Lauren subtypes of advanced gastric cancer influence survival and response to chemotherapy: real-world data from the AGAMENON National Cancer Registry

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BACKGROUND: The choice of chemotherapy in HER2-negative gastric cancer is based on centre’s preferences and adverse effects profile. No schedule is currently accepted as standard, nor are there any factors to predict response, other than HER2 status. We seek to evaluate whether Lauren type influences the efficacy of various chemotherapies and on patient overall survival (OS).

METHODS: We have conducted a multicenter study in 31 hospitals. The eligibility criteria include diagnosis of stomach or gastroesophageal junction adenocarcinoma, HER2 negativity, and chemotherapy containing 2–3 drugs. Cox proportional hazards regression adjusted for confounding factors, with tests of ‘treatment-by-histology’ interaction, was used to estimate treatment effect.

RESULTS: Our registry contains 1303 tumours analysable for OS end points and 730 evaluable for overall response rate (ORR). A decrease in ORR was detected in the presence of a diffuse component: odds ratio 0.719 (95% confidence interval (CI), 0.525–0.987), \( P = 0.039 \). Anthracycline- or docetaxel-containing schedules increased ORR only in the intestinal type. The diffuse type displayed increased mortality with hazard ratio (HR) of 1.201 (95% CI, 1.054–1.368), \( P = 0.0056 \). Patients receiving chemotherapy with docetaxel exhibited increased OS limited to the intestinal type: HR 0.65 (95% CI, 0.49–0.87), \( P = 0.024 \), with no increment in OS for the subset having a diffuse component. With respect to progression-free survival (PFS), a significant interaction was seen in the effect of docetaxel-containing schedules, with better PFS limited to the intestinal type subgroup, in the comparison against any other schedule: HR 0.65 (95% CI, 0.50–0.85), \( P = 0.015 \), and against anthracycline-based regimens: HR 0.64 (95% CI, 0.46–0.88), \( P = 0.046 \).

CONCLUSIONS: As a conclusion, in this registry, Lauren classification tumour subtypes predicted survival and responded differently to chemotherapy. Future clinical trials should stratify effect estimations based on histology.

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Advanced gastric cancer (AGC) is a complex, heterogenous entity that encompasses tumors with varying histologies, molecular profiles, and behaviours. Lauren's histological classification differentiates between intestinal type (IT), with the presence of gland formations, and diffuse type (DT), with a pattern of poorly cohesive cells, high invasiveness, and on occasion, the presence of signet ring cells. This histological classification is relevant from a prognostic, epidemiological, and pathogenic perspective (Lauren, 1965). The two histotypes differ in their clinical and molecular features to the point of representing distinct entities (Shah et al., 2011; Tan et al., 2011; Ma et al., 2016). Thus, DT tumors are often genomically stable, although they tend to harbour characteristic mutations in genes that participate in adhesion, chromatin integrity, or cell motility, such as the E-cadherin gene (CDH1) and Ras homologue gene family, member A (RhoA), as well as fusions involving the gene that codes for claudin-18 and Rho GTPase activating protein 6 (CLDN18-ARHGAP6), among others (Cancer Genome Atlas Research Network, 2014). In contrast, IT tumors exhibit aneuploidy or other genetic features more frequently, the most relevant ones being certain mitotic and signalling pathways, such as human epidermal growth factor receptor 2 (HER2) (Hofmann et al., 2008; Cancer Genome Atlas Research Network, 2014).

In cancers overexpressing or amplifying HER2, the combination of cisplatin–fluoropyrimidine–trastuzumab is considered to be the treatment of reference and is, to date, the schedule that has achieved the best results with median overall survival (mOS) of 13.8 months (Bang et al., 2010). In HER2-negative cancers, different combinations of platin with fluoropyrimidine attain mOS rates that rarely exceed 12 months, and overall response rates (ORR) that range between 35 and 45%. The addition of a third cytotoxic (epirubicin or docetaxel) is not able to reach mOS >12 months, while increasing toxicity (Wagner et al., 2010). At present, the choice of treatment schedule for HER2-negative tumors is based on the centre’s preferences and adverse effects profile, with no chemotherapy deemed standard across-the-board (Duo-Ji et al., 2017). Therefore, identifying factors that modify response to drugs and guide clinical decisions continues to be a pressing concern.

Despite the fact that the Lauren classification is more than 50 years old (Lauren, 1965), the predictive effect of each histological subtype on various end points related to the efficacy of chemotherapy has yet to be definitively elucidated, since most important pivotal trials in western populations did not report predefined subgroup analyses based on these criteria. This has led to these pathological subtypes being treated equally (Van Cutsem et al., 2006; Cunningham et al., 2008). In the case of AGC, most data available from Asian populations suggest that histological heterogeneity correlates to sensitivity to specific drugs, opening the door to personalised therapies (Koizumi et al., 2008, 2014; Boku et al., 2009; Narahara et al., 2011). However, the evidence is still weak, with interaction tests that were often non-significant or simply not reported, as addition to having limited sample sizes.

