Kasr. El-Ain. J. of Clin. Oncol. Nucl. Med.
Vol.2, no.2, Apr. 2006:21-24

NEMROCK

Original Article

EVALUATION OF GEMCITABINE–DE GRAMONT REGIMEN IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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ABSTRACT

HCC is a neoplasm of high degree of malignancy and quite unfavorable prognosis. In Egypt, HCC is now a common malignancy which usually develops on top of liver cirrhosis of viral origin in 82% of cases. Egypt has one of the highest prevalence rates of HCV infection in the world. Both HCV and HBV infections increase the risk of HCC. Treatment of HCC depends mainly on extent of disease, the presence or absence of cirrhosis as well as degree of hepatic dysfunction. Most patients who show evidence of liver failure are seldom suitable for any active treatment. HCC is found to be resistant to conventional chemotherapy, cytabine analogues (gemcitabine) is a new anticancer agent with acceptable toxicity profile which demonstrated antineoplastic activity in many solid tumors. Few clinical trials have shown that gemcitabine appears to have antitumor activities for HCC.

This is a clinical trial done on 60 patients with HCC to evaluate the role of gemcitabine with de Gramont regimen.

Overall response rate was 10% (5% CR and 5% PR), 20% SD and DP in 70% of patients, TDP was two months. Toxicity was accepted with grade III and IV hepatic toxicity in 10% of patients and grade III and IV hematologic toxicity in 6.6%.

Although this regimen has an acceptable toxicity profile, but it did not add much to outcome of HCC like most chemotherapeutic combinations which also carry poor response and survival rates. Studies using newer regimens and targeted therapies as well as efforts to prevent HCV and HBV infections are required to combat such aggressive disease.

Key Words: Hepatocellular carcinoma, gemcitabine, de gramont

INTRODUCTION

HCC is a neoplasm of high degree of malignancy and quite unfavorable prognosis. Its frequency is tripled over the last 30 years[1] .It is considered one of the leading cancers worldwide being the forth most common cancer and the third most common cause of cancer death with an estimated 500,000 deaths each year[2]. Chronic infection with either hepatitis B or hepatitis C, alcohol consumption, and aflatoxin ingestion are known risk factors for HCC[3] .

In Egypt, HCC is now a common malignancy which usually develops on top of liver cirrhosis of viral origin in 82% of cases[4] . Egypt has one of the highest prevalence rates of HCV infection in the world. Both HCV and HBV infections increase the risk oh HCC in Egyptian patients while isolated Schestosoma infestation does not increase that risk. Because of the very high prevalence rate of HCV in general Egyptian population, it account for most cases of HCC in Egypt. The estimated attributable fraction of HCC from HCV is 48% in the general population[5]. Male: female ratio is 7:1 and age range between 40-59 years[6].

Treatment of HCC depends mainly on extent of disease, the presence or absence of cirrhosis as well as degree of hepatic dysfunction. Most patients who show evidence of liver failure are seldom suitable for any active treatment[7]. HCC is found to be resistant to conventional chemotherapy, cytabine analogues (gemcitabine) is a new anticancer agent with acceptable toxicity profile which demonstrated antineoplastic activity in many solid tumors. Few clinical trials have shown that gemcitabine appears to have antitumor activities for HCC, but the overall survival remains to be improved[8].

Aim of the Study:

To evaluate the role of gemcitabine with de gramont regimen in the treatment of Hepatocellular carcinoma.

PATIENTS AND METHODS

This clinical trial was done in the period between March 2005 and May 2006 on 60 patients with HCC

who were treated at Menofia Clinical Oncology Hospital (30 patients), Menofia Health Insurance (10 patients) and Arab Organization of Industerlization Hospital, Cairo (20 patients).

Eligibility Criteria:

1. Age range between 40 and 70 years.
2. No major organ dysfunction.
3. Histopathological proof of HCC, or radiological evidence of hepatic focal lesion with serum alpha-fetoprotein more than 500ng/dl.
4. No prior chemotherapy.
5. Serum bilirubin not more than 3mg/dl.
6. Satisfactory hematological, hepatic and renal functions.
7. Performance status not less than 50% on Karnofisky Scale.
8. Informed patient consent was signed by the patients before study entry.

Eligible Patients Received the Following Regimen:

- Gemcitabine 1250mg/m² IV infusion over 2 hours on D1.
- Calcium leucovorin 200mg/m² IV infusion over half an hour on D1, 2.
- 5-FU 400mg/m² IV shot on D1, 2.
- 5-FU 600mg/m² IV continuous infusion over 22 hours on D1, 2.

  Antiemetics were given before chemotherapy.

Treatment was repeated every two weeks till disease progression or occurrence of high grade (III and IV) toxicities according to ECOG toxicity criteria.

All Patients Underwent Pretreatment Evaluation as Follow:

- Thorough clinical examination.
- Laboratory investigations including CBC, LFTs, RFTs, and tumor marker (alpha-fetoprotein).
- Radiological examination in the form of pelvi-abdominal CT with contrast.

All these investigations were done before each treatment except for alpha-fetoprotein and CT which were done every two months.

Response to treatment was assessed according to WHO response criteria. Toxicity was assessed according to ECOG toxicity criteria.

