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4'Epidoxorubicin (Epirubicin) as A Single Agent in Advanced Primary Hepatocellular Carcinoma

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SUMMARY : 4'-Epidoxorubicin (Epirubicin) is a new anthracycline analogue which has activity in a variety of cancers. Advanced primary hepatocellular carcinoma is a rapidly fatal neoplasm. Studies with doxorubicin (Adriamycin) in Africa and Asia have shown a response rate around 30-50% with modest gains in median survivals in patients who responded. We report here our experience with epirubicin in advanced primary hepatocellular carcinoma.

We treated 13 patients with advanced primary hepatocellular carcinoma with epirubicin using a dose schedule of 60 mg／m^2 at the beginning and gradually escalated to 90 mg／m^2 as tolerated. All patients had no prior chemotherapy. Median age was 51 years with range of 31 to 70 years. Cardiotoxicity was serially monitored with radionuclide multigated left ventriculogram. Objective responses were observed in 3 (23%) patients of the 13 evaluable patients. The median duration of these responders was 30 weeks (range 20 to 42). The overall median survival was 11 weeks. Two patients had cardiotoxicity as measured by a significant fall in left ventricular ejection fraction. The toxicities are much less than doxorubicin and better tolerated. We feel that epirubicin has definite activity in primary hepatocellular carcinoma even in patients with advanced disease.

INTRODUCTION

Primary hepatocellular carcinoma is the third most common cancer in Singapore [1]. Patients often present in the advanced stage of their disease and very often curative surgical resection is not feasible. Chemotherapy and radiation therapy have been employed with varying and limited success. There are various chemotherapeutic agents which have some activity. Doxorubicin (Adriamycin) is probably the most active agent for treating primary hepatocellular carcinoma[2-6]. However doxorubicin produced significant gastro- intestinal side effects and has a dose limiting cardiotoxicity when the cumulative dose exceeds 500 mg／m^2. In recent years, various analogues of doxorubicin have been developed in an attempt to reduce these adverse reactions and improve the therapeutic efficacy[7,8]. 4'Epidoxorubicin is an epimer of doxorubicin with a different configuration of the hydroxyl (OH) group in the C_4 position of the amino sugar[9].

This study is aimed at evaluating the therapeutic efficacy and toxicities of 4'Epidoxorubicin in advanced hepatocellular carcinoma. In this report, we present our experience of using 4'Epidoxorubicin in advanced primary hepatocellular carcinoma.

PATIENTS CHARACTERISTICS

Number of Patients		13
Sex Ratio (M:F)		5:1
Age (Mean)		51
(Range)		31-70
Stages	I	2
	II	4
	III	7
Median number of courses		3
Range		1-14
Objective Response (complete)		0
(partial)		3 (23%)
(stable disease)		5
Median duration of response		30 weeks
Overall median survival		11 weeks
Median survival for responders		41 weeks
Median survival for non responders		8 weeks
Adverse Effects :		
Nausea	5 (38%)	
Vomiting	2 (15%)	
Alopecia	9 (69%)	
Myelosuppression	3 (23%)	
Cardiac toxicity	2 (15%)	

MATERIALS AND METHOD

Thirteen patients entered into this study were fully evaluable. The patients were entered on Nov 1984 and results analysed in January 1986. All patients had histological confirmation of primary hepatocellular carcinoma and they all had measurable disease at the start of treatment. The patients had one or more of the following investigations done after diagnosis (a) radionuclide liver scan (b) computerised tomography of the liver (c) hepatic arteriogram (d) serum alphafetoprotein (e) electrocardiogram (f) multigated left ventriculogram (MUGA scan) (g) haemogram (h) liver function tests including bilirubin, albumin, serum alanine aminotransferase, serum aspartate aminotransferase and alkaline phosphatase.

The inclusion criteria for entry into this study were (i) age below 70 years (ii) biopsy proven primary hepatocellular carcinoma (iii) no prior chemotherapy (iv) no evidence of heart disease (v) normal bilirubin (vi) expected survival of at least 4 weeks.

CLINICAL STAGING

All patients entered in study were clinically staged modified from Primack et al's staging system[10].

Stage I *: When patients have one or more of the following features* :

(a)asymptomatic (b) hepatomegaly with no ascites, oedema and jaundice (c) normal prothrombin time (PT) and partial thromboplastin time (PTT) and serum albumin$>$3.5 g/dl.

