UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

IMPACTO DA COMBINAÇÃO DE CISPLATINA, 5-FLUOROURACIL INFUNDIDO EM BOLUS E ÁCIDO FOLÍNICO EM PACIENTES COM CÂNCER GÁSTRICO AVANÇADO

Rafael Corrêa Coelho

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Dissertação apresentada como requisito parcial para obtenção do título de Mestre em Medicina: Ciências Médicas, da Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Medicina: Ciências Médicas.

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RESUMO

Introdução: O câncer gástrico (CG) é a quarta causa mais comum de câncer e a segunda causa de morte por câncer no mundo. Os derivados da platina e as fluoropirimidinas são os principais medicamentos utilizados no tratamento de primeira linha paliativo do CG avançado.

A utilização de 5-Fluorouracil (5-FU) em bolus demonstrou ser eficaz em diversos estudos pré-clínicos e clínicos, com desfechos semelhantes aos protocolos em infusão contínua, porém com maior facilidade de administração dado a ausência de necessidade de internação hospitalar e bombas de infusão. Por tal motivo, o protocolo PFL, um regime quimioterápico combinando cisplatina (CDDP), 5-FU infundido em bolus e ácido folínico, foi incorporado no Instituto Nacional de Câncer (INCA).

Objetivo: Este estudo visa avaliar os desfechos clínicos de pacientes com câncer gástrico avançado tratados com o protocolo PFL no cenário de primeira linha paliativo.

Materiais e métodos: Estudo de coorte retrospectiva avaliando 109 pacientes com câncer gástrico avançado tratados em primeira linha paliativa com CDDP 80mg/m^2(D1) + 5- FU 400mg/m^2 infundido em bolus (D1,D8,D15,D22) + ácido folínico (LV) 20mg/m^2 (D1,D8,D15,D22), em ciclos de 4 semanas, no período de Janeiro de 2008 a Dezembro de 2014.

Resultados: A idade média foi de 54 anos (24-80) e 53,2% eram homens. O estadiamento ao diagnóstico foi: E IIA 2,7%, E IIB 2,7%, E IIIA 1,8%, E IIIB 5,5%, E IIIC 5,5% e E IV 80,8%. Os sítios mais comuns de metástase foram peritônio 45%, linfonodos 32,1%, fígado 22%, pleura 5,5% e

pulmão 2,8%. O número médio de ciclos recebidos por paciente foi de 4 (1-11). Respostas completas foram alcançadas em 6,4%, respostas parciais em 14,7% e doença estável em 14,7% dos pacientes. A sobrevida livre de progressão mediana foi de 6,3 meses (5,08-7,58) e sobrevida global mediana de 8,3 meses (6,79-9,87). Trinta e quatro (31,2%) pacientes estavam vivos em 1 ano e 8 (7,3%) em 2 anos. Reduções de dose foram necessárias em 9,1% e as toxicidades mais comuns foram náuseas 72%, vômitos 50%, fadiga 35%, diarreia 29%, constipação 12 %, mucosite 11% e neutropenia 11%. Entre todos os eventos adversos, aqueles de grau 3 e 4 corresponderam a 26,6% e 3,7%, respectivamente. Três pacientes apresentaram neutropenia G4. Apenas 27 pacientes (24,8%) receberam segunda linha de tratamento paliativo.

Conclusão: O protocolo de quimioterapia combinando CDDP, 5-FU infundido em bolus e LV é ativo em pacientes com câncer gástrico avançado e pode ser uma alternativa quando os tratamentos em infusão contínua de 5-FU não possam ser utilizados por limitações técnicas e/ou orçamentárias.

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Palavras chave: câncer gástrico metastático, quimioterapia, câncer gástrico avançado, tratamento paliativo de primeira linha

ABSTRACT

Introduction: Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death worldwide. Platinum agents and fluoropyrimidines are the main compounds used in first line setting for advanced GC. Given the activity of bolus 5-fluorouracil (5-FU) administration showed in many pre-clinical and clinical studies, similar outcomes when compared to infusional protocols and the convenient schedule without the need of hospitalization or infusion pumps, PFL protocol, a chemotherapy regimen combining cisplatin (CDDP), 5-FU in bolus infusion and leucovorin (LV), was incorporated at the Brazilian National Cancer Institute (INCA). This study aims to evaluate the outcomes of PFL regimen in first line setting for treating patients with advanced gastric cancer.

Materials and methods: Retrospective cohort study evaluating 109 patients with advanced GC treated in a first line setting with CDDP 80mg/m^2(D1) + 5- FU 400mg/m^2 in bolus injection (D1,D8,D15,D22)+ LV 20mg/m^2 (D1,D8,D15,D22) in 28-day cycles from January 2008 to December 2014.

Results: The median age was 54 years (24-80), 53.6% were male. Tumor staging at initial diagnosis was: E IIA 2.7%, E IIB 2.7%, E IIIA 1.8%, E IIIB 5.5%, E IIIC 5.5% and E IV 80.8%. The most common metastatic sites were peritoneum 45%, lymph nodes 32.1%, liver 22%, pleura 5.5% and lung 2.8%. The median of cycles received per patient was 4 (1-11). Complete responses were achieved in 6.4% and partial responses in 14.7%. Median PFS was 6.3 months (5.08 – 7.58) and median OS was 8.3 months (6.79 – 9.87). Thirty-four

(31.2%) patients were alive in 1-year and 8 (7.3%) in 2-years. Dose reduction was necessary in 9.1% and the most common toxicities were nausea 72%, vomiting 50%, fatigue 35%, diarrhea 29%, constipation 12%, stomatitis 11% and neutropenia 11%. Grade 3 and 4 adverse events corresponded to 26.6% and 3.7%, respectively. Three patients had neutropenia G4. Only 27 patients (24.8%) received second line treatment.

Conclusion: Chemotherapy protocol combining CDDP, 5-FU in bolus injection and LV is active in advanced gastric cancer and could be an alternative for 5-FU continuous infusion protocols in institutions with limited resources and low budget which is the reality of many nations all over the world.

Key Words: metastatic gastric cancer, advanced gastric cancer, chemotherapy, first line treatment

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LISTA DE ABREVIATURAS EM PORTUGUÊS

QT- Quimioterapia

CG- Câncer gástrico

PS- Performance status

PFL- Combinação de cisplatina, 5-fluorouracil infundido em bolus e leucovorin

CDDP – Cisplatina

5-FU – 5- Fluorouracil

LV - Leucovorin

TR - Taxas de resposta

SG - Sobrevida global

SLP - Sobrevida livre de progressão

E – Estadio

G - Grau

HR - Razão de risco

IC - Intervalo de confiança

INCA - Instituto Nacional de Câncer

CF – Cisplatina e 5-fluorouracil

CEA – Antígeno carcinoembrionário

APAC- Autorização de procedimentos de alta complexidade

FAM – 5-FU, adriamicina e mitomicina

FAMTX – Metrotrexate, 5-Fluorouracil e adriamicina

ECF - Epirrubicina, cisplatina e 5-fluorouracil

DCF - Docetaxel, cisplatina e 5-fluorouracil

EOF - Epirrubicina, oxaliplatina e 5-Fluorouracil

ECX - Epirrubicina, cisplatina e capecitabina

EOX - Epirrubicina, oxaliplatina e capecitabina

FLO - 5-Fluorouracil, leucovorin e oxaliplatina

FLP - 5-Fluorouracil, leucovorin e cisplatina

CS - Cisplatina e S-1

LISTA DE ABREVIATURAS EM INGLÊS

GC – Gastric cancer

INCA – Brazilian National Cancer Institute

PFL – Combination of Cisplatin, 5-Fluorouracil in bolus injection and Leucovorin

5-FU – 5 – Fluorouracil

CDDP – Cisplatin

LV – Leucovorin

E – Staging

G – Grade

PFS – Progression Free Survival

OS – Overall Survival

AGC – Advanced Gastric Cancer

ECOG - Eastern Cooperative Oncology Group

PS – Performance status

CR – Complete response

PR – Partial response

PD – Progressive disease

SD – Stable disease

DCF – Docetaxel, cisplatin and 5-Fluorouracil

CF – Cisplatin and 5 – Fluorouracil

ECF – Epirrubicin, cisplatin and 5-Fluorouracil

ECX - Epirrubicin, cisplatin and capecitabine

EOF- Epirrubicin, oxaliplatin and 5-Fluorouracil

EOX - Epirrubicin, oxaliplatin and capecitabine

FLP - 5-Fluorouracil, leucovorin and cisplatin

FLO - 5-Fluorouracil, leucovorin and oxaliplatin

FLOT – 5-Fluorouracil, leucovorin, oxaliplatin and docetaxel

XP - Capecitabine and cisplatin

CS1 - Cisplatin e S-1

CX – Cisplatin and capecitabine

T – Trastuzumab

TTP – Time to progression

RR – Response rate

IP – Infusion pump

IH – In hospital

HR – Hazard ratio

CI – Confidence interval

FUTP - Fluorouridine 5'-triphosphate

TS - Thymidilate synthase

FdUMP - 5- fluoro-2' deoxyuridine-5' monophosphate

NS – Normal saline

D5W - 5% glucose solution

SUMÁRIO

1. INTRODUÇÃO

Para o Brasil, estimam-se 13.540 casos novos de câncer gástrico entre homens e 7.750 nas mulheres para cada ano do biênio 2018-2019. Esses valores correspondem a um risco estimado de 13,11 casos novos a cada 100 mil homens e 7,32 para cada 100 mil mulheres. Entre homens, é o quarto mais incidente e o sexto entre as mulheres. [1] A última estimativa mundial apontou a ocorrência de, aproximadamente, 1 milhão de casos novos de câncer gástrico para o ano de 2012, configurando-se como a quarta causa mais comum de câncer em homens (631 mil casos novos) e quinta em mulheres (320 mil casos novos). Mais de 70% dos casos ocorrem em países em desenvolvimento, sendo a incidência cerca de duas vezes maior no sexo masculino e dois terços dos casos diagnosticados tardiamente, caracterizado por doença localmente avançada ou disseminada à distância. [2,3,4]

Diversas drogas são consideradas ativas contra o câncer gástrico (CG), como os derivados da platina (ex.: cisplatina e oxaliplatina), flouropirimidinas, irinotecano, taxanos e terapias alvo (ex.: trastuzumabe e ramucirumabe). [5,6] Contudo, apesar das possibilidades terapêuticas disponíveis, o prognóstico de pacientes com CG avançado continua reservado variando em torno dos 12 meses. [6]

