

Role of Chemotherapy in Advanced Gastric Cancer: Review from a Latin American Perspective

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Abstract

Gastric cancer (GC) is the fourth most common neoplasm and the second leading cause of cancer-related death worldwide. In Latin America (LA), the burden of this disease is higher and is the leading cause of cancer death in some countries. Chemotherapy is the standard treatment for advanced-stage GC. However, the best regimen for specific populations, such as LA, is as yet unknown. Cisplatin and fluoropyrimidine continue to be the standard of care in light of the findings of phase III studies, while docetaxel, cisplatin, and 5-fluorouracil (5-FU) are alternatives for patients with suitable overall health. Oxaliplatin or irinotecan with fluoropyrimidine can also be used in elderly patients who are not candidates for cisplatin, or have a limited performance status. This review examines studies conducted in LA. Patients from LA are under-represented in multicenter trials of chemotherapy and targeted therapies. The major challenges currently lie in implementing strategies in which patients are selected on the basis of regional, racial or molecular characteristics, to consider the molecular subtype of GC for enrolment, and in selecting patients according to prognostic factors to optimize the benefits of chemotherapy.

Keywords

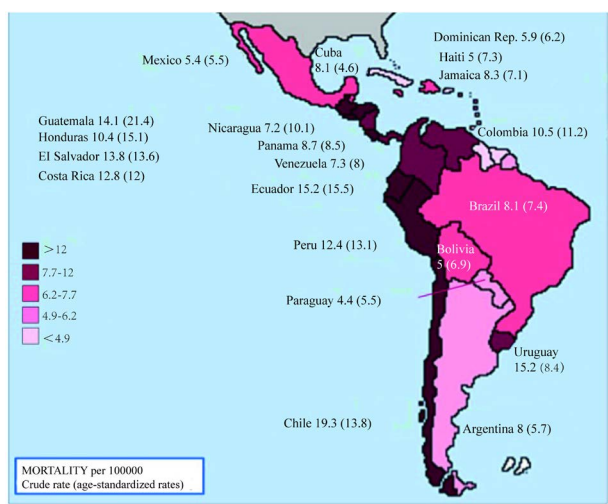
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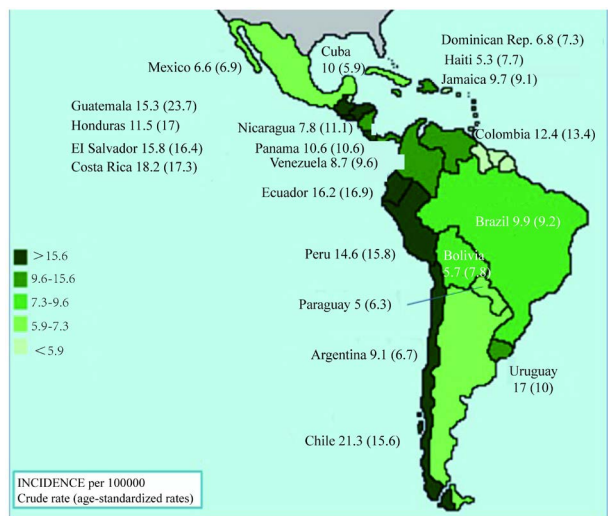
1. Introduction

GC remains the fourth most common cancer and is second leading cause of cancer-related death worldwide, exceeded only by lung cancer [1]. The facts that over 70% of these cases occur in low-income countries and that the mortality rate in young cohorts in developed countries has risen [2] suggest that gastric cancer may be among the top ten causes of death by 2030 [3]. Latin American populations (LAP) include people who live in Central and South America, as well as immigrants from these countries in the United States (US), Europe (EU), and other countries. LA’s total population is 606 million and rising; for example, the US includes 50.5 million people from LA, which represents 16.3% of the total population and is the fastest growing minority group in that country [4].

In LA, GC is a highly relevant disease given its prevalence, incidence, and associated mortality. In contrast to the US and EU, cancers related to infectious agents (liver cancer, stomach cancer, and cervix cancer) are exceedingly prevalent in LAP. GC remains common throughout many countries in Central and South America; for instance, in Chile, GC is the leading cause of cancer-related death in men and women combined [5] [6]. **Figure 1** illustrates the different mortality and incidence rates from GC in the different countries in LA.



(a)



(b)

Figure 1. Map of mortality (a) and incidence (b) of GC in Latin America. The data are expressed as the crude rate (age-standardized rate) per 100000 inhabitants.

