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Second-Line Therapy in the Treatment of Metastatic Gastric Cancer

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ABSTRACT

Gastric cancer continues to be one of the most prevalent malignancies. It is estimated that it is the fifth most frequent malignancy, and is considered the third mortality cause worldwide due largely to the fact that more than 70% of the cases are detected in advanced stages where, although first-line therapy has shown benefits in terms of survival, many of these patients showed disease progression, which raises the challenge of optimizing subsequent lines of therapy and developing new and better therapeutic options.

The role of second-line therapy has been widely discussed due to the fact that although there is evidence regarding the benefits of some drugs such as docetaxel, paclitaxel, and irinotecan in second-line therapy, and that this benefit has shown a reduction of approximately 18% in the risk of death, there is still a concern regarding the toxicity profile, and an adequate choice of the best drugs as regards efficacy, toxicity, and patient characteristics continues to be a topic of discussion.

The following review explores the most recent data published about the role of chemotherapy as second-line therapy, as well as the clinical trials performed with target therapies showing promising results, which will allow for the improvement of gastric cancer treatment. (J CANCEROL. 2016;3:91-104)

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INTRODUCTION

Gastric cancer continues to be one of the most important causes of mortality from cancer. In spite of a decrease in incidence, it is estimated that 22,220 new cases of gastric cancer were diagnosed in the USA in 2015, with approximately 10,990 deaths; in addition, it continues to be one of the most important causes of mortality in the world, with 70% of cases presenting in advanced stages[1].

The incidence of gastric cancer worldwide varies according to geographic region, so that countries such as the USA and parts of Europe have achieved a decrease in incidence. However, the incidence in Mexico shows a trend towards increasing in the coming decades so that gastric cancer continues to be an important health problem, being the third cause of cancer-related deaths in subjects older than 20 years[2].

The mortality rate from gastric cancer in males is 6.4 cases per 100,000 inhabitants, compared with 4.7 cases per 100,000 inhabitants in females[2].

At present, up to 80-90% of patients in Mexico are diagnosed in advanced stages when the tumor cannot be resected[2].

Although there is no consensus regarding a first-line approach, some concepts derived from meta-analyses are clear, such as Wagner, et al., which showed a significant improvement in terms of overall survival (OS) with regimes including fluoropyrimidine, cisplatin, and anthracyclines (HR: 0.82; 95% CI: 0.73-0.92)[3].

As for the role of triplets in the treatment of advanced or metastatic gastric cancer, it should be mentioned that several studies have been performed with the purpose of examining whether the addition of a third drug may have a positive impact in terms of survival. One of the studies analyzing the efficacy of triplets, the TAX 325 trial, which included 445 patients and compared cisplatin/fluorouracil vs. docetaxel, cisplatin, and fluorouracil, reported better response rates (25 vs. 37%; $p = 0.01$), time to progression (3.7 vs. 5.6 months; $p \leq 0.01$), and OS (8.6 vs. 9.2 months; $p = 0.02$). However, this same arm showed higher rates of grade 4 neutropenia (82 vs. 57%) and febrile neutropenia (30 vs. 12%). Considering the latter, several modifications to this schedule have been performed in order to maintain efficacy, but with an improved toxicity profile. This raises the possibility of including triplets as a treatment option in carefully selected patients (adequate functional status, preserved nutritional status)[4].

Another interesting study was the REAL-2 trial, which assessed whether capecitabine and oxaliplatin could constitute alternatives to the treatment with 5-fluorouracil and platinum, respectively[5].

A total of 1,002 patients were randomized 2:2 to the following treatment schedules: epirubicin, cisplatin, 5-fluorouracil (ECF) or capecitabine (ECX), or a triplet including epirubicin, oxaliplatin, fluoropyrimidine (EOF) or capecitabine (EOX). The primary objective was non-inferiority in terms of OS; no significant differences were observed as regards disease-free interval or overall responses to treatment. However, in the secondary analysis of OS, a greater survival was reported for EOX than ECF (95% CI: 0.66-0.97; $p = 0.02$), which allowed the authors to conclude that capecitabine and oxaliplatin are as effective as 5-fluorouracil and platinum in the first-line treatment of metastatic or advanced gastric cancer[5].

The above presents the advancements that have occurred in first-line therapy, and how these advancements have lead to an improvement in OS and symptom control for patients with gastric cancer. However, the duration of response is less than one year in more than half of the patients. It is generally clear that first-line chemotherapy regimes must be based on platinum and fluoropyrimidines. Given these limitations in first-line therapy, there is

a need for the addition of molecular targets that achieve better results[6].

