MINIREVIEWS

Adjuvant therapy for gastric cancer: What have we learned since INT0116?

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Abstract

Gastric cancer is one of the main cancer-related causes of death worldwide. The curative treatment of gastric cancer consists of tumor resection and lymphadenectomy. However, surgical treatment alone is associated with high recurrence rates. Adjuvant treatment strategies have been studied over the last decades, but there have been controversial results from the initial studies. The pivotal INT0116 study demonstrated that the use of adjuvant chemoradiotherapy with 5-fluorouracil increases relapse-free and overall survival, and it has been adopted across the Western world. The high toxicity of radiochemotherapy and suboptimal surgical treatment employed, with fewer than 10% of the patients submitted to D2 lymphadenectomy, were the main study limitations. Since its publication, other adjuvant treatment modalities have been studied, and radiochemotherapy is being refined to improve its efficacy and safety. A multimodal approach has been demonstrated to significantly increase relapse-free and overall survival, and it can be offered in the form of perioperative chemotherapy, adjuvant chemoradiotherapy or adjuvant chemotherapy, regardless of the extent of lymphadenectomy. The objective of the present review is to report the major advances obtained in the last decades in the adjuvant treatment of gastric cancer as well as the perspectives of treatment based on recent knowledge of the molecular biology of the disease.

Key words: Stomach neoplasms; Adjuvant radiotherapy; Adjuvant chemotherapy; Histology; Genes erbB-2

Core tip: Adjuvant therapy of gastric cancer significantly improves overall survival. The most accepted adjuvant therapy in the Western world is chemoradiotherapy according to the pivotal INT0116 study. However, in the time following its publication, other adjuvant treatment modalities have been discussed, and significant improvements have been obtained in our understanding of the multimodal approach of gastric cancer. The present review reports on the major advances obtained in the last decades in the adjuvant treatment of gastric

cancer as well as the perspectives of treatment based on recent knowledge of the molecular biology of the disease.

INTRODUCTION

Gastric cancer is the fourth most common malignant neoplasm in the world, and it ranks at the same position as a cancer-related cause of death[1]. Its carcinogenesis is intimately related to environmental factors, especially those involving diet, as reflected by the geographic distribution of the disease[2]. Eastern countries, Eastern Europe and Latin America are high risk areas for the development of gastric cancer, whereas Southeast Asia, North America and Australia are low risk areas[1].

The risk factors involved in the development of gastric cancer vary according to the histological type of the tumor[3]. The Laurén intestinal-type is closely related to infection with *Helicobacter pylori*[4], especially the cagA+ subtype, gastroesophageal reflux disease and obesity[3]. The Laurén diffuse-type does not involve clearly defined environmental risk factors. The Laurén diffuse-type is associated with a mutation of the CDH1 gene, which is responsible for e-cadherin expression, and is the histological type that is usually detected in genetic syndromes associated with gastric cancer[5].

The curative treatment for gastric cancer consists of tumor resection and lymphadenectomy[6]. However, surgical treatment alone is associated with high recurrence rates[7,8]. A multimodal approach has been demonstrated to significantly increase relapse-free and overall survival[9], and it can be offered in the form of perioperative chemotherapy, adjuvant chemoradiotherapy or adjuvant chemotherapy. The use of adjuvant chemotherapy in the treatment of gastric cancer is estimated to reduce the risk of death by approximately 20%[9].

Adjuvant treatment strategies have been studied over the last decades, but initial studies have generated controversial results due to the methodological limitations and use of toxic chemotherapy regimens. In 2001, the pivotal INT0116 study demonstrated that the use of adjuvant chemoradiotherapy with 5-fluorouracil increases relapse-free and overall survival, albeit with high toxicity[10]. The main limitation of the study was the type of surgical treatment employed, which was considered to be suboptimal considering that fewer than 10% of the patients underwent D2 lymphadenectomy, the standard of care[11].

The INT0116 study represented a milestone in the treatment of gastric cancer and has been adopted across the Western world. Since its publication, other adjuvant treatment modalities have been discussed, and chemoradiotherapy is being refined to improve its efficacy and safety.

The objective of the present review is to report on the major advances in the last decades for the adjuvant treatment of gastric cancer as well as the perspectives of treatment based on our recent knowledge of the molecular biology of the disease.