The large proportion of GC patients who are diagnosed at stage IV and limited access to standard treatment may account for the high mortality associated with CG in LA. In the Dutch Eindhoven Cancer Registry, 50% of patients were diagnosed with stage IV disease, and this proportion did not change between 1990 and 2007 [7]. However, these data are not available for many countries in LA, except in Brazil where the diagnosis of advanced GC is observed in 85% of cases [8]. However, these data are not available for many other countries in LA.

The present review analyzes standard chemotherapy and factors associated with it in metastatic GC with a special focus on trials and experiences in LA.

2. Methods

We performed a review of the literature published in English, Spanish, or Portuguese on chemotherapy and advanced GC. The search was performed in PubMed, The Cochrane Library, EMBASE, and LILACS without date limits. The search strategy included different combinations of the following terms: “metastatic or advanced GC”, “stomach cancer”, “stomach neoplasms”, “esophagogastric junction cancer”, “Hispanic Americans”, “Latin American”, “chemotherapy”, “targeted therapy”, “Clinical trials”, and “Phase III study”. In topics without consistent Phase III studies, Phase II trials or case series reports published in or presented at relevant meetings were likewise included. Articles were also identified by searching the major oncology congress databases, including those of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), International Gastric Cancer Association (IGCA), Chilean Society of Medical Oncology (SCOM), and Latin American Society of Gastrointestinal Oncology (SLAGO).

Bibliographic references from selected papers also served as sources of additional information.

3. Chemotherapy Compared to Best Supportive Care

In the 1990s, at least three randomized studies were published that had been designed to verify whether chemotherapy had any benefit in the treatment of advanced GC compared to best supportive care (BSC) [9]-[11]. In these trials, drug combinations containing 5-FU showed a 61% increase in survival with a hazard ratio (HR) of 0.39. The median survival time of the chemotherapy-treated groups was 9 - 11 months compared to 3 - 4 months in the groups without chemotherapy; this difference was significant. BSC compared to chemotherapy has not been studied in LA, despite the high relevance of GC. However, in a considerable proportion of patients, BSC is the primary treatment; for example, in the registry of the Colombian “Instituto de Cancerología” 27% of patients with newly diagnosed GC were treated exclusively with BSC [12]. A meta-analysis published in 2010 examined thirty-five trials with a total of 5726 patients analysed for overall survival (OS) analysis. The comparison of chemotherapy versus BSC consistently demonstrated a significant benefit of chemotherapy in terms of OS (HR, 0.37; 95% confidence interval (CI), 0.24 - 0.55) [13]. These results confirmed chemotherapy as the standard treatment for GC worldwide, and chemotherapy was adopted by SLAGO [14] and the SCOM guidelines.

4. Combination Chemotherapy in GC (Table 1)

4.1. Classic Regimens

Fluoropyrimidine and cisplatin were studied in randomized clinical trials in GC with the basic regimen of cisplatin 100 mg/m² on day 1 and 5-FU 1000 mg/m²/day by continuous infusion (Ci) on days 1 - 5 every 4 weeks (FP4w); patients showed a response rate (RR) of 41% (95% CI: 28% - 54%) [15]. FAM (5-FU, adriamycin, and mitomycin) had a 15% RR and OS of almost 9 months [16]. FAMTX (5-FU, adriamycin, and methotrexate) showed a RR of 8% - 41% and median survival time of 5 - 10 months [17]. The epirubicin, cisplatin, and 5-FU regimen (ECF) was compared to FAMTX and exhibited improved RR (46% vs. 21%, $P = 0.00003$), median OS (8.7 vs. 6.1 months, $P = 0.0005$), and two-year survival rate (14% vs. 5%, $P = 0.03$) [18].

FAMTX was compared to FP4w and ELF (etoposide, leucovorin, and 5-FU). Disease control (response rate plus stable disease) was 55% for ELF, 46% for FAMTX, and 63% for FP4w. ELF showed a median OS of 7.2 months; FAMTX, 6.7 months, and FP4w, 7.2 months [19].

These results led FP4w and ECF to be considered the standard of care and were adopted in academic centers in LA; however, generally due to patient fragility, the proportion of patients with malnutrition and cost, FP4w was more extensively used.

Table 1. Selected phase III trials of first-line chemotherapy and/or targeted therapies in advanced GC.