The treatment of gastric cancer continues to be a challenge, and in spite of the advancements achieved in its treatment, a large percentage of patients still show disease progression; hence, new second-line therapy strategies are required[6,7].

ROLE OF CHEMOTHERAPY IN SECOND-LINE THERAPY FOR ADVANCED GASTRIC CANCER

Efforts have recently focused on attempting to improve survival outcomes for patients with gastric cancer in second-line therapy. Some phase II and III studies have been performed in which chemotherapy as sole agent was compared to best supportive care (BSC). Although these studies have shown modest activity as sole agents with drugs including taxanes (paclitaxel or docetaxel) and irinotecan, these studies have some limitations such as biases due to study design, sample size, and population heterogeneity[7,8].

Studies allowing an analysis of the role of chemotherapy as second-line therapy have been performed[7,8].

One of these studies is the AIO trial, performed in 2011. Chemotherapy consisted of irinotecan 250 mg/m^2 every three weeks in patients with an ECOG of 0-2. The study was terminated early after 40 patients had been enrolled due to the small enrollment because patients opposed randomization. Twenty-one patients received irinotecan and 19 patients received best supportive care, with a median OS of 4.0 vs. 2.4 months (HR: 0.48; p = 0.0012). Irinotecan showed a significant improvement in decreasing the risk of death and symptom improvement. However, the sample size was too small[9].

Another study assessing the efficacy of second-line therapy in gastric cancer is the Korean study by Kang, et al., which enrolled 212 patients with an ECOG of 0-1, randomized at a ratio of 2:1 to irinotecan 150 mg/m^2 every two weeks or docetaxel 60 mg/m^2 every three weeks, as per investigator preference, plus BSC or BSC alone. Median OS with chemotherapy was 5.3 vs. 3.8 months (HR: 0.66; p = 0.007), with a decrease of 34% in the risk of death. No statistically significant differences were observed between the two chemotherapy regimens (6.5 vs. 5.2 months)[10].

Another study was the COUGAR-2 trial, which enrolled 168 patients with an ECOG 0-1, who progressed during chemotherapy or within six months of chemotherapy completion, based on fluoropyrimidines and platinum. Patients were randomized to a treatment arm with docetaxel 75 mg/m^2 every three weeks plus active symptom control or active symptom control alone. Median OS was greater in the docetaxel arm compared with active symptom control at 5.2 vs. 3.6 months (HR: 0.67; p = 0.01). Although toxicity was greater in patients receiving docetaxel, especially neutropenia, infections, and febrile neutropenia, quality of life was better in patients receiving chemotherapy[11].

In 2013, Kim, et al. presented a meta-analysis of these three trials in order to answer the question of whether chemotherapy as second-line therapy was more effective than best supportive care. They found that 410 patients were eligible for analysis, of which 150 received docetaxel and 81 received irinotecan. Based on the results of this meta-analysis, there is a decrease of 36% in the risk of death (HR: 0.64; p < 0.0001) regardless of treatment type[12].

Other studies, such as the WJOG 4007 trial, compared second-line chemotherapy in 219 patients, weekly paclitaxel 80 mg/m^2 on day 1, 8, and 15 every four weeks, with irinotecan 150 mg/m^2 every two weeks. Irinotecan was not superior to paclitaxel in terms of median survival (8.4 vs. 9.5 months; HR: 1.13; p = 0.38). The greater survival reported in these studies may be due to

the exclusion of patients with severe peritoneal carcinomatosis, which is a factor for worst prognosis[13].

The phase II trial with PEP02 (MM-398) randomized subjects 1:1:1 to three treatment arms comparing PEP02 as monotherapy (novel formulation of liposomal irinotecan) or in combination with docetaxel or irinotecan as second-line therapy. One hundred and thirty-two patients were assigned to PEP02 120 mg/m^2, irinotecan 300 mg/m^2, or docetaxel 75 mg/m^2 every three weeks. No differences were reported regarding overall response (13.6 vs. 6.8 vs. 15.9%, respectively), and OS and progression-free survival (PFS) were similar among the three treatment groups. Median OS was 7.3 vs. 7.8 vs. 7.7 months with PEP02, irinotecan, and docetaxel, respectively, while PFS was 2.7 vs. 2.6 vs. 2.7 months, respectively[14].

