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Clinicopathological, Epidemiological and Outcome of Treatment of Advanced Gastric Cancer in Egypt: Single Institution Experience

Ahmed Gabballah [1], Manal Moawad [1], Mohamed Yassin [1], Manal M. El-Mahdy[2] and Nancy El-wasly[1]

1. *Clinical Oncology Department, Ain Shams University, Cairo, Egypt.*
2. *Pathology Department, Ain Shams University, Cairo, Egypt.*

Corresponding Author:
Ahmed Gaballah
Clinical Oncology Dept., Faculty of Medicine, Ain Shams University
Abbasia, Cairo 11555, Cairo, Egypt
Tel. +201066882266,
Email drgaballah@gmail.com

Abstract

Background: Gastric cancer is the 3rd cause of cancer-related deaths. In Egypt, it is 12th regarding incidence and cancer-related deaths. About 65% of patients present with advanced diseases with 5-year survival rates 5-30%. Several prognostic factors had been identified for gastric cancer including age, HER-neu and pathological features.

Methods: Retrospective analysis of advanced gastric cancer patients at Ain Shams university, treated between January 2011 and December 2014 with retrospective analysis of HER-neu.

Results: Median age was 52. 55% were male and 57% were smokers. 58% of patients had performance status. The main presenting symptom was vomiting. Diffuse pattern was predominant (66.7%) and high grade tumor (61%). Liver was the most common site of metastasis (31%). HER2-neu was positive in 10.5%. Median OS was 7 months with significantly better survival in young patients (<45years), non-smokers, intestinal-type, patients with metachronous metastasis (> 6 months DFS) with P value 0.003, 0.0001, 0.03, 0.039. DCF, 5FU/LCV and ECX were the most commonly used protocols with ORR of 44%. No protocol was superior in terms of ORR, PFS or OS. Thirty-four patients received 2nd line chemotherapy; Docetaxel- or Irinotecan-based. They had similar ORR, PFS and OS. Patients who received ≥2 lines of chemotherapy had better OS (P 0.002). HER2-neu positivity negatively impacted survival (P 0.014).

Conclusion: Advanced gastric cancer is potentially incurable. Several prognostic factors may predict outcome; including age, smoking, pathological type and HER2-neu. As long as the general condition permits, sequential lines of treatment should be offered to improve patients' survival.

Introduction

Gastric cancer is the third leading cause of cancer death worldwide, with the highest rates reported in East Asia, South America and Eastern Europe. It is relatively uncommon in the United States, causing an estimated 10.000 deaths per year.[1] Stomach cancer is most frequently diagnosed among people aged 65-74. [2] At the Egyptian National Cancer Institute (ENCI) the median age of gastric cancer in the Egyptian population is 56 years. The incidence rises with age and 55% of cases occur between 50 and 70 years of age.[3] Age standardized incidence rate are about twice as high in men as in women.[4]

Approximately, 50% of advanced gastric cancers arise in the distal stomach (the pyloric part of the stomach), frequently involving the lesser curvature and 16% occur in the proximal stomach (cardia, the upper third of the body and fundus). [5] In one large series, the gross appearance of gastric cancer was type 1 (polypoid) is 7%, type 2 (fungating mass) is 36%; type 3 (ulcer) is 25%; and type 4 (infiltrating) is 26%. The most common macroscopic type is type II; fungating tumor, which are frequently located in the lesser curvature.[6]

HER2 is overexpressed or amplified in less than quarter of advanced gastric cancer cases.[7] In gastric cancer overexpression and amplification of HER2, occur in 20-30% of intestinal and < 10% of diffuse/signet ring gastric cancers [8]. HER2 overexpression is directly correlated with poorer outcome in gastric cancer.[7]

Docitaxel-Cisplatin-5Fluorouracil (DCF) combination or one of its modification, are the most commonly used protocols in the treatment of advanced and metastatic gastric cancer with median OS of 9.2 months.[9] Another alternative is the Epirubicin-Cisplatin-5Fluorouracil (ECF) or its modification.[10] in meta-analysis of COUGAR-02, AIO trials and TCOG GI-0801 trial, it was noticed that patients received 2nd line chemotherapy

has significantly lower risk of death with p value < 0.0001. This was evident in Docitaxel combinations (p= 0.004) and Irinotecan combination (p = 0.0004), although most or response was stable disease 46%.[11]

Patients and Methods

In this retrospective analysis, the medical records at Clinical Oncology department, Ain Shams University from January 2011 till December 2014 were reviewed for metastatic and locally advanced gastric and gastro-esophageal cancer. The clinic-epidemiological data e.g., age, sex, performance status (PS), operative details, pathological information and treatment pattern and outcome were collected.