Phase III Trial	Author	Year	N	Treatment Arms	ORR (%)	mPFS (m)	mOS (m)
Royal Marsden (18)	Webb A	1997	256	ECF FAMTX	45 21	7.4 3.4	8.9 5.7
EORTC (19)	Vanhoefer U	2000	399	ELF FP4w FAMTX	9 20 12	3.3 4.1 3.3	7.2 7.2 6.7
V325 (20)	Ajani JA	2007	445	DCF FP4w	37 25	5.6 3.7	9.2 8.6
Chinese trial (23)	Wang J	2015	243	mDCF FP3w	48.7 33.9	7.2 4.9	10.2 8.5
ML 17032 (24)	Kang YK	2009	316	XP FP3w	46 32	5.6 5.0	10.5 9.3
REAL-2 (25)	Cunningham E	2008	1002	ECF ECX EOF EOX	40.7 46.4 42.4 47.9	6.2 6.7 6.5 7.0	9.9 9.9 9.3 11.2
AIO (26)	Al Batran SE	2008	220	FLO FLP	34.8 24.5	5.8 3.9	10.7 8.8
French trial (31)	Dank M	2008	333	IFL FP4w	31.8 25.8	5.0 4.2	9.0 8.7
FFCD-Unicancer-GERCOR (32)	Guimbaud R	2014	416	FOLFIRI-ECX ECX-FOLFIRI	39.2 37.8	5.3 5.8	9.5 9.7
TOGA (40)	Bang YL	2010	594	X(FU)P X(FU)P-T	35 47	5.5 6.7	11.1 13.8
TRIO-013/LOGiC (41)	Hech R	2013	545	XOx XOx-L	40 53	5.4 6.0	10.5 12.2
AVAGAST (46)	Otshu A	2011	774	X(FU)P X(FU)P-Bev	37.4 46	5.3 6.7	10.1 12.1
AVATAR (47)	Shen J	2015	202	XP XP-Bev	33.7 40.7	6.0 6.3	11.4 10.5
EXPAND (43)	Lordick F	2013	904	XP XP-Cet	30 30	4.4 5.6	9.4 10.7
REAL-3 (44)	Waddell T	2013	553	EOX EOX-Pan	42 46	7.4 6.0	11.3 8.8

mPFS: Median progression free survival; Bev: Bevacizumab; W: Weeks; ORR: Overall response rate; XOx: Capecitabine; Oxaliplatin; DCF: Docetaxel, cisplatin, 5-FU; N: Number of patients; ECF: Epirubicin, cisplatin, 5-FU; FLO: 5-FU, Leucovorin, oxaliplatin; mOS: Median overall survival; FAMTX: 5-FU, adriamycin, Methotrexate; m: Modified; L: Lapatinib; X(FU); P: Capecitabine or 5-FU and Cisplatin; FLP: 5-FU, leucovorin, cisplatin; Pan: Panitumumab; XP: Capecitabine, Cisplatin; IFL: Irinotecan, 5-FU, leucovorin; Cet: Cetuximab; T: Trastuzumab; Paclit-W: Paclitaxel weekly; NR: Not registered; EOX: Epirubicin, Oxaliplatin, Capecitabine; ELF: Epirubicine, leucovorin, 5-FU; ECX: Epirubicin, cisplatin, capecitabine; FOLFIRI: 5-FU, leucovorin, Irinotecan.

4.2. Third-Generation Regimens

DCF: The V325 clinical trial compared docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1 and 5-FU 750 mg/m²/d by Ci on days 1 - 5 every 3 weeks (DCF) with FP4w. DCF had a higher RR (36.7% vs. 25.4%), TTP (5.6 vs. 3.7 months), OS (9.2 vs. 8.6 months), clinical benefit and improved quality of life ($p < 0.02$) than FP4w [20] [21]. There was no difference in treatment-related deaths and the high percentage of febrile neutropenia and/or neutropenic infection declined from 29% to 12% with the administration of granulocyte colony-stimulating factor. However, due to its high toxicity (neutropenia grade 3/4, 69%), the modified DCF regimen (mDCF) was developed and was included in more studies [22], in addition to being considered standard of care for

the Chinese population [23].

In LA, the DCF scheme is used in reference and academic centers and m DCF is the most commonly used regimen in younger patients with good performance status (PS).