Another topic to be discussed is polychemotherapy versus monochemotherapy. To date, two Asian randomized trials have been performed with the purpose of assessing the role of polychemotherapy versus monochemotherapy in advanced gastric cancer. A Korean phase II study comparing modified FOLFIRI (irinotecan 150 mg/m^2 plus leucovorin 20 mg/m^2 IV on day 1, followed by 5FU 2,000 mg/m^2 after 48 hours) vs. irinotecan monotherapy at 150 mg/m^2 every two weeks, in patients progressing during or after first-line chemotherapy based on platinum, taxanes, or fluoropyrimidines. The primary objective was to assess OS, and the secondary objective was to assess PFS. Fifty-two of the 59 enrolled patients were assessed for response, which was 17.2 vs. 20% in patients treated with irinotecan and mFOLFIRI, respectively. Median PFS and median OS were 2.2 and 5.8 months, respectively, for irinotecan, and 3.0 and 6.7 months for mFOLFIRI[15].

A Japanese phase III study, TCOG GI-0801, compared irinotecan 60 mg/m^2 plus cisplatin 30 mg/m^2 every two weeks (BIRIP schedule) versus irinotecan 150 mg/m^2 monotherapy every two weeks. One hundred and thirty patients refractory to first-line S1 were enrolled, with a median PFS of 3.8 vs. 2.8 months (HR: 0.68; p = 0.03). In a subgroup analysis, in patients naive to platinum-containing agents, median PFS was greater in the BIRIP arm (6.4 vs. 4.2 months; HR. 0.60; p = 0.0786). Rates of OS and overall response (OR) were not improved with combined therapy compared with irinotecan monotherapy. This study only included Japanese patients, and more than 40% had not received chemotherapy with platinum-containing agents before being admitted in the study, so these data are not considered real for Western patients[16].

Sequential polychemotherapy: the phase III trial FFCD-GERCOR-FNCLCC03-07 enrolled 416 patients. The group that received FOLFIRI as first-line therapy, followed by ECX as second-line therapy, showed longer time to failure (22.1 vs. 18.5 weeks; HR: 0.77; p = 0.008), but OS was similar (9.5 vs. 9.7 months) compared with the opposite sequence[17].

A Korean phase III study performed by Kim, et al., which was terminated early due to insufficient enrollment, randomized 58 patients to first-line docetaxel/cisplatin every three weeks until progression, followed by FOLFIRI (Arm A) or the opposite sequence (Arm B). No differences were observed in global response, control rate, first PFS, and second PFS, as well as OS[17].

The above data provides an overview of the efforts being made in trying to improve treatment outcomes in patients progressing with a first-line therapy, and in developing a strategy that will allow better treatment outcomes. However, consensus has not been reached regarding the best treatment strategy for these patients, taking into consideration that the above data only examine chemotherapy; other therapeutic options, including molecular targets, are discussed below[18].

ROLE OF TARGETED THERAPIES IN SECOND-LINE THERAPY FOR ADVANCED GASTRIC CANCER

In recent years, efforts have focused on developing new treatment strategies that will allow better outcomes, including new molecular targets. A review considering the signaling pathways targeted by these therapies is performed[19].

The carcinogenesis of gastric cancer is complex and has not been fully characterized. Numerous signaling pathways are affected, including:

- Signaling pathways directed to the epidermal growth factor receptor (EGFR)
- Signaling pathways directed to anti-EGFR tyrosine kinase inhibitors
- Signaling pathways directed to anti-HER2 signaling
- Vascular endothelial growth factor (VEGF) signaling pathways
- Signaling pathways directed to overexpression via c-Met
- Signaling pathways directed to mammalian target of rapamycin (mTOR)
- Signaling pathways of checkpoint inhibitors

The above has given rise to the development of new treatment options targeting these signaling pathways.

EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

CLINICAL OUTCOMES OF AGENTS TARGETED TO THE EPIDERMAL GROWTH FACTOR RECEPTOR SIGNALING PATHWAY

Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor frequently activated in different malignancies, playing an important role in oncogenesis. The EGFR includes ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4).

The EGFR remains in an auto-inhibition state in the absence of ligands with EGF transforming growth factor alpha (TGF-α)[19].

After binding to the ligand, receptors are homodimerized or heterodimerized with other members of the ErbB family. This dimerization triggers the autophosphorylation of EGFR's intracellular domain, which triggers the subsequent activation of the internal signaling pathways. Said pathway is involved in several processes such as proliferation, angiogenesis, metastasis, and resistance to apoptosis[19].

Undoubtedly, EGFR is a molecular target. Numerous studies have shown an increase in EGFR expression and a correlation with poor prognosis. An overexpression of EGFR was observed in a small study in 27% of gastric cancer patients, also associated with prognosis[20].

On the other hand, the EGFR pathway has been established as part of the therapeutic armamentarium in other malignancies such as colon cancer, head and neck cancer, squamous non-small cell lung cancer (NSCLC), and it is precisely the expression of EGFR that provides the rationale for clinical trials in gastric cancer[20,21].

