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Original Article

Paliative Chemotherapy Based in Etoposide Leucovorin and 5 FluoroUracil (ELF) Using Leucovorin in Low Dose in the Treatment of Patients with Advanced Gastric Cancer

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Abstract

A great percentage of diagnosed gastric cancer cases are encountered in advanced stages with distant metastases. In these cases, the standard treatment is palliative chemotherapy. In the ELF chemotherapy regime, the dose of leucovorin (Lv) varies from 300 to 500mg/m^2. However, there are no studies that demonstrate therapeutic equivalence between high and low doses of Lv. **Objective:** Retrospectively analyze the response rates and toxicity profile of the ELF scheme with low doses of Lv offered to patients with metastatic gastric cancer. **Materials and Methods:** Evaluated were patients treated with etoposide (120mg/m^2/day), Lv (20mg/m^2/day) and 5-fluorouracil (500mg/m^2/day), D1 and D3 cycles repeated every three weeks. **Results:** Sixty-eight patients were treated, 69% men, with median age of 60.24 years. Occurred six complete responses (8.8%), five partial responses (7.4%) and 38.2% of the patients presented stable disease. The median overall survival was 9.15 months (95% CI 6.06-12.95), while patients with overall response was 16.05 months (95% CI 10.48-21.63) and in those that presented stable disease or progression was 9.01 months (95% CI 4.71-13.31; p=0.669). Grade III and IV low frequency toxicity was observed. **Conclusions:** In the present sample, the ELF regime with low-dose leucovorin presented an excellent toxicity profile. In spite of the low response rate, the respondent patients presented an equivalent overall survival to the other regimens of the literature.

Keywords: Etoposide; Leucovorin; 5-fluorouracil; Stomach Neoplasms; Metastasis

Introduction

Gastric cancer represents the second leading cause of cancer worldwide and the second leading cause of cancer death.[1] In the year 2008, there were an estimated 21,500 new cases in the USA (10,880 deaths) and 21,800 new cases in Brazil.[2] A great majority of the cases continue to be diagnosed in an advanced phase of the disease. According to data from Surveillance Epidemiology and End Results (SEER), the median 5-year survival of 15.4% in 1973 increased to 21.8% in 1997 in the USA.[3-5]

For localized disease, surgery is the therapeutic modality capable of offering a cure perspective. However, even in the cases with complete resections, locoregional and distant recurrences still occur. Neoadjuvant and adjuvante treatments based on radiotherapy and chemotherapy have been providing an improvement in the overall and progression-free survival rates.[6-8] For the metastatic disease at diagnosis, chemotherapy has a relevant role in the palliation of symptoms but also is capable to alter the rates of overall survival.[9-11] In that scenario, the median survival varies from 7.5 to [12] months among the patients treated with chemotherapy

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and from 3 to 5 months when only clinical support is offered. The 12-month survival rate varies from 35% to 40% for those who received chemotherapy, versus 10% for the control group. Some studies relate a benefit to quality of life.[12-15]

With the objective of improving the results in the response rate, survival and quality of life, several studies have analyzed the combination of drugs with known activity as a single agent. Phase II studies demonstrate higher response rates when compared to monotherapy regimens.[16-30] However, among the regimens with polichemotherapy, there is a significant variation in the toxicity profile, where some more active regimens are more toxic. The combination of etoposide, leucovorin and 5-fluorouracil (ELF) is active and well tolerated, especially in the senior population with low clinical performance and bearers of comorbidities.[2] The recommended dose of leucovorin is 300mg/m^2, but there are studies with smaller doses (150mg/m^2) with response rates of 32% and median survival of 10 months.[31] Leucovorin (Lv) is a biomodulador of 5-fluorouracil (5-FU) and promotes a greater tumorous cytotoxicity.[32] On the other hand, this potential can also add a larger hematological toxicity. In the treatment of colon cancer, a *meta-analysis* analyzed nine studies comparing 5-FU isolated versus 5-FU/Lv, where a substantial difference was observed in the response rates in favor of the use of the combination (23% and 11%; p <0.001), but without survival benefit.[33] Also in colorectal cancer, a direct comparison among the leucovorin schemes of high-dose (500mg/m^2) versus low-dose (20mg/m^2) didn't demonstrate a difference in terms of efficacy; however, a lower incidence of diarrhea in the low-dose group was evidenced.[34] In metastatic gastric cancer, there are no studies that demonstrate the therapeutic equivalence between low and high leucovorin doses.