After obtaining the approval of the ethical committee of the department of clinical oncology, Ain Shams University, patients with age ≥ 18, locally advanced & metastatic gastric or gastro-esophageal junction cancer were included. Follow-up data of at least 6 months after initiation of treatment was mandatory to include patients in the analysis except those with recorded date of death before this time.

The 38 available paraffin blocks were analyzed for HER2-neu status using IHC. This was carried out using anti-HER2-neu (4B5) antibody (Ventana medical systems, Inc. Tucson, AZ, USA) as the 1ry antibody on a Ventana Bechmark XT automatic staining system and Hematoxyline was used as a counterstain. Score 0 and +1 were considered negative and score +3 was considered positive. For patients with score +2 , further HER2 amplification analysis was carried out using SISH.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Qualitative data were presented as number and percentages while quantitative data were presented as median and interquartile range (IQR). The comparison between two groups regarding qualitative data were done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. Kaplan Meier survival analysis with Log Rank Analysis was used to correlate progression free survival and overall survival to the other studied parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
P > 0.05: Non significant
P < 0.05: Significant
P < 0.01: Highly significant

Results

Description of population

Eighty-one files were retrieved with 53 patients were eligible for survival analysis in intention to treat population. Additionally, 38 paraffin blocks were available for analysis of HER-2neu status.

The median age of patients was 52 years (range 25-81). Twenty eight patients (34.6%) were younger than 45 years old.

Fifty-five (55.6%) of patients were males. 56.8% of patients were smokers.

Vomiting was the main presenting symptom. It represents 40.7% followed by epigastric pain 37% and the least common is weight loss 3.7%. Most of the patients (58%) had good performance status (≤ ECOG 2).
Most common site of primary tumor was gastric antrum (33.5%), followed by gastric body (29.1%) and the least common was fundus (9.8%).

The most common macroscopic pattern was fungating mass (type II) representing 44.4% followed by diffuse thickening (type IV) 28.4% then ulcer (type III) 27.2%, while the most common microscopic pattern was diffuse pattern representing 66.7%. High grade tumors represented 61.7%.

Twenty-seven (33.3%) patients presented with stage IV gastric cancer form the start; while the rest developed metastasis at a later stage. Liver was the most common site of metastases representing 39.5% followed by peritoneum, lung, bone and adnexa; 31.6%, 24%, 15% and 10% respectively. The least common was brain 2.6% (Fig. 1).

From the 38 available paraffin blocks for analysis, HER2-neu was positive (score +3 by IHC) in only 4 cases (10.5%) and negative (score 0 or +1) in 33 cases and one case was equivocal (score +2) which was proved negative by SISH (figure 1).
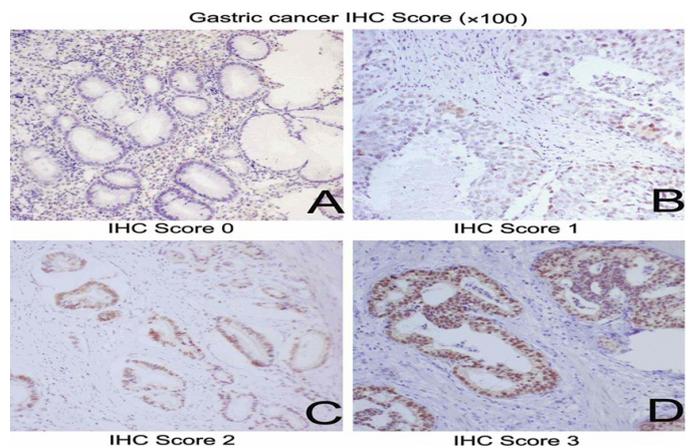

Fig. 1: Gastric cancer IHC score (x100), A) IHC score 0; B) IHC score +1; C) IHC score +2; D) IHC score +3.
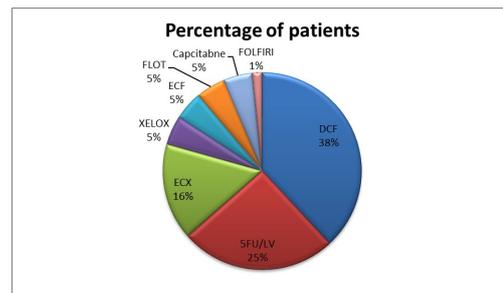

Fig.2: Different types of chemotherapy used in the first line setting.

Treatment Outcome

Sixty-three patients received 1st line chemotherapy (Figure 2). The most commonly used chemotherapy protocol was DCF in 38.1% of patients followed by 5FU/LV in 25.4% then ECX (Epirubicin-Cisplatin-Capcitabine) in 15.87%. The clinical benefit rate (CBR) was 88.8%; half of it was stable disease (SD) in 44.4% of patients. Median number of cycles was 2 (IQR 2-4) and ranged from 1-8 cycles. The median progression free survival (PFS) was 5 months. There was no difference between the 3 protocols in terms of CBR, PFS or OS.