XP: The ML 17032 phase III study showed similar OS for cisplatin 80 mg/m² on day 1 and oral capecitabine 1000 mg/m² twice daily on days 1 to 14 every 3 weeks (XP) in comparison to 5-FU 800 mg/m²/day by Ci on days 1 - 5 and cisplatin 80 mg/m² on day 1 every 3 weeks (FP3w) as first-line treatment. Median OS times were 10.5 and 9.3 months for XP and FP3w, respectively (unadjusted HR, 0.85; 95% CI, 0.64 - 1.13; P = 0.008) [24] (24). XP was combined with epirubicin (ECX) in a phase III clinical trial in advanced GC, and it was concluded that Capecitabine can replace 5-FU [25].

In LA, oral capecitabine is extensively used because it can replace the continuous infusion of 5-FU, which avoids the inconvenience and complications associated with central venous access and portable pumps; additionally, it shortens hospital stays.

Oxaliplatin regimens: The REAL-2 study tested the efficacy of oxaliplatin and capecitabine in a 2 × 2 non-inferiority trial. A total of 600 randomized patients were treated with one of four different regimens: ECF, EOF (epirubicin, oxaliplatin and 5-FU), ECX, or EOX (epirubicin, oxaliplatin and capecitabine). The regimens containing capecitabine showed favorable OS compared to those containing 5-FU (10.9 vs. 9.6 months; HR, 0.86; 95% CI, 0.75 - 0.99). Regimens with oxaliplatin displayed favorable OS compared to those with cisplatin (10.4 vs. 10.1 months). However, this difference was not statistically significant (HR, 0.92; 95% CI, 0.80 - 1.05). Serious side effects (approximately 40%) appeared with both cisplatin (neutropenia and thromboembolism) and oxaliplatin (diarrhea and neuropathy) [25].

The AIO (Arbeitsgemeinschaft Internistische Onkologie) group compared 5-FU 2600 mg/m² as a 24-hour infusion, leucovorin 200 mg/m² and oxaliplatin 85 mg/m² every 2 weeks (FLO regimen) to 5-FU 2000 mg/m² as a 24-hour infusion, leucovorin 200 mg/m², and cisplatin 50 mg/m² every 2 weeks (FLP combination). Increased progression-free survival (PFS) (FLO, 5.8 months vs. FLP, 3.9 months; p = 0.077) and OS (FLO, 10.7 vs. FLP, 8.8 months) was showed. However, FLO appeared to reduce hematological and cardiovascular toxicity in elderly people; therefore, oxaliplatin may be an alternative to cisplatin for the treatment of advanced GC in these patients [26]. The FOLFOX regimen (bolus 5-FU 400 mg/m², LV 200 mg/m², and 5-FU 600 mg/m² by 24-hour Ci on days 1 and 2 and oxaliplatin 85 mg/m² on day 1 every 2 weeks), a regimen that is widely used in LA, particularly in colorectal cancer, presented a good toxicity profile in a Chilean population with RR of 72.4% and median OS of 12.4 months [27]; the update of these results showed similar results, proving this scheme to be both active and safe [28] (28) (Table 2).

Table 2. Efficacy and selected toxicities of oxaliplatin and fluoropyrimidines in first-line chemotherapy in advanced GC.

Chemotherapy	Oxaliplatin and Fluoropyrimidine
Number of Patients	113
Response Rate % (95% CI)	62 (48 - 69)
mPFS (95% CI)	7.1 (6.1 - 8.2)
mOS (95% CI)	9.6 (7.8 - 11.3)
OS at 1 year (%)	51.3
Neutropenia Grade 3/4 (%)	13
Febrile Neutropenia (%)	3
Vomiting Grade 3/4	3
Death (60 days)	1

Oral capecitabine 1000 mg/m² twice daily on days 1 - 14 and oxaliplatin 130 mg/m² on day 1 every 3 weeks (XELOX) produced similar results to those with oxaliplatin and 5-FU, with a 42% RR, 5.8 month TTP, and 11.1 months OS [29]. The toxicity profile differed (more diarrhea and neuropathy; less thrombosis and neutropenia), but was not inferior to that of cisplatin regimens. In elderly patients, XELOX displayed similar results [30].

In LA, the FOLFOX regimen is broadly used instead of FP4w regimens, especially in elderly patients or those who are not candidates for cisplatin-containing regimens.