SURGICAL TREATMENT

Surgical treatment is the therapeutic modality with the possibility of a cure for patients with gastric cancer[6]. It consists of tumor resection with wide margins and lymphadenectomy. D2 lymphadenectomy is the most recommended nodal dissection, which is related to its lower rate of locoregional recurrence and lower death rate from gastric cancer, but it may involve a higher risk of postoperative complications[11,12].

The risk of recurrence after surgical treatment depends on the initial stage of the disease, histological type and surgical radicality[6]. The risk of recurrence is higher if the tumor invasion is deeper into the gastric wall, especially when the serosa is involved, as well as with the presence of nodal involvement. It is also known that the Laurén diffuse-type and the presence of microscopic residual disease are associated with a higher risk of recurrence[6]. Studies have reported variable data according to the investigated population, but the largest series in the literature demonstrated recurrence risks ranging from 20% to 40% after resections performed for curative purposes[7,8]. The pattern of recurrence also varies according to the sample studied. Patients who undergo more limited nodal dissection and who have microscopic residual disease tend to have a higher risk of locoregional and peritoneal recurrence. The presence of poorly differentiated tumors with more extensive nodal involvement is associated with a higher risk of distant metastases. Strategies for adjuvant treatment have been planned based on the analysis of the risk and pattern of disease recurrence.

ADJUVANT CHEMORADIOTHERAPY

Since the publication of the INT0116 study, which demonstrated an improvement in the overall survival with adjuvant chemoradiotherapy, the treatment strategy published in that report was adopted as one of the major therapeutic options in Western countries. Before the publication of this study, the standard treatment was gastrectomy alone due to the methodological limitations and use of highly toxic

chemotherapy regimens in previous clinical studies, which has raised doubts about the benefits of adjuvant treatment.

The major limitation of the INT0116 study is the surgical treatment that was adopted[10]. The authors performed D2 lymphadenectomy in fewer than 10% of the patients, which is likely to leave microscopic residual nodal disease in most patients and would justify the survival benefit with the addition of radiotherapy. However, a potential benefit when evaluating the role of adjuvant treatment in patients who did not undergo a standardized surgical technique would be that we can reflect on the results for when D2 lymphadenectomy is not routinely performed. The update of the study after a median follow-up of 10 years supported the initial data with convincing results[13]. A gain of 8 mo in the relapse-free survival (27 mo *vs* 19 mo; HR = 1.51, 95%CI: 1.25-1.83) and in the overall survival (35 mo *vs* 27 mo; HR = 1.32, 95%CI: 1.10-1.60) has convinced the medical community to adopt this approach as one of the preferred adjuvant treatments.

A negative aspect of the treatment proposed by the INT0116 study is its toxicity. The incidence of grade 3 or higher hematologic toxicity in 54% and gastrointestinal toxicity in 33% of the patients, with a treatment-related mortality of 1%, has indicated the need for improving the treatment safety.

The absence of standardization for lymphadenectomy raises questions about the efficacy of combined treatment for patients who undergo D2 lymphadenectomy, even though the study did not detect differences in the benefit of adjuvant treatment according to the type of lymphadenectomy. Retrospective studies have supported the findings of the INT0116 study and have demonstrated the efficacy of fluoropyrimidine-based chemoradiotherapy in patients who undergo D2 lymphadenectomy[14,15].

Aiming to improve the safety and efficacy of chemoradiotherapy treatment, the RTOG 0114 study compared two therapeutic regimens, which were both associated with 45 Gy radiotherapy, *i.e.*, paclitaxel and cisplatin (PC) *vs* paclitaxel, cisplatin and 5-fluorouracil (PCF)[16]. Two chemotherapy cycles were applied, which was followed by radiotherapy concurrent with PC or PCF. The patients treated with the triple regimen had an incidence of 59% for a toxicity of grade 3 or higher, which led to the premature closure of this study arm. The patients treated with the PC regimen showed a 2-year disease-free survival of 52%, which was lower than the results of the INT0116 study. Therefore, the RTOG 0114 study did not increase the gains compared to standard treatment.

The most relevant study about the role of chemoradiotherapy that has been published in the time following the INT0116 study was the ARTIST trial, which compared adjuvant chemotherapy alone, consisting of six cycles of capecitabine and cisplatin (XP), to combined treatment with capecitabine

and radiotherapy at the dose of 45 Gy in 25 fractions, with two cycles of XP before and after the combined phase[17]. All 458 patients underwent D2 lymphadenectomy. The arms of the study showed similar 3-year disease-free survival (HR = 0.74; 95%CI: 0.52-1.05) and overall survival (HR = 1.13; 95%CI: 0.77-1.64). However, combined treatment was superior to chemotherapy alone when the subgroup of patients with positive lymph nodes was analyzed (HR = 0.70; 95%CI: 0.49-0.99), which was also true when the subgroup of patients with intestinal-type histology was evaluated (HR = 0.44; 95%CI: 0.23-0.84). This result supports the hypothesis of the benefit of radiotherapy in the adjuvant treatment of gastric cancer.

