personalized treatment also in this group of tumors. However, further investigations are needed in order to evaluate the role of HER2 in small bowel carcinomas and to eventually design prospective randomized trials with target therapies in this field.

3.3. Gastrointestinal Stromal Tumors (GIST)

Several small series in Europe and USA found no GIST patient to be positive for HER2. Yan et al. examined 37,992 patients with diverse cancer types, including 143 GIST. Nevertheless, no GIST expressed a positive HER2 status [40]. Likewise, another trial including 94 GIST failed to show gene amplification for HER2 [41]. However, a small Egyptian study including 32 patients showed a 43.7% positivity in HER2 status [42]. Additionally, it reported that high-risk grade, tumor size, mitotic count, and increased risk of relapse were significantly correlated with HER2 positivity. Interestingly, a large study from China [43] involving 453 GIST patients showed a positive HER2 status in 52.3% of patients, even if the author used a non-conventional scoring system for the HER2 assessment.

Therefore, the role of HER2 in GIST is not still defined. However, further investigations also exploring the heterogeneity of HER2 expression according to ethnicity could be of interest.

3.4. Biliary Tract Cancer and Pancreatic Cancer

3.4.1. Biliary Tract Tumors

Cancers of the biliary tract includes different kind of tumors, which are intrahepatic and extrahepatic cholangiocarcinoma and gallbladder carcinoma. The highest incidence rates are reported in India, Pakistan, Korea, Japan, and some South American countries [44]. Surgery is considered the only curative approach; however, only few patients have an early stage amenable to surgical resection at diagnosis. Therefore, the majority of patients are diagnosed with a locally advanced disease; those patients show high recurrence rates even after adjuvant chemotherapy [45].

Regarding the molecular profile, the knowledge about carcinogenesis and genetic alterations in the biliary tract cancers is still incomplete. However, some reports in the literature have showed an HER2 overexpression in 10–82% biliary tumors [46]. Additionally, a metanalysis showed a higher HER2 overexpression in extrahepatic than intrahepatic cholangiocarcinoma (19% versus 4.8%). Among patients with HER2 overexpression, almost 60% of patients has HER2 amplification too [47]. Another case series showed an HER2 positivity in 16.6% of gallbladder cancer [48].

The role of HER2 as predictive or prognostic biomarker is still unclear in the field of biliary tract cancers. In this regard, Vivaldi et al. did one of the largest retrospective mono-institutional analysis of 100 patients with biliary tract tumors after curative surgery [49]. HER2 positivity was found in 11% of patients and was associated with a poorer disease-free survival (DFS): 10.6 versus 20.9 months in HER2 positive and HER2 negative patients, respectively. However, the HER2 status alone did not affect the OS. Another Japanese analysis evaluated the HER2 status in samples from 454 patients with biliary tract cancers who had undergone to curative surgery (intrahepatic cholangiocarcinoma: 110 patients, perihilar extrahepatic cholangiocarcinoma: 67, distal extrahepatic cholangiocarcinoma: 19, gallbladder carcinomas: 80, ampullary carcinomas: 79) [50]. HER2 positivity was seen in 14.5% of tumors (intrahepatic cholangiocarcinoma: 3.7%, perihilar extrahepatic cholangiocarcinoma: 3%, distal extrahepatic cholangiocarcinoma: 18.5%, gallbladder carcinomas: 31.3%, ampullary carcinomas: 16.4%) [50]. Unlike the work by Vivaldi et al. [49], in this analysis HER2 positive tumors were mainly differentiated with low rate of invasion. Therefore, the prognostic role of HER2 is still unclear.

