LONG TERM (FIVE-YEAR) SURVIVAL FOLLOWING RADICAL SURGICAL TREATMENT PLUS ADJUVANT CHEMOTHERAPY (FAM) IN ADVANCED GASTRIC CANCER: A CONTROLLED STUDY

Cláudio Bresciani, Joaquim Gama-Rodrigues, Victor Strassmann, Dan L. Waitzberg, Mitsunori Matsuda and Henrique Walter Pinotti

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BRESCIANI C et al. - Long term (five-year) survival following radical surgical treatment plus adjuvant chemotherapy (FAM) in advanced gastric cancer. A controlled study. **Rev. Hosp. Clín. Fac Med. S. Paulo 55** (4):129-136, 2000.

Several drugs and their associations are being used for adjuvant or complementary chemotherapy with the aim of improving results of gastric cancer treatment. The objective of this study was to verify the impact of these drugs on nutrition and on survival rate after radical treatment of 53 patients with gastric cancer in stage III of the TNM classification. A control group including 28 patients who had only undergone radical resection was compared to a group of 25 patients who underwent the same operative technique followed by adjuvant polychemotherapy with FAM (5-fluorouracil, Adriamycin, and mitomycin C). In this latter group, chemotherapy toxicity in relation to hepatic, renal, cardiologic, neurological, hematologic, gastrointestinal, and dermatological functions was also studied.

There was no significant difference on admission between both groups in relation to gender, race, macroscopic tumoral type of tumor according to the Borrmann classification, location of the tumor in the stomach, length of the gastric resection, or response to cutaneous tests on delayed sensitivity. Chemotherapy was started on average, 2.3 months following surgical treatment. Clinical and laboratory follow-up of all patients continued for 5 years. The following conclusions were reached: 1) The nutritional status and incidence of gastrointestinal manifestation were similar in both groups; 2) There was no occurrence of cardiac, renal, neurological, or hepatic toxicity or death due to the chemotherapeutic method per se; 3) Dermatological alterations and hematological toxicity occurred exclusively in patients who underwent polychemotherapy; 4) There was no significant difference between the rate and site of tumoral recurrence, the disease-free interval, or the survival rate of both study groups; 5) Therefore, we concluded, after a 5-year follow-up, chemotherapy with the FAM regimen did not increase the survival rate.

DESCRIPTORS: **Gastric Cancer. Chemotherapy. Gastrectomy. Survival. FAM regimen.**

The survival rate of patients undergoing surgical treatment of gastric cancer in the Western World is disappointing, especially when compared to Japanese centers[1]. Such a difference may be explained by the low number of patients with early diagnosis in the Western World, while in Japan most patients are operated on while still early cancer carriers[2]. Since the results of surgery in patients with advanced gastric cancer are disappointing, it is natural that other therapeutic modalities that may either complement or replace surgery are being researched. Systemic neoplastic chemotherapy is the best hope for neutralizing microscopic neoplastic foci, which are impossible to extirpate during surgery[3,4,5].

From the Department of Gastroenterology, Hospital das Clínicas, Faculty of Medicine, University of São Paulo.

It has not yet been established in the literature that chemotherapy, either with single or multiple drugs, increases the survival rate, although the more responsive patients to this treatment are those who live longer[6]. The objective of using the chemotherapeutic scheme is to increase survival, provided that it does not produce significant side-effects that may impair the quality of life of patients who undergo surgery for gastric cancer[7].

The objectives of this study are: 1) to investigate the effect of the FAM (5-fluorouracil, Adriamycin, and mitomycin C) regimen—as well as its toxicity—on the postoperative nutritional status of patients; 2) to analyze the impact of polychemotherapy with FAM on the 5-year survival rate of patients undergoing radical surgical treatment for stage III gastric cancer (TNM classification).