There are two kinds of agents targeting EGFR available in clinical practice: monoclonal antibodies, which recognize EGFR's extracellular domain (cetuximab, panitumumab, nimotuzumab), and

small molecules such as tyrosine kinase inhibitors (TKI), which block intracellular signaling of EGFR (gefitinib and erlotinib)[21,22].

We shall examine the data obtained with monoclonal antibodies (mAbs) such as cetuximab, panitumumab, and nimotuzumab.

Two phase II clinical trials had shown promising results in gastric cancer, with median survival of 9-11 months, which gave rise to the development of the phase III trials EXPAND and REAL-3[22].

The EXPAND trial randomized 904 gastric cancer patients to receive placebo or cetuximab plus a chemotherapy schedule with cisplatin/capecitabine. The primary endpoint was PFS, and secondary endpoints included OS, response rate (RR), and toxicity. No statistically significant differences were observed between treatment groups (PFS: 5 months; OS: 10 months; RR: 30%), and a trend to lower survival was observed when cetuximab was added. Toxicity was similar, except for an increase in rash in the cetuximab group[23].

Another phase II trial explored the role of cetuximab combined with docetaxel/oxaliplatin, with or without cetuximab, as first-line therapy in the treatment of gastric cancer, showing negative results. It should be noted that this trial allowed the analysis of the RAS mutation test although, as in other studies, no conclusions could be drawn about the prognostic value of RAS as a response biomarker[24].

The REAL 3 trial randomized 503 patients to receive treatment with placebo or panitumumab with the EOX chemotherapy schedule (epirubicin, oxaliplatin, capecitabine). Oxaliplatin and capecitabine dosages were reduced in the panitumumab arm due to the toxicity observed in previous studies. The primary objective was the analysis of overall survival, and the secondary objectives included PFS, overall responses, and toxicity[25].

As in EXPAND, the addition of a molecular target showed negative results, which caused the early termination of the study[25].

The third monoclonal antibody targeting EGFR is nimotuzumab, which has been extensively investigated in gastric cancer, showing great promise. The phase II trial of nimotuzumab combined with cisplatin/S1 has shown inferior results in those patients receiving the target therapy with nimotuzumab[26].

In addition to the previously discussed outcomes, some trials have included anti-EGFR antibodies in chemo/radiotherapy regimes in locally advanced stages, where these trials have almost uniformly shown an increase in toxicity without a clear benefit in terms of OS.

CLINICAL OUTCOMES OF ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS GEFITINIB AND ERLOTINIB

Tyrosine kinase inhibitors such as gefitinib and erlotinib have been assessed in gastric cancer, but no benefit has been shown, although multiple phase II trials suggest benefit, which gave way to the development of the phase III trial COG (NCT01243398), which enrolled 450 patients with gastric or gastro-esophageal junction (GEJ) cancer of adenocarcinoma or squamous histology, who had progressed under first-line therapy based on platinum/fluoropyrimidine. No significant improvement in PFS was observed (1.6 months for gefitinib vs. 1.2 months for placebo), and more importantly, the primary endpoint, OS, was not different between both treatment groups (3.7 months). An improvement in odynophagia was reported, although the remaining symptoms showed no changes[27].

In spite of the negative results in the COG trial, a small subgroup with rapid response and disease control suggests that a biomarker has not been identified[27].

The TRANS COG analysis assessed the predictive value of a number of EGFR copy numbers gained (CNG) in 295 patients treated in COG. The CNG were analyzed using a FISH test, where 46 patients (15.6%) with evidence of CNG showed an improvement in OS, PFS, and disease control. Of note, 38% of the patients with CNG treated with gefitinib had survived at six months, and 13% had survived at 12 months, which is comparable to the results obtained in other trials; thus it can be concluded that EGFR CNG may constitute a predictive factor. However, additional studies will be required before considering gefitinib as a standard of care[27].

In summary, although preclinical trials with agents targeting EGFR seemed very promising, the phase III studies have been negative. Interestingly, other clinical settings where EGFR inhibition has been beneficial have had biomarkers associated to response; for example, wild-type RAS in colorectal cancer, and EGFR mutation in lung cancer, although this doesn't seem relevant in gastric cancer.

CLINICAL OUTCOMES IN MONOCLONAL ANTIBODIES TARGETING EPIDERMAL GROWTH FACTOR RECEPTOR 2: TRASTUZUMAB, TRASTUZUMAB-EMTANSINE, AND PERTUZUMAB

Epidermal growth factor receptor 2 (HER2) is the second member of the ErbB family, which is strongly involved in the pathogenesis of gastric cancer.