Against this background, the aim of this study has been to ascertain whether Lauren type modified response to several chemotherapy regimens used in clinical practice. To this end, ‘real world’ data from a National AGC Registry have been used.

MATERIALS AND METHODS

Patients. All the patient data are from a national registry of consecutive cases of AGC that began recruitment in 2014 (AGAMENON Study), with the participation of one Chilean and 30 Spanish centres. The main characteristics of this registry, method, and data collection criteria have been previously reported (Carmona-Bayonas et al., 2016, 2017; Jiménez-Fonseca et al., 2016; Custodio et al., 2017). Briefly put, AGAMENON is a non-interventionist registry sponsored by the investigators themselves; the diagnostic and therapeutic patterns were those implemented according to the clinical practice of each centre. The data are gathered by means of a web-based data collection tool (http://www.agamenonstudy.com/). This tool has multiple filters and a system of queries, to ensure the reliability of the data in real time. The researchers are systematically instructed on the requirements of the registry and the information is regularly monitored remotely and the cases are closed after they are validated.

Basically, eligibility criteria for OS end points include a histologically confirmed diagnosis of resectable, locally advanced, or metastatic adenocarcinoma of the stomach or gastroesophageal junction; furthermore, patients must have received a minimum of one course of polychemotherapy containing two or three drugs. The population that is eligible for objective tumour response analysis also required the presence of initially measurable disease, with at least one objective evaluation at three months, according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Adenocarcinomas of the oesophagus were excluded from this analysis, despite their molecular similarities with gastric cancer with chromosomal instability (Cancer Genome Atlas Research Network, 2017), given the epidemiological and molecular differences, and specific treatment patterns. We also excluded HER2-positive tumours (immunohistochemistry 3+ or 2+, and fluorescent in situ hybridisation-positive), as they represent a different biological reality with standard treatment. Other exclusion criteria were <6 months since the end of adjuvant or perioperative treatment, the absence of other synchronous primary cancers, and the absence of at least 3 months of follow-up (except for the patients who died during this period). The study was approved by a multicenter Research Ethics Committee. All patients still alive at the time of data collection provided written, signed, informed consent.

Variables. The primary end point of this study was ORR as per RECIST 1.1 criteria locally evaluated according to the usual practice at the centre. Secondary end points were OS and progression-free survival (PFS) defined as the time between treatment initiation and tumour progression or all-cause mortality, censoring patients lost to follow-up. The chemotherapy regimens used in each histological type are those that represent patterns of real-world clinical practice at the various centres (Supplementary Annex Table 1). The following strata were established for pairwise comparisons of chemotherapy schedules: two-agent with cisplatin–fluoropyrimidine, two-agent containing oxaliplatin–fluoropyrimidine, regimens with irinotecan, three-agent with anthracyclines, and docetaxel-containing schedules. The Lauren classification was locally assessed as routinely performed at each centre, and no centralised review was carried out. Tumours with signet ring cells were classified as diffuse according to International Agency for Research on Cancer (IARC) criteria (Hamilton and Aaltonen, 2000). As possible confounding factors, we considered 17 routinely available baseline clinical-pathological variables proven to predict survival in at least one previous publication (Custodio et al., 2017). In addition, univariate analyses were performed to verify that these variables had prognostic significance and to exclude other potential factors (Supplementary Annex Table 2).

Statistical methods. The Cochran–Mantel–Haenszel (CMH) test was used to evaluate the null hypothesis of ORR being independent of Lauren type and controlling for kind of chemotherapy. The heterogeneity across sites was evaluated with the I2 statistic. The homogeneity of the odds ratio for each treatment was analysed by the Breslow–Day test. To assess the effect of each treatment (hazard ratio (HR)) for each end point in subgroups defined by the Lauren classification, the Cox proportional hazards regression was used, adjusted for interaction tests (treatment type by-Lauren), and
the previously named confounding factors. Interaction tests make it possible to detect whether the observed effect of treatment is significantly different in each Lauren subtype (Simon, 1982; Barraclough and Govindan, 2010). All statistical assessments were two-sided and P-values <0.05 were deemed significant. The Holm–Bonferroni method was used for multiple comparisons. Prior data from the literature indicate that the ORR for IT tumours is ~45%. If the true ORR for DT tumours were 25% lower, some 626 patients would be required, using χ² statistics in order to reject the null hypothesis that responses in those subtypes are equal, with a statistical power of 80%, and a Type I error probability of 5% (Fleiss et al, 1980). Statistical analyses were performed using RStudio (RStudio, Inc., Boston, MA, USA), including survival, base, epitools, and forest plot packages.