Based on the evidence of the studies in colorectal cancer, a chemotherapy scheme was elaborated with the same doses of etoposide and 5-fluorouracil of conventional ELF; however, with a reduced dose (20mg/m^2) of leucoorin. Thus, the objective of the present study was to carry out a retrospective analysis of the response rates, as well as the toxicity profile of the ELF scheme, with low leucovorin doses offered to the patients with metastatic gastric cancer treated and accompanied by clinical oncology services of Hospital A.C.Camargo and Hospital Santa Marcelina, São Paulo, Brazil.

Materials and Methods

Retrospectively evaluated were 68 patients (47 men; 21 women) diagnosed with gastric cancer, locally advanced, nonresectable (19) or metastatic (49) (Table 1) treated first-line with chemotherapy based on the ELF scheme with low-dose leucovorin (August 1999 to May 2005): etoposide (120mg/m^2/day), leucovorin (20mg/m^2/day) and 5-fluorouracil (500mg/m^2/day),

Table 1 - Clinical characteristics of 68 patient bearers of gastric cancer, nonresectable or metastatic at diagnosis

Variable	Category	N (%)
Median age (years)	60.24 (23.1-82.56)	
Gender	Masculine	47 (69.1)
	Feminine	21 (30.9)
Condition at diagnosis	M0, nonresectable	19 (27.9)
	M1	49 (72.1)
Gastrectomy	Yes	43 (63.3)
	No	25 (36.7)
Metastases sites at diagnosis	Peritoneum	34 (50.0)
	Liver	28 (41.2)
	Lymph nodes	25 (36.8)
	Lung	4 (5.9)
	Bone	4 (5.9)
	Ovary	2 (2.9)
	Pleural	1 (1.5)
	Brain	1 (1.5)

administrated via intravenous for three consecutive days and repeated every three weeks. Response evaluation was made each three cycles only in the patients with measurable lesions according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria.35 Descriptive statistical analysis was done with percentages, averages and median. The survival rates were calculated by Kaplan-Meier method. Chemotherapy toxicity was evaluated through the NCI CTC version 2.0 toxicity scale in all patients who received at least one chemotherapy cycle.

Results

The median number of ELF cycles was four (variation: 1 to 7). Fifty-seven percent of the patients received four cycles. Of the 68 patients, 46 (67.6%) were evaluated for response to chemotherapy; occurred six complete responses (8.8%), five partial responses (7.4%), overall response of 16.5%, 26 cases of stable disease (38.2%) and nine cases of progression (13.2%).

The median survival was 9.15 months (95% IC 6.06-12.95) (Figure 1).

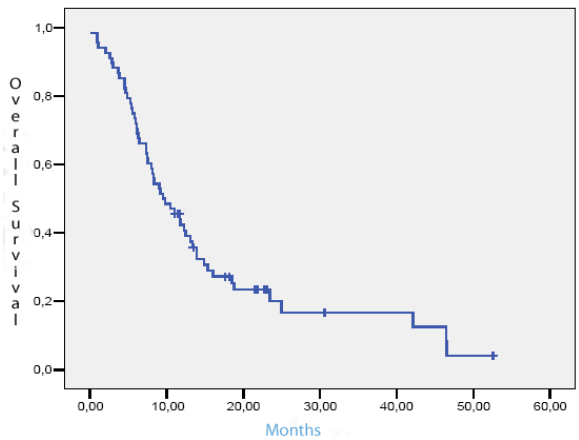

Figure 1 - Overall survival for 68 patient bearers of gastric cancer, nonresectable or metastatic at diagnosis, treated with ELF regime with low doses of Leucovorin (20mg/m^2).

Patients that reached overall response presented median survival of 16.05 months (95% IC 10.48-21.63), versus 9.01 months (95% IC 4.71 to 13.31) for those that presented stable disease or progression (p=0.669). There was no difference in the median rates of survival between the group with metastase at diagnosis (14.96 months) and the group with locally advanced nonresectable disease (16.81 months; p=0.961).

In total, 268 chemotherapy cycles were carried out. As for the ELF toxicity profile with low-dose leucovorin, grade III and IV low frequency toxicity was observed as side effect, principally: nausea (4.4%); vomiting (3%); neutropenia (4.4%) and diarrhea (2.9%). The other more frequent toxicities, all grade II, were alopecia (39.7%), mucositis (19.1%), nausea (25.0%), vomiting (8.8%), leukopenia (5.9%), neutropenia (8,8%),anemia (5,9%),thrombocytopenia (2,9%) and diarrhea (2.9%). There were no febrile leukopenia episodes (Table 2).

Table 2 - Toxicity profile observed in 68 patient bearers of gastric cancer, nonresectable or metastatic at diagnosis, treated with ELF regime with low doses of Leucovorin (20mg/m^2).