Pacientes submetidos a tratamento quimioterápico apresentam aumento na sobrevida global (SG) quando comparados àqueles submetidos a cuidados paliativos exclusivos em primeira [7,8,9] e

segunda linhas de tratamento. [10,11,12] Em meta-análise que comparou o tratamento com quimioterapia (QT) em primeira linha a cuidados paliativos exclusivos, encontrou-se uma razão de risco (HR) de 0,39 (95% CI, 0.28 a 0.52; P<.001) para sobrevida global em favor da quimioterapia se traduzindo em um ganho de, aproximadamente, 6 meses. [13]

A combinação de cisplatina e fluorouracil (CF), ou o regime triplo baseado nesta combinação são uns dos principais esquemas de primeira linha para tratamento com uma taxa de resposta de cerca de 40%. Em 2008, o papel da oxaliplatina e capecitabina foi estabelecido através da demonstração de que estes tem eficácia semelhante à cisplatina e fluorouracil, respectivamente, porém com um perfil de toxicidade melhor. [14,15,16]

A segunda linha de tratamento é muitas vezes difícil de ser instituída, pois os pacientes podem apresentar piora expressiva do estado geral após a primeira linha de tratamento, relacionadas tanto às toxicidades inerentes da terapia citotóxica, comorbidades e/ou progressão da doença de base. Meta-análise neste contexto evidenciou uma HR para SG nos pacientes tratados com QT de 0.73 (95% CI, 0.58 a 0.96) quando comparados a pacientes submetidos a cuidados paliativos, e, para aqueles pacientes com performance status (PS) 0 e 1, a HR foi de 0.57 (95% CI, 0.36 a 0.91). [18]

O tratamento quimioterápico, como já referido acima, se mostra como principal opção de tratamento para pacientes com CG avançado;

contudo, não existe na literatura estudo comparando diretamente o uso de 5-Fluorouracil em bolus versus em infusão contínua no cenário de câncer gástrico avançado. O racional para este estudo é de que a utilização de 5-Fluorouracil (5-FU) em bolus demonstrou ser eficaz em diversos estudos pré-clínicos e clínicos, com desfechos semelhantes aos protocolos em infusão contínua, porém com maior facilidade de administração dado a ausência de necessidade de internação hospitalar e bombas de infusão. [19-25] Por tal motivo, o protocolo PFL, um regime quimioterápico combinando cisplatina, 5-FU infundido em bolus e ácido folínico, foi incorporado no Instituto Nacional de Câncer (INCA).

Este estudo visa avaliar os desfechos clínicos de pacientes com câncer gástrico avançado tratados com o protocolo PFL no cenário de primeira linha paliativo.

2. REVISÃO DA LITERATURA

2.1 Estratégias para localizar e selecionar as informações

Esta revisão da literatura está focada nos desfechos, toxicidades e formas de administração relacionados ao tratamento quimioterápico paliativo em câncer gástrico, em especial regimes de primeira linha. A estratégia de busca envolveu os dados epidemiológicos divulgados nos sites do Instituto Nacional de Câncer e da Agência Internacional de Pesquisa do Câncer bem como as seguintes bases de dados: LILACS, Embase e PubMed. Todos os artigos publicados até 3 de fevereiro de 2018 foram incluídos, data da última atualização da revisão.

Foram realizadas buscas através dos termos:

PUBMED

("stomach neoplasms"[MeSH Terms] OR "stomach neoplasms"[All Fields] OR "gastric cancer"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR “neoplasm metastasis"[All Fields] OR "metastasis"[All Fields]) AND ("drug therapy"[Subheading] OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR "chemotherapy"[All Fields]) AND ("Survival"[Mesh] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh] OR "mortality"[Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR “response rate”) AND ((“Clinical Trial” AND “Phase II”) OR (“Clinical Trial” AND “Phase III”) OR “Randomized Controlled Trial”)

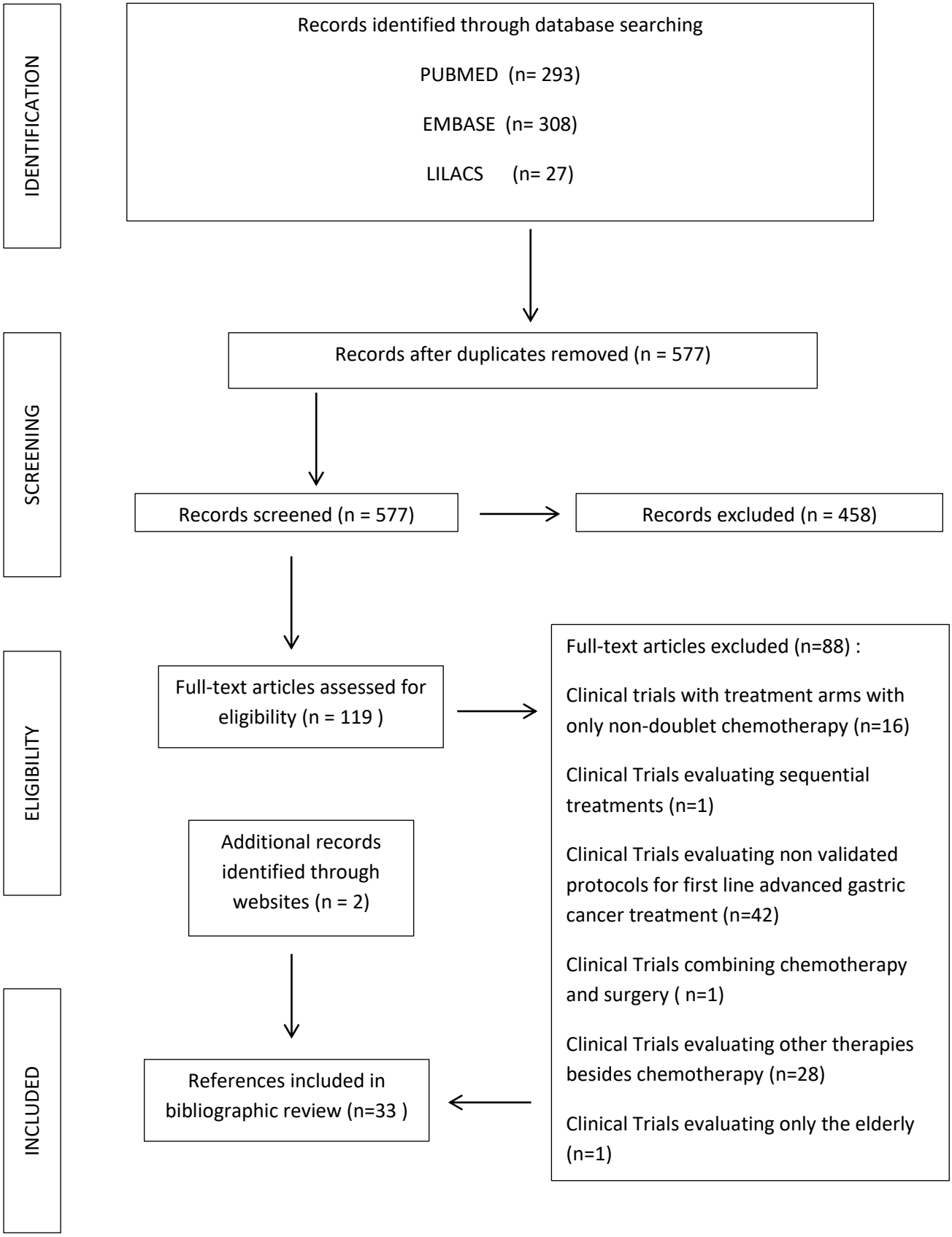
EMBASE

('advanced cancer'/mj OR 'advanced cancer' OR 'cancer, advanced') AND ('stomach cancer'/mj OR 'cancer, stomach' OR 'gastric cancer' OR 'stomach cancer') AND ('chemotherapy'/mj OR 'chemotherapeutics' OR 'chemotherapy' OR 'therapy'/mj OR 'combination therapy' OR 'disease therapy' OR 'disease treatment' OR 'diseases treatment' OR 'disorder treatment' OR 'disorders treatment' OR 'efficacy, therapeutic' OR 'illness treatment' OR 'medical therapy' OR 'medical treatment' OR 'multiple therapy' OR 'polytherapy' OR 'somatotherapy' OR 'therapeutic action' OR 'therapeutic efficacy' OR 'therapeutic trial' OR 'therapeutic trials' OR 'therapeutics' OR 'therapy' OR 'therapy, medical' OR 'treatment effectiveness' OR 'treatment efficacy' OR 'treatment, medical') AND ('overall survival'/mj OR 'overall survival' OR 'progression free survival'/mj OR 'progression free' OR 'progression free survival') AND ('randomized controlled trial'/mj OR 'controlled trial, randomized' OR 'pragmatic clinical trial' OR 'pragmatic clinical trials' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled')

LILACS

(tw:(gastric cancer)) OR (tw:(stomach neoplasm)) AND (tw:(chemotherapy)) OR (tw:(treatment)) AND (tw:(metastatic)) OR (tw:(advanced disease)) AND (tw:(randomized clinical trial)) OR (tw:(clinical trial))

FIGURA 1. Estratégia de busca de referências bibliográficas (Flow Chart)



2.2 **Revisão da literatura**

O prognóstico de pacientes com neoplasia gástrica é reservado, com uma expectativa de vida média de 4 meses quando tratados com tratamento de suporte paliativo exclusivo e 12 meses quando submetidos a tratamento quimioterápico. A quimioterapia além de aumentar a expectativa de vida dos pacientes, melhora sua qualidade de vida, e, portanto, deve-se oferecida àqueles com bom performance status (PS) e função orgânica preservada. [7,8,13]

Em relação ao tratamento combinando agentes quimioterápicos versus quimioterápicos isolados, há ganho em sobrevida global de 1.6 meses favorecendo a combinação (HR 0.82; 95% IC 0.74 - 0.90; 1914 participantes). [13]

No início da década de 80, foi publicado estudo prospectivo avaliando o papel da combinação de 5-FU, doxorrubicina e mitomicina (FAM) em 62 pacientes. A duração média da remissão foi de 9 meses e a SG mediana nos pacientes respondedores alcançou os 12.5 meses. Naqueles que não responderam, a SG reduziu para 3.5 meses e a SG global do estudo foi de 5.5 meses. [26]

O esquema FAM se tornou referência até 1991, quando estudo multicêntrico, randomizado, fase 3 comparou um novo protocolo combinando metrotrexate, 5-FU e adriamicina (FAMTX) com o esquema vigente. Foram incluídos 213 pacientes com CG avançado; a taxa de resposta foi estatisticamente superior [41% x 9%

(P<0.0001)], bem como a sobrevida global [mediana, 42 semanas x 29 semanas (P = 0.004)] para o braço tratado com FAMTX. [27]