RESULTS

Patients. At the data cutoff (June 2017), the registry comprised 2203 patients treated with first-line chemotherapy between January 2008 and March 2017, of which 1303 were evaluable for survival end points and 730 for tumour response. The patient selection process is presented in Figure 1. It is worth noting that the exclusion of HER2-positives (281 tumours) conditions the distribution of the Lauren histological types in this series (37% IT, 50%, DT, and 13% not classified). The analysis of histological results by centres reveals the presence of slight heterogeneity (I² = 25%, P = 0.115) (Supplementary Annex Table 3). The remaining baseline characteristics of the cohort are displayed in Table 1. The disease was initially categorised as measurable by RECIST 1.1 criteria in 71%, while 56% had measurable disease at baseline and evaluable at 3 months. Briefly put, the schedules were: oxaliplatin–fluoropyridines (35%), anthracycline-containing triplets (26%), docetaxel-based schedules (15%), cisplatin–fluoropyrimidines (15%), irinotecan-based regimens (2%), and other (5%) (Supplementary Annex Table 1). As regards the docetaxel-based schedules, 76% (145 of 197) were triple-agent regimens.

ORR according to Lauren histological type. A total of 730 patients had measurable and response-evaluable disease (Figure 1).

*Categories are not mutually exclusive

Figure 1. Flowchart of patients in the registry. HER2 = human epidermal growth factor receptor 2.
across chemotherapy strata (Breslow–Day test, heterogeneity was observed regarding ORR in each Lauren type chemotherapy is shown in Figure 2. In this analysis, no overall $P = 0.843$), significantly decreased: common odds ratio 0.522 (95% CI, 0.323–0.88), compared to anthracycline-based combinations vs chemotherapy with or without irinotecan. In contrast, a significant interaction was seen in the comparison of oxaliplatin-containing double-chemotherapy vs cisplatin; likewise, the same is true for with or without anthracyclines. In contrast, the interaction tests revealed an observable subgroup effect in OS benefit for schedules incorporating docetaxel. In comparison to the rest of the population, patients receiving chemotherapy with docetaxel exhibited increased mOS limited to IT: HR 0.65 (95% CI, 0.49–0.87), $P = 0.024$.

On the other hand, at the data cutoff point, 1040 events of progression had been recorded in 1303 patients (80%). All told, no significant differences were detected in mPFS based on Lauren type: 6.1 months (95% CI, 5.6–6.5) for IT, 6.2 months (95% CI, 5.6–6.5) for DT, and 5.4 months (95% CI, 4.4–6.3) for unclassified tumours, with a log-rank test of $\chi^2 = 3.3$, $df = 2$, $P = 0.191$. In the case of the effect of chemotherapy on PFS for each subgroup, the difference in estimates is reported in Figure 3. In line with the survival analysis, no differences were detected in subgroups (HR for PFS for two-agent chemotherapy based on oxaliplatin or cisplatin; likewise, the same is true for with or without anthracyclines. In contrast, a significant interaction was seen in the effect of docetaxel-containing schedules, with significantly better PFS limited to the IT, in the comparison against any other schedule: HR 0.65 (95% CI, 0.50–0.85), $P = 0.015$, and in comparison to anthracycline-based regimens: HR 0.64 (95% CI, 0.46–0.88), $P = 0.046$ (Figure 4).
pronounced activity in IT vs DT (Al-Batran et al, 2016). This conclusion is also in line with the result of another neoadjuvant study, the NeoFLOT trial, a phase II that also found FLOT was more active in predominantly IT, as quantified in terms of complete or near complete ORR (Schulz et al, 2015). In turn, our data are compatible with the results of the V325 clinical trial that concluded that adding docetaxel to cisplatin–fluorouracil significantly improved OS, although this analysis was not stratified based on histology (Van Cutsem et al, 2006). Nevertheless, given the toxicity of these schedules, it would be worthwhile to corroborate the risk-benefit in DT in future clinical trials.

Insofar as triple-agent regimens are concerned, this analysis constitutes a refinement of other previous reports from the AGAMENON registry in which it was suggested that three-drug regimens (both epirubicin- and docetaxel-based) were associated with a discrete increase in OS: HR 0.84 (95% CI, 0.72–0.98; P = 0.035) (Carmona-Bayonas et al, 2016), although this beneficial effect disappeared when the comparison was confined to anthracyclines-based triplets vs platin–fluoropyrimidine double-agent therapies: HR 0.91 (CI, 95%, 0.76–1.08; P = 0.226) (Carmona-Bayonas et al, 2017). Indeed, here we confirm that the absence of incremental benefit in survival-related outcomes apparently involved with the addition of anthracyclines to platin–fluoropyrimidine double-agent therapies does not vary significantly according to the underlying histological subtype. Our series illustrate that more intense schedules with docetaxel increase PFS, compared to schedules with anthracyclines; however, we propose the hypothesis that this benefit is limited to the IT subgroup and it is possible that it does not occur in DT, which would have to be corroborated in the future.