Another interesting finding of the ARTIST trial is related to the safety of the therapeutic regimen used. When the chemoradiotherapy and chemotherapy groups were compared with respect to grade 3 and 4 toxicity, 48% *vs* 40% neutropenia, 12% *vs* 12% nausea, 3% *vs* 3% vomiting and 1% *vs* 2% diarrhea were observed, respectively. These rates are more favorable when compared to the INT0116 study findings. It should be emphasized that 5-HT$_3$ inhibitors for the prophylaxis of nausea and vomiting were not used in the INT0116 study because they were not yet available at the time of study initiation. The greater hematological and gastrointestinal toxicity of bolus 5-fluorouracil (5-FU) is well known compared to infusional 5-FU and capecitabine[18]. Replacement with capecitabine may have been responsible for the greater tolerance observed in the ARTIST study. Therefore, even though partially favorable, the efficacy and safety data indicate that the XP regimen with capecitabine and concurrent with radiotherapy could be a regimen adopted for the adjuvant treatment of gastric cancer.

In addition to the ARTIST trial, two other randomized trials and a meta-analysis have tried to elucidate the comparison of chemoradiotherapy to adjuvant chemotherapy in patients with gastric cancer who undergo D2 lymphadenectomy[19-21]. A phase Ⅲ, single institution Korean study with 90 patients, which was prematurely stopped due to low recruitment, demonstrated a reduced risk of locoregional relapse with the addition of radiotherapy to chemotherapy and an equivalent overall survival[19]. The therapeutic regimens followed the guidelines of the INT0116 study, including the use of 5-FU and folinic acid alone in the arms treated with adjuvant chemotherapy. Both treatments showed a similar toxicity profile.

A phase Ⅲ Chinese study on 404 patients, which used 5-FU according to the INT0116 study, while associating radiotherapy with the intensity-modulated radiotherapy technique also demonstrated a reduced risk of relapse (HR = 1.35; 95%CI: 1.03-1.78); the study's authors reported a median relapse-free survival of 50 mo in the combined treatment group *vs* 32 mo in the chemotherapy group, but there was no impact

Ref.	Treatment	*n*	D	DFS	OS	Toxicities G3-G4
Park *et al*[17]	XP *vs* XP/XRT/XP	458	D2	0.74 (0.52-1.05)	1.13 (0.77-1.64)	N 12%, V 3% in both groups
Kim *et al*[19]	FL/FL + RT/FL *vs* FL	90	D2	60.9% *vs* 50.0%	65.2% *vs* 54.6%	Hem 25%, GI 11.4% *vs* Hem 19.6%, GI 17.4%
Zhu *et al*[20]	FL/FL + IMRT/FL *vs* FL	404	D2	1.35 (1.03-1.78)	1.24 (0.94-1.65)	Leuco 7.5%, N 2.7% *vs* Leuco 7.3%, N 0%

Table 1 Randomized clinical trials comparing adjuvant chemoradiotherapy *vs* chemotherapy

D: Lymphadenectomy; DFS: Disease-free survival; OS: Overall survival; XP: Capecitabine + Cisplatin; FL: 5-Fluorouracil + Leucovorin; Hem: Hematological; GI: Gastrointestinal; N: Nausea; V: Vomiting; Leuco: Leucopenia.

on overall survival (HR = 1.24; 95%CI: 0.94-1.65)[20]. There was no difference between groups with respect to toxicity. The most frequent adverse effects were neutropenia (31% *vs* 25% in the chemoradiotherapy *vs* chemotherapy group, respectively) and diarrhea (38% *vs* 30%) (Table 1).

A meta-analysis evaluating the comparison of adjuvant chemoradiotherapy *vs* chemotherapy in patients with gastric cancer who underwent D2 lymphadenectomy demonstrated an increase in relapse-free survival (HR = 0.72; 95%CI: 0.59-0.89) and locoregional relapse-free survival (HR = 0.53; 95%CI: 0.32-0.87) in favor of combined treatment[21]. Three randomized studies were selected[17,19,20], including a total of 895 patients, who were all from Asian countries, and there was no benefit in terms of the distant metastasis-free survival and overall survival. There was no difference in the toxicity between groups.

