Evaluation of Response, Tolerability and Toxicity of New Chemotherapeutic Regimen in Advanced Gastric Cancer

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Abstract

Background: This study testing the effectiveness, toxicity and tolereability of new chemotherapeutic regimen (consist of Irinotecan 5-FU and Leucovorin) in locally advanced and metastatic Gastric Cancer.

Patients and Methods: Patients with locally advanced gastric cancer (at least stage 3) or metastatic gastric cancer that no treated previously with chemotherapeutic agents entered onto this study. Treatment consist of 6-12 cycles (every 2 weeks) with Irinotecan (CPT-11) 140mg/m^2 iv, Lecovorin 100mg/m^2 iv, followed by 5-FU 400mg/m^2 (in4hours) and then 5-FU 1200m^2 (ci in 48h), all cycles given every 2 weeks and repeated at least for 6 cycles(6-12 cycles**).**

Results: Ten (10) patients were enrolled and eligible patients received this protocol therapy. The over all response rate was 60% and 10% complete response, and 50% with partial response and 10% stable disease. Median survival was 13 months and median event free survival was 8 months. The major toxicity was Neutropenia (grade 4) in 3 cases (30%), that two cases died in neutropenic sepsis feature. Grade 4 anemia was observed in one case that needs to transfusion therapy. Other mild side effect and toxicity of this protocol therapy were: Grade 1 neutropenia (10%), mild thrombocytopenia (10%),mild diarrhea (40%)mild nausea and vomiting (60%)and lethargia and mucositis were not seen.

Conclusion: This protocol consist of Irinotecan iv bolus that followed with Leucovorin and 5-FU in 4h and then 5-FU in 48h ci is very active in patients with locally advanced and metastatic Gastric Cancer. Diarrhea and mucositis were less than other reports. Future trials in large series need to documented effectiveness and tolereability and toxicity of this new protocol.

Keywords: Irinotecan, Leucovorin, 5fluorouracil, Gastric cancer

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Introduction

Gastric cancer is the most common malignancy in digestive system in the majority of countries. Gastric cancer is the one of the most common causes of death with malignancy.(1) Although systemic chemotherapy has been proven to prolong survival when compared with the best supportive care alone.(2-5) The prognosis was very poor and 5 years survival with the best supportive care was 10-15% respectively.(4)

After diagnosis of gastric cancer, gold standard therapy is curative surgery and adjuvant treatment with every stage of malignancy. Although this treatment is gold standard therapy but this management possible in less than 30% of patients and over 705 of patients presented in advanced disease with stage 3 and stage 4.(7)

Chemotherapy approach is very important in advanced gastric cancer.

Four studies compared chemotherapy modality to only supportive care in patients with advanced gastric cancer.(17)

The first study was done in 1993 (with Morad and et al) that compared 30 patients with advanced gastric cancer that those received FAMTX regimen

With ten patients with advanced disease and treated only with supportive care.

In the end of study Morad and coworker concluded that median survival in chemotherapy group 9 months and in only supportive care were 3 months with P-value <0.001.(18)

Other study was done in 1995 with Piernone and coworker that compared in 21 patients with advanced gastric cancer that treated with

FAMTX (5-FU, Epirubicin and MTX) with 20 patients with advanced disease that treated only with supportive care. In the end of study Piernone

And coworker concluded that median survival in chemotherapy group was 12 months and in other group was 3 months (P value <0.001).(19)

Other study was done with Glimlymous and coworker in 1997 that evaluated 31 patients with advanced gastric cancer that those received chemotherapy with ELF (Epirubicin, 5-FU, Leucovorin) and compared with 30 patients with advanced disease and treated with only supportive care.

The result of this study revealed 8 months median survival in chemotherapy group and 5 months in supportive care group (P value <0.12). (21)

These studies revealed the efficacy of chemotherapy in patient with advanced gastric cancer when compared with only supportive care. Median survival for chemotherapy group was 10 months and median survival for supportive care was 3.5 months. These studies confirmed that chemotherapy was superior to only supportive care.

CPT-11 (Irinotecan) has demonstrated marked anti tumor activity against a variety of neoplastic cell lines, including several gastrointestinal types. A japans trial of single agent drug in gastric carcinoma reported a response rate of 23% (20).

Patients and Methods

Patients that to entered to this study had the following criteria:

1- Documented pathologic report of adenocarcinoma histology
2- Locally advanced or metastatic disease (at least stage 3)
3- Non respectable tumor (based on CT scan, Endoscopy and Laparatomy)
4- No prior chemotherapy
5- Karnofsky score > or =70
6- Written informed consent given
7- Good hematologic profile (absolute granulocyte >2000 and platelet >100'000/mm^3)
8- Good liver function (serum bilirubin <1.5 mg/dl, AST & ALT<3 upper limit on normal range)
9- Good renal function (serum creatinine <1.5 mg/dl).