As for individuals who received only double-agent schedules, the data obtained about patients with measurable and response-evaluable disease in our registry were unable to provide statistical evidence that the oxaliplatin–fluoropyrimidines regimens yielded higher ORR in IT than cisplatin–fluoropyrimidine. In this regard, a small, phase II trial have recently suggested that microarray-based tumour molecular profiling is predictive of differential platin sensitivity (Yong; et al, 2017). The method consisted of testing a genetic signature developed in a cohort from the National Cancer Centre of Singapore that classified tumours into two genomic subtypes, one intestinal and another diffuse, with greater sensitivity.
to oxaliplatin and cisplatin, respectively (Tan et al., 2011). Nevertheless, concordance with the Lauren histological classification in this study was only 65%; hence, its correspondence with our data is questionable. Furthermore, for survival end points, we have not either detected interactions between the type of platin and histology. In any case, we have not been able to demonstrate greater sensitivity to cisplatin in the DT; our overall impression is that clinical–molecular correlations require more extensive clinical validations.

Insofar as the generalisability and reproducibility of these results are concerned, one of the most salient characteristics of our series is the exclusion of HER2-positive tumours, which have distinctive traits: (1) a single, standard treatment with platin–fluoropyrimidine–trastuzumab (Bang et al., 2010) and (2) preponderance of IT (Huang et al., 2013). These aspects condition the histological distribution in our cohort that has a higher rate of diffuse tumours which eliminates systematic errors, but prevents the evaluation of response in DT tumours with only unmeasurable, peritoneal miliary dissemination, which presumably constitutes less chemo-sensitive diseases (Yoon et al., 2016).

Our study has certain limitations. Some of them are contingent to any result based on subgroup analyses, for example, increased type II errors when the alternative hypothesis is correct (Barraclough and Govindan, 2010). Therefore, this kind of report must necessarily be interpreted with caution. Although the Holm–Bonferroni method is used to control the family-wise error rate due to multiple comparisons, it also reduces statistical power; thus, the existence of small differences cannot be ruled out. Other limitations are common to all analyses of registries with ‘real world’ data. Most of the data are retrospective with the inherent issues of accuracy, although in this case, the end points used (ORR, PFS, and OS) are solid variables that tend to be reliably reflected in patient histories. Nonetheless, one uncertainty is that there is no common pathology protocol to evaluate histopathological classification. In fact, the lack of a centralised pathology examination has been a constant limitation in conducting clinical trials addressing chemotherapy in AGC, casting clear doubts on the interpretation and applicability of ‘average’ results in the study population.
Consequently, we believe it is important that future clinical trials substitute for it was obtained from all patients before they were informed of all variables that could modify response to drugs must be validated; p.g., histology. In this regard, our data support the hypothesis that histopathological heterogeneity is reflected as specific sensitivity to different cytotoxics (Koizumi et al., 2008; Ajanı et al., 2009; Boku et al., 2009; Narahara et al, 2011). Furthermore, we believe it is important that future clinical trial protocols with chemotherapy for AGC contemplate stratification by Lauren type.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Hansson L-E, Lindgren A, Nyren O (1996) Can endoscopic biopsy specimens from endoscopic biopsies (Hansson et al., 1996; Shibata et al., 2001). Despite this, our rate of unclassified tumours is within the range reported by other authors (Pölkowksi et al., 1999). On the other hand, a centralised evaluation of radiological response was not performed. Nevertheless, the chemosensitivity data are compatible with the information from other similar series (Schulz et al., 2015; Al-Batran et al., 2016). Another relevant aspect is that, given the diversity of the chemotherapy regimens in this registry, we have evaluated them as drug-based groups, taking into account their common characteristics, although it is possible that the specific schedules differ somewhat in efficacy profiles, for example, dose-dependent and periodicity of the regimen. Furthermore, we have not assessed the impact of histology on second-line chemotherapy in this analysis, which could also affect OS, particularly after the introduction of ramucirumab in recent times in clinical practice.

In short, in light of the difficulty in choosing first-line chemotherapy for a patient with HER2-negative AGC, the effect of all variables that could modify response to drugs must be validated; p.g., histology. In this regard, our data support the hypothesis that histopathological heterogeneity is reflected as specific sensitivity to different cytotoxics (Koizumi et al., 2008; Ajanı et al., 2009; Boku et al., 2009; Narahara et al, 2011). Consequently, we believe it is important that future clinical trial protocols with chemotherapy for AGC contemplate stratification by Lauren type.

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