Os derivados da platina em CG foram consolidados através do estudo prospectivo publicado por Webb et al., o qual randomizou 274 pacientes e comparou os tratamentos com epirrubicina, cisplatina e fluorouracil (ECF) e FAMTX, até então este último era o esquema de eleição para tratamento deste grupo de pacientes. A resposta global foi de 45% [IC 95% (36 – 54%)] com ECF e 21% [IC 95% (13 – 29%)] com FAMTX (P<0.0002); a SG mediana foi de 8.9 meses para o braço com ECF e 5.7 meses para o FAMTX (P=0.0009). [28]

Baseado nos estudos acima referidos e outros que se sucederam, a epirrubicina foi incorporada ao tratamento do CG avançado, sendo ainda utilizada em alguns países. No entanto, o seu uso está em decréscimo devido às controvérsias em relação ao seu real benefício quando combinada com derivados da platina e fluoropirimidinas; há evidências a favor de seu uso como a meta-análise da Cochrane (HR 0.77; 95% IC 0.62a 0.95, 501 participantes) [13]; e contra, como a meta-análise publicada pelo GASTRIC group na qual não se evidenciou benefício do uso de antraciclinas quando combinadas com 5-FU e/ou derivados da platina em relação a aumento da sobrevida livre de progressão (HR = 0.92; 95% IC 0.82–1.04) e sobrevida global (HR = 0.97; 95%CI 0.87–1.09). A última é considerada de maior relevância por ter utilizado os dados de pacientes individualmente. [29]

A associação de docetaxel à cisplatina e ao 5-FU foi avaliada no estudo fase II/III (V325). Foram randomizados 445 pacientes entre os braços: docetaxel, cisplatina e 5-FU (DCF) e cisplatina + 5-FU (CF). O tempo para progressão de doença e sobrevida global foram maiores com DCF, sendo a redução no risco de progressão de 32% (log-rank p<0.001) e de 23% no risco de morte (log-rank P= 0.02). Contudo, apesar dos desfechos favoráveis, o DCF não é utilizado com grande frequência na prática clínica devido às toxicidades potenciais (69% de efeitos adversos grau 3 e 4 para o grupo tratado com DCF versus 59% para aqueles tratados com CF). [17]

O estudo REAL 2 avaliou através de um desenho fatorial 2 x 2, regimes baseados em epirrubicina nos quais o 5-FU foi substituído pela capecitabina e a cisplatina foi substituída por oxaliplatina. Os quatro regimes estudados foram: epirrubicina, cisplatina e 5-Fluorouracil (ECF), epirrubicina, oxaliplatina e 5-Fluorouracil (EOF), epirrubicina, cisplatina e capecitabina (ECX) e epirrubicina, oxaliplatina e capecitabina (EOX). As taxas de resposta, sobrevida livre de progressão e sobrevida mediana não apresentaram diferenças estatisticamente significativas entre os tratamentos avaliados pelo estudo. Conclui-se que capecitabina e oxaliplatina são tão efetivos quanto 5-FU e CDDP, respectivamente, em pacientes com neoplasia esofagogástrica avançada sem tratamentos prévios. [15]

Outro estudo também confirmou que a cisplatina pode ser substituída por oxaliplatina através da comparação entre 5-FU, LV e

oxaliplatina (FLO) com 5-FU, LV e cisplatina (FLP). Foram randomizados 220 pacientes, FLO foi associado a menor incidência de efeitos adversos graves e não graves. Na população geral do estudo não houve diferença estatisticamente significativa em sobrevida livre de progressão e sobrevida global. No entanto, avaliando a população de pacientes acima de 65 anos, o regime FLO resultou em maiores taxas de resposta (41.3% versus 16.7%; P= 0.012), tempo para falha de tratamento (5.4 v 2.3 meses; P < .001), SLP (6.0 v 3.1 meses; P = .029) e SG (13.9 v 7.2 meses) quando comparado com o regime FLP, respectivamente. [14]

O S-1 é uma medicação extensamente estudada e utilizada no cenário de CG avançado na Ásia. Ela consiste na combinação oral de tegafur (uma prodroga do fluorouracil), gimeracil (inibidor da dihidropirimidina desidrogenase) e oteracil (inibidor da fosforilação intestinal do fluorouracil). A inibição dupla de enzimas de degradação das fluoropirimidinas aumenta as concentrações do citostático no sangue e tecidos tumorais. O estudo SPIRITS avaliou o tratamento de S-1 isolado e em combinação com cisplatina, demonstrando um aumento na sobrevida global com a combinação (13 versus 11 meses - HR 0.77; 95% IC 0.61-0.98; P=0.04). [30]

Tabela 1: Principais estudos clínicos de fase III avaliando regimes quimioterápicos de primeira linha para câncer gástrico avançado ou metastático. [31]

	Regime terapêutico	Número de pacientes	Proporção com resposta ao tratamento	Sobrevida global (meses)
MacDonald et al, 1980 [26]	Fluorouracil, doxorubicina e mitomicina	62	42%	5.5
Webb et al, 1997 [28]	Epirrubicina, cisplatina e fluorouracil ***x*** fluorouracil, doxorrubicina, e metotrexato	111 x 108	45% x 21%	8.9 x 5.7
Van Cutsem et al, 2006 [17]	Cisplatina and fluorouracil *x* docetaxel, cisplatina, and fluorouracil	133 x 137	24% x 24%	8.2 x 9.6
Cunningham et al, 2008 [15]	Epirrubicina, cisplatina e fluorouracil ***x*** epirrubicina, cisplatina e capecitabina ***x*** epirrubicina, oxaliplatina e fluorouracil ***x*** epirrubicina, oxaliplatina e capecitabina	263 x 250 x 245 *x* 244	41% x 46% x 42% x 48%	9.9 x 9.9 x 9.3 x 11.2
Al-Batran et al, 2008 [14]	Fluorouracil, àcido folínico e cisplatina ***x*** fluorouracil,ácido folínico e oxaliplatina	108 x 112	25% x 35 %	8.8 x 10.7
Ajani et al, 2010 [32]	Cisplatina e fluorouracil ***x*** cisplatina e S-1	526 x 527	32% x 29%	7.9 x 8.6

A fim de comparar a eficácia do S-1 com o 5-FU, o estudo FLAGS randomizou 1053 pacientes em dois grupos: cisplatina e S-1 (CS1) e cisplatina e 5-FU (CF). A SG não apresentou diferença estatisticamente significativa: 8.6 meses no grupo CS1 e 7.9 meses no CF (HR, 0.92; 95% IC, 0.80 - 1.05; P =0.20); contudo, o perfil de segurança do regime CS1 foi superior com menores taxas de neutropenia grau 3/4 (32.3% v 63.6%), neutropenia complicada (5.0% v 14.4%), mucosite (1.3% v 13.6%), hipocalemia (3.6% v 10.8%) e mortes relacionadas ao tratamento (2.5% v 4.9%; P < .05). [32]

O irinotecano é também ativo no CG avançado, contudo não é aprovado para uso em primeira linha, pois não demonstrou superioridade aos regimes baseados em platina. [33-37] O papel das terapias alvo em CG avançado também vem sendo avaliado nos

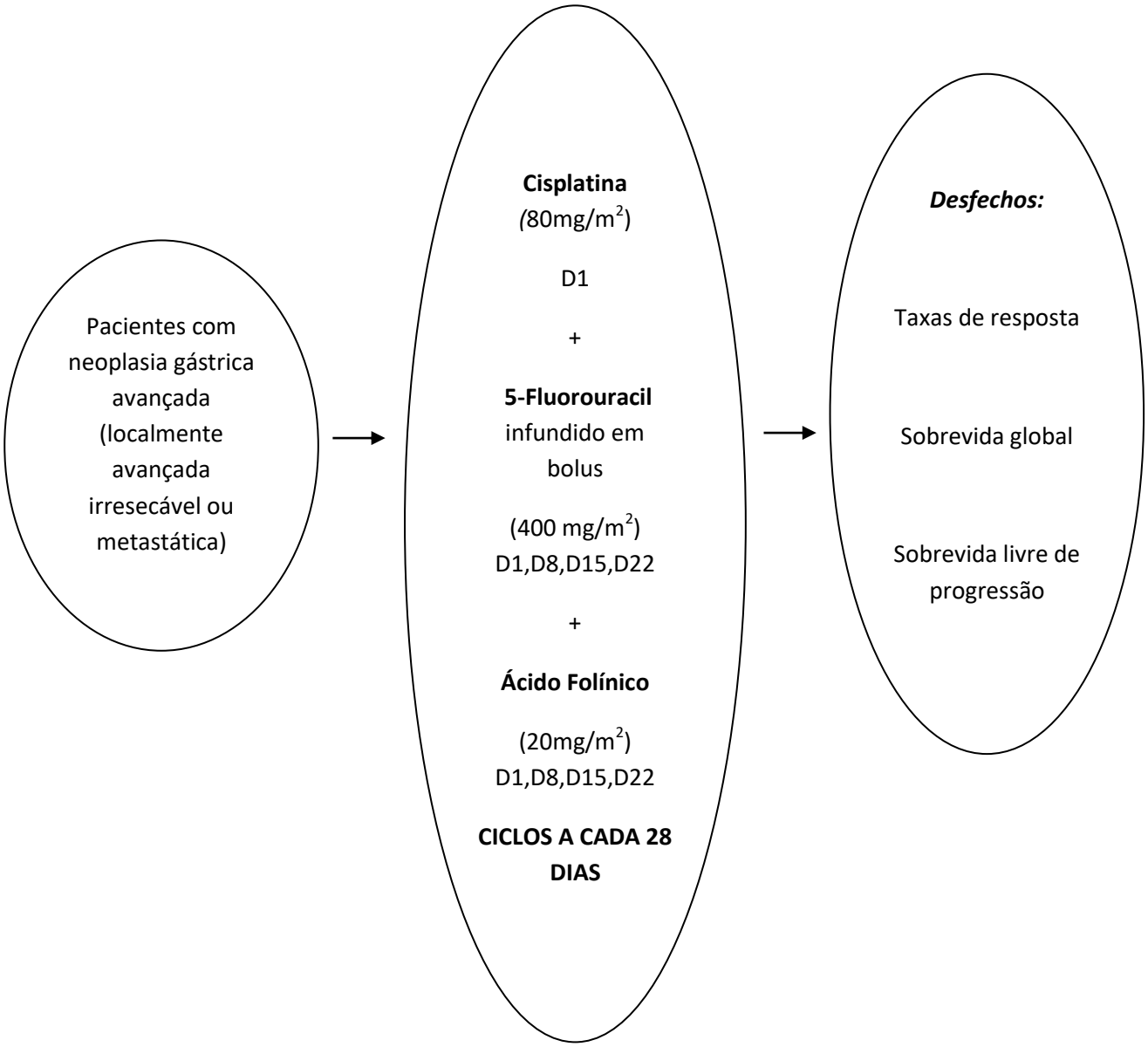
últimos anos, contudo seu uso ainda é bastante restrito. Na primeira linha de tratamento paliativo, o trastuzumabe foi aprovado, após os resultados publicados do estudo ToGA, para aqueles pacientes com hiperexpressão da proteína HER 2 (até 20 % do pacientes com CG avançado). Este estudo randomizou 594 pacientes em dois braços: todos pacientes receberam até 6 ciclos de cisplatina combinada com capecitabina ou fluorouracil sendo que 298 receberam trastuzumabe e 296 apenas quimioterapia). A sobrevida global mediana foi de 13.8 meses no grupo que recebeu trastuzumabe (95% IC 12–16) versus 11.1 meses no grupo controle (95% IC; 10–13) (HR 0•74; 95% IC 0•60–0•91; p=0•0046). Os eventos adversos não foram estatisticamente diferentes entre os grupos. [38]

Os estudos EXPAND, REAL 3 e AVAGAST avaliaram o papel dos anti-EGFR e anti-VEGF em primeira linha de tratamento, contudo seus resultados não demonstraram benefício. [39-41]

Em relação ao presente projeto de pesquisa vale salientar que não há na literatura dados robustos avaliando o papel da quimioterapia com 5-Fluorouracil administrado em bolus sendo aplicado de forma semanal no câncer gástrico avançado.

