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Efficacy and safety of chemotherapy in older *versus* non-older patients with advanced gastric cancer: A real-world data, non-inferiority analysis

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ABSTRACT

Objective: Advanced gastric cancer (AGC) is a common neoplasm in older adults. Nevertheless, there are few specific management data in the literature. The aim of this study was to assess non-inferiority of survival and efficacy-related outcomes of chemotherapy used in older *vs* non-older patients with AGC.
Materials and Methods: We recruited 1485 patients from the AGAMENON registry of AGC treated with polychemotherapy between 2008–2017. A statistical analysis was conducted to prove non-inferiority for overall survival (OS) associated with the use of chemotherapy schedules in individuals ≥70 *vs.*<70 years. The fixed-margin method was used (hazard ratio [HR]<1.176) that corresponds to conserving at least 85% efficacy. Results: 33% (n = 489) of the cases analyzed were ≥70 years. Two-agent chemotherapies and combinations with

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oxaliplatin (48% *vs.* 29%) were used more often in the older patients, as were modified schedules and/or lower doses. Toxicity grade 3–4 was comparable in both groups, although when looking at any grade, there were more episodes of enteritis, renal toxicity, and fatigue in older patients. In addition, toxicity was a frequent cause for discontinuing treatment in older patients. The response rate was similar in both groups. After adjusting for confounding factors, the non-inferiority of OS associated with schedules administered to the older *vs.* younger subjects was confirmed: HR 1.02 (90% CI, 0.91–1.14), P (non inferiority) = 0.018, as well as progression-free survival: HR 0.97 (90% CI, 0.87–1.08), P(non-inferiority) = 0.001.
Conclusion: In this AGC registry, the use of chemotherapy with schedules adapted to patients ≥ 70 years provided efficacy that was not inferior to that seen in younger cases, with comparable adverse effects.

1. Introduction

While the incidence and overall death rates associated with advanced gastric cancer (AGC) have decreased over the last four decades [1], cancer of the stomach comprises the fourth most common neoplasm and the third leading cause of cancer mortality in Europe [2]. According to data from the *Surveillance, Epidemiology, and End Results* (SEER) program, the median age at diagnosis is 68 years and one third of all individuals diagnosed are over the age of 70 [3]. Given that population aging is accelerating in the West, this epidemiological profile is expected to intensify.

At present, chemotherapy has proven a clear clinical benefit in individuals with AGC [4]. However, older participants are underrepresented in most clinical trials; the median age of AGC clinical trial participants is between 54 and 65 years [5]. It is therefore doubtful that these data can be extrapolated to real subjects who may be ten to twenty years older.

Most of the data available regarding chemotherapy in older patients with ACG are pooled subgroup analyses from clinical trials with few participants in these age ranges. Furthermore, these clinical trials looked at chemotherapeutic regimens currently considered to be obsolete. Trumper et al. conducted a pooled analysis of three trials and concluded that chronological age *per se* should not be considered a contraindication to the use of chemotherapy. There were no differences with respect to efficacy or grade 3–4 toxicities based on age. However, indications of selection bias were seen, with only 24% of the cohort over the age of 70, and no patients over the age of 80 being treated with platin-based schedules [6]. In contrast, a second pooled analysis of eight clinical trials by the *North Central Cancer Treatment Group* carried out by Jatoi et al. concluded that the rate of serious adverse events (neutropenia, asthenia, infection,and stomatitis) was much higher in people >65 years, although survival-related outcomes did not vary based on age. The authors concluded that more tolerable treatment regimens needed to be developed for this, *a priori*, more vulnerable population [7].

Despite all this, the debate surrounding the efficacy and safety of chemotherapy for AGC in older individuals remains open, since real-world patients may be more frail and have more comorbidities compared to the highly selected populations of the previously mentioned clinical trials. Moreover, a percentage of these patients can be expected to have received pragmatically modified, less intense schedules compared to the standard schedules evaluated in clinical trials [8].

Thus, registry-based cohort studies address real-world safety concerns by examining serious toxicities and risk-benefit ratios in larger series of older subjects. With this rationale, the aim of this study has been to assess the non-inferiority of survival-and efficacy-related outcomes of the chemotherapy schemes used in older patients compared to non-older patients, as well as to compare safety, in a national AGC registry.

2. Patients and Method

2.1. Study Design and Participants

Patients are from the AGAMENON database, a national registry of consecutive cases of AGC, in which 30 Spanish centers and one Chilean center have participated. The study design, characteristics, method, and data quality criteria have been widely communicated elsewhere [9–13]. AGAMENON is a non-interventionist database sponsored by the investigators themselves. Data are collected by means of a web-based data collection tool (http://www.agamenonstudy.com/). This tool consists of several filters and a system of queries, to assure data reliability in real time. The researchers are methodically trained on the requirements of the registry and the information is regularly monitored remotely, closing cases after validation.

Eligibility criteria included adult patients (≥eighteen years) with histologically confirmed, unresectable or metastatic gastric, gastro-esophageal junction (GEJ), or distal esophageal adenocarcinoma and who received first line chemotherapy with two or three drugs. Esophageal adenocarcinomas were eligible for this analysis because of their molecular similarity to gastric cancer [14]. Two populations were chosen: one to analyze survival-and safety-related end points and another one to examine objective tumor response-related endpoints. The two requisites for the populations analyzable for objective tumor response were the presence of initially measurable disease and at least one objective evaluation three months later, according to *Response Evaluation Criteria in Solid Tumors* (RECIST 1.1) criteria. Exclusion criteria included: the absence of at least three months of follow-up (except for those subjects who died prior to the three-month evaluation), less than six months since completion of an eventual adjuvant or neoadjuvant therapy, and the presence of other synchronous cancers. Participants treated with single-agent chemotherapy were excluded.

2.2. Variables and Outcomes

The primary outcome of this analysis was overall survival (OS), defined as the interval between initiating first-line chemotherapy and demise for any cause. Secondary outcomes were the percentage of patients (with initially measurable disease) who obtained an objective response as per RECIST version 1.1 criteria; progression-free survival (PFS), defined as the time elapsed between initiation of first-line chemotherapy and progression ordemise, and safety in keeping with the *National Cancer Institute Common Toxicity Criteria*, version 3.0 [15]. "Older patient" was defined as being 70 years old or older. The chemotherapys chedules were the ones chosen in real-life clinical practice. To compare schedules with each other, five strata were established: two-agent chemotherapies with cisplatin-fluoropyrimidine; two-agent chemotherapy with oxaliplatin-fluoropyrimidine; schedules with irinotecan; triple-agent therapy with anthracyclines; and docetaxel-based schedules. Dose intensity (DI) was defined as the amount of drug administered per unit of time, expressed as milligrams per square meter (mg/m^2) weekly. Cumulative dose was defined as the total dose and reported as total mg/m^2 administered. Relative dose intensity (RDI) was considered to be the DI administered with respect to the planned dose intensity for each schedule. Twenty-two prognostic variables deemed important in gastric cancer in at least one previous study [12] were collected in the registry as possible confounding factors.

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