PATIENTS AND METHODS

The study included 53 patients with advanced stage III gastric adenocarcinoma (TNM classification of UICC)[8]. All patients underwent level D2 radical resection. This terminology was adopted following a suggestion of the German authors and acceptance by the Japanese (Japanese Classification of Gastric Carcinoma – Japanese Research Society for Gastric Cancer, 1995)[9] instead of the previous terminology – R2 – currently reserved to identify radicality.

After the operation the patients entered a controlled prospective and non-randomized study, with two groups as follows: Group I (FAM), including 25 patients who, besides having undergone surgical treatment, received adjuvant polychemotherapy under the FAM regime; Group II, control (C), made up of 28 patients who only underwent surgical treatment.

The average age of patients in Group I (FAM) was 51.80 (±10.39) and in Group II (C) 56.93 (±7.30) years (Student's test t= 2.09; p= 0.0205). Patients of both groups had the same stage (III) gastric cancers, and the distribution according to gender, race, Borrmann macroscopic classification, tumor location in the stomach, length of gastrectomy, and immune response to skin tests did not reach statistical significance, establishing that the population in both groups were uniform (Table 1).

Criteria of Exclusion

1) Patients with preoperative metastatic lesions (detected through physical examination, radiographic, ultrasonographic, or laparoscopic methods, or even by intraoperative verification).

2) Patients with heart, hepatic, renal or respiratory failure, infection, anemia, or malnutrition that could not be corrected before surgery.

Postoperative Clinical and Laboratory Evaluation

The sequence of clinical evaluation and complementary exams carried out for the patients in the two groups is shown in Table 2.

Table 1 - Stratification of patients according to gender, race, Borrmann, neoplasia location, length of gastrectomy, and skin sensitivity tests.

		Group I (FAM)		Group II (Control)		Statistical
		Number	%	Number	%	Study*
Gender	Male	15	60.00	21	75.00	x^2=1.36
	Female	10	40.00	7	25.00	p=0.2429 NS
Race	Yellow	3	12.00	5	17.86	x^2=0.35
	White	17	68.00	18	64.28	p=0.8353
	Black	5	20.00	5	17.86	NS
Borrmann	I	1	4.16	3	10.71	x^2=1.53
	II	3	12.50	4	14.29	p=0.6732
	III	18	75.00	17	60.71	NS
	IV	2	8.33	4	14.29	
Neoplastic Location in the stomach	1/3 proximal	2	8.00	2	7.14	x^2=1.20
	1/3 medial	4	16	8	28.57	p=0.8774
	1/3 distal	14	56.00	13	46.43	NS
	+ 1 region**	3	12.00	3	10.71	
	Stump	2	8.00	2	7.14	
Length of gastrectomy	Subtotal	15	60.00	17	60.71	x^2=0.40
	Total	5	20.00	7	25.00	p=0.8184
	Enlarged tot.***	5	20.00	4	14.29	NS
Skin Tests	Non-reactor	3	16.66	8	33.33	x^2=1.48
	Reactive	15	83.33	16	66.66	p=0.2241 NS

* Statistical Test: two-tailed x^2

** More than one region in the stomach

*** Total gastrectomy, splenectomy, and partial pancreatectomy.

NS: Without statistical difference

Evaluation of nutritional status was made according to the parameters suggested by Seltzer et al.[10]: ideal body weight percentage (IBW%), serum albumin and number of lymphocytes, triceps skin fold measure (TSF%), and arm muscular circumference (AMC%).

Chemotherapeutic method

The patients in Group I (FAM) were admitted to the protocol after 2.36 ± 0.64 months on average following surgical treatment.

The dose and regime of the in-clinic applications of chemotherapeutic drugs were planned for 6 cycles that lasted 28 days each, as shown in Table 3.

The criteria for changing the chemotherapeutic doses were based on the hematological toxicity levels verified by the number of white globules and/or platelets on the day of drug application (Table 4).

In case of progression of disease, toxicity, or intolerance to medication, the treatment was interrupted, and a lack of response to the FAM protocol was recorded.

The following methods were routinely used to detect disease progress: clinical examination, thoracic X-ray, gastroduodenal endoscopy, and abdominal ultrasound.

