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Radiation Therapy in Liver Cancer and Systemic 5-Fluorouracil

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Abstract

The effect of systemic 5-fluorouracil (5-FU) after hepatic irradiation (RT) was evaluated in 37 randomized patients with primary hepatocellular carcinoma. All patients underwent hepatic irradiation of 24-30 Gy. 5 FU was induced for 20 patients (500 mg/ day for 5 consecutive days intravenously every 4 weeks). First cycle induced during hepatic irradiation. No significant response was observed ($p > 0.1$).

Introduction

PRIMARY Hepatocellular Carcinoma (PHC) is one of the ten most prevalent cancers in the world [1]. PHC is considered a highly malignant tumor with a poor prognosis. It is usually not resectable and there is no other effective treatment [2]. A large number of therapeutic trials have been realized but most of their conclusions are not convincing because they are usually not controlled not controlled , not randomized or they include a small number of patients [2].

Case and Wartin in 1924 [3] were the first to report the usefulness of hepatic irradiation in patients with metastatic disease. Since then, several authors have reported results of hepatic irradiation both in metastatic disease and in primary liver cancer [4]. The chemotherapeutic management of primary carcinoma of the liver has posed a formidable challenge to medical oncologists worldwide [5]. Patients with hepatic cellular carcinoma or cholangiocarcinoma frequently have a variety of medical conditions including bleeding disorders, poor nutrition, and liver failuer which complicate treatment attempts. Furthermore, these tumors have been relatively resistant to available chemotherapeutic drugs [5].

It is too early to tell whether a combination of radiotherapy and chemotherapy will increase survival. A synergistic cell killing effect by 5-FU, and radiation was

recorded both in animal models and in vitro [6]. A time dependent enhancement of cell killing was found if human tumor cells were exposed to 5-FU, for 48 hours following the radiation exposure [7]. Experimental and clinical data indicate an extreme complexity in the treatment modalities [6].

The current study was undertaken to evaluate the synergistic cell killing effect of 5- Fluorouracil to external radiation in primary hepatocellular carcinoma.

Patients and Methods

The patients of the study included all cases of hepatocellular carcinoma attended to Kasr Ei-Eini Center of Radiation Oncology and Nuclear Medicind, Cairo University (Nemrock). during the period January 1990 to July 1991. The total number of these patients was 41.

At clinical examination, the duration of earlier illnesses was recorded. Apart from clinical evaluation, levels of serum bilirubin, alkaline phosphatase, serum aminotransferase, albumin and tests for alphafetoprotein (AFB) were carried out.

The lobar distribution of PHC was determined using the most accurate method available for a given patient. The methods were computed tomography (CT) ultrasonography and Tc 99m imaging.

The presence of metastasis was determined from routine chest radiography, a skeletal survey and CT.

Complete blood picture with platelet count were performed prior to the start of treatment.

Treatment :

The forty-one patients in the study were randomized to external hepatic irradiation with or without systemic 5-FU. Hepatic irradiation was delivered to opposed anterior and posterior fields to a dose of 24-30 Gy per 15 days / 3 weeks using Cobalt-60 or linear accelerator.

In twenty patients 5-FU, (500 mg/day for 5 consecutive days intravenously every 4 weeks). The first cycle induced during (RT) treatment with 5-FU, was continued when evidence of tumor progression observed.

Response criteria :

The tumor size was evaluated before any active treatment by liver/spleen scan, abdominal ultrasonography. There were no complete responses, partial response (P. R) is defined as reduction of tumor size by 50% using two perpendicular measurements, or at least a 33% decrease in the sum of linear measurement of the liver below the costal margin in right and left mid clavicular lines and below the xyphoid process. A fall in serum chemistries was not acceptable as response criteria.

Results

Of the 41 patients studied, 35 were male and 6 female, making a male-female ratio of about 6:1. The mean age of presentation was 54 ± 11 years.

The commonest three symptoms of presentation were abdominal pain (71% of the 41 patients), abdominal swelling (33%) and ascites (21%). Other presenting symptoms were jaundice, weight loss, anorexia and malaise. Metastases were found in 5 cases, localized in the lung (three cases) and spine (two cases).

As illustrated in table (1), 95% cases showed alterations in liver function tests, singly or in combination. The most common alteration was a raised aminotransferase value. AFP was positive in 75% of cases (table 1), ultrasound examination of abdomen revealed a solitary intrahepatic lesion in 21 cases, multiple foci in 10 and diffuse lesions in four cases.

The grade of PHC was available only in 25 cases. 60% of these cases were grade II, 28% grade III and 12% grade I, (Table 2).