3. **MARCO CONCEITUAL**

Figura 2. Marco conceitual esquemático do estudo PFL



4. JUSTIFICATIVA

O câncer gástrico é um importante e emergente problema de saúde que quando diagnosticado tardiamente apresenta prognóstico ominoso. A maioria dos tratamentos é idealizada e testada nos países desenvolvidos; contudo, a realidade das nações em desenvolvimento é diferente, o que pode dificultar a incorporação de protocolos de tratamento com benefício comprovado.

Neste cenário, adaptações de protocolos estabelecidos podem ser necessárias para que os pacientes sejam submetidos a tratamento eficaz, porém adequado para a realidade econômica e estrutural do país onde o tratamento será executado.

No Instituto Nacional do Câncer do Brasil (INCA), assim como em diversos hospitais no Brasil e em outros países, existe restrição no número de leitos bem como dificuldades na aquisição de ferramentas e aparelhos para tratamentos dos mais diversos tipos. Os protocolos de quimioterapia utilizados como padrão de tratamento para neoplasia gástrica, em sua grande maioria, utilizam o 5-fluorouracil em infusão contínua, necessitando de internação hospitalar e/ou bombas de infusão, o que pode ser um fator limitante.

O tratamento com infusão do citotóxico 5-Fluorouracil, em bolus, é uma alternativa que facilita a administração de protocolos de quimioterapia podendo manter a eficácia do tratamento semelhante a de regimes em infusão contínua.

5. OBJETIVOS

5.1 Objetivo primário

Avaliar a sobrevida global em pacientes com neoplasia gástrica avançada submetidos a tratamento de primeira linha com o esquema PFL.

5.2 Objetivos secundários

Avaliar a sobrevida livre de progressão em pacientes com neoplasia gástrica avançada submetidos a tratamento com o esquema PFL.

Avaliar o perfil de toxicidade dos pacientes submetidos ao tratamento com o esquema PFL.

Verificar os índices de resposta clínica e/ou por imagem de acordo com os critérios Recist 1.1 ao regime terapêutico estudado.

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7. **ARTIGO**

Cisplatin, 5-Fluorouracil in bolus injection and Leucovorin in first line therapy for advanced gastric cancer as alternative to protocols with infusional 5-Fluorouracil

7.1 **ABSTRACT**

Introduction: Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death worldwide. Platinum agents and fluoropyrimidines are the main compounds used in first line setting for advanced GC. Given the activity of bolus 5-fluorouracil (5-FU) administration showed in many pre-clinical and clinical studies, similar outcomes when compared to infusional protocols and the convenient schedule without the need of hospitalization or infusion pumps, PFL protocol, a chemotherapy regimen combining cisplatin (CDDP), 5-FU in bolus infusion and leucovorin (LV), was incorporated at the Brazilian National Cancer Institute (INCA). This study aims to evaluate the outcomes of PFL regimen in first line setting for treating patients with advanced GC.

Materials and methods: Retrospective cohort study evaluating 109 patients with advanced GC treated in a first line setting with CDDP 80mg/m^2(D1) + 5- FU 400mg/m^2 in bolus injection (D1,D8,D15,D22)+ LV 20mg/m^2 (D1,D8,D15,D22) in 28-day cycles from January 2008 to December 2014.

Results: The median age was 54 years (24-80), 53.6% were male. Tumor staging at initial diagnosis was: E IIA 2.7%, E IIB 2.7%, E IIIA 1.8%, E IIIB 5.5%, E IIIC 5.5% and E IV 80.8%. The most common metastatic sites were

peritoneum 45%, lymph nodes 32.1%, liver 22%, pleura 5.5% and lung 2.8%. The median of cycles received per patient was 4 (1-11). Complete responses were achieved in 6.4% and partial responses in 14.7%. Median PFS was 6.3 months (5.08 – 7.58) and median OS was 8.3 months (6.79 – 9.87). Thirty-four (31.2%) patients were alive in 1-year and 8 (7.3%) in 2-years. Dose reduction was necessary in 9.1% and the most common toxicities were nausea 72%, vomiting 50%, fatigue 35%, diarrhea 29%, constipation 12%, stomatitis 11% and neutropenia 11%. Grade 3 and 4 adverse events corresponded to 26.6% and 3.7%, respectively. Three patients had neutropenia G4. Only 27 patients (24.8%) received second line treatment.

Conclusion: Chemotherapy protocol combining CDDP, 5-FU in bolus injection and LV is active in advanced gastric cancer and could be an alternative for 5-FU continuous infusion protocols in institutions with limited resources and low budget which is the reality of many nations all over the world.

Key Words: metastatic gastric cancer, advanced gastric cancer, chemotherapy, first line treatment

7.2 **INTRODUCTION**

Gastric cancer (GC) is a major health problem and it is the fourth most common cancer and the second leading cause of cancer death worldwide. More than 950,000 new diagnoses are made every year. An estimated 720,000 patients died from gastric cancer in 2012. [1,2] In Brazil, 13.540 GC new cases are expected for men and 7.750 for women in 2018, being the fourth more incident in men and the sixth in women. [3]

The prognosis for patients with advanced GC is poor, with median survival ranging from 4 months when treated only with best supportive care to around 12 months when treated with cytotoxic chemotherapy with or without target therapies. [4,5,9-16] The basis for chemotherapeutic protocols for first line setting in advanced GC are platinum compounds and fluoropyrimidines; in addition, these components can be combined with others as taxanes and antracyclines, for example. (9-16)

5-Fluorouracil (5-FU) may be administered by intravenous (IV) bolus or as a continuous infusion (CI) and each protocol influences its pharmacologic behavior and cytotoxic effects involving RNA and DNA synthesis. (17) 5-FU can be incorporated into nuclear RNA in the form of fluorouridine 5'-triphosphate (FUTP) (18) and its impact on DNA synthesis is mainly through the inhibition of thymidilate synthase (TS) by 5- fluoro-2' deoxyuridine-5' monophosphate (FdUMP) (19) and, to a lesser extent, through its incorporation into DNA. (20) Sobrero et al. highlight the role of decreased TS inhibition in the mechanism of resistance to infusional 5-FU, in contrast to the role of decreased incorporation of 5-FU into RNA in the mechanism of resistance to in bolus 5-FU. (21)

In vivo pharmacokinetic comparison of bolus versus CI 5-FU administration shows that the latter results in more constant drug levels in the plasma. (22) Given that the cytotoxicity of 5-FU is optimal during cell division, the constant drug levels achieved by CI ensure that a larger number of cells are exposed to 5-FU during the cell cycle. (23) The superiority of CI 5-FU administration when compared to bolus infusion in the setting of metastatic colorectal cancer is highlighted in a meta-analysis of 7 randomized studies based on 1219 individual patient data. (24) The CI resulted in a higher response rate (RR) (22 vs. 14 %, $p = 0.002$) and a small but significant survival difference (12.1 vs. 11.3 months, $p = 0.039$). None of the individual trials included in the meta-analysis had reported a significant survival benefit. (24) Regarding gastric cancer, there is no trial comparing these two administration modes directly.

Given the activity of bolus 5-FU administration showed in many pre-clinical and clinical studies, similar outcomes when compared to infusional protocols (17-24) and the convenient schedule without the need of hospitalization or infusion pumps, PFL protocol, a chemotherapy regimen combining cisplatin (CDDP), 5-FU in bolus infusion and leucovorin (LV), was incorporated at the Brazilian National Cancer Institute (INCA).

This retrospective study aims to evaluate the outcomes of an advanced GC chemotherapy protocol with 5-FU bolus infusion and no need of hospitalization or infusion pumps.

7.3 **MATERIALS AND METHODS**

All the patients included in the present study were treated after their consent from January 2008 to December 2014 at the INCA (Rio de Janeiro,

Brazil). This study was approved by the INCA's Ethics in Human Research Committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

This retrospective cohort study evaluated advanced GC patients defined as those with metastatic or unresectable disease. The disease had to be documented by imaging and treated in first line setting with CDDP 80mg/m^2 (D1) + 5-FU 400mg/m^2 (D1,D8,D15,D22) + LV 20mg/m^2 (D1,D8,D15,D22) in 28-day cycles (PFL regimen). CDDP was diluted in 400mL of normal saline (NS) and mannitol 20% 100 mL, being infused over 60 minutes followed by LV diluted in 100 mL of 5% glucose solution (D5W) over 15 minutes and 5-FU in bolus diluted in 100 mL of NS after LV. Hydration and electrolytes reposition were performed previously and post CDDP infusion.

Clinical data were collected from medical records; demographics, Eastern Cooperative Oncology Group (ECOG) performance status (PS), clinical and imaging stages, tumor characteristics, prior neo-adjuvant and adjuvant treatments, adverse events, response, progression free-survival (PFS) and overall survival (OS) were evaluated.

Response to treatment was assessed using clinical and radiological criteria as follows: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). The radiological evaluation was based on the Response Evaluation Criteria in Solid Tumors, version 1.1 [6], with a frequency determined by the assistant physician.

Evaluation of drug toxicities was standardized according to the National Cancer Institute Common Toxicity Criteria, version 3.0 [7].