RESULTS

Statistical analysis showed similarity in the distribution of patients concerning the nutritional status in both study groups, with the exception of the number of lymphocytes at the moment of admission to the protocol, since Group I (FAM) was made up by a larger number of patients with moderate or severe malnutrition than the Group II (Control Group).

During the follow-up period through the third chemotherapy cycle, no statistical significance between the study groups in relation to the 5 nutri-

Table 2 - Sequence of clinical evaluation and the time of each post-operative complementary exam.

	Pre-chemo-therapy	Each Cycle	3rd cycle	6th cycle	At the end of each year
Anamnesis	**X**	**X**			**X**
Physical exam	**X**	**X**			**X**
Weight check	**X**	**X**			**X**
Height check	**X**				
Activity check (ECOG Scale)	**X**	**X**			**X**
Nutritional Status check	**X**	**X**			**X**
Complete hemogram and platelet count	**X**	**X**			**X**
Hepatic function testing*	**X**		**X**	**X**	**X**
Renal function testing**	**X**		**X**	**X**	**X**
Radiological thorax exam	**X**		**X**	**X**	**X**
Per-oral endoscopic exam	**X**		**X**	**X**	**X**
Ultra-sound exam	**X**			**X**	**X**
Electrocardiogram	**X**		**X**	**X**	
Late sensitivity skin testing***	**X**				

*Hepatic function testing: alkaline phosphatase, aspartate amino transferase, alanine amino transferase, gammaglutamyl-transpeptidase, total and fraction proteins and bilirubin.
**Renal function testing: Urea and creatinine.
***Late sensitivity skin testing: PPD, trichophytin, yeast, and Varidase.
ECOG: Eastern Cooperative Oncology Group.

Table 3 - Chemotherapy regime (FAM): doses, sequence,* and time of application of drugs during treatment.

	Doses (mg/m^2)	Cycles 1,3, and 5 Days 1	8	Cycles 2,4 and 6 Days 1	8
5-Fluorouracil	600	**X**	**X**	**X**	**X**
Adriamycin	30	**X**	-	**X**	-
Mitomycin	10	**X**	-	-	-

* the treatment was planned for six 28-day sequential cycles.
X = Chemotherapic application.

Table 4 - Adequacy of chemotherapeutic doses in accordance with the number of white globules and platelets.

FAM (Dose %)	White globules ($Nº/mm^3$)	Platelets ($Nº/mm^3$)
100	> 4,000	> 100,000
50	2,500 - 4,000	75,000 - 100,000
0	< 2,500	< 75,000

tional parameters considered was observed. The same was observed in the 6th cycle, except in relation to IBW%, because Group I (FAM) was made up of a larger number of patients with normal check (two-tailed X^2 test $p < 0.05$).

In the first and second years of follow-up, no statistically significant difference between the groups in relation to the nutritional parameters was observed. Likewise, no statistically significant difference was observed between the groups in the third year, except in relation to IBW% in Group I (FAM), which was made up by a larger number of eutrophic patients (two-tailed X^2 test $p < 0.05$).

The synthesis of the nutritional evaluation in the different periods of study in accordance with the 5 parameters is shown on Table 5.

Table 5 - Nutritional evaluation comparison between the FAM and control groups.

	IBW%	TSF%	AMC%	Lymphocytes	Albumin
Admission	NS	NS	NS	NS	S (FAM<C)
3rd C/P	NS	NS	NS	NS	NS
6th C/P	S (FAM>C)	NS	NS	NS	NS
1st year	NS	NS	NS	NS	NS
2nd year	NS	NS	NS	NS	NS
3rd year	S (FAM>C)	NS	NS	NS	NS

Statistical analysis: X^2 two-tailed test.
NS: No statistical difference.
S: Presence of statistical difference.
IBW%: Ideal body weight percentage TSF%: Triceps skin fold percentage.
AMC%: Arm muscular circumference percentage.
C/P: Cycle (FAM) or Period (Control).

Table 6 - Frequency of postoperative gastrointestinal manifestations in the two study groups*.