A second meta-analysis evaluating the same comparison, but with a higher number of patients (6 trials with a total of 1171 patients), had similar results[22]. Chemoradiotherapy was associated with an increase in disease-free survival (HR = 1.48; 95%CI: 1.08-2.03). However, there was no difference in overall survival (HR = 1.27; 95%CI: 0.95-1.71). An analysis of five trials demonstrated no statistically significant differences in the toxicities between the two groups.

ADJUVANT CHEMOTHERAPY

Studies evaluating the role of adjuvant chemotherapy in gastric cancer used to be characterized by small sample sizes of patients, low recruitment, highly toxic chemotherapy regimens, and methodological limitations. With improvement in the clinical studies and treatment regimens, it has been possible to observe the benefits of adjuvant therapy. A meta-analysis based on individual data for 3838 patients demonstrated an 18% relative risk reduction in death (HR = 0.82; 95%CI: 0.76-0.90) with the use of adjuvant chemotherapy[9]. Group analysis did not identify differences when treatment modalities were analyzed, *i.e.*, monotherapy or polychemotherapy. Therefore, it is not possible to identify the best chemotherapy regimen. However, considering only one study included did not have fluoropyrimidines in its regimen, the recommendation is that when adjuvant chemotherapy alone is chosen, the regimen should

include 5-FU or oral fluoropyrimidines.

The practice of adjuvant chemotherapy is more common in Eastern countries. Since the publication of the INT0116 study, the relevant studies that have evaluated the role of adjuvant chemotherapy were conducted on this population. The reproducibility of these data in the Western population is being debated in view of the distinct surgical practices, different biological characteristics of the tumors and different patterns of recurrence between populations.

The use of S-1, an oral fluoropyrimidine, for adjuvant treatment was investigated in the ACTS-GC study, which involved 1059 patients with disease stages II and III who were submitted to curative resection associated with D2 lymphadenectomy; one group received surgical treatment followed by systemic therapy for 1 year, and a second group was treated with surgery alone[23,24]. The use of adjuvant S-1 permitted a 34% relative risk reduction of death (HR = 0.66; 95%CI: 0.54-0.82) as well as a 5-year overall survival of 71.7%, compared to 61.1% for the group that underwent surgical treatment alone[24]. Together with this marked survival gain, treatment safety was observed, including low rates of grades 3 and 4 toxicity (6.0% anorexia, 3.7% nausea, and 3.1% diarrhea)[23].

As in the ACTS-GC study, the CLASSIC trial evaluated the use of adjuvant oral fluoropyrimidines in patients who underwent curative resection in combination with D2 lymphadenectomy[25]. Only patients from South Korean, Chinese and Taiwanese centers participated in the study, and relapse-free survival was the primary endpoint. The study randomized 1035 patients to surgical treatment alone and to surgical treatment followed by 6 mo of adjuvant XELOX (oral capecitabine 1000 mg/m^2 twice daily on days 1 to 14 plus intravenous oxaliplatin 130 mg/m^2 on day 1 of each cycle). The systemic treatment was associated with a 44% relative risk reduction of relapse within 3 years (HR = 0.56; 95%CI: 0.44 to 0.72), which is a higher value than the 35% reduction reported in the ACTS-GC study (HR = 0.65; 95%CI: 0.53-0.79). The XELOX regimen resulted in higher grades 3 and 4 toxicity (56% *vs* 6% for the group with surgery alone) as well as 22% neutropenia, 8% nausea and 8% thrombocytopenia (Table 2).

Extrapolation of data obtained in studies of metastatic disease shows that the combination of fluoropyrimidines and platins has greater therapeutic activity than monotherapy. The comparison of 5-FU

Table 2 Randomized clinical trials comparing adjuvant chemotherapy *vs* observation

Study	Treatment	n	D	DFS	OS	Toxicities G3-G4
ACTS-GC[23,24]	S-1 *vs* observation	1059	D2-3	0.65 (0.53-0.79)[a]	0.66 (0.54-0.82)[a]	Anorexia 6%, N 3.7%
CLASSIC[25]	XELOX *vs* observation	1035	D2	0.56 (0.44-0.72)[a]	NR	Leuco 22%, N 8%