Patients receiving PFL regimen for second line advanced GC, neoadjuvant and/or adjuvant setting were excluded, as well as patients with another primary cancer (except non-melanoma skin cancer) and data absence in medical charts.

A budget estimative to each main first line chemotherapeutic regimen per cycle was performed considering only the value of drugs, hospitalization and/or devices. This study was not designed for a cost-effectiveness analysis. The standard body surface for estimating treatment costs was 1.85 m^2. The drugs, devices and procedures prices are those currently applied to the Brazilian Public Health System. Protocols with the need of prolonged infusion had the value of hospital diary (US$ 110.76 per day) or infusion pump device (48h – US$ 45.23 and 96h – US$ 45.41) added. Those who received the treatment through an infusion pump must have added the catheter implantation costs of US$ 251.75 to the value described on table 2. To calculate the costs in US dollars the conversion rate of US$ 1.00 = R$ 3.25 was applied.

OS was estimated from the time of the first day infusion of PFL regimen until death or, for living patients, the last available follow-up, and PFS was measured from the date of the PFL treatment beginning to either first progression or death or the date of last contact for patients who are alive and progression-free, in both cases using the Kaplan-Meier method. All descriptive analyses were performed with the SPSS software, version 18.0.

7.4 **RESULTS**

A hundred and nine patients were eligible for the study (Figure 1). Tumor characteristics at diagnosis and epidemiological data are described in table 1.

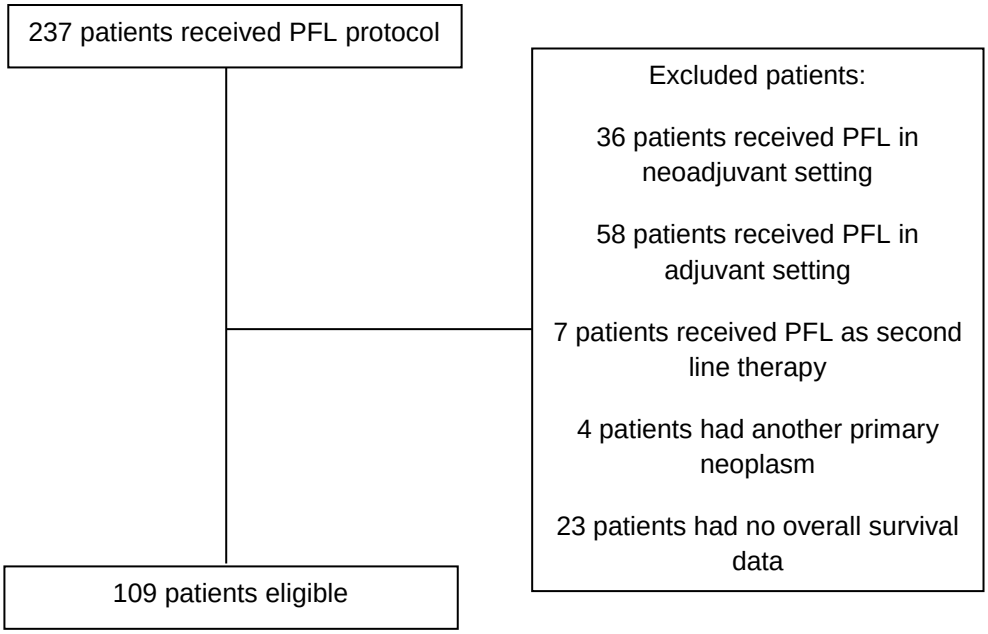

Figure1. Flow chart of eligible patients for the study.

Table 1. Baseline and tumor characteristics of the total study population (N=109).

Characteristics	*n (109)*	*%*
Age, years		
Median	54	
Range	24-80	
Sex		
Male	58	53.2
Female	51	46.8
Schooling		
Illiterate	7	6.4
≤ 8 years	63	57.8
> 8 years	39	35.8
Race		
White	77	70.6
Black	10	9.2
Mulatto	22	20.2
Former smoker		
Yes	54	49.5
Former drinker		
Yes	17	15.6
Differentiation grade		
Grade 1	3	2.8
Grade 2	31	28.4
Grade 3	70	64.2
Unknown	5	4.6
Performance status		
≤ 1	95	87.2
2	12	11
3	2	1.8
Unresectable disease	21	19.2
Metastatic sites		
Peritoneum	49	45
Lymph nodes	35	32.1
Liver	24	22
Pleura	6	5.5
Lung	3	2.8
Other	59	52.1

Regarding the treatment, the median of cycles received per patient was 4 (1-11). The medium interval between the radiological evaluations was four months. Seven patients (6.4%) achieved CR, sixteen (14.7%) had PR, 16 (14.7%) SD and 54 (49.5%) PD. Sixteen patients (14.7%) had no responses described in medical records.

The median PFS was 6.3 months (5.08 – 7.58) and median OS was 8.33 months (6.79 – 9.87) (Figure 2). Thirty-four (31.2%) patients were alive in 1-year and 8 patients (7.3%) in 2-years.

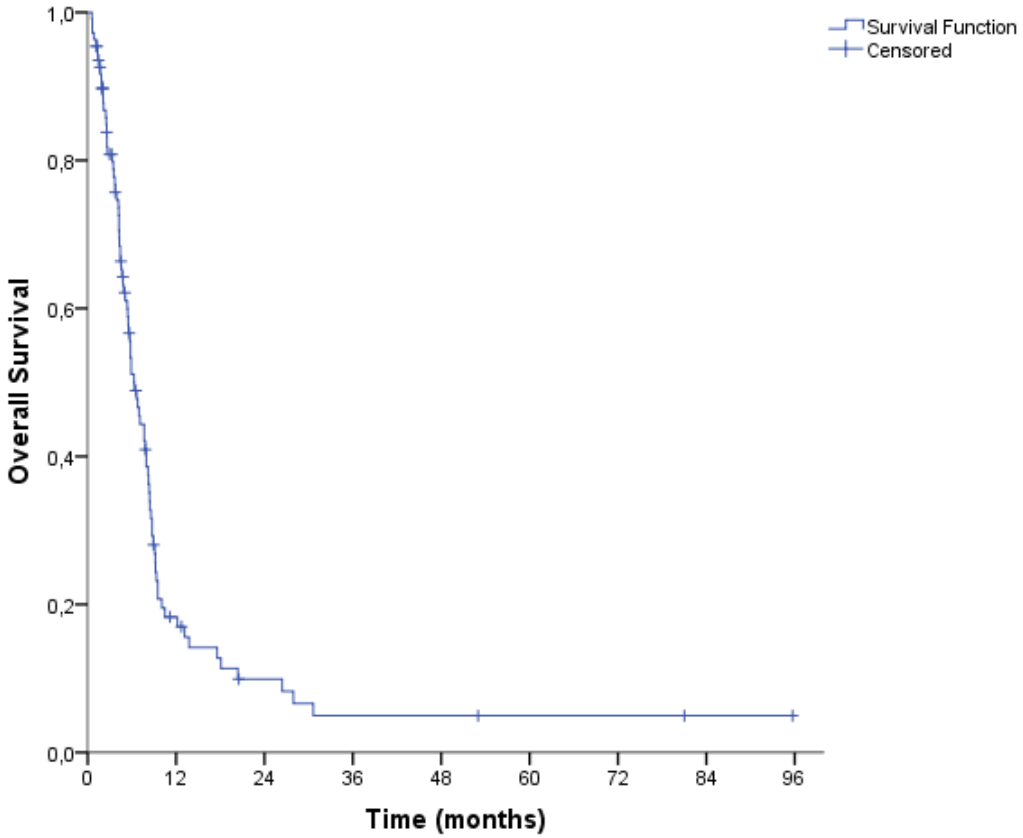

Figure 2. Overall Survival among advanced GC patients treated with palliative PFL.

No differences were found in PFS and OS between patients with non-metastatic and metastatic gastric cancer at diagnosis. Table 2 describes the outcomes of PFL regimen and compares it with important phase 2 and 3 clinical trials evaluating the role of platinum compounds and 5-FU in advanced GC.

Table 2. Clinical studies evaluating chemotherapy in first line setting of advanced gastric cancer.

References	Number of patients	Treatment regimen	Toxicities	Response Rate	Progression Free Survival (months) or Time to progression (months)	Overall Survival (months)	Treatment Costs per cycle (US$)
Coelho et al, 2018 Retrospective study	***PFL 109***	***Cisplatin (CDDP) (80mg/m^2) D1*** ***5- Fluorouracil (5-FU) (400 mg/m^2) D1,D8,D15,D22*** ***Leucovorin (LV) (20mg/m^2) D1,D8,D15,D22*** ***every 4 weeks***	***G3 and G4 adverse events to 26.6% and 3.7%, respectively. The most common toxicities were nausea 72%, vomiting 50%, fatigue 35%, diarrhea 29%, constipation 12%, stomatitis 11% and neutropenia 11%.***	***CR - 6.4%*** ***PR - 14.7%***	***PFS*** ***6.3*** ***(95% CI, 5.08 - 7.58)***	***8.33*** ***(95% CI, 6.79 - 9.87)***	***131.69***
Van Cutsem et al, 2006 [9] Phase 3 trial	DCF 221 *CF* 224	DCF Docetaxel 75 mg/m^2 and CDDP 75 mg/m^2 (day 1) plus 5-FU 750 mg/m^2/d (days 1 to 5) every 3 weeks CF CDDP 100 mg/m^2 (day 1) plus 5-FU 1,000 mg/m^2/d (days 1 to 5) every 4 weeks	Grade 3 to 4 treatment-related adverse events occurred in 69% (DCF) *v* 59% (CF) Frequent grade 3 to 4 toxicities for DCF *vs* CF were: neutropenia (82% *vs* 57%), stomatitis (21% *vs* 27%), diarrhea (19% *vs* 8%), lethargy (19% *v* 14%). Complicated neutropenia was more frequent with DCF than CF (29% *v* 12%).	DCF CR - 2% PR - 35% CF CR - 1% PR - 24%	Primary endpoint TTP DCF - 5.6 CF - 3.7 (HR 1.47; 95% CI, 1.19 - 1.82; log-rank p < 0.001; risk reduction 32%)	DCF – 9.2 CF - 8.6 (HR 1.29; 95% CI, 1.0 - 1.6; log-rank *p* = *0*.02; risk reduction 23%).	DCF 395.70 IP 713.23 IH CF 156.92 IP 474.46 IH
Cunningham et al, 2008 [10] Phase 3 noninferiority trial	ECF 263 ECX 250 EOF 245 EOX 244	ECF – Epirrubicin 50 mg/m^2 + CDDP 60 mg/m^2 + 5-FU 200 mg/m^2 daily every 3 weeks ECX - Epirrubicin 50 mg/m^2 + CDDP 60 mg/m^2 + capecitabine 1250mg/m^2/day every 3 weeks EOF - Epirrubicin 50 mg/m^2 + Oxalipatin 130 mg/m^2+ 5-FU 200 mg/m^2 daily every 3 weeks EOX - Epirrubicin 50 mg/m^2 + Oxalipatin 130 mg/m^2+ capecitabine 1250mg/m^2/day every 3 weeks	Toxic effects of capecitabine and fluorouracil were similar. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhea and neuropathy.	ECF CR - 4.1% PR - 36.6% ECX CR - 4.2% PR - 42.2% EOF CR - 2.6% PR - 39.8% EOX CR - 3.9% PR - 44%	ECF PFS – 6.2 ECX PFS – 6.7 EOF PFS – 6.5 EOX PFS – 7	Primary endpoint ECF 9.9 ECX 9.9 EOF 9.3 EOX 11.2	ECF 565.92 ECX 262.00 EOF 654.00 EOX 349.85