	Group I (FAM) Nº = 25	Group II (C) Nº = 28	Statistical Study (square x)	
Nausea	8	2	x^2=3.83	p=0.0503 NS
Vomiting	6	5	x^2=0.04	p=0.8327 NS
Diarrhea	4	5	x^2=0.08	p=0.8519 NS

* Observed during the 6 cycles for the FAM Group and 6 periods for the Control Group.

Table 7 – Types and frequency of dermatological changes in the two study groups.

	Group I (FAM) Nº = 25	Group II (C) Nº = 28
Alopecia	7	0
Hyperchromic stains on fingers	2	0
Purplish fingernails	2	0

Table 8 - Frequency of hematological alterations in the two study groups.

	Group I (FAM)	Group II (C)	Statistical Study (square x)	
Leucopenia	75	0	-	-
Anemia	7	4	x^2=1.28	P=0.7421 NS

Effects of Chemotherapic Drugs

The gastrointestinal manifestations, even if observed only once in each patient after operation for both groups, are shown in Table 6.

Types and frequency of dermatological complications are shown in Table 7. All these complications reverted spontaneously (Table 7).

Neurological, cardiac, hepatic, or renal toxicity was not presented by any patient.

Hematological alterations were more often seen in patients who received chemotherapy, with leucopenia being the most frequent manifestation (Table 8). In one case myelodepression motivated interruption of chemotherapy after the first cycle.

Due to either leucopenia or anemia, patients in Group I (FAM) received on average 74.4% of the total planned dosage of 5-fluorouracil, 78.9% of Adriamycin, and 86.0% of mitomycin C.

Disease-free interval and tumoral recurrence

In patients who underwent adjuvant treatment by the FAM regimen, the average disease-free interval was 27.15 ± 22.35 months.

In the control group, the average disease-free interval was 23.07 ± 22.21 months (Student's t test = 0.6700 and p = 0.2520); therefore, there was no statistically significant difference between the two groups of patients.

Gastrointestinal tumor recurrence was not detected by endoscopic examination in any patient of both groups. Tumoral recurrence site in the two groups is shown on Table 9.

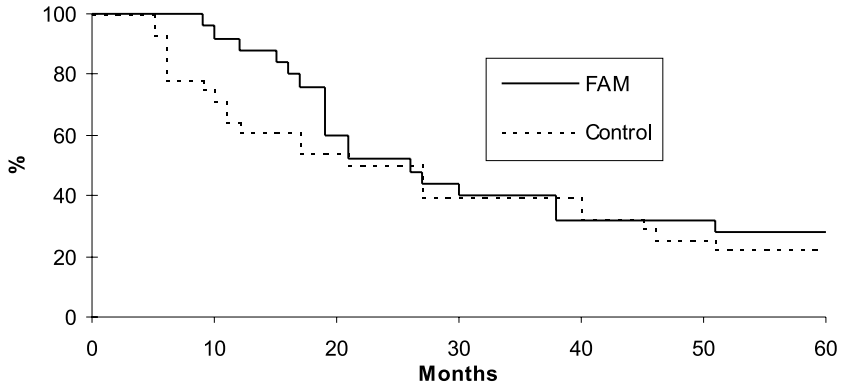
Survival

The average survival in patients in group I (FAM) was 33.08 ± 19.43 months, and in group II (C) was 28.75 ± 21.40 months (Student's t test = 0.77 p = 0.2231 NS). The 5-year survival rate

Table 9 - Tumoral recurrence site during the 5-year postoperative follow-up.

Site of recurrence	Group I (FAM)		Group II (C)	
	Nº	%	Nº	%
Carcinomatosis	11	61.11	17	77.27
Hepatic	5	27.77	4	18.18
Bone	1	5.55	1	4.54
Lung	1	5.55	0	0.00
Total	18	100.00	22	100.00

x^2 test: $x^2 = 2.02$ $p = 0.5689$ NS



Graph 1 - Survival Curve Kaplan-Meier Method.

by the direct method (UICC TNM General Rules) for Group I (FAM) was 28.0% and for Group II (C) was 21.4%.