The overexpression of HER2 is a marker of poor prognosis, and is associated with a high relapse rate in patients with breast cancer. However, in gastric cancer HER2 is controversial; for example, the six first-line trials involving 381 patients with gastric cancer were retrospectively analyzed, and the multivariate analysis indicated that the HER2 status was not an independent prognostic factor. However, two studies (ToGA and EXPAND) suggest that a positive HER2 status carries a favorable prognostic factor in those negative to HER2, even when they are treated with chemotherapy alone[28].

Trastuzumab is a monoclonal antibody that recognizes an extracellular epitope in the HER2 receptor. The registration study of trastuzumab for the first-line therapy of gastric cancer (ToGA) included patients with unresectable or metastatic gastric or GEJ cancer who were stratified according to HER2 expression determined by a combination of IHQ and FISH. The trial enrolled 3,665 people, of whom 810 (22%) had HER2 expression; 584 of these patients (80% gastric and 20% GEJ) were randomized to standard chemotherapy with intravenous cisplatin/5-fluorouracil or oral capecitabine vs. a treatment arm with cisplatin/fluoropyrimidine plus trastuzumab at 8 mg/kg in the first cycle, and subsequently at 6 mg/kg every three weeks[28].

Survival results show a clear benefit in favor of the trastuzumab treatment arm, with an OS of 13.8 months for trastuzumab vs. 11.1 months for chemotherapy alone, and PFS of 6.7 vs. 5.5 months. As for the toxicity profile, trastuzumab is well tolerated and no differences were observed in the toxicity profiles, including cardiac events.

In a previously planned exploratory analysis in HER2-positive (IHC 2+/FISH+ or IHQ 3+) patients, HER2-positive patients derived the greatest benefit from trastuzumab treatment (OS 16 months for trastuzumab vs. 11.8 months for chemotherapy)[29].

Undoubtedly, the results of the ToGA trial have led to exploring the potential role of trastuzumab

in gastric cancer, taking into consideration the examination of alternative treatment regimes. However, the role of trastuzumab as first-line therapy is being explored and, as mentioned before, in those patients positive to HER2.

Nonetheless, new treatment strategies are required in order to overcome resistance to trastuzumab, either *de novo* or acquired, by understanding the molecular biology of the HER family[28,29].

Trastuzumab emtansine

Trastuzumab emtansine (T-DM1) is a conjugated monoclonal antibody containing trastuzumab with a high microtubule-inhibiting potential.

T-DM1 constitutes a monotherapy that overcomes resistance in patients previously treated with trastuzumab.

There are ongoing phase II/III multicentric, randomized, adaptive, second-line trials in patients previously treated with first-line trastuzumab in order to assess the efficacy of T-DM1 compared with standard therapy (docetaxel/paclitaxel as per the investigator's choice)[28,29].

Lapatinib

Lapatinib is a potent dual inhibitor of TKI or HER2 and blocks the EGFR pathway associated to cascade signaling. Since this agent had achieved positive outcomes in breast cancer by overcoming resistance to trastuzumab, it was considered for gastric cancer in TYTAN, a phase III study that randomized 261 Asian patients who had shown progression to first-line chemotherapy, to placebo, or to lapatinib combined with paclitaxel. Ninety-five percent of the patients had not received anti-HER2 therapy; those who received lapatinib showed an increase in response rate (27 vs. 8% in favor of the lapatinib arm). However, in terms of survival, only a trend towards improvement with no statistical significance was observed, with an OS of 11.0 vs. 8.9 months, and a PFS of 5.4 vs. 4.4 months. A subanalysis showed some benefit in patients with HER2 (FISH-positive)[30,31].

Another small German study (NCT01145404) randomized HER2-positive patients confirmed by FISH to second-line therapy with capecitabine, placebo, or lapatinib. The primary endpoint of the trial, response rate, was not achieved, and survival was similar across treatment arms[32].

Results in both studies show no benefit from adding lapatinib either in first-line or second-line therapy for gastric cancer.

CLINICAL OUTCOMES OF THE VASCULAR ENDOTHELIAL GROWTH FACTOR SIGNALING PATHWAY

Of great interest among the molecular targets in this scenario are those drugs against angiogenesis. It has been shown that the positive regulation of VEGF is associated with a more aggressive disease, and that the positive regulation of VEGF-A, VEGF-C, and VEGF-D is observed in gastric cancer and is associated with a poor prognosis for patients.

VEGF and signaling and angiogenesis mediated by VEGFR-2 contribute to the pathogenesis of gastric cancer. Moreover, circulating VEGF levels are associated with greater tumor aggressiveness and lower survival.