Al-Batran et al, 2008 [11] Phase 3 trial	FLP 108 FLO 112	FLP - 5-FU 2.000 mg/m^2 via 24-hour infusion, LV 200 mg/m^2 weekly, and CDDP 50 mg/m^2 every 2 weeks. FLO- 5-FU 2.600 mg/m^2 via 24-hour infusion, LV 200 mg/m2, and oxaliplatin 85 mg/m^2 every 2 weeks	FLO was associated with significantly less (any grade) anemia (54% vs 72%), nausea (53% vs 70%), vomiting (31% vs 52%), alopecia (22% vs 39%), fatigue (19% vs 34%), renal toxicity (11% vs 34%), thromboembolic events (0.9% v 7.8%), and serious adverse events related to the treatment (9% vs 19%). FLP was associated with significantly less peripheral neuropathy (22% vs 63%)	FLP 24.5% FLO 34.8%	Primary endpoint PFS FLO vs FLP (5.8 v 3.9, respectively; p = 0.077)	FLP 8.8 FLO 10.7	FLP 329.54 FLO 251.83
Al-Batran et al, 2008 [12] Phase 2 trial	FLOT 54	FLOT - oxaliplatin 85 mg/m2, LV 200 mg/m2, and docetaxel 50 mg/m2, each as a 1- to 2-h i.v. infusion followed by FU 2600 mg/m2 as a 24-h continuous infusion every 2 weeks	Frequent (>10%) grade 3 or 4 toxic effects included neutropenia in 26 (48.1%), leukopenia in 15 (27.8%), diarrhea in 8 (14.8%), and fatigue in 6 (11.1%) patients. Complicated neutropenia was observed in two (3.8%) patients.	Primary endpoint (n = 52) CR – 3.8% PR – 53.8 %	PFS 5.2 (95% CI, 4.4 – 8.4)	11.1 (95% CI, 9.3-17.3)	FLOT 395.67 IH
Kang et al, 2009 [13] Phase 3 noninferiority trial	XP 160 CF 156	XP - CDDP (80 mg/m2 i.v. day 1) plus oral capecitabine (1000 mg/m2 b.i.d., days 1-14) CF- CDDP (80 mg/m2 i.v. day 1) plus 5-FU (800 mg/m2/day by continuous infusion, days 1-5) (FP) every 3 weeks	The most common treatment-related grade 3/4 adverse events in XP versus FP patients were as follows: neutropenia (16% versus 19%), vomiting (7% versus 8%), and stomatitis (2% versus 6%).	XP RR – 46% (95% CI, 38 - 55) CF RR – 32% (95% CI, 24 - 41) Odds Ratio 1.80 (95% CI, 1.11 – 2.94; p = 0.020)	Primary endpoint PFS XP (n = 139) - 5.6 FP (n = 137) - 5.0 HR 0.81 (95% CI, 0.63 - 1.04; p < 0.001; noninferiority margin of 1.25)	NA	XP 166.15 CF 474.46 IH 127.07 IP
Ajani et al, 2010 [14] Phase 3 trial	CF 526 CS1 527	CF – 5-FU 1,000 mg/m2/24 hours for 120 hours and CDDP at 100 mg/m2 intravenously on day 1, repeated every 28 days CS1 S-1 at 50 mg/m2divided in two daily doses for 21 days and CDDP 75 mg/m2 i.v. on day 1 every 4 weeks	Significant safety advantages were observed in the CS1 arm compared with the CF arm for the rates of grade 3/4 neutropenia (32.3% vs 63.6%), complicated neutropenia (5.0% vs 14.4%), stomatitis (1.3% vs 13.6%), hypokalemia (3.6% vs 10.8%), and treatment-related deaths (2.5% vs 4.9%; P < .05).	CF (n = 402) RR – 31.9% CS1 (n = 385) RR – 29.1% (Fisher's exact test p = 0.40)	PFS CS1 (n = 521) 4.8 CF (n = 508) 5.5 (HR 0.99; 95% CI, 0.86 - 1.14)	Primary endpoint CS1 (n = 521) 8.6 CF (n = 508) 7.9 (HR 0.92; 95% CI, 0.80 - 1.05; p = 0.20).	CF 156.95 IP 459.08 IH CS1 S1 is not available in Brazilian Public Health System

Yun et al, 2010 [15] Phase 2 trial	CX 45 ECX 44	XP - CDDP 75 mg/m2 iv on day 1 and capecitabine 1000 mg/m2 bid po on days 1-14) ECX - Epirubicin 50 mg/m2 plus CX every 3 weeks	There was no relevant difference in the occurrence of overall grade 3 or 4 toxicities between the XP and ECX arms (80% versus 78%, respectively; P = 0.516). However, none in the XP and 12% in the ECX arm discontinued treatment because of toxicity.	XP 38% ECX 37%	Primary Endpoint PFS XP – 6.4 ECX – 6.5 (p = 0.863)	NA	XP 166.15 ECX 262.00
Bang et al, 2010 [16] Phase 3 trial	XP or CF plus trastuzumab (T) 298 XP or CF alone 296	XP- CDDP 80 mg/m² on day 1 was given by intravenous infusion. Capecitabine 1000 mg/m² was given orally twice a day for 14 days followed by a 1-week rest CF - Fluorouracil 800 mg/m² per day was given by continuous intravenous infusion on days 1–5 of each cycle. Chemotherapy was given every 3 weeks for six cycles. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks until PD, unacceptable toxicity, or withdrawal of consent.	The most common adverse events in both groups were nausea (trastuzumab plus chemotherapy, 197 [67%] vs chemotherapy alone, 184 [63%]), vomiting (147 [50%] vs 134 [46%]), and neutropenia (157 [53%] vs 165 [57%]). Rates of overall grade 3 or 4 adverse events (201 [68%] vs 198 [68%]) and cardiac adverse events (17 [6%] vs 18 [6%]) did not differ between groups.	XPT or CFT CR – 5% PR – 42% XP or CF CR – 2% PR – 32% Odds Ratio for PR 1·52 (1·09 – 2·14; X^2 test p = 0·0145)	PFS XPT or CFT 6·7 (6 – 8) XP or CF 5·5 (5 – 6) HR 0·71 (0·59 – 0·86) p = 0·0004	Primary endpoint XPT or CFT - 16 (95% CI, 15 – 19) XP or CF – 11.8 (95% CI, 10 - 13) HR 0·65 (95% CI, 0·51 – 0·83)	XP 166.15 CF 474.46 IH 127.07 IP Trastuzumab is not available in Brazilian Public Health System for advanced gastric cancer treatment

CR – Complete response PR – Partial response SD – Stable disease PD – Progressive disease RR – Response rate TTP – Time to progression PFS – Progression free survival OS – Overall survival

Pts – patients IP – costs bases in patients receiving treatment by infusion pump IH – patients receiving treatment in hospital HR – Hazard ratio CI – confidence interval

The most common toxicities were nausea 72%, vomiting 50%, fatigue 35%, diarrhea 29%, constipation 12%, stomatitis 11% and neutropenia 11%. Of all adverse events, grade 3 and 4 corresponded to 26.6% and 3.7%, respectively. Three patients had neutropenia G4, one had febrile neutropenia G4 and one died of dehydration from diarrhea. Adverse events are described in table 3.

Table 3: Prevalence and grade of adverse effects (%)

Adverse event	Grade				
	All grades	1	2	3	4
Nausea	72	39	28	5	0
Vomiting	50	33	12	5	0
Fatigue	35	23	8	4	0
Diarrhea	29	21	6	1	0
Constipation	12	10	2	0	0
Stomatitis	11	8	3	0	0
Neutropenia	11	1	2	5	3
Neuropathy	6	5	1	0	0
Anemia	6	0	4	2	0
Ototoxicity	5	3	0	2	0
Thrombocytopenia	5	2	3	0	0
Myalgia	5	5	0	0	0
Febrile neutropenia	4	0	0	3	1
Renal dysfunction	4	1	1	2	0
Skin toxicity	3	3	0	0	0

Three patients were re-exposed to PFL regimen after progressive disease and only 27 patients (24.8%) received second line treatment. Three were treated with oxaliplatin based regimen and 18 with isolated irinotecan.

7.5 **DISCUSSION**

GC is a major concern in emergent countries since its burden remains very high in Asia, Latin America, and Central and Eastern Europe. (1-3) Low educational status, negligence, limited access to public health system, social disparities, scarce resources, high prevalence of smoking and alcoholism and dietary habits are important factors influencing this epidemiological data.

Chemotherapy is a well-established treatment in advanced GC, improving the quality of life and OS. (4,5,9-15,24) In the present article, it was evaluated the effectiveness of bolus 5-FU administration in first line treatment for advanced GC.

The patients' outcomes with PFL protocol were in the range of those already published in literature as shown in Table 2. (9-16) The OS was 8.33 months (95% CI; 6.79 – 9.87) and PFS 6.3 months (95% CI; 5.08 – 7.58). Some explanations for the timeframe proximity of these two outcomes are the low number of patients receiving second line treatment, i.e. only 27 patients (24.8%), and the absence of imaging exams time standardization.

The RR was also similar to other trials showing 21.1% of patients with tumor reduction after treatment. The PD proportion was greater than what was found in literature (9-16), reaching 49.5% of patients; nonetheless, this could be related to the absence of standardization in time to imaging and clinical evaluations for response assessment. As a consequence, patients without symptoms could have their imaging evaluation postponed, and despite having

responses or a SD, they would be considered as non-responders taking into consideration that imaging was performed only during the symptomatic phase of a PD. This hypothesis is reinforced in this retrospective study because the main endpoint, OS, is within the range of the three main phase III trials evaluating CDDP and 5-FU combination which is 7.9 to 8.6 months (9, 14).