The survival curves were calculated by Kaplan-Meyer's method and are shown in Graph 1.

In the initial phase (up to 21 months) a numerically higher survival rate was observed in patients in Group I (FAM).

The statistical study of the survival rates, comparing both groups by the Wilcoxon's method did not show any difference between the two curves either considering just the first 21 months (W* = 1.21 p = 0.1131 NS) or during the whole period of study (W* = 1.14 p = 0.1271 NS).

DISCUSSION

The preliminary assessment of the results of combined chemotherapy (FAM regimen) suggested that better survival rates could be obtained for patients operated on for advanced gastric cancer without increased significant or severe side effects[11,12,13].

The objective of this study was to verify the influence of the use of the polychemotherapy (FAM) regime in patients undergoing radical surgical treatment of gastric cancer. The antineoplastic treatment was planned to be an adjuvant; it was accepted that the operative technique standardization in the 53 patients had reached its goal concerning surgical radicality. The justification for the use of the adjuvant polychemotherapeutic regimen relies on the survival rates after radical surgical treatment in patients with stage III tumors, which are between 19% and 33%[14,15,16,17]. It is also known that the response rate to this chemotherapeutic scheme varies from 7% to 42%[12,18,19,10,21]. Therefore, over 50% of the patients surely did not respond to the treatment.

Because the statistical analysis indicated that the two groups studied were homogeneous in relation to the main clinical and laboratory variables, and all patients had gastric cancer in the same stage, it is reasonable to accept the obtained results as effectively indicative of the only distinctive variable, i.e., the FAM regimen.

After surgery, gastrointestinal complaints were frequent but easily controlled clinically with symptomatic medication. We observed that patients in the control group showed the same degree of gastrointestinal symptoms as the group receiving the antineoplastic drugs (Table 6). This observation may be explained as a consequence of the physiologic modifications of the digestive transit after gastric resection.

Neurological, renal, hepatic, or cardiologic toxicity signals or infection were not observed during the follow-up period. Nor was any physical activity difference between groups observed as evaluated by the ECOG scale. The behavior similarity was remarkable in both groups in relation to the 5 nutritional parameters: measurement of weight, albuminemia, number of serum lymphocytes, triceps skin fold, and arm muscular circumference.

The differences between the groups, certainly arising from the use of the FAM regime, were the temporary reduction of the lymphocyte number in 72% of cases and the dermatological manifestations in 40%. The dermatological finding motivated us to change the pattern of administration of chemotherapeutic drugs. Since they were more frequent when high doses of 5-fluorouracil are used, the occurrences of hyperchromic staining and purplish fingernails must be monitored.

Cartei et al.[22] observed the presence of moderate leucopenia and plateletopenia in spite of using the FAM regimen in higher doses. Apparently the degree of leucopenia is not significantly influenced by the doses

given, but rather by the individual sensitivity to chemotherapeutic drugs[21]. In own study, 74.4% of the planned dose of 5-fluorouracil, 78.9% of the planned dose of Adriamycin, and 86.0% of the planned dose of mitomycin C were given. A similar observation was described by MacDonald et al.[12], in which the average quantity of planned dosage started at 89% (first cycle), but was progressively reduced to only 71% of the planned dose by the sixth cycle.

In this study, the patients started polychemotherapy 2.3 months on average after surgical treatment; this time is longer than that established by the review by Schlag's[23] and Torelli et al.[24] of some studies carried out in Japan. However, several Western study groups started chemotherapy only in the postoperative period and with an interval similar to that used in the present investigation[24, 25]. The early introduction of treatment could, theoretically, favorably affect the survival results; however, the Hallisey et al.[26] studies failed to prove that hypothesis.