Statistical Analysis:

data were collected, revised, verified, and then edited by SPSS statistical package version 10 with assessment of Kaplan Meyer survival analysis.

RESULTS

60 patients were enrolled in this study, patient demographics are listed in table 1.

Table 1: showing patient characteristics (gender, age, risk factors and performance status).

Characteristic	No.	%
Sex		
Male	48	80
Female	12	20
Total	60	100%
Male: female ratio	4:1	
Age		
Range	45:64	
SD	5.6	
Mean	52 years	
Risk factors		
HCV & liver cirrhosis	57	95
HBV & liver cirrhosis	3	5
Total	60	100%
PS		
90%	6	10
80%	9	15
70%	21	35
60%	18	30
50%	6	10
Total	60	100%

PS: Performance status.

Tumor Characteristics were as Follow:

Tumors 3cm or less were present in 36 patients (60%), tumors more than 3cm in 24 patients (40%). A single hepatic focal lesion was present in 42 patients (70%) and multiple hepatic focal lesions were present in 18 patients (30%). Number of cycles given ranged from 1 to 12 cycles (average four cycles), 6 patients (10%) completed 12 cycles. Response rate was as follows: Three patients (5%) had CR, three patients (5%) had PR, 12 patients (20%) had a stationary disease and 42 patients (70%) had disease progression.

Median time to disease progression was 2 months; Median survival was four months (range 1-13 months).

Toxicity:

In general this regimen was well tolerated with grade III and IV hepatic toxicity occurring in 10% of patients. Grade III and IV hematological toxicity occurred in four patients (6.6%), renal toxicity in two patients (3.3%). (Tables 2,3)

Table 2: The percentage of hepatocllular carcinoma patients with different tumor responses to the gemcitabine with de gramont regimen.

Response	CR	PR	SD	PD
Patient NO	3	3	12	42
Percent	5%	5%	20%	70%

CR: Complete remission, PR: Partial Remission, SD: Stable disease, PD: Progressive disease

Table 3: The toxicities assessed on the 60 patients during receiving the gemcitabine with de gramont regimen.

Toxicity	Patient No.	%
Hematological		
Grade 1&2	24	40%
Grade 3&4	4	6.6%
Hepatic		
Grade 1 &2	30	50%
Grade 3 &4	6	10%
Renal		
Grade 1 &2	4	6.6%
Grade 3 &4	2	3.3%
GIT		
Grade 1 &2	36	60%
Grade 3 &4	6	10%

GIT: Gastro-intestinal tract.

DISCUSSION

HCC is a disease of rising incidence and mortality among many developing countries. New and innovative ways to combat this disease are therefore needed as a priority. Historically, improved diagnostic methods and treatment options have had only a small impact on patient survival. One year survival rates have only increased from 14% to 23% over the past two decades, while 5 year survival rates remain poor (5%). Patients with the longest survival are those with early stage disease at diagnosis to whom potentially curative therapies may be offered[9]. But still HCC carries a very poor prognosis with different treatment modalities especially with advanced stage disease. Fuchs et al.[10] reported a study on 30 patients with advanced HCC using gemcitabine as a single agent weekly for three weeks followed by one week rest; there was no CR or PR, 30% of patients had a stable disease. Another study done by Yang T et al.[11] on 34 patients with HCC using a combination of gemcitabine 1250mg/m² on D 1 and 8 and doxorubicin 60 mg/m² on D1, 4 patients (11.8%) had partial response, six patients (17.6%) had minor response, 9 patients (26.5%) had a stable disease and fifteen patients (44.1%) had disease progression. Taieb et al.[12] evaluated a regimen containing gemcitabine and oxaliplatin on 21 patients with HCC, 48% of patients had stable disease and the remaining patients had disease progression, there was no CR or PR. A combination of gemcitabine and cisplatin was assessed by T-S Yang et al.[12], on 47 patients, one patient (2%) had CR, 9 (19%) PR, 8 MR (17%) (Moderate Response), 8 (17%) SD, 17 (36.2%) DP and four were not evaluated. Response rate was 21.3% median survival was 6.4 months. In our study, overall response rates (CR and PR) was 10% and stationary disease 20% which is comparable to response rates of most of trials using gemcitabine whether as a single agent or in combination with other chemotherapeutic drugs. Time to disease progression in our study was two months which also is comparable to that of other trials using gemcitabine combinations[9,10].

This regimen has an acceptable toxicity with grade III and IV toxicity not more than 10% of cases. By revising these results, it seems that choosing a regimen that has acceptable toxicity profile is important in HCC as most patients are fragile from liver cirrhosis that's commonly associated with the disease and reaching minor response even in the form of a stationary disease may be a good target.

CONCLUSION

HCC has a rising incidence and mortality most probably as a result of high incidence of HCV and HBV infections. Gemcitabine–de Gramont regimen, although has an acceptable toxicity, but still carries a low response rates in HCC like most chemotherapeutic combinations which carry poor response and survival rates. So, until today, an optimal regimen has not been defined for patients with HCC. More studies on newer regimens and targeted therapies are required to improve response rate and survival. Also, efforts should be directed towards prevention of such aggressive disease that carries low response rate through prevention of HCV and HBV infections that proved to be major etiologic factors.

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