Toxicities were manageable and treatment was well tolerated. The most common adverse events were nausea and vomiting; the explanation for the high prevalence of these two toxicities, besides the high dose of CDDP, is that from 2008 until 2011, there were no neurokinin 1 and 5-HT_3 antagonists for vomiting prophylaxis at INCA; the latter was introduced routinely only after 2012. Neutropenia occurred in 13.76% of patients. The concern about adverse events is related to the different toxicities between bolus and infusional 5-FU schemes. A meta-analysis revealed that grade 3 and 4 hematologic toxicity (most commonly neutropenia) was 7 times more common in patients who received bolus infusion ($p < 0.0001$). The risks of severe diarrhea, nausea/vomiting, and stomatitis were not different among the 2 groups. The risk of developing hand-foot syndrome was almost doubled with 5-FU CI (adjusted RR 1.87) (25).

In terms of costs per cycle, PFL may be a cheaper alternative than the majority of other regimens as described in table 2. The reductions in costs and time spent in infusion could expand the access to treatment to hospitals with low budget and little infrastructure.

The retrospective methodology, absence of a strict control in the intervention group, missing data in patients' records, lack of standardized chemotherapeutic regimens in neoadjuvant, adjuvant and second line settings,

and absence of a strict interval for imaging response evaluation are the main limitations in this study.

The strongest points are that it is a large cohort evaluating a group of patients with advanced GC receiving only one chemotherapeutic regimen and it shows how the treatment for GC is in real life scenario, outside a clinical trial.

PFL protocol is feasible, well tolerated and has outcomes in line with main phase 3 trials (9-16). It is necessary to stress that the main objective of this study was not to directly compare the outcomes of this retrospective cohort with those clinical trials already published. However, PFL could be an alternative for those institutions which lack resources to offer the standard of care protocols, widening treatment access to patients.

7.6 **CONCLUSION**

Chemotherapy protocol combining CDDP, 5-FU in bolus injection and LV could be an alternative for 5-FU continuous infusion protocols in institutions with limited resources and low budget which is the reality of many nations all over the world.

FUNDING

This work did not receive any specific grants from funding agencies in the public, commercial or not-for-profit sectors.

ETHICAL APPROVAL

This study was approved by the Ethics in Human Research Committee of the Brazilian National Cancer Institute and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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8. **CONSIDERAÇÕES FINAIS**

O protocolo PFL, combinando a infusão de 5-Fluorouracil em bolus, cisplatina e ácido folínico se mostrou ativo como tratamento em primeira linha para pacientes com neoplasia gástrica avançada.

A sobrevida global mediana do estudo de 8.33 meses (95% CI; 6.79 – 9.87) foi semelhante aos resultados de estudos fase III os quais avaliaram o papel da poliquimioterapia em primeira linha paliativa para câncer gástrico avançado, contudo utilizando regimes de infusão contínua.

O protocolo PFL é de fácil utilização, possui baixo custo e boa tolerância, podendo ser alternativa para tratamento de câncer gástrico metastático em hospitais que possuem limitações para administrar regimes quimioterápicos com fluorouracil em infusão contínua ou capecitabina.

9. PERSPECTIVAS FUTURAS

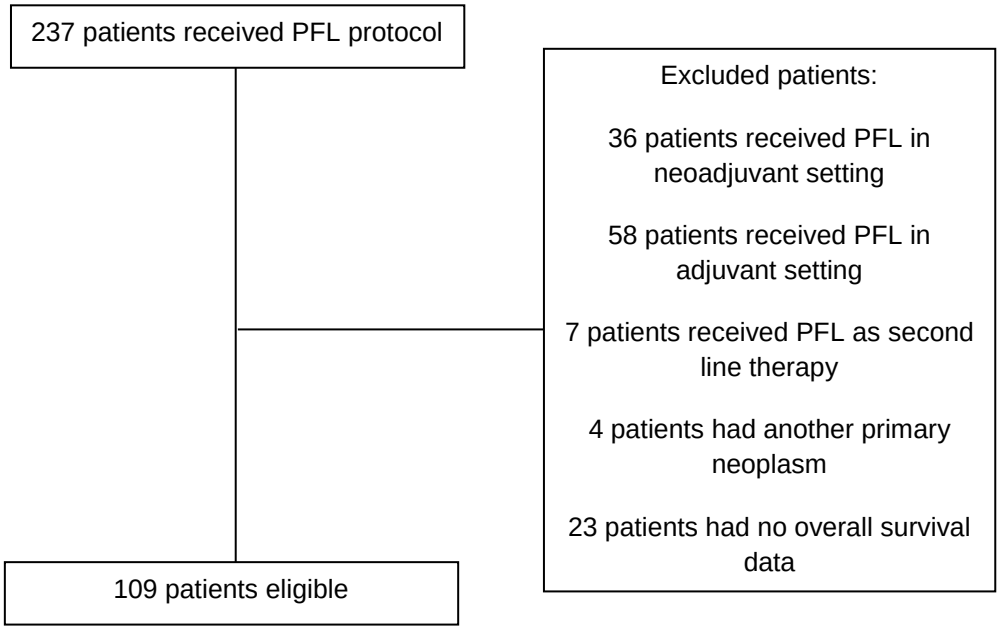
Em um mundo ideal, todos os pacientes, de todos os lugares, deveriam receber os melhores tratamentos para suas doenças. Infelizmente, está-se bastante distante desta realidade e alternativas para democratizar e ampliar o acesso a tratamentos são sempre bem vindas.

O objetivo deste trabalho se cumpriu ao mostrar que um regime quimioterápico de baixo custo, boa tolerabilidade e fácil administração é ativo contra uma neoplasia tão prevalente como o câncer gástrico.

Portanto, o protocolo de quimioterapia PFL é mais uma alternativa para auxiliar os pacientes com câncer gástrico avançado em locais onde a infusão contínua de 5-FU ou o uso de capecitabina não é factível.

10. **ANEXOS:**

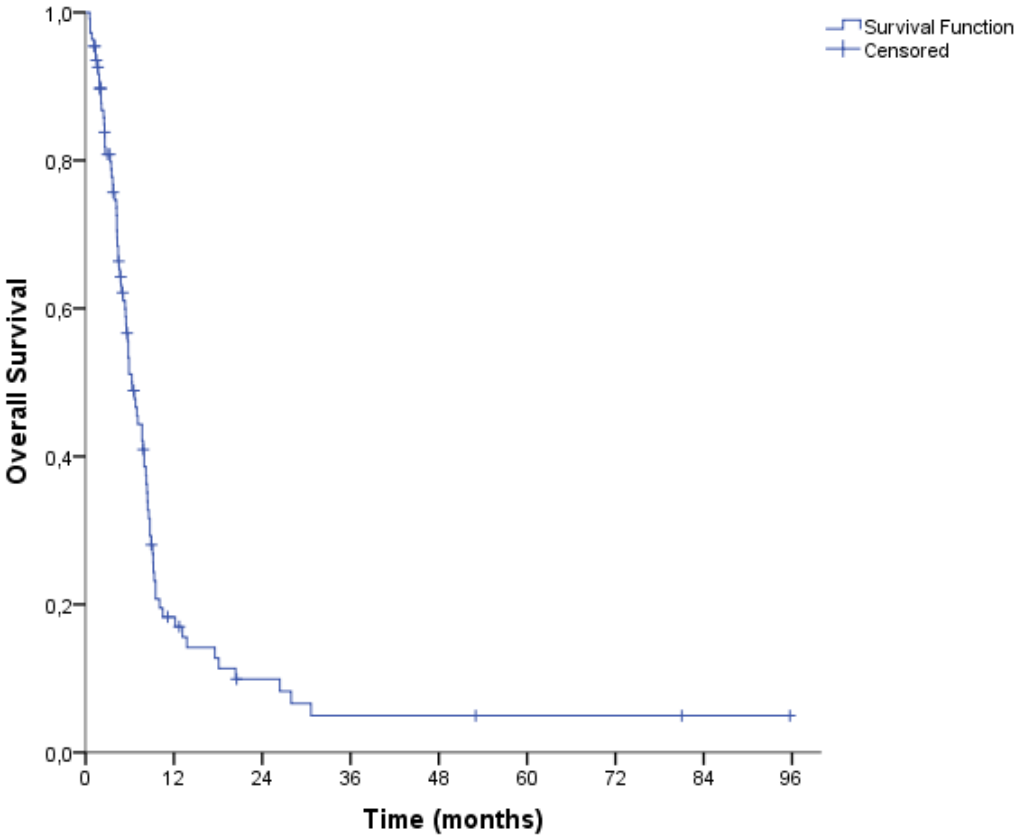
10.1 **Figure1**. Flow chart of eligible patients for the study.



10.2 **Table 1.** Baseline and tumor characteristics of the total study population (N=109).

Characteristics	*n (109)*	*%*
Age, years		
Median	54	
Range	24-80	
Sex		
Male	58	53.2
Female	51	46.8
Schooling		
Illiterate	7	6.4
≤ 8 years	63	57.8
> 8 years	39	35.8
Race		
White	77	70.6
Black	10	9.2
Mulatto	22	20.2
Former smoker		
Yes	54	49.5
Former drinker		
Yes	17	15.6
Differentiation grade		
Grade 1	3	2.8
Grade 2	31	28.4
Grade 3	70	64.2
Unknown	5	4.6
Performance status		
≤ 1	95	87.2
2	12	11
3	2	1.8
Unresectable disease	21	19.2
Metastatic sites		
Peritoneum	49	45
Lymph nodes	35	32.1
Liver	24	22
Pleura	6	5.5
Lung	3	2.8
Other	59	52.1

10.3 **Figure 2.** Overall Survival among advanced GC patients treated with palliative PFL.



10.4 **Table 2.** Clinical studies evaluating chemotherapy in first line setting of advanced gastric cancer.