Regarding survival rates, there was no statistical difference between groups at the 5-year follow-up; only a higher numerical, but not statistical significant, survival was observed up to 21 months after surgery among the patients receiving chemotherapy. This result allows the supposition of some activity of the drugs on the remaining neoplastic cells that is not intense enough to confirm the hypothesis formulated by Macdonald et al.[12] that the objective response to the therapy would correspond to an increase in the survival rate. This finding reinforces the concept of Hallisey et al.[27] that was endorsed by Hermans et al.[28] based on a 11-study analysis—that postoperative adjuvant chemotherapy should not be routinely used .

In the extensive experience of the University of Georgetown group with the FAM protocol[29], an increase in survival was not observed, although a high response percentage was detected. Therefore, it is plausible to emphasize the proposal made by Clark & Slevin[30], Kelsen[31], Macdonald & Gohmann[6], Treat et al.[29], Murad et al.[32] and Douglas[33], who advocate that research for new drugs and new therapeutic trials are required to improve results of radical treatment of gastric cancer.

CONCLUSIONS

Nutritional status and incidence of gastrointestinal manifestations after surgical treatment of gastric cancer were similar in the control group and in patients treated by polychemotherapy (FAM).

There was neither occurrence of cardiac, renal, neurological, or hepatic toxicity nor of death arising from the chemotherapeutic method per se.

Dermatological alterations and hematological toxicity occurred exclusively in patients who received the polychemotherapy, and these had minimal clinical expression.

At the 5-year follow-up, there was no difference between the rate and site of the tumoral recurrence, the disease-free interval, and the survival rate between study groups.

Therefore, chemotherapy under the FAM regimen does not increase survival rate; it is not recommended for routine use, but rather only for established study protocols.

RESUMO

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BRESCIANI C e col. – Sobrevivência tardia (cinco anos) após tratamento cirúrgico radical e quimioterápico adjuvante (FAM) em câncer gástrico avançado: estudo controlado. **Rev. Hosp. Clín. Fac. Med. S. Paulo 55** (4):129-136, 2000.

Várias são as drogas e associações propostas tanto para a quimioterapia adjuvante como complementar visando melhorar os resultados do tratamento do câncer gástrico. Com o objetivo de se analisar o impacto sobre o estado nutricional e o índice de sobrevivência no tratamento de 53 doentes com câncer gástrico do estádio III da classificação TNM, comparou-se um grupo controle composto de 28 doentes submetidos apenas a ressecção radical com outro grupo tratado com a mesma conduta operatória seguida de poliquimioterapia adjuvante pelo regime FAM (5-fluorouracil, adriamicina e mitomicina C) e composto de 25 doentes. Nestes últimos averiguou-se também a toxicidade das drogas antineoplásicas quanto à função hepática, renal, cardiológica, neurológica, hematológica, gastrointestinal e dermatológica. Por meio de análise estatística afastou-se desigualdade entre os dois grupos de estudo quanto ao sexo, raça, tipo tumoral macroscópico da classificação de Borrmann, localização da neoplasia no estômago, extensão da ressecção gástrica e resposta às provas cutâneas de sensibilidade retardada na admissão. O tratamento quimioterápico foi iniciado em média 2,3 meses após o tratamento cirúrgico. Os doentes foram acompanhados clíni-

ca e laboratorialmente pelo período de 5 anos tendo se chegado às seguintes conclusões: 1) Foram semelhantes em ambos os grupos de estudo a evolução nutricional e a incidência de manifestações gastrintestinais; 2) não ocorreu toxicidade cardíaca, renal, neurológica ou hepática e tampouco óbito em decorrência do método quimioterápico em si; 3) alterações dermatológicas e mielotoxicidade ocorreram exclusivamente nos doentes que se submeteram à poliquimioterapia; 4) não houve diferença significante entre o índice e a sede da recidiva tumoral, o tempo livre de doença e os índices de sobrevivência dos dois grupos de estudo após cinco anos de seguimento portanto, a quimioterapia pelo esquema FAM não incrementa o referido índice.

DESCRITORES: Câncer gástrico. Quimioterapia. Gastrectomia. Sobrevivência. Esquema FAM.

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