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Intravenous Adriamycin and External Radiation Therapy for Treatment of Hepatocellular Carcinoma

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Abstract

Twenty-four patients with primary malignant hepatocellular carcinoma (PHC), treated with either external radiation therapy alone (group I), or external radiotherapy with Adriamycin (group II), were evaluated. The median survival was eight months for group I and six months for group II. The partial response rate was 46% for group I and 45% for group II. Acute and subacute toxicities developed in group II patients. We found that external radiation therapy alone can palliate primary hepatocellular carcinoma for a reasonable duration and single agent Adriamycin chemotherapy does not add any further improvement.

Introduction

PRIMARY hepatocellular carcinoma (PHC) is considered a highly malignant tumor with a poor prognosis [1]. Many unrandomized trials were carried out but did not show any statistically significant results.

Since the favorable experience of Olweny et al. [2], Adriamycin has been widely used in the treatment of PHC. Adriamycin has an anti-tumor activity against PHC. Olweny et al. [2], reported that all of the 11 evaluated Ugandan patients with hepatoma responded to 60 mg/m^2 Adriamycin chemotherapy given by I.V. bolus, at three week intervals. Their median survival was eight months (range 1-13 months).

However, Choi and Lee [3], in a subsequent study, using the same regimen, did not report achieving comparable favorable results.

Locally applied external radiotherapy, either alone or in combination with chemotherapy, frequently leads to significant improvement in primary and metastatic cancer of the liver. Mostly, it has a palliative

effect in metastatic disease and may play an equally palliative role in unersectable primary liver tumors [4,5,6].

This current study was carried out to evaluate the addition of intravenous Adriamycin to external hepatic irradiation for the treatment of unresectable primary hepatocellular carcinoma, versus external hepatic irradiation alone.

Patients and Methods

During the period 1988 till 1990, 24 patients suffering from PHC were evaluated. The diagnosis of PHC was based on histopathology in 22 patients; serum alpha-fetoprotein (AFP) levels higher than 500 ng/ml and/or concordance of clinical, biological and morphologic data (alpha fetoprotein assay, ultrasonography, angiography and/or Computed Tomography) in the two remaining patients.

The durations of earlier illness, proper clinical evaluation and main presenting symptoms were recorded. Levels of serum bilirubin, alkaline phosphatase, serum albumin and other liver enzymes were also estimated. An ultrasound examination and/or Computed Tomography examination of the liver was made to detect the extent of hepatic involvement.

Patients had no detectable cardiac disease either clinically or by electrocardiography, echocardiography or by systolic ejection study before the administration of Adriamycin. Karnofsky performance status [7] was 50% or more. None had received any previous specific treatment for PHC either by surgical resection, chemotherapy or external radiation therapy.

In group I (13 patients), external radiation therapy was the only treatment employd. Radiation treatment was directed to the whole liver through opposed anterior and posterior fields. Planned tumor doses of 24-30 Gy were aimed, at 160-180 cGy daily, 5 treatments/week. The mean tissue dose was calculated at midline. The radiation therapy was given using Cobalt 60 machine or 10 MV Megavoltage Linear Accelerator.

In group II (11 patients), the same radiation therapy was given, followed by a two-week rest interval then Adriamycin chemotherapy was given intravenously at three week intervals. The initial dose was 60 mg/m^2. If this dose was well tolerated then the subsequent doses were increased to 75 mg/m^2. The dose of Adriamycin was reduced by 1/3 or 1/2 if the patient could not tolerate the drug (grade III and IV neutropenia and vomiting according to the WHO staging system [8], or if serum bilirubin and/or prothrombin time deteriorated or was initially elevated. Adriamycin was stopped if neutropenia did not return to its pre-treatment level within three weeks time, or when there was any symptom or sign of cardiotoxicity.

All patients were followed up monthly. During each visit, the following parameters were checked; Complete blood count, Liver function tests and AFP level. Tumor size was also assessed clinically and if there was any sign of tumor regression, ultrasonography and/or computer tomography was done.

Tumor response was assessed clinically, by ultrasound, or by C.T. according to the WHO staging system for the response [8]. In subjects with pre-treatment raised AFP levels; reassessment of the AFP was done.

Chest radiographs and skeletal survey

or bone scan were done to exclude the development of new metastatic lesions.

Results

The clinical, demographic data i.e. complaints, pre-treatment biochemical and serological parameters of both groups are listed in table (1). There was no significant statistical difference between both groups. The survival time is defined as the time from the first day of treatment and the time of the patients' death or lost follow up.