After selection of patients on basis of these criteria the study was begin. The order of drug administration was every two weeks of: Irinotecan (CPT-11) with dose of 140 mg/m^2 iv over 90 min Followed by Lecovorin (100 mg/m^2 bolus infusion) and then 5-FU (400 mg/m^2/4h and then 1000 mg/m^2 ci/48 h). Doses could be adjusted during a cycle of therapy based on the most severe toxicity that observed since the prior treatment or at the start of the a new cycle (with toxicity graded: according to the National Cancer Institute (NCI). During a cycle of therapy, doses of CPT-11 and 5-FU were reduced 20% for grade 2 toxicity and held for grade 3-4 toxicity. Once the adverse event had resolved, treatment was resumed, with a 20% dose reduction for a previous grade 3 toxicity and a 40% reduction for grade 4 toxicity.

Table 1. Patient Characteristics (n=10)

Age (median age)	55(27-75)
Gender	
Male	7 (70%)
Female	3 (30%)
Performance status score	
70	4
80	3
90	3
Disease extension	
Locally advance	5
Metastatic	5
Site of metastasis	
Lymph node	4
Liver	2
Peritoneum	3
Ovary	1

Standard efficacy of objective tumor response rates, time to tumor progression (TTP) and survival were assessed. Lesion were measured at baseline with endoscopy and imaging (CT scan) and after cycles of 6 and 12 of treatment repeated.

Results

Ten patients were enrolled and treated with this protocol and are evaluated for toxicity. Patients' characteristics are listed in table 1. The median age was 55 years (27-75), and there were the majority of cases male (70%) and 30% were female. Metastatic disease documented in 5 cases and other were locally advanced disease. Metastatic sites include: lymph node, peritoneum, liver and ovary. The median courses of chemotherapy were 9 cycles (5 patients 12 cycles, one case 8 cycles, 3 cases 6 cycles and one patient received 7 cycles).

Therapeutic toxicity

Patients received a median of nine (9) treatment cycles.33% of patients experienced dose reduction or delayed treatment to drug-related side effects.

Adverse event are listed in table 2.

Table 2. Adverse events

Hematologic Grade		
Neutropenia	4	1-4
Neutropenic fever	2	4
Anemia	5	1
Thrombocytopenia	1	1
Gastrointestinal		
Neusea&vomiting	6	1
Anorexia	8	Mild
Diarrhea	4	1
Hepatic	0	-
Lethargia	0	-
Stomatitis	0	-
Palmar plantar erythema	0	-

The most important toxicity was Neutropenia that observed in 3 cases (33%). Other common toxicity include: nausea and vomiting in 8 cases (77%) with mild symptom and well tolerated with supportive care.
Two patients (<20%) died of toxicity (neutropenia grade 4 and then neutropenic sepsis).

Discussion

The majority of gastric cancer presented in advanced disease and no standard combination chemotherapy regimen represents for treatment of metastasis and locally advanced disease.
The evaluation of response rate and toxicity of this protocol was done in multiple center and these studies revealed response rate of 34% with median survival about 10.7 months.
Dr Bougatt (in 2000) was studied 74 patients with this protocol and different doses.
These patients received.
Irinotecan (80 mg/m^2), Leucovorin (500 mg/m^2/2h) and then 5-FU (2000 mg/m^2), this protocol repeated every week for 6 weeks. In this study 2 cases with complete response and 44% with survival over than 12 months.
Common toxicities include: Neutropenia 25%, Febrile neutropenia 5%, Neusea and vomiting 60% Diarrhea 24% (26).
Other study was done with Blank in 36 patients with advanced gastric cancer. Protocol was Irinotecan (125 mg/m^2), Leucovorin 20mg/m2 and 5-FU 500mg/m2 weekly for 4 weeks and then rest for 2 weeks.
Response rate was 22% with 19% partial response and 3% complete response. Median survival was 7.6 months. Four cases died during treatment.
The reason of death in 3 cases was toxicity of treatment and one case died with other cause.
Toxicities in this study were include: Neutropenia 36%, Diarrhea 28%, Infection 14%, Vascular event 14%. The all of death related to toxicity was due to neutropenic sepsis.(4)
In other study that was done with Asserson in 38 patients with median age 59 years, response rate 29% (2 cases with complete response and 5 cases with partial response and 34% with stable disease).
The doses of drugs were Irinotecan 180 mg/m^2, 5-FU 400 mg/m^2 bolous and then 1200 mg/m^2/ci in 48 hours and leucovorin 125mg/m^2.
The efficacy of this protocol in decreased of dysphagia was 78.6% Reflux 60%, pain 54.5 % anorexia 64.35, weight loss 72.7%. Toxicities were include: Anemia (grade 3 & 4) 13.2%, Neutropenia 26.4%, Febrile neutropenia 5.2%, Stomatitis 2.6%, Neusea and Vomiting 13.2% and diarrhea was 7.9%. Median free event survival was 3.7 months and median survival was 6.4 months.(28)
Two trials testing CPT-11 with 5-FU and Leucovorin in advanced gastric cancer were reported at the 2001 meeting of the American Society of Clinical Oncologist.(21,22) A randomized phase 2 study combined CPT-11 either CDDP or 5-FU and Folinic acid.(21) The CPT-11 /5-FU arm had the serious toxicities:
Neutropenia 25%, febrile neutropenia 5%, and diarrhea 24%.The arm was reported to have an over all response rate (ORR) of 42% (compared with 28% for the CDDP containing arm).
A second trial with CPT-11, 5-FU and Leucovorin was done.(23)
And grade 3-4 toxicities reported for all patients included:
Neutropenia 28%, diarrhea 17% and infection 7%. The ORR in untreated patients was similar to that in the current trial (23%), with a median survival for all patients were 6.3 months.
In our study: Results of the patients that treated with this protocol revealed, 60% response rate (50% relative response and 10% complete response). M/F was 7/3, 20% response in female and 40% in male. Median age was 55 years. 5 cases had under 60 years old and 5 cases that has over 60 years old. In lower than 60 years old the response rate was 30% that the same of other group.
Karnofsky score in 4 cases was70 and in other cases was >70. The metastatic disease in 5 cases and 5 cases with locally advanced disease.
In our study median survival was 13 months(5.3-20.7) with CI 95% and event free survival (EFS) was 8 months with CI=95% (0-18.3m).