After progression thirty-four patients only were able to receive 2nd line chemotherapy. The most commonly used was docitaxel-based representing 47.1% followed by irinotecan-based (29.4%). The median number of cycles in the 2nd line setting was 2 (IQR 1-3, range 1-6) and the CBR was 82.4% with stable disease in 47.06%. The PFS was 2 months. Also there was no difference in CBR, PFS or OS between the 2 different chemotherapy regimens.

Survival analysis

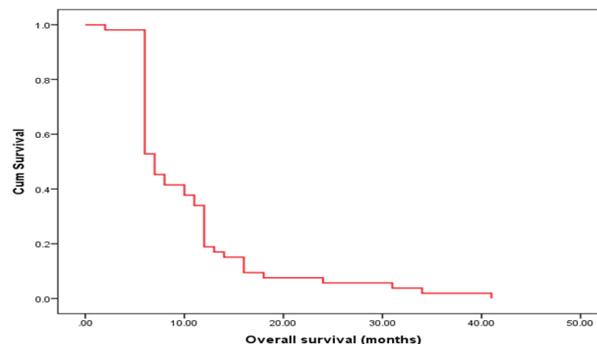Median OS of our population was 7 months (CI 95%, SE

Fig. 3: Overall survival of 53 patients in ITT population (Kaplan-Meier curve).

0.725, 5.579-8.421) (figure 3). It was found that young patients (≤ 45 years), non-smokers, microscopic intestinal type and patients with meta-chronous metastases (with DFS > 6 months) had statistically significant better OS with p values; 0.003, 0.0001, 0.03 and 0.039 respectively) (Figure 4). Moreo-
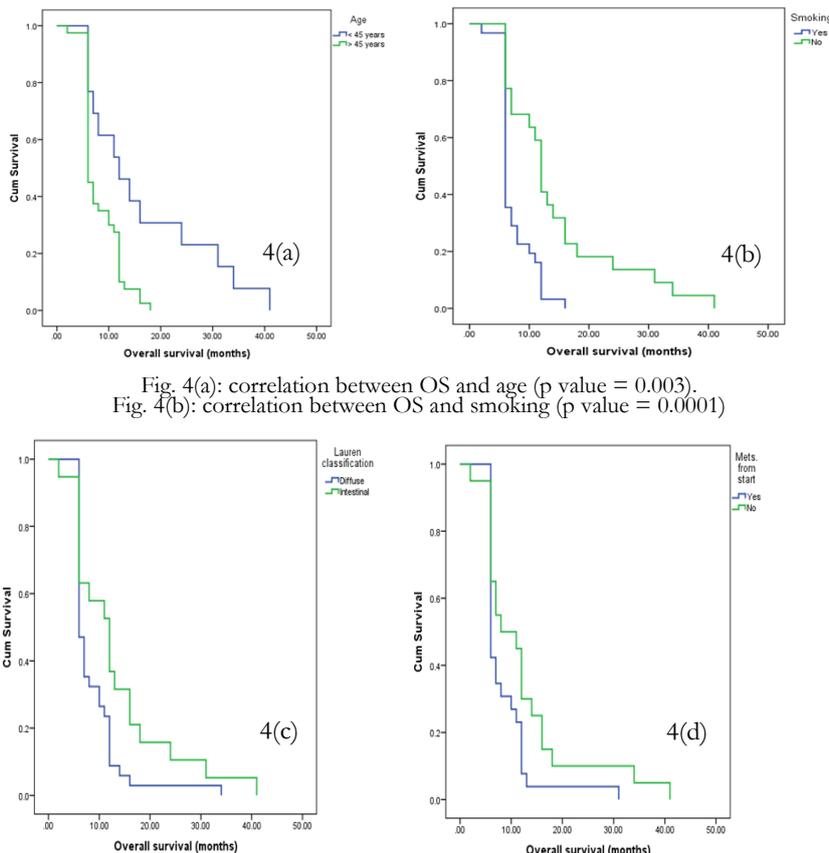

Fig. 4(a): correlation between OS and age (p value = 0.003).
Fig. 4(b): correlation between OS and smoking (p value = 0.0001)

Fig. 4(c): Correlation between OS and microscopic subtype (p value = 0.03).
Fig. 4 (d): correlation between OS and different timing of metastasis (p value = 0.039).