References	Number of patients	Treatment regimen	Toxicities	Response Rate	Progression Free Survival (months) or Time to progression (months)	Overall Survival (months)	Treatment Costs per cycle (US$)
Coelho et al, 2018 Retrospective study	***PFL 109***	***Cisplatin (CDDP) (80mg/m^2) D1*** ***5- Fluorouracil (5-FU) (400 mg/m^2) D1,D8,D15,D22*** ***Leucovorin (LV) (20mg/m^2) D1,D8,D15,D22*** ***every 4 weeks***	***G3 and G4 adverse events to 26.6% and 3.7%, respectively. The most common toxicities were nausea 72%, vomiting 50%, fatigue 35%, diarrhea 29%, constipation 12%, stomatitis 11% and neutropenia 11%.***	***CR - 6.4%*** ***PR - 14.7%***	***PFS*** ***6.3*** ***(95% CI, 5.08 - 7.58)***	***8.33*** ***(95% CI, 6.79 - 9.87)***	***131.69***
Van Cutsem et al, 2006 [9] Phase 3 trial	DCF 221 *CF* 224	DCF Docetaxel 75 mg/m^2 and CDDP 75 mg/m^2 (day 1) plus 5-FU 750 mg/m^2/d (days 1 to 5) every 3 weeks CF CDDP 100 mg/m^2 (day 1) plus 5-FU 1,000 mg/m^2/d (days 1 to 5) every 4 weeks	Grade 3 to 4 treatment-related adverse events occurred in 69% (DCF) *v* 59% (CF) Frequent grade 3 to 4 toxicities for DCF *vs* CF were: neutropenia (82% *vs* 57%), stomatitis (21% *vs* 27%), diarrhea (19% *vs* 8%), lethargy (19% *v* 14%). Complicated neutropenia was more frequent with DCF than CF (29% *v* 12%).	DCF CR - 2% PR - 35% CF CR - 1% PR - 24%	Primary endpoint TTP DCF - 5.6 CF - 3.7 (HR 1.47; 95% CI, 1.19 - 1.82; log-rank p < 0.001; risk reduction 32%)	DCF – 9.2 CF - 8.6 (HR 1.29; 95% CI, 1.0 - 1.6; log-rank *p* = *0*.02; risk reduction 23%).	DCF 395.70 IP 713.23 IH CF 156.92 IP 474.46 IH
Cunningham et al, 2008 [10] Phase 3 noninferiority trial	ECF 263 ECX 250 EOF 245 EOX 244	ECF – Epirrubicin 50 mg/m^2 + CDDP 60 mg/m^2 + 5-FU 200 mg/m^2 daily every 3 weeks ECX - Epirrubicin 50 mg/m^2 + CDDP 60 mg/m^2 + capecitabine 1250mg/m^2/day every 3 weeks EOF - Epirrubicin 50 mg/m^2 + Oxalipatin 130 mg/m^2+ 5-FU 200 mg/m^2 daily every 3 weeks EOX - Epirrubicin 50 mg/m^2 + Oxalipatin 130 mg/m^2+ capecitabine 1250mg/m^2/day every 3 weeks	Toxic effects of capecitabine and fluorouracil were similar. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhea and neuropathy.	ECF CR - 4.1% PR - 36.6% ECX CR - 4.2% PR - 42.2% EOF CR - 2.6% PR - 39.8% EOX CR - 3.9% PR - 44%	ECF PFS – 6.2 ECX PFS – 6.7 EOF PFS – 6.5 EOX PFS – 7	Primary endpoint ECF 9.9 ECX 9.9 EOF 9.3 EOX 11.2	ECF 565.92 ECX 262.00 EOF 654.00 EOX 349.85

Al-Batran et al, 2008 [11] Phase 3 trial	FLP 108 FLO 112	FLP - 5-FU 2.000 mg/m^2 via 24-hour infusion, LV 200 mg/m^2 weekly, and CDDP 50 mg/m^2 every 2 weeks. FLO- 5-FU 2.600 mg/m^2 via 24-hour infusion, LV 200 mg/m2, and oxaliplatin 85 mg/m^2 every 2 weeks	FLO was associated with significantly less (any grade) anemia (54% vs 72%), nausea (53% vs 70%), vomiting (31% vs 52%), alopecia (22% vs 39%), fatigue (19% vs 34%), renal toxicity (11% vs 34%), thromboembolic events (0.9% v 7.8%), and serious adverse events related to the treatment (9% vs 19%). FLP was associated with significantly less peripheral neuropathy (22% vs 63%)	FLP 24.5% FLO 34.8%	Primary endpoint PFS FLO vs FLP (5.8 v 3.9, respectively; p = 0.077)	FLP 8.8 FLO 10.7	FLP 329.54 FLO 251.83
Al-Batran et al, 2008 [12] Phase 2 trial	FLOT 54	FLOT - oxaliplatin 85 mg/m2, LV 200 mg/m2, and docetaxel 50 mg/m2, each as a 1- to 2-h i.v. infusion followed by FU 2600 mg/m2 as a 24-h continuous infusion every 2 weeks	Frequent (>10%) grade 3 or 4 toxic effects included neutropenia in 26 (48.1%), leukopenia in 15 (27.8%), diarrhea in 8 (14.8%), and fatigue in 6 (11.1%) patients. Complicated neutropenia was observed in two (3.8%) patients.	Primary endpoint (n = 52) CR – 3.8% PR – 53.8 %	PFS 5.2 (95% CI, 4.4 – 8.4)	11.1 (95% CI, 9.3-17.3)	FLOT 395.67 IH
Kang et al, 2009 [13] Phase 3 noninferiority trial	XP 160 CF 156	XP - CDDP (80 mg/m2 i.v. day 1) plus oral capecitabine (1000 mg/m2 b.i.d., days 1-14) CF- CDDP (80 mg/m2 i.v. day 1) plus 5-FU (800 mg/m2/day by continuous infusion, days 1-5) (FP) every 3 weeks	The most common treatment-related grade 3/4 adverse events in XP versus FP patients were as follows: neutropenia (16% versus 19%), vomiting (7% versus 8%), and stomatitis (2% versus 6%).	XP RR – 46% (95% CI, 38 - 55) CF RR – 32% (95% CI, 24 - 41) Odds Ratio 1.80 (95% CI, 1.11 – 2.94; p = 0.020)	Primary endpoint PFS XP (n = 139) - 5.6 FP (n = 137) - 5.0 HR 0.81 (95% CI, 0.63 - 1.04; p < 0.001; noninferiority margin of 1.25)	NA	XP 166.15 CF 474.46 IH 127.07 IP
Ajani et al, 2010 [14] Phase 3 trial	CF 526 CS1 527	CF – 5-FU 1,000 mg/m2/24 hours for 120 hours and CDDP at 100 mg/m2 intravenously on day 1, repeated every 28 days CS1 S-1 at 50 mg/m2divided in two daily doses for 21 days and CDDP 75 mg/m2 i.v. on day 1 every 4 weeks	Significant safety advantages were observed in the CS1 arm compared with the CF arm for the rates of grade 3/4 neutropenia (32.3% vs 63.6%), complicated neutropenia (5.0% vs 14.4%), stomatitis (1.3% vs 13.6%), hypokalemia (3.6% vs 10.8%), and treatment-related deaths (2.5% vs 4.9%; P < .05).	CF (n = 402) RR – 31.9% CS1 (n = 385) RR – 29.1% (Fisher's exact test p = 0.40)	PFS CS1 (n = 521) 4.8 CF (n = 508) 5.5 (HR 0.99; 95% CI, 0.86 - 1.14)	Primary endpoint CS1 (n = 521) 8.6 CF (n = 508) 7.9 (HR 0.92; 95% CI, 0.80 - 1.05; p = 0.20).	CF 156.95 IP 459.08 IH CS1 S1 is not available in Brazilian Public Health System

Yun et al, 2010 [15] Phase 2 trial	CX 45 ECX 44	XP - CDDP 75 mg/m2 iv on day 1 and capecitabine 1000 mg/m2 bid po on days 1-14) ECX - Epirubicin 50 mg/m2 plus CX every 3 weeks	There was no relevant difference in the occurrence of overall grade 3 or 4 toxicities between the XP and ECX arms (80% versus 78%, respectively; P = 0.516). However, none in the XP and 12% in the ECX arm discontinued treatment because of toxicity.	XP 38% ECX 37%	Primary Endpoint PFS XP – 6.4 ECX – 6.5 (p = 0.863)	NA	XP 166.15 ECX 262.00
Bang et al, 2010 [16] Phase 3 trial	XP or CF plus trastuzumab (T) 298 XP or CF alone 296	XP- CDDP 80 mg/m² on day 1 was given by intravenous infusion. Capecitabine 1000 mg/m² was given orally twice a day for 14 days followed by a 1-week rest CF - Fluorouracil 800 mg/m² per day was given by continuous intravenous infusion on days 1–5 of each cycle. Chemotherapy was given every 3 weeks for six cycles. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks until PD, unacceptable toxicity, or withdrawal of consent.	The most common adverse events in both groups were nausea (trastuzumab plus chemotherapy, 197 [67%] vs chemotherapy alone, 184 [63%]), vomiting (147 [50%] vs 134 [46%]), and neutropenia (157 [53%] vs 165 [57%]). Rates of overall grade 3 or 4 adverse events (201 [68%] vs 198 [68%]) and cardiac adverse events (17 [6%] vs 18 [6%]) did not differ between groups.	XPT or CFT CR – 5% PR – 42% XP or CF CR – 2% PR – 32% Odds Ratio for PR 1·52 (1·09 – 2·14; X^2 test p = 0·0145)	PFS XPT or CFT 6·7 (6 – 8) XP or CF 5·5 (5 – 6) HR 0·71 (0·59 – 0·86) p = 0·0004	Primary endpoint XPT or CFT - 16 (95% CI, 15 – 19) XP or CF – 11.8 (95% CI, 10 - 13) HR 0·65 (95% CI, 0·51 – 0·83)	XP 166.15 CF 474.46 IH 127.07 IP Trastuzumab is not available in Brazilian Public Health System for advanced gastric cancer treatment

CR – Complete response PR – Partial response SD – Stable disease PD – Progressive disease RR – Response rate TTP – Time to progression PFS – Progression free survival OS – Overall survival

Pts – patients IP – costs bases in patients receiving treatment by infusion pump IH – patients receiving treatment in hospital HR – Hazard ratio CI – confidence interval

10.4 **Table 3.** Prevalence and grade of adverse effects (%)*

Adverse event	Grade				
	All grades	1	2	3	4
Nausea	72	39	28	5	0
Vomiting	50	33	12	5	0
Fatigue	35	23	8	4	0
Diarrhea	29	21	6	1	0
Constipation	12	10	2	0	0
Mucositis	11	8	3	0	0
Neutropenia	11	1	2	5	3
Neuropathy	6	5	1	0	0
Anemia	6	0	4	2	0
Ototoxicity	5	3	0	2	0
Thrombocytopenia	5	2	3	0	0
Myalgia	5	5	0	0	0
Febrile neutropenia	4	0	0	3	1
Renal dysfunction	4	1	1	2	0
Skin toxicity	3	3	0	0	0

* Considering valid information

11. STROBE

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Página
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	37
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	38,39
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	39 40
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	40
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	40
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	40 41
		(*e*) Describe any sensitivity analyses	

Continued on next page

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			Página
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	43
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	44
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	45
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	45
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	46-49
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	50

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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