[a]P < 0.05, adjuvant chemotherapy *vs* observation. D: Lymphadenectomy; DFS: Disease-free survival; OS: Overall survival; XELOX: Capecitabine + Oxaliplatin; N: Nausea; Leuco: Leucopenia; NR: Not reported.

and leucovorin to 5-FU, leucovorin and adjuvant oxaliplatin (FOLFOX4) was performed in a randomized, single-institution study of only 80 patients[26]. The combined regimen led to an increase in relapse-free survival (30.0 mo *vs* 16.0 mo, P < 0.05) and overall survival (36.0 mo *vs* 28.0 mo, P < 0.05), and there were similar rates of adverse events, except for a higher incidence of peripheral neuropathy in the FOLFOX4 group.

Therefore, even though meta-analysis data do not demonstrate the superiority of polychemotherapy over adjuvant monotherapy in gastric cancer, recent studies that were not included in the cited meta-analysis suggest that as for metastatic disease, the combination of fluoropyrimidines and platins has a potentially greater reduction in the risk of death than fluoropyrimidines alone[26].

The absence of data on the overall survival in the CLASSIC study does not prevent the adoption of this regimen in clinical practice in view of data favoring disease-free survival as a surrogate endpoint of the overall survival in the adjuvant treatment of gastric cancer[27].

PERIOPERATIVE CHEMOTHERAPY

The high recurrence rates associated with the exclusive surgical treatment of gastric cancer are explained by the early occurrence of micrometastases. The combination of systemic and surgical treatment is justified by the imperative need to treat micrometastases. The start of systemic treatment before the surgical procedure is intended to provide early treatment for micrometastases as well as have the potential benefit of increasing the rates of resection by reducing the tumor size; additional goals are a complete pathological response, evaluation of therapeutic sensitivity *in vivo* and better tolerability of the systemic treatment in the absence of postoperative complications.

Based on these principles, the strategy of perioperative systemic treatment was proposed, including the use of treatment regimens known to be active for treating advanced disease and the use of chemotherapy both before and after surgical treatment. The main clinical study evaluating this strategy is the MAGIC study, involving 503 patients with gastric or distal esophagus adenocarcinoma[28]. The patients were randomized to a group of perioperative treatment (three cycles of the ECF regimen - epirubicin, cisplatin

and 5-fluorouracil - before and after surgery) and to a group of surgery alone. The use of perioperative treatment was associated with a reduced risk of relapse (HR = 0.66; 95%CI: 0.53-0.81) and of death (HR = 0.75; 95%CI: 0.60-0.93). The group of patients who underwent perioperative treatment had a higher rate of curative resection (79% *vs* 70%, P = 0.03), smaller tumors (T1-T2: 51% *vs* 36%, P = 0.002) and lower nodal involvement (N0-N1: 84% *vs* 70%, P = 0.01) upon anatomopathological study. The main adverse effects related to chemotherapy were myelotoxicity (23% and 27% grades 3 and 4 neutropenia during the preoperative and postoperative phase, respectively), nausea and vomiting.

An aspect that reflects the difficulty of perioperative treatment with the ECF regimen is that only 41% of the patients randomized to this group were able to complete the entire treatment schedule proposed. The administration of 5-FU in an infusional regimen lasting 21 d per cycle is difficult to execute in clinical practice. However, the recent availability of capecitabine and oxaliplatin, combined with the demonstration of the equivalent efficacy of the ECF regimen and of regimens in which replacement with these more recent drugs is possible, has increased the feasibility of perioperative treatment in clinical practice[29].

The ACCORD-07 study followed the MAGIC study and evaluated the efficacy and safety of perioperative treatment consisting only of platins and fluoropyrimidines, without the addition of anthracycline agents, in 224 patients[30]. Only 25% of the patients in this study had gastric cancer. The remaining patients had esophageal or esophagogastric junction tumors. The patients received 2 or 3 cycles of CF (cisplatin and infusional 5-FU) preoperatively and 3 or 4 cycles postoperatively, resulting in a total of 6 cycles. As also observed in the MAGIC study, perioperative treatment with the CF regimen was associated with a reduced risk of relapse (HR = 0.65; 95%CI: 0.48-0.89) and a reduced risk of death (HR = 0.69; 95%CI: 0.50-0.95). The patients who underwent perioperative chemotherapy also presented with higher rates of curative resection (87% *vs* 74%, P = 0.004), although there was no significant difference between the groups in terms of the pathological stage. The CF regimen showed the expected grades 3 and 4 toxicity as well as 20% neutropenia and 9% nausea and vomiting in the preoperative phase (Table 3).