Table (1): Features of Laboratory and Ultrasonic Examination.

Features	No. of patients	Positive or Abnormal (%)
Liver function tests:		
Bilirubin	38	18 (47)
Alkaline phosphatase	38	36 (95)
Aminotransferase	38	36 (95)
AFP	16	12 (75)
Ultrasonic :	35	
Solitary		21 (60)
Multiple		10 (28)
Diffuse		4 (12)

Table (2); Grades of Differentiation in 25 Cases of PHC.

Grade	No. of cases (%)	
grade I	3	(12)
grade II	15	(60)
grade III	7	(28)

Objective Tumor Response :

Forty-one patients entered this study. Four patients were excluded from analysis, due to marked deterioration of their general condition, diffuse liver disease. Patients characteristics of the 37 Patients received complete treatment were summarized in table 3. Pretreatment Performance status (ECOG scale) [normal activity] to 4

[completely bedridden] was relatively comparable between the two groups of patients those received radiation therapy only and those who received radiation therapy and systemic 5 FU. (table 3).

Table (3): Patients Characteristics (37 Patients Received Active Treatment).

Characteristic	Treatment	
	R.T. No. of patients (%)	RT + CT No. of patients (%)
Sex :		
Male	15 (88)	18 (90)
Female	2 (12)	2 (10)
Age :		
Greater than 60	7 (42)	8 (40)
Less than 59	10 (58)	12 (60)
performance status (ECOG) :		
0	0	0
1	2 (12)	3 (15)
2	7 (41)	9 (45)
3	3 (18)	4 (20)
unknown	5 (29)	4 (20)
Tumor grade :		
I	1 (6)	2 (10)
II	8 (27)	7 (35)
III	3 (18)	4 (20)
unkmown	5 (29)	7 (35)
Status of primary:		
solitary	10 (59)	12 (60)
multiple	7 (41)	8 (40)

R.T. Radiation therapy CT : 5 - F.U (systemic)
ECOG : Eastem Cooperative Oncology Group

Among the 17 patients receiving radiation therapy only, 7 (41%) patients had objective partial tumor responses. These responses have lasted from 1 to 10 months with mean of 5.4 ± 3.3 months. whilein, the 20 patients received systemic 5 FU with radiation therapy. 9 (45%) patients only had objective partial tumor response. Such response lasted from 1 to 12 months with mean of 6 ± 4.5 months. No response difference was observed statistically between both groups ($p > 0.1$) Table (4).

Discussion

The role of radiotherapy in the treatment of hepatic tumors is growing. There is opportunity to combine irradiation with intra-arterial or systemic chemotherapy of isotopic therapy and - in some situations - with surgery.

The partial response rate to external irradiation of the current series was 41% a figure in agreement with Glimelius [6], who recorded that liver irradiation at a dose between 20 - 30 Gy results in palliaion for more than half of the patients.

The response was not significantly increased when systemic 5 FU was added.

Laboratory and clinical data suggest that postirradiation 5-FU may allow for radiosensitization by depletion of thymidylate synthetase and DNA repair enzymes with evidence suggesting that 5-FU radiosenitization is a cellular condition developing gradually in the 24 hours or more after

radiation exposure [8]. By inhibiting RNA synthesis, 5-FU may prevent radiation-induced sublethal damage repair [9].

The theoretical necessities for 5-F U radiosensitization are continuous exposure 24 hours after radiation exposure in the highest possible drug concentration. Such as intraarterial administration [8].

However, a major limitation of intra-arterial 5-FU for the treament of malignant hepatoms is the short duration of response seen in most patients. In addition, technical problems and complications from the repeated placement of angiographic catheters for intra-arterial administration, or the complications of laparotomy to surgically position catheters in this patients population, comprise major obstacles to this form of treatment.

In conclusion the results of this study were disappointing in view of the small proportion of patients who experienced clinically meaningful tumor responses. Although some patients had definite tumor reduction, neither the frequency nor duration of response appear to warrant the use of this systemic chemotherapy regimen in the treatment of malignant hepatoma.

Future progress in the chemotherapeutic management of malignant hepatoma will require the development of drugs with substantially greater antitumor activity.

Furthermore combination of regional chemotherapy and external irradiation still needs further investigation.

Table (4) Objective Response in 37 Patients with

Response	Treatment RT (N = 17)	RT + CT (N = 20)
Complete Response	0 (0%)	0 (0%)
Partial response	7 (41%)	7 (45%)
No Response	10 (59%)	10 (55%)
Mean duration of Response (Months)	5.4 ± 3.3	6. ± 4.5

R.t. : Radiation therapy

CT : 5 - fluorouracil *systemic

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