Comparison of this study to other studies

In our study the number of patients were lower than other studies. The median age in this study was lower than other study (55 years to 59 years in Blank and Asserson studies). Response rate in this study was 60% that exceed of other reports (in Bouggat study 34%, Blank study was 22% and in Asserson study was 29%).
The median survival was 13 months that was over the other study.
In study of Bouggat was 10.7 months, in Blank experience was 7.6 months and in Asserson report was 6.4 months.
Event free survival was 8 months, and this parameter in Blank study was 4.4 months, and 3.7 months in Asserson study.
Complete response in our study was one case (10%)

and this parameter in Blank study was one case (3%) two cases in Asserson study (5%) and two cases in Bouggat study (3%).
Relief of symptoms observed in the majority of cases. Relief of reflux and anorexia were the same of other studies (60%), Dysphagia in 70% of cases and in other studies was 78.6%, pain 60 % to 54.4%, in Asserson study.
The median courses of treatment were 9 cycles (6-12) and in Asserson study was 5.5 courses (1-19), and in Blank study was 3 cycles (1-8) and in Bouggat study was 6 cycles.
Treatment related mortality was 20% that this problem in Blank study was 8% and in Asserson study was 0%. Every two cases that died in this protocol therapy had Karnofsky status about 70 and although had eligible criteria for this study but performance status was not good.
The cause of treatment related mortality in this study was neutropenic sepsis.
In over all serious complication were:
3 cases with grade 4 neutropenia (30%),and in Asserson 26%, and Bouggat 25% and in Blank study was 36%.
Febrile neutropenia was 20% and in Asserson and Blank study was (15.85 and 145) and in Bouggat study was 5%. This assessment revealed that febrile neutropenia in this study was more than other study.
Lethargia in our experience was 0% and in Asserson 15.8% grade 4 lethargia was observed. Grade 4 anemia observed in one case and this parametyer in Asserson study was 13.2% and in Blank study was 11%.
Mild and self limited diarrhea was observed in 40% of patients,and grade 3&4 diarrhea not seen in this study. In Asserson study diarrhea observed in 52.6% and grade 4 diarrhea observed in 7.9% and this complication observed in 27% of patients and grade 4 was observed in 3.4% in blank experience.
Mild and limited nausea and vomiting in 60% of patients were observed. This side effect in 68.4% of Assreson study was observed.
In our study stomatitis, palmar erythema, alopecia and neuropathy did not seen but these side effects in Asserson study was: 15.8%, 13.2%, 65.8%, 26.4%.
Vascular event such as thromboembolic event in Blank study was 11% and renal complication in Blank study was 3% and these side effect in our study was 0% and not observed.

Conclusion

This protocol therapy consist of Irinotecan, 5-FU and Leucovorin is very active in patients with locally advanced and metastatic Gastric cancer.
Grade 3-4 neutropenia similar to those that observed in patients that receiving this protocol for colorectal cancer but mucositis and diarrhea lethargy and palmar plantar erythema were less than other reports.
This study revealed the effectiveness and tolerability and acceptable toxicity of this protocol therapy.
Future trials in large series need to document effectiveness and tolerability and toxicity of this new protocol.

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