FOLFIRI/IFL: IFL was compared to FP4w in a French phase III trial. For IFL versus FP4w, RR values were 31.8% and 25.8%; TTP was 5.0 months and 4.2 months ($p = 0.088$), and OS rates were 9.0 and 8.7 months, respectively [31]. The IFL group exhibited a superior safety profile, making this regimen a suitable alternative for fragile patients or co-morbidities that limit the use of cisplatin.

The FOLFIRI regimen (irinotecan 180 mg/m², LV 400 mg/m², and bolus 5-FU 400 mg/m² on day 1 and 5-FU 2400 mg/m² for 46 hrs every 2 weeks) was evaluated in two sequences with ECX (FOLFIRI-ECX versus ECX-FOLFIRI). There were no differences in PFS or OS [32]. The potential benefit and improved tolerability of irinotecan-based regimens make IFL or FOLFIRI good choices for prolonging the chemotherapy treatment period and for combinations with new targeted agents in GC. In LA, the FOLFIRI regimen has been used as second-line treatment for patients with a PS < 2.

4.3. New Molecular Targeted Drugs in Advanced Gastric Cancer

GC over-expresses a large number of proteins and exhibits the amplification of genes involved in transduction and cellular growth. The molecular classification of GC in 3 or 4 subgroups provides for an understanding of the clinical differences and variable responses to chemotherapy in patients with a similar disease based on classic parameters [33] [34]. This molecular classification elucidates new therapeutic options based on molecular subtype or new molecular targets. The findings of The Cancer Genome Atlas Research Network included Epstein-Barr virus-associated GC; this group accounts for 23% of GC cases in LA [35] and these patients probably have a better prognosis [36].

Molecular targets are being tested in different populations in LA; for example, HER2 positivity in intestinal GC was 12% in Peru [37] and 16.4% in Chile [38]. These percentages are lower than the previously reported 24% in the validation study by Hoffman *et al.* [39], which raises the biological differences in different regions.

Phase III clinical trials using targeted agents are being developed; some of the published studies are described below.

Anti-HER/ErbB2: The TOGA trial used capecitabine 1000 mg/m² administered orally twice per day for 14 days, followed by a 1-week rest, or fluorouracil 800 mg/m² per day by continuous intravenous infusion on days 1 - 5 of each cycle, cisplatin 80 mg/m² on day 1 by intravenous infusion, and trastuzumab by intravenous infusion at 8 mg/kg on day 1 of the first cycle followed by 6 mg/kg every 3 weeks until disease progression [40]. A total of 22.1% (584) of the patients were HER2+ and were randomized to receive treatment with (294 patients) or without (290 patients) trastuzumab. The results of the study established a clear benefit of chemotherapy with trastuzumab in terms of OS (13.5 vs. 11.1 months; $p = 0.0048$). Fifty-two of these patients were from LA and showed a clear benefit of trastuzumab (HR, 0.44; 95% CI, 0.21 - 0.90). The TRIO-013/LOGIC trial exhibited a benefit in terms of PFS but not OS in HER2-positive patients treated with lapatinib and XELOX as first-line therapy [41]. The promising results obtained with trastuzumab led to the development of other phase II and III trials with trastuzumab or new anti-HER-2-targeted agents, such as lapatinib, pertuzumab, trastuzumab, emtansine (TDM-1), afatinib or dacomitinib, in combination with different chemotherapies (ECX, ECF, XP, XELOX, or FOLFOX). These trials are currently active, recruiting or in the process of being reported [42].

Anti-EGFR1: Two phase III studies, the EXPAND trial [43] (cisplatin and capecitabine with or without cetuximab) and the REAL-3 trial [44] (EOX with or without panitumumab), exhibited no benefit in PFS or OS. A small number of patients from LA were included in the EXPAND trial.

Anti-VEGF: The AVAGAST study (XP with and without bevacizumab) did not accomplish its primary endpoint of extending OS in patients treated with bevacizumab [45]; however, subgroup analyses demonstrated significantly longer OS in patients from non-Asian regions. Furthermore, a biomarker study showed that plasma VEGF-A and tumor neuropilin-1 are strong candidate biomarkers for predicting clinical outcome in patients with AGC who are treated with bevacizumab [46]. A subgroup of Pan-American patients (19%) benefited from the addition of bevacizumab, with a median OS rate of 11.5 versus 6.8 months (HR, 0.63; 95% CI, 0.43 - 0.94).

The AVATAR trial in a Chinese population yielded similar results to AVAGAST [47].