Study	Treatment	n	D	DFS	OS	Toxicities G3-G4
MAGIC[28]	ECF *vs* observation	503	D1-2	0.66 (0.53-0.81)[a]	0.75 (0.60-0.93)[a]	Leuco 27.8%, N 12.3%
ACCORD-07[30]	CF *vs* observation	224	NR	0.65 (0.48-0.89)[a]	0.69 (0.50-0.95)[a]	Leuco 20.2%, N 9.2%

Table 3 Randomized clinical trials comparing perioperative chemotherapy *vs* observation

[a]$P < 0.05$, perioperative chemotherapy *vs* observation. D: Lymphadenectomy; DFS: Disease-free survival; OS: Overall survival; XELOX: Capecitabine + Oxaliplatin; N: Nausea; Leuco: Leucopenia; NR: Not reported.

INDIVIDUALIZED TREATMENT

HER2 and adjuvant treatment

HER2 overexpression and/or amplification is a controversial prognostic factor in gastric cancer, but its predictive value for the use of trastuzumab, an anti-HER2 monoclonal antibody, was demonstrated in the ToGA study, which involved patients with locally advanced or metastatic disease[31]. The addition of trastuzumab to cisplatin plus fluoropyrimidines in HER2-positive patients reduced the relative risk of death by 26% (HR = 0.74; 95%CI: 0.60-0.91), permitting an increase in overall survival from 11.1 to 13.8 mo. In exploratory analysis, the risk reduction was more pronounced in the HER2-enriched population, with 3+ or 2+ immunohistochemistry and FISH-positive status. In this population, the addition of trastuzumab increased survival from 11.8 to 16.0 mo (HR = 0.65; 95%CI: 0.51-0.83). The ToGA study was the first to permit the inclusion of a monoclonal antibody in the treatment of advanced gastric cancer, leading to the approval of the drug in several countries. No published prospective studies have evaluated the use of anti-HER2 therapies in the adjuvant treatment of gastric cancer. Ongoing phase II trials are evaluating the combination of capecitabine, oxaliplatin and trastuzumab in the neoadjuvant and adjuvant setting of HER2-positive gastric cancer patients (clinicaltrials.gov NCT 01748773, NCT01130337). The potential predictive value of HER2 expression to adjuvant therapies was obtained through the use of an exploratory analysis of relevant clinical trials.

The INT0116 study, by performing an immunohistochemical evaluation of 148 patients and FISH in 258 of the 556 patients, failed to identify the prognostic value of HER2 expression and/or amplification[32]. Among the patients with HER2 amplification (*n* = 28), there was no survival benefit with the use of adjuvant chemoradiotherapy (HR = 1.44; 95%CI: 0.44-4.75). In patients without HER2 amplification (*n* = 230), adjuvant chemoradiotherapy resulted in a significant increase in overall survival (HR = 1.58; 95%CI: 1.17-2.14), which was also demonstrated in the general population. In view of the small patient sample, the absence of a benefit from adjuvant treatment based on 5-fluorouracil concurrent with radiotherapy in patients with HER2 amplification should be interpreted with caution.

The evaluation of the HER2 status in the MAGIC study revealed data similar to that of the INT0116 study[33]. Of the 503 patients included in the study, 415 had their specimens evaluated for HER2 status. The hypothesis that HER2 overexpression and/or amplification would influence the sensitivity to the adjuvant therapy regimen based on anthracyclines was not confirmed. The HER2 status was not a prognostic factor in the MAGIC study nor was it a predictive factor for response to the ECF regimen. HER2-positive and HER2-negative patients had similar benefits after exposure to perioperative chemotherapy (interaction, *P* = 0.77).

An exploratory analysis of the ACTS-GC study also did not demonstrate an influence of the expression and/or amplification of HER2 on the prognosis for a population of patients with gastric cancer, and the benefit obtained with the administration of adjuvant S-1 did not vary according to HER2 status[34]. Of the 1059 patients included in the study, 829 were retrospectively evaluated in terms of the expression and/or amplification of HER2. A total of 113 patients (13.6%) were considered to be HER2-positive and, within this group, the use of adjuvant S-1 reduced the relative risk of death with the same magnitude as that observed in the HER2-negative group (HR = 0.63; 95%CI: 0.48-0.83 in HER2-negative; and HR = 0.63; 95%CI: 0.33-1.19 in HER2-positive).