Toxicity	N	%
Nausea grades III & IV	3	4.4
Vomiting grades III & IV	2	3.3
Neutropenia grades III & IV	3	4.4
Diarrhea grades III & IV	2	2.9
Alopecia grade II	27	39.7
Mucositis grade II	13	19.1
Nausea grade II	17	25.0
Vomiting grade II	6	8.8
Leukopenia grade II	4	5.9
Neutropenia grade II	6	8.8
Anemia grade II	4	5.9
Thrombocytopenia grade II	2	2.9
Diarrhea grade II	2	2.9

Discussion

Studies with single-drug therapeutic regimens for the treatment of advanced gastric cancer demonstrate response rates between 6% and 49%. The principle agents are antimetabolics (5-fluorouracil and methotrexate), oral antimetabolics (capecitabine, uracil-tegafur and S-1), antibiotics (mitomycin C, doxorubicin and epirubicin), heavy metals (cisplatin and carboplatin), taxols (paclitaxel and docetaxel) and camptotecan (irinotecan and topotecan).[2,12-17] With the intention of improving the response rates, survival and the quality of life, other studies have been analyzing the drug combinations. In this context, randomized studies were elaborated with the objective of evaluating the best therapeutic regimen. In the EORTC (European Organization for Research and Treatment of Cancer) study there was a comparison among ELF (etoposide, 5-fluorouracil and leucovorin), FUP (5-fluorouracil and cisplatin) and FAMTX (5-fluorouracil, methotrexate, doxorubicin and leucovorin). There was not a significant difference among the groups in terms of response and survival.[36] The TAX 325 study randomized patients to receive DCF (docetaxel, cisplatin and 5-fluorouracil) or FUP. Superior response rates and

survival was demonstrated in the group that received DCF.[37] In this same line, Webb et al.[38] randomized patients to receive FAMTX or ECF (epirubicin, cisplatin and 5-fluorouracil). FAMTX was more beneficial than ECF for survival and response rates; however, DCF as well as ECF, present high probability of presenting grave toxicity. Thus, DCF and ECF are recommended to patient bearers of gastric cancer with good performance status and young age. However, these regimens still were not compared with less toxic regimens, like ELF. Moehler et al.[39] conducted a randomized study comparing ELF with a new combination of drugs; ILF (irinotecan, high dose of 5-fluorouracil and leucovorin). ILF presented a greater response rate, but there was no difference in terms of overall survival.

The ELF regimen has been described as less toxic than other chemotherapeutic regimens and with similar antitumorous activity in patients with metastatic gastric cancer. This scheme presents a response rate of 53%, with 12% complete response and a survival median that varies from 7.1 to 11.5 months.[36,40] In spite of this consideration, alterations in this regimen have been made with the intention to diminish toxicity and increase the response rate, as well as median survival. In the study done by Chiou et al.,[40] the time of 5-FU and Lv infusion increased from 3 to 5 days, with etoposide in 100 mg/m^2/day dose for 3 days. A response level of 46% was observed in patients with measurable lesions and median survival of 7 months. Another study showed that the dose increase of the infusion of 5-FU and Lv did not increase the response level (40% vs. 36%) nor did it prolong survival.[38] In another study involving 42 patients with advanced gastric cancer, conventional ELF treatment was observed to obtained an overall response of 32% (95% CI 19-48%), with 7% complete remission. The median response duration was 4 months, the median time for progression was 5 months and overall survival of 10 months. No grade IV toxicity was observed.[38] In our study, the ELF scheme with low-dose Lv provided median survival of 9.15 months, equivalent to the aforementioned studies. The survival rate found was also similar to other non-randomized phase II studies. The overall response rate was 16.5% and in 38.2% of the patients, stable disease was observed. In spite of a response rate inferior to that mentioned in the literature (32% to 56%), it was observed that the patients who reached overall response presented a median survival of 16.05 months, superior to that found in other studies (7.1 to 11.5 months).[31,36,40-41] Additionally, the low-dose ELF scheme presented a toxicity profile slightly inferior to the data already cited. There were grade III and IV low-frequency toxic effects, which resulted in no febrile leukopenia internments or any other side effects. We conclude that the ELF scheme with low-dose Lv should be considered among the treatment regimens of gastric cancer, locally advanced, nonresectable or metastatic, constituting a particularly interesting option for the palliative treatment of patients that present unfavorable clinical conditions in the use of last generation regimens.

Considering the reality of the public health systems of developing countries and the high incidence of gastric cancer in advanced stages, the use of protocols of lower-cost and toxicity brings relevant contribution. The ELF scheme with 20mg/m^2 of leucovorin is an option that should be studied and compared in phase III studies.

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