Regarding the therapeutic application, up to date there are no randomized controlled trials in the field of biliary tract cancers showing efficacy of anti-HER2 agents. In fact, all the evidence about their activity in those tumors are retrospective or at an early stage of development, such as preclinical (in vitro and in vivo models) or from phase I trials [51]. In particular, in a retrospective series from a single institution, 14 patients with metastatic HER2 positive biliary tract cancers (9 gallbladder cancer patients and 5 cholangiocarcinoma patients) had received trastuzumab, lapatinib, and pertuzumab, alone or in association with chemotherapy [52]. In this experience, the authors recorded a complete response in one patient with gallbladder cancer, whereas 4 patients had a partial response by RECIST. The median duration of response was 40 weeks. No response was seen in patients affected by HER2 positive cholangiocarcinoma, even if they had higher proportion of HER2 overexpression or mutation. However, these results should be considered with caution due to the limitations of the study, mainly related to the heterogeneity of treatment and the retrospective design. Another case report describes a good response by using trastuzumab in combination with Paclitaxel in the second line treatment of a patients affected by HER2 positive metastatic gallbladder cancer. Then, lapatinib plus FOLFOX was evaluated in a phase I trial, regardless of HER2 status, showing partial responses in 2/34 patients [53].

Among phase II trials, the California consortium and the MyPathway trial are the best match for anti-HER2 treatments in this field [54][55]. In the first one, 19 patients with advanced biliary tract tumors were treated with lapatinib. However, no objective responses were seen in those patients and only five patients had a stable disease as best response at the radiological assessment [54]. The MyPathway trial is an open label basket trial aiming to find the genomic peculiarities of each kind of tumors in order to develop a personalized target therapy for each alteration. It included 11 patients with HER2 positive biliary tract tumors (eight patients had HER2 amplifications and three had somatic mutations), showing good responses after treatment with the target anti-HER2 agents trastuzumab and pertuzumab (four patients had a partial response and five patients a stable disease as best response) [55]. Then, another basket trial (SUMMIT) evaluated the use of neratinib in patients with HER2 positive solid tumors, including nine patients with HER2 positive biliary tract tumors, who had a 22% overall response rate (ORR) [56].

In conclusion, the evidence regarding a potential role of HER2 in the field of biliary tract cancers is immature at the time of writing. Therefore, further phase III trials are needed in order to consider HER2 as a potential target for effective target treatments in this field.

3.4.2. Pancreatic Cancer

The prevalence and diagnostic criteria for HER2 status in pancreatic cancer remain unclear as well as its role as predictive or prognostic biomarker. In general, few experiences have reported an HER2 positivity in 24–26% of pancreatic adenocarcinomas [57]. Additionally, the data available in the literature showed no correlation between the HER2 status and the outcome in pancreatic cancer patients [58].

Regarding the therapeutic implications of HER2, preclinical studies have evaluated the role of trastuzumab in human pancreatic cancer cell lines both in vitro and in vivo [59]. Cells with high level of HER2 positivity had the best response to treatment, whereas there were no significant responses in those with low HER2 expression. A similar anti-tumor effect of trastuzumab was seen in another in vitro study in combination with gemcitabine, causally related to HER2 level expression [60]. Moving from the preclinical to the early drug development field, a phase II study evaluated the efficacy of using trastuzumab in combination with capecitabine in 17 HER2 positive pancreatic cancer [57]. The trial showed a median OS and PFS of 23.55 and 6.9 months, respectively, without improvement in the outcomes if compared with the “historical” data of chemotherapy alone [57].

Another single arm study by Safran et al. evaluated the response rates by using Trastuzumab and gemcitabine in 34 patients with metastatic HER2 positive pancreatic adenocarcinoma [61]. Thirteen patients had >50% reduction of CA 19–9 levels; median OS was 7 months, and 1-year OS rate was 19%. Nevertheless, trastuzumab appeared not to give a benefit if compared with chemotherapy (gemcitabine) alone.

In conclusion, the evidence regarding a potential role of HER2 in the field of pancreatic cancers is immature and not conclusive at the time of writing. Therefore, further phase III trials are needed in order to consider HER2 as a potential target for effective target treatments in this field.

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