Histological type and adjuvant treatment

Despite the recognized existence of distinct histological subtypes in gastric adenocarcinoma, with different risk factors and carcinogenesis, there is no individualized adjuvant therapy approach according to histological type.

The updates to the INT0116 study suggested, in the subgroup analysis, the absence of a benefit of adjuvant chemoradiotherapy in patients with the Laurén diffuse-type[10]. However, the interaction test did not show statistical significance.

The ARTIST trial demonstrated similar findings in a recent update, which revealed the absence of a benefit of chemoradiotherapy in patients with Laurén diffuse-type[17], which was also the case in a subgroup analysis. These findings, together with the INT0116 study, allow for the development of a hypothesis that patients with Laurén diffuse-type histology have little to no benefit from adjuvant chemoradiotherapy. However, given the known statistic limitations of the subgroup analysis, it cannot be generalized to clinical practice.

An ongoing phase Ⅱ/Ⅲ study (clinicaltrials.gov NCT01717924) is evaluating therapeutic strategies in patients with signet ring cell gastric adenocarcinoma. The patients will be randomized to perioperative treatment (3 cycles of ECF before and after surgical treatment) or to primary surgical treatment followed by 6 cycles of adjuvant ECF. This study may help clarify the best treatment approach for this subgroup of patients with gastric cancer.

Disease stage and adjuvant treatment

To date, there are no randomized studies that support the adjuvant treatment of gastric cancer directed for each stage of the disease. Through the lessons learned from breast and colon cancers, each stage of disease is expected to derive different benefits from adjuvant therapy. Based on the subgroup analysis of relevant clinical trials, greater disease stages may have lower benefits from adjuvant therapy, which is not statistically significant[13,23].

Ongoing clinical trials are trying to propose a stage-specific directed therapy. A phase Ⅲ study evaluating only stage IB gastric cancer patients randomized patients to adjuvant capecitabine *vs* observation (clinical trials.gov NCT01917552). Three randomized clinical trials are currently underway to evaluate adjuvant therapy only in patients with stage Ⅲ disease (clinicaltrials.gov NCT01618474, NCT01935778, NCT00182611). Adjuvant intraperitoneal chemotherapy with mitomycin C has been investigated together with systemic chemotherapy in a phase Ⅲ study in serosa-positive disease (clinical trials.gov NCT02205008).

POTENTIAL BIOMARKERS

Gene amplification is the most common genetic alteration in gastric cancer[35]. Most of these targetable driver mutations involve human receptor tyrosine kinases. Clinical studies evaluating the prognostic role of these overexpressed receptors and the use of tyrosine kinases inhibitors have been conducted in recent years. While these studies have been performed for advanced disease, the receptors are potential therapeutic targets in the adjuvant setting.

Fibroblast growth factor receptor (FGFR) is a transmembrane receptor tyrosine kinase family[35,36], which is represented by four members (FGFR1-4) that are involved in cell signaling by interacting with fibroblast growth factors (FGFs). The activation of FGFRs by FGFs leads to the autophosphorylation and activation of several downstream signaling pathways, including mitogen-activated protein kinase and phosphoinositide 3-kinase/akt/mTOR/p70S6kinase, which are crucial effectors in oncogenic signaling[35]. Studies have demonstrated FGFR2 amplification in 4% to 6% of gastric cancer patients, and it seems to be a prognostic factor in gastric cancer because patients harboring this genetic alteration have a poor survival rate[37,38]. FGFR2 inhibitors, such as ponatinib[39], dovatinib[40] and AZD4547[41], have activity against FGFR2-amplified cell lines *in vitro*. A randomized phase Ⅱ trial comparing AZD4547 to paclitaxel as a second-line treatment of advanced gastric cancer harboring FGFR2 polysomy or amplification is currently underway (clinicaltrials.gov NCT01457846).

The mesenchymal-epithelial transition (MET) receptor is also a transmembrane receptor tyrosine kinase that belongs to the hepatocyte growth factor receptor family[35]. It is estimated that 2% to 4% of gastric cancer patients have MET-amplification[41-43], which seems to confer poor prognosis[42]. In a report of four gastric cancer patients with advanced disease and MET-amplification, two responded to crizotinib, but the response had a limited duration[42]. Also disappointing was the use of foretinib in MET-amplified gastric cancer patients; none of the 69 patients treated with foretinib responded to this tyrosine kinase inhibitor[43]. One promising strategy for targeting MET is through monoclonal antibodies that bind to the MET receptor or to the circulating ligands for MET, such as hepatocyte growth factor. Onartuzumab, a MET antibody, is currently being tested with mFOLFOX6 in advanced gastric cancer patients who are HER2-negative and MET-positive based on immunohistochemistry (clinicaltrials.gov NCT01662869).