Several preclinical trials have shown an improvement in the control of tumor growth and metastases, or through the inhibition of the VEGF pathway. In terms of overexpression of VEGF in gastric cancer, this has been related to tumor aggressiveness and poor outcomes, as has been shown in colon cancer[33].

CLINICAL OUTCOMES OF AGENTS TARGETING THE VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR PATHWAY (MONOCLONAL ANTIBODIES)

The addition of an agent targeting VEGF to chemotherapeutic regimes has shown an improvement in malignancies such as colon cancer and others, which has led to the rationale for use of ramucirumab in gastric cancer. A wide variety of monoclonal antibodies targeting VEGF have been tested in gastric cancer, with or without bevacizumab, ramucirumab, and ziv-aflibercept, and among the TKIs targeting VEGF we find regorafenib, sunitinib, sorafenib, and afatinib[33].

Bevacizumab is a monoclonal antibody targeting VEGF-A. Some preclinical trials have been performed in various tumors with the purpose of evaluating its efficacy. Specifically in gastric cancer, a phase II study in combination with irinotecan/cisplatin/bevacizumab observed response in two thirds of patients, with a PFS of 8.2 months and an OS of 12.3 months, which is favorable as compared with historical controls[33].

These promising phase II clinical trials provide the rationale for performing phase III clinical trials such as the AVAGAST study, which evaluated the efficacy of first-line bevacizumab. The primary objective, the improvement in OS, was not achieved (OS: 12.1 months with bevacizumab vs. 10.1 months with placebo). Regarding PLP and response rates, these showed improvement for the bevacizumab arm[34].

The AVATAR study subsequently assessed the efficacy of bevacizumab in combination with a regime containing capecitabine + cisplatin in patients with gastric and GEJ. The trial enrolled 220 patients, and results showed no difference in terms of OS or progression-free interval in the bevacizumab compared with the placebo arm[35].

Two first-line clinical trials in gastric cancer failed to show efficacy in terms of OS.

Other anti-angiogenic drugs have shown efficacy in gastric cancer, specifically as second-line therapy, that being the case of ramucirumab[36].

Ramucirumab is a fully humanized monoclonal antibody targeting the VEGF[36].

Two large clinical trials have assessed the efficacy of ramucirumab in terms of OS in patients with progression under a first-line therapy. These trials are REGARD and RAINBOW, which provide the most robust data and the best available evidence in the second-line setting since the trials enrolled the largest number of patients and they were adequately designed and conducted, double-blind, placebo-controlled trials that achieved the primary endpoint of improvement in OS, and also showed a consistent improvement in the progression-free interval, maintaining quality of life[36].

The REGARD trial sets a precedent regarding the efficacy of ramucirumab in patients with advanced gastric cancer of the gastroesophageal joint, adenocarcinoma subsequent to disease progression during or after first-line therapy based on platinum/fluoropyrimidine. Results showed benefit in terms of OS, with a 22% decrease in the risk of death[36].

RAINBOW is a global phase III, randomized, double-blind trial of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of advanced gastric cancer or adenocarcinoma of the GEJ after first-line therapy with any doublet based on platinum/fluoropyrimidines with or without anthracyclines (epirubicin or doxorubicin)[37].

The primary objective of the RAINBOW trial was to assess OS, and the secondary objectives were to assess the following: PFS, time to progression (TTP), overall response rates, patient-reported results, safety, pharmacokinetic profile, immunogenicity, and pharmacokinetic parameters of ramucirumab[37].

As regards results, RAINBOW showed that ramucirumab combined with paclitaxel reduced the risk of death by 19% in this population (HR: 0,807; 95% CI: 0.678-0.962; p = 0, 0169), which represents a 31% increase in median survival in the paclitaxel plus ramucirumab arm[37].

The statistical significance, effect size, and robustness of the results of the OS analysis were reported by means of a pre-specified sensitivity analysis, which consistently showed hazard ratios between 0.745 and 0.822, all $p < 0.05$[37].

In addition, the disease control rate reported a response of 80% for the ramucirumab plus paclitaxel vs. 64% for paclitaxel alone (p = 0, 0001)[37].

Recent results of ramucirumab combined with paclitaxel have shown a consistent benefit in terms of OS, progression-free interval, response rate, and disease control, with an adequate safety profile, as was previously stated, without a detrimental effect in patient quality of life[37].

The RAINBOW trial represents the most complete quality of life database in the treatment of advanced gastric cancer after initial chemotherapy reported to date, and shows that an advantage in survival associated with ramucirumab combined with paclitaxel occurred without worsening quality of life. Hazard ratios on the TTD and EORTC QLQ-C30 scales numerically favored the ramucirumab plus paclitaxel arm[37].