Ramucirumab is a fully humanized IgG1 monoclonal antibody targeting VEGF receptor-2. Its clinical activity as a second-line therapy for advanced GC was verified in the REGARD study. In this trial, 335 patients were randomized to BSC versus ramucirumab. The HR for OS was 0.776 (95% CI, 0.603 - 0.998; $p = 0.0473$). Median OS was 5.2 months for ramucirumab and 3.8 months for placebo [48]. The RAINBOW study of ramucirumab combined with paclitaxel in second-line therapy documented a significant increase in OS, establishing it as the new standard in this setting [49]. Forty-one patients in the REGARD and 23 in the RAINBOW trials were from LA.

Anti-PI3K-AKT-mTOR: This pathway has often been found to be activated in gastric cancer. A specific inhibitor of this pathway, everolimus, was evaluated in a phase III trial (GRANITE-1) in patients with two or more lines of treatment versus BSC. Median OS was 5.39 months with everolimus versus 4.34 months with BSC (HR, 0.90; 95% CI, 0.75 - 1.08; $P = 0.1244$); thirty-five Hispanic or Latino patients were included in this trial [50]. More studies are required with new inhibitors as first-line therapies, especially in patients with mTOR activation. The particular relevance of this pathway has been demonstrated in the new molecular classification of GC.

Anti-HGF-c-MET: This pathway has become an increasingly interesting target in many types of cancer. In gastric cancer, c-MET amplification is observed in 2% of patients. High MET expression, as determined by immunohistochemistry, may predict a clinical benefit from rilotumumab plus ECX in gastric cancer patients and may be associated with poor prognosis in ECX-treated patients [51]. A phase III clinical trial with rilotumumab is ongoing and includes centers in Mexico and Brazil.

5. Prognostic Factors in Patients with Advanced GC Treated with Chemotherapy

Prognostic models help to determine which patients will have a poor prognosis with standard treatment and in what circumstances alternative treatment strategies should be developed. Prognostic models for advanced cancer can also be used to stratify patients into subgroups in clinical trials to compare uniform groups of patients and contribute to the decision-making process involving physicians and patients.

In advanced GC, several studies have evaluated prognostic factors associated with worse survival.

European Population: The Royal Marsden Hospital's prognostic index has been validated in a larger sample. It was evaluated in a cohort of 1080 patients with advanced GC who were recruited in 3 clinical trials using chemotherapy. Mean OS of this cohort was 7.9 months. In the multivariate analysis, 4 prognostic factors were significantly associated with worse prognosis: performance status (PS) based on the Eastern Cooperative Oncology Group (ECOG) score ≥ 2 (HR, 1.58), the presence of peritoneal metastases (HR, 1.33), alkaline phosphatase ≥ 100 U/I (HR, 1.41), and the presence of liver metastases (HR, 1.41) [52].

Patients without any of these characteristics were classified as low risk, those with 1 or 2 variables were categorized as intermediate risk, and the high risk group comprised patients with 3 or 4 characteristics. Median survival times for the three groups were 11.8, 7.4, and 4.1 months, respectively. This prognostic index was validated with data from the REAL-2 trial, confirming its discriminatory capacity [53].

A Netherlands-based study evaluated 350 patients with advanced esophageal tumors who were treated with palliative cisplatin-based chemotherapy in 6 different phase I and phase II studies. The factors associated with worse prognosis in this series were ECOG PS ≥ 2 , elevated LDH, the presence of unresectable loco-regional disease, and the presence of disseminated metastatic disease [54].

Korean Population: Kim *et al.* evaluated 304 patients with advanced GC who were treated at a single center with cisplatin-based chemotherapy. In the multivariate analysis, the authors detected 5 factors associated with poor prognosis: poor performance status (HR, 1.46), elevated bilirubin (HR, 2.04), peritoneal metastases (HR, 1.73), bone metastases (HR, 3.11), and more than one metastatic site (HR, 1.22). This model enabled patients to be stratified into three prognostic groups with 1-year survival rates of 34.6%, 20.7%, and 1.7%, respectively ($p < 0.0001$) [55].

At Samsung Medical Center, a retrospective analysis was conducted of 1455 gastric cancer patients receiving first-line chemotherapy. In the multivariate analysis, they found 6 predictors that were associated with worse prognosis based on relative risk (RR): no prior gastrectomy (RR, 1.1), albumin < 3.6 g/dl (RR, 1.2), alkaline phosphatase > 85 U/l (RR, 1.2), ECOG PS ≥ 2 (RR, 1.6), bone metastases (RR, 1.4), and ascites (RR, 1.4). This model classified patients into 3 prognostic categories, with median OS times of 12.5, 7, and 2.8 months [56].