Epithelial growth factor receptor (EGFR) is a member of the HER receptor family that is over-expressed in a variable proportion of patients with gastric cancer[44-47], but gene amplification was found in only a small proportion of patients (2%)[44,47]. The strategy of inhibition of the EGFR pathway through both monoclonal antibodies and tyrosine kinase inhibitors in gastric cancer has been frustrating. Randomized trials using cetuximab[48], panitumumab[49], nimotuzumab[50] and erlotinib[51] in an unselected population of patients showed no clinical benefit. However, an evaluation in an enriched population may reveal new data.

PERSPECTIVES

The recent molecular characterization, including the identification of driver mutations in malignant neoplasms over the last decades and the resulting significant therapeutic impact, may contribute to modifying the adjuvant treatment of gastric cancer in the coming years. Monoclonal antibodies and tyrosine-kinase inhibitors are currently limited to advanced disease and are not used in adjuvant therapies, except for imatinib in GIST and trastuzumab in breast cancer. The recent incorporation of trastuzumab in the treatment of HER2-positive patients with advanced gastric cancer is currently being evaluated in the adjuvant treatment of early disease (clinicaltrials. gov NCT01130337, NCT01748773). Other anti-HER2 drugs, such as pertuzumab, which has recently been incorporated into the treatment for breast

cancer, are being investigated in advanced gastric cancer (clinicaltrials.gov NCT01774786) and, if they demonstrate a beneficial effect, they may be investigated in adjuvant treatment.

Currently, the association of systemic and surgical treatment has been incorporated into clinical practice, but the existence of distinct therapeutic options raises the question of which one is the best and when they should be used. The strategy of adjuvant chemotherapy has been rarely investigated in western countries and merits reproduction of the studies conducted in eastern countries, where this therapeutic modality has been evaluated more extensively.

Studies comparing the three most frequently adopted treatment strategies (adjuvant chemoradiotherapy, perioperative chemotherapy and adjuvant chemotherapy) are currently underway and will bring interesting updates in the next few years (clinicaltrials. gov NCT00407186, NCT01534546, NCT01761461, NCT01989858, NCT01516944, NCT00591045, NCT01665274, and NCT01640782).

In recent years, the chemotherapy regimen used in the INT0116 study has been criticized because bolus infusion of 5-FU is in disuse due to its greater toxicity compared to infusional 5-FU or capecitabine. When adjuvant chemoradiotherapy is performed, the recommendation is to replace bolus 5-FU with infusional regimens or with capecitabine or to follow the therapeutic regimen adopted in the ARTIST study, which includes the combination of cisplatin and capecitabine concurrent with radiotherapy. Studies that are currently underway are investigating the increased efficacy of chemoradiotherapy when, potentially, more effective regimens are used (clinicaltrials.gov NCT00052910).

CONCLUSION

Since the publication of the pivotal INT0116 study in 2001, important contributions have been made to the adjuvant treatment of gastric cancer. The main limitation of the original study, suboptimal surgical treatment, was corrected in later studies demonstrating that chemoradiotherapy prolongs the survival of patients who undergo D2 lymphadenectomy. The equivalent efficacy of chemotherapy and chemoradiotherapy that was demonstrated in the ARTIST study, albeit with better performance of the combined treatment in the subgroup of patients with positive lymph nodes and in the Laurén intestinal-type histology, shows that more than ten years after the original report, treatment based on chemoradiotherapy continues to be one of the main options of adjuvant treatment. The therapeutic options have also been expanded on the basis of studies evaluating the role of perioperative chemotherapy and adjuvant chemotherapy.

There is a need to investigate and identify the prognostic and predictive factors in early gastric cancer

to obtain the benefits already achieved in treating breast and colon cancer, for which there is a greater therapeutic individualization of adjuvant treatment with distinct benefits of adjuvant treatment according to tumor specificities. Therefore, randomized clinical trials in gastric cancer that consider the heterogeneity of gastric adenocarcinoma are needed.

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