Fig. 4: Kaplan-Meier curves of different prognostic factors in correlation with survival.
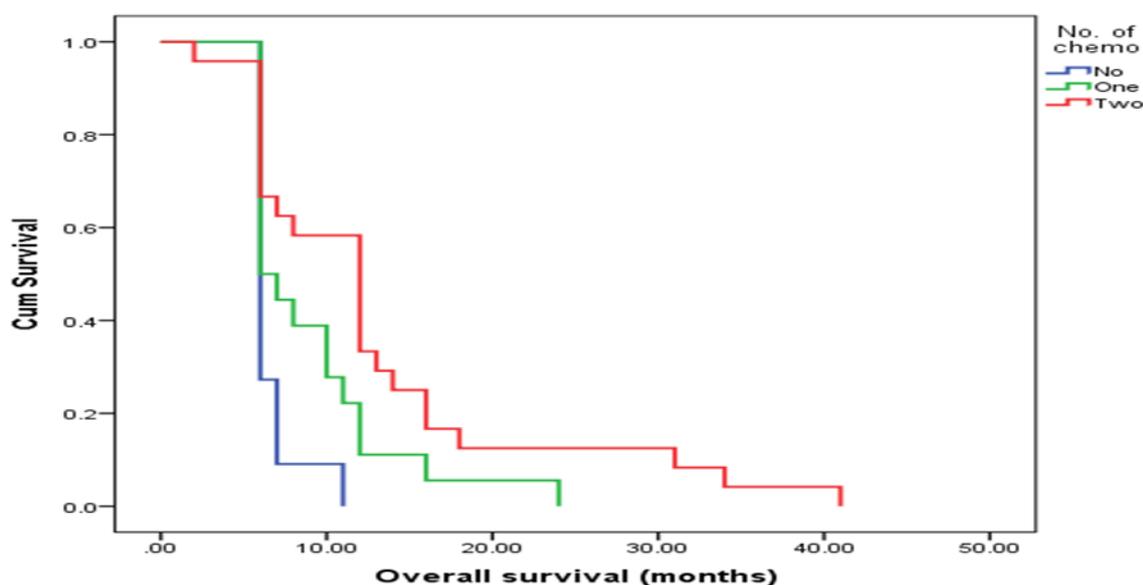
Fig. 5: Kaplan-Meier curve of correlation between OS and numbers of chemotherapy lines (p value = 0.002).

ver, patients who received ≥ 2 lines of chemotherapy had statistically significant better OS compared to one line or best supportive care (12, 7 and 6 months respectively with p value = 0.002) (figure 5).

Also HER2-neu positivity negatively impact OS with median OS of 6 months compared to 10 months in HER2 negative population (p value 0.014). Of note, all the patients included in this analysis did not receive any anti-HER2 therapy.

In multi-variant analysis HER2-neu positivity had no statistically significant difference in expression with different clinico-epidemiological or pathological factors.

Discussion

The median age of the patients in our analysis is 52 years old which is like the Egyptian NCI report by Alielden [3]; it was 56 years old and lower than the SEER report of Eastern population where the peak incidence is between 65-74 years.[2]

There are many prognostic factors that have been identified for gastric cancer. We found that younger population (< 45) are doing better with higher median OS 12 months compared to 6 months for patients ≥ 45 years. This data was similar to data from Dongyun et al [12] where young population (≤44) has statistically significant better OS. Also smoking history was positive in more than half of our series and this had negative impact on survival and this data was supported by other trials as Delpisheh et al.[13] In Vauhkonen et al[14] review of pathological subtypes, intestinal type was the predominant type in 60% of patients which is totally opposite our data where diffuse type was found in 2/3 of cases and it was negatively affecting survival.

HER2-neu was found to be positive in 8-34% of gastric cancer patients in different trials and it was positive in 10.5% of our cohort and it was negatively correlated with median OS. The HER2-neu positivity was more common in intestinal type and GEJ in comparison to diffuse type or gastric cancer [8] [15], but this was not evident in our study where HER2-neu positivity was equally distributed between different cohort groups.

The treatment of advanced and metastatic gastric cancer is difficult with median OS around 7-10 months.[9] The best CBR from 1st or 2nd line chemotherapy in the advanced gastric cancer setting is stable disease with response rate (RR) of around 40% in the 1st line setting. In our retrospective analysis, the median OS was 7 months statistically significant higher survival for patients received more than one line of chemotherapy in the metastatic setting. This data was also previously proved in meta-analysis of COUGAR-02, AIO trials and TCOG GI-0801 trials and was published by Kim et al, where the risk of death was decreased with both 2nd line irinotecan-based chemotherapy (p = 0.0004) and docetaxel-based regimens (p = 0.004).[11]

Conclusion

Advanced gastric cancer is an aggressive disease which is potentially incurable. A lot of prognostic factors had been identified including age, pathological type, smoking, and other biomarkers like HER2-neu. Improving the quality of life of the patient and his performance status by multidisciplinary supportive care team is an important aim; in order to be able to deliver multiple lines of chemotherapy which may improve the patient survival.

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