The RAINBOW study population included patients with poorly differentiated tumors (55.9%), disease progression within six months of first-line therapy initiation (76.1%), and metastatic disease (97.4%), with approximately a third of patients with at least three metastatic sites (33.7%). In addition, 43.3% of the patients had liver metastases, 47.4% had peritoneal metastases, and 35.6% had ascites[37].

Another strategy targeting VEGFR is ziv-aflibercept, whose mechanism of action is directed to inhibiting VEGFR1 and VEGFR2, which theoretically offers an advantage, and taking into account the results of the VELOUR trial, in which aflibercept showed efficacy in colon cancer, the decision was made to evaluate its efficacy as second-line therapy for metastatic gastric cancer. A phase II trial is presently ongoing with the purpose of evaluating the role of ziv-aflibercept in combination with FOLFOX as second-line therapy. These results should prove interesting[38].

CLINICAL OUTCOMES OF AGENTS TARGETING THE VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR PATHWAY (TYROSINE KINASE INHIBITORS)

Tyrosine kinase inhibitors (TKI) are small molecules, representing the second group of drugs targeting the angiogenesis pathway. Most of these agents affect multi-kinases simultaneously; however, it has been difficult to elucidate the exact mechanism of action of these small molecules. We shall analyze their role in the second-line therapy of gastric cancer[39].

Sorafenib is a multi-target inhibitor targeting BRAF, VEGF, PDGFR, and Ras/Raf/MERK/ERK. A phase II trial evaluated the efficacy of sorafenib plus oxaliplatin as second-line therapy. A total of 40 patients were enrolled. Complete response was observed in 2.5%, stable disease in 47.2%; observed adverse events were neutropenia 9.8%, thrombocytopenia 7.3%, neurotoxicity 4.9%, and diarrhea 4.9%, with a PFS of three months, and OS of 6.5 months[39].

Two angiogenesis inhibitors, sunitinib and sorafenib, have shown anti-angiogenic activity. Both agents have been assessed in the treatment of gastric cancer, unfortunately with poor activity and substantial toxicity. The two agents failed to show usefulness in the treatment of gastric cancer, both in the first and second lines of therapy, either as monotherapies or combined with chemotherapy,

even though the combination of docetaxel/sunitinib showed an improvement compared with chemotherapy alone (41.0 vs. 14.3%). At present, there are no ongoing trials[39,40].

Regorafenib is a multi-kinase with activity against VEGFR1-3 and TIE2, which was assessed in gastric cancer in the phase II trial INTEGRATE, which randomized patients with gastric cancer who had been treated with one or more lines of chemotherapy to regorafenib 160 mg daily for 21 or 28 days vs. placebo. The progression-free interval was short (11.1 weeks for regorafenib vs. 3.9 weeks for placebo), with a statistically significant difference; the difference was not statistically significant in terms of OS[41].

Other studies with regorafenib in gastric cancer are ongoing: NCTC02241720 (regorafenib as second-line monotherapy), NCT01913639 (regorafenib + FOLFOX as first-line therapy), and NCT02234180 (regorafenib as adjuvant therapy after neo-adjuvant chemotherapy and nodule-positive surgery). These studies should define the role of regorafenib in the treatment of gastric cancer.

CLINICAL OUTCOMES OF TARGETED AGENTS VIA CMET

The tyrosine kinase receptor targeting MET is a proto-oncogene regulating cellular growth, survival and migration. When the hepatocyte growth factor binds to MET, it directs the dimerization of MET and the phosphorylation of the residues of the tyrosine kinase domain, which directs the downstream stimulation of bioactive molecules and the stimulation of proliferation, survival and migration. This deregulation of HGF/MET promotes tumor growth and metastases[42].

A high expression of c-MET has been observed associated with intestinal histology, comparatively with diffuse tumors ($p = 0.04$), invasion deepness, neural invasion ($p = 0.002$), and advanced stages[42,43].

On the other hand, authors such as Ha, et al. have observed that the overexpression of c-MET is associated with shorter OS and progression-free intervals compared with those without c-MET expression, and a significant difference was found as regards OS between patients positive to c-MET and negative to c-MET (11.9 vs. 14.2 months). The multivariate analysis also showed that a positive c-MET status constitutes a prognostic factor of OS (HR: 1.30; 95% CI: 1.02-1.67; $p = 0.037$). These patients might benefit from molecular targets directed to c-MET[42,43].