Stage II *: When patients have one or more of the following features* :

(a) hepatomegaly with oedema but no ascites and oesophageal varices (b) jaundice with bilirubin$<$3.5 mg/dl and (c) normal PT and PTT and serum albumin$>$3.5 g/dl.

Stage III *: When patients have one or more of the following features* :

(a) marked cachexia (b) hepatic encephalopathy (c) ascites and oesophageal varices (d) jaundice with bilirubin$>$3.5mg/dl (e) leucopenia or thrombocytopenia (f) serum albumin $<$3.5g/dl (g) distant metastasis.

CHEMOTHERAPY REGIME

4'Epidoxorubicin is given intravenously at 60 mg/m^2 and repeated every three weeks. At each subsequent dose, if patient tolerates, the dose is escalated to 90 mg/m^2. Toxicities were evaluated according to the WHO criteria. Serial MUGA cardiac scans were done to detect cardiotoxicity.

Table 1. Clinical Data

Patient	Age (YRS)	Sex	Stage at diagnosis	No. of courses	Status	Survival (weeks)
1	31	M	III	4	DEAD	11
2	56	M	I	14	DEAD	52
3	55	F	III	11	DEAD	43
4	55	M	III	3	DEAD	11
5	64	M	II	3	DEAD	12
6	61	M	III	1	DEAD	4
7	40	M	I	2	DEAD	9
8	70	M	II	2	DEAD	23
9	49	M	II	3	DEAD	8
10	49	F	II	8	ALIVE	31^+
11	52	M	III	3	DEAD	9
12	39	M	III	3	ALIVE	8^+
13	49	M	III	1	ALIVE	7^+
	MEAN 51	M : F 5 : 1	I 2 II 4 III 7		DEAD 10 ALIVE 3	MEDIAN 11

RESULTS

The clinical profile, number of courses of chemotherapy given and survival are summarised in Table 1. The mean age was 51 years with range of 31 to 70 years. The male : female sex ratio was 5 : 1.

Majority of the patients were in Stage III. 10 patients have died at time of analysis. Objective responses were obtained in three (23%) of the 13 patients with no complete responders. Five of the patients had stabilisation of their disease for a median duration of six weeks (range 4 to 11 weeks). The median duration for partial responders was 30 weeks (range 20^+ to 42 weeks). The overall median survival was 11 weeks. However, the median survival for the responders was 41 weeks and 8 weeks for the nonresponders. Two patients showed significant decrease of left ventricular ejection fraction as measured by multigated cardiac angiography. The cumulative dosages of 4'epidoxorubicin in these two patients were 810 mg/m^2 and 1000 mg/m^2 respectively. Overt clinical cardiac failure was not encountered in these patients.

TOXICITIES

4'Epidoxorubicin was fairly well tolerated by most patients. The toxicities are summarised in Table 2.

Table 2. Toxicities of 4'Epidoxorubicin

	No. of Patients (N=13)	Percent
NAUSEA	5	38
VOMITING	2	15
ALOPECIA	9	69
STOMATITIS	2	15
MYELOSUPRESSION WBC (<2500/CMM)	3	23
THROMBOCYTOPENIA (<75000/CMM)	1	8
CARDIAC TOXICITY	2	15

The gastrointestinal side effects were minimal to moderate. About 69% experienced moderate to severe alopecia. Myelosuppression was seen only in 3 patients.

DISCUSSION

The preliminary results of this study show that 4'epidoxorubicin as a single agent has activity for patients with advanced primary hepatocellular carcinoma. The overall response rate of 4'epidoxorubicin in patients with no prior chemotherapy was 23%, which is com-

parable to the rate achieved with doxorubicin. The patients with clinical Stage I disease appeared to show a better response rate.

The toxicities of 4'epidoxorubicin are much less than doxorubicin and is much better tolerated. Two cardiac toxicities were encountered which were detected by multigated cardiac angiography.

4'epidoxorubicin is a worthwhile chemotherapeutic agent for palliative treatment of patients with advanced primary hepatocellular carcinoma. These preliminary findings suggest that 4'epidoxorubicin could be considered for combination chemotherapy or use at higher does schedule or intrahepatic arterial infusion in future studies.

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