CLINICAL STUDIES IN ASIAN PATENTS WITH IRRESECTIBLE PRIMARY HEPATOCELLULAR CARCINOMA TREATED BY ADRIAMYCIN AND PREDNISOLONE ALONE OR IN COMBINATION WITH 5-FLUOROURACIL, VINCRISTINE AND PREDNISOLONE

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SYNOPSIS

A prospective study of 65 patients with irresectible histology-confirmed primary hepatocellular carcinoma was done over a one-year period. Only those patients who had non serious medical condition(s) were selected for entry into a randomised clinical study to evaluate the effectiveness of Adriamycin and Prednisolone alone or Adriamycin combined with 5-Fluorouracil, Vincristine and Prednisolone. There were a total of 34 treated patients. The comparison groups were (a) 15 "no treatment" — patients who refused treatment and (b) a historical group of 38 patients.

Clinical remission was achieved in 32% of patients having Adriamycin (40mg/m^2) given every 4 weeks. 6/17 (35%) showed remission on Adriamycin alone and 5/17 (29%) showed remission on the combination regime. Survival with either regime was better than the historical group ($p < 0.001$) (median survival 16 weeks and 6 weeks respectively) and against the no treatment group ($p < 0.001$).