Only the Royal Marsden Hospital prognostic index has been validated in the setting of a clinical trial, such as

the REAL-2 study, but none of the prognostic indices have been validated independently in real clinical practice. The Royal Marsden Hospital prognostic factor has been evaluated in European and Asian populations without targeted therapy associated with chemotherapy.

LA population: Specific studies of prognostic factors in patients with advanced GC treated with chemotherapy have not been performed; however, the AGAMENON study organized by a Spanish and Chilean collaborative group is assessing prognostic factors in the real clinical practice of patients with advanced GC treated with chemotherapy and/or targeted therapy in a multicenter study. The data that prompted this study were presented at ESMO. Spanish and Chilean populations were included and eight independent prognostic factors were identified in the multivariate analysis (**Table 3**): two or more chronic co-morbidities (HR, 1.19; 95% CI, 1.04 - 1.36), ECOG performance status ≥ 2 (HR, 1.40; 95% CI, 0.99 - 2.14), the presence of signet ring cells (HR, 1.37; 95% CI, 1.07 - 1.72), HER2-overexpressing tumors treated with trastuzumab (HR, 0.71; 95% CI, 0.50 - 0.96), two or more sites of metastatic disease (HR 1.26; 95% CI, 1.08 - 1.63), carcinoembryonic antigen (CEA) ≥ 20 ng/ml (HR, 1.32; 95% CI, 1.23 - 1.69), the presence of bone metastasis (HR, 1.99; 95% CI, 1.37 - 2.87) and ascitis (HR, 1.67; 95% CI, 1.26 - 2.21). These variables were integrated into a prognostic index that classified patients into low (n = 84) (Group 1), moderate (n = 324) (Group 2), and high (n = 42) (Group 3) risk categories, with median OS times of 13.9 months in Group 1, 8.9 months in Group 2, and 6.2 months in Group 3; these differences in OS were statistically significant (p < 0.001) [57], a validation study is ongoing (**Table 4**).

6. Conclusions

People in LA have a very real health problem related to advanced CG. It is estimated that in the upcoming years, GC may gain in relevance due to increased risk factors, such as increased longevity, increased obesity, the lack of programs to identify GC in high-risk populations, the high rate of infection and re-infection with *Helicobacter pylori*, and limited access to health systems.

Table 3. Risk factors for overall survival (OS) identified in a multivariate analysis.

Risk Factor (RF)	HR	95% CI
Comorbidities, ≥ 2	1.19	1.04 - 1.36
ECOG, ≥ 2	1.40	0.99 - 2.14
Signet Ring Cells, >50%	1.37	1.07 - 1.72
Her2 Treated with Trastuzumab	0.71	0.50 - 0.96
Metastatic Sites, ≥ 2	1.26	1.08 - 1.63
CEA, ≥ 20	1.32	1.23 - 1.69
Bone Metastases	1.99	1.37 - 2.89
Ascitis	1.67	1.26 - 2.21

Table 4. Three groups of risk with differences in median OS (mOS) based on the eight risk factors.

Prognostic Index	mOS	p
Group 1: Low (0 RF)	13.4	
Group 2: Moderate (1 - 2 RF)	8.9	<0.001
Group 3: High (>2 RF)	6.2	

Despite considerable advances in the chemotherapeutic treatment of GC, mortality of advanced GC in LA remains high. People from LA are under-represented in multicenter clinical trials and specific studies in this population are rare, with the exception of isolated reports of experience in research centers. Finally, not a single report of targeted therapies in this population exists.

The identification of specific molecular subtypes and risk factors that are more prevalent in people from LA using TCGA has revealed specific characteristics of this population that require further analysis and specific studies to assess the true impact of treatments and chemotherapy regimens.

Everyday, patients who do not meet the conditions for clinical trials, as well as those with chronic and acute co-morbidities, advanced age, and poor PS are not included in clinical trials, and therefore, the effect they may have on the final prognosis of advanced GC has not been evaluated. It is possible that these patients respond differently than clinical trial subjects. In this sense, the AGAMENON study is moving in the right direction by evaluating prognostic factors in real clinical practice with a clear role for persons from LA. We hope that this is merely the first of many studies on the impact of treatment on populations where advanced GC is the top priority, as it is in LA.

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