Rilotumumab (AMG102) is a fully humanized monoclonal antibody of immunoglobulin G, type 2 (IgG2) against the human hepatocyte growth factor, dispersion factor (HGF/SF), which blocks the HGF/SF ligand for this MET receptor, inhibiting HGF/SF/MET which orchestrates cellular activities[43,44].

Two phase II clinical trials have been performed as first-line therapy in metastatic gastric cancer, in which results have shown an improvement in PFS, with an apparent correlation between cMET status and treatment response.

These trials encouraged the development of a phase III trial, RILOMET-1, performed in treatment-naive, HER2-positive and c-MET-negative patients. However, the trial was terminated early due to poor outcomes in the rilotumumab arm. In the end, the analysis showed worse survival, progression-free intervals, and response rates for patients treated with rilotumumab[43,44].

A similar study is ongoing, RILOMET-2, in an Asian population, although results are not yet available.

CLINICAL OUTCOMES OF AGENTS TARGETING MAMMALIAN TARGET OF RAPAMYCIN

The mTOR inhibitors are targeted to inhibit the activation of the mTOR protein, which is a serine/

threonine kinase of 289 kDa. The mTOR protein family has pleiotropic functions, and is involved in regulating the initiation of messenger RNA transcription and translation into protein, in response to amino acid intracellular concentrations and other essential nutrients. It is involved in the organization of the actin cytoskeleton, membrane traffic, protein degradation, protein kinase C signaling, and ribosome biogenesis. This pathway regulates essential signaling pathways and is involved in coupling the growth stimulus and the cellular cycle progression.

The activation of PI3K/Akt/mTOR is associated with chemo-resistance and poor survival, and is frequent in gastric cancer, observed in around 30% of patients.

Everolimus is an oral mTOR inhibitor, with a high affinity for the intracellular FKBP12 receptor, which has shown tumor activity in multiple malignancies, including gastric cancer. Thus, phase II clinical trials with everolimus have been performed in previously treated patients with metastatic gastric cancer. Fifty-three patients were enrolled, of which 45% showed disease control. The PFS was 2.7 months and OS was 10.1 months (95% CI: 6.5-12.1 months).

This study was the rationale for the development of a phase III trial, GRANITE-1, which showed median OS and PFS of 5.4 vs. 5.3 months ($p = 0.124$) for everolimus vs. placebo, and a progression-free interval of 1.7 vs. 1.4 months (HR: 0.66; 95% CI: 0.56-0.78), respectively. This study found that everolimus showed no improvement in the treatment of gastric cancer in second- and third-line therapies.

CLINICAL OUTCOMES OF CHECKPOINT INHIBITORS

These agents block immunological checkpoints directed to antigens associated to cytotoxic lymphocyte T and the programmed cellular death protein 1 (PD-1/PDL1), which has shown promising results in other malignancies.

These strategies involve the manipulation of the immune system's normal function signaling pathways.

Considering the positive results observed in other malignancies such as melanoma, phase II studies have been performed with the purpose of assessing the efficacy of pembrolizumab in gastric cancer.

Pembrolizumab is a monoclonal antibody targeting PD-1, which is expressed in gastric cancer.

CONCLUSIONS AND FUTURE PERSPECTIVES

Gastric cancer is a frequent neoplasia in Mexico, Latin America, and Asia. It represents the first cause of death by intestinal tumors in Mexico. It presents in clinical stage IV in 60-70% of cases, with a median age of 58-62 years according to a reviewed reference.

The primary treatment is based on combined chemotherapy. Almost all patients initially treated with chemotherapy will eventually experience disease progression, and more than half of those patients will be candidates to systemic treatment. Pain and weight loss are the main symptoms at diagnosis. Between 20 and 40% of patients with advanced disease under first-line systemic therapy will be candidates to second-line therapy, with median survivals reported of 5.6 months and response rates of 13%.

Until recently, there have been no new and effective therapies approved for the second-line therapy available in gastric cancer. Ramucirumab is considered as standard management in patients with advanced gastric adenocarcinoma who have

progressed to first-line chemotherapy, according to all the efficacy data, such as PFS, OS, and continued impairment of the activity level in ECOG, with improved response rates when combined with paclitaxel, maintaining quality of life. Future scenarios to consider are immunotherapy and other signaling pathways present in gastric carcinoma.

We believe that ramucirumab is an example, although there is undoubtedly much that needs to be improved as regards OS in advanced gastric cancer, strengthening timely detection in high-risk regions, and management of *H. pylori* eradication, approaches that will jointly decrease the incidence and mortality of this terrible disease.

DISCLOSURE OF INTERESTS

The authors have no significant financial relationships to disclose.

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