Fig. (1) shows the analysis of the survival of patients categorized by the method of therapy. Patients of group I had a median survival of 8±1.5 months, versus 6±2.5 months for group II patients and the difference was not statistically significant.

Table (3) shows that the acute toxicity in group I was in the form of nausea and grade 1 vomiting; while in group II it was as nausea and grade 3 and 4 vomiting and persisted for 1-14 days after each course. Alopecia developed in all patients of group II and was mild in 81% and severe in 19% of patients. None of the patients of group I developed bone marrow suppression, while in group II, 90% of patients developed grade 1-3 neutropenia, within 10-14 days from starting treatment. In 27.3%, the neutropenia was severe (grade 4), i.e., less than $1x10^9$ cell/1. Cardiotoxicity as heart failure, developed in one patient of group II and the Adriamycin treatment was suspended.

Table (1): Clinical and Demographic Data of Patients of both Group I and II.

	Group I	Group II
Number	13	11
Male: female	11.2	10.1
Median age (y)	52	57
Median time from presentation to ttt (months)	3	4.5
Chief complatint (%)		
1- Upper abdominal pain	55	56.5
2- Abdominal distension	21.7	21.7
3- Abdominal mass	13.3	15.3
4- other	10	6.5
Mean Karnofsky scale	0.65	0.6
Median AFP level	600	700
Tumor grade (%)		
I	15.3	18.2
II	46.1	45.4
III	15.3	9.1
Unknown	23.3	27.3

Table (2): Objective Response in Patients of both Group I and II.

	Method of treatment	
Response	Group I	Group II
Complete	0%	0%
Partial	46%	45%
No response	54%	55%

Table (3): Toxicity from Therapy in Groups I and II.

Toxicity	Group I	Group II
Nausea and vomiting (grade III and IV)	15.3%	100%
Alopecia	0%	100%
Neutropenia	0%	90%
Cardiotoxicity	0%	9%
Transient fever	23%	45.5%

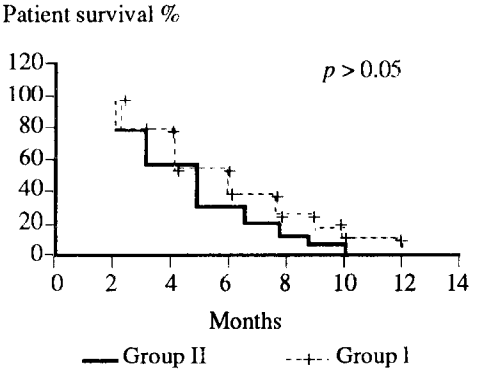

Fig. (1): Patient survival (months) categorized by treatment modality.

Discussion

Most patients with PHC present late with unresectable disease and to date, an effective and safe palliative treatment has not been found.

Choi et al. [5] reported, in a randomized controlled clinical trial of different modalities for the treatment of unresectable PHC against a control group receiving only symptomatic therapy (group I), hepatic dearterialization (group II), hepatic artery ligation and cannulation for infusion of chemotherapeutic agents (group III), hepatic artery ligation and portal vein cannulation for chemotherapeutic agents infusion (group IV) and external irradiation (group V). The results suggested that none of the modalities studied offered symptomatic palliation or better survival compared to the symptomatic treatment alone.

In our study, the survival for group receiving radiotherapy alone (group I) was better, compared to the group receiving radiotherapy with Adriamycin chemothrapy. However, the median survival increased by only two months. This may be attributed to the toxic effect of Adriamycin, by neutropenia.

Our results agree with those reported by Lai et al. [9], concluding that diminished survival is observed more in the Adriamycin group compared to the no treatment group.

The partial response rates, 46% in group I and 45% in group II, may be attributed to the better tolerated external radiation therapy.

In our study, serious side effects as bone marrow suppression were observed in group II patients, especially with larger doses of Adriamycin. This agrees with earlier results of Leff et al. [10]. Cardiotoxicity of Adriamycin, a complication that is unpredictable and difficult to detect early [11,12,13], occurred only in one patient and unfortunately was fatal.

This study shows that external radiation therapy represents a less toxic weapon to

palliate unresectable PHC. Adriamycin did not add any appreciable benefit when used as an adjuvant to radiotherapy in the management of non resectable PHC. Our study thus encourages the use of other less toxic chemotherapeutic agents and other modalities of treatment like immunomodulatory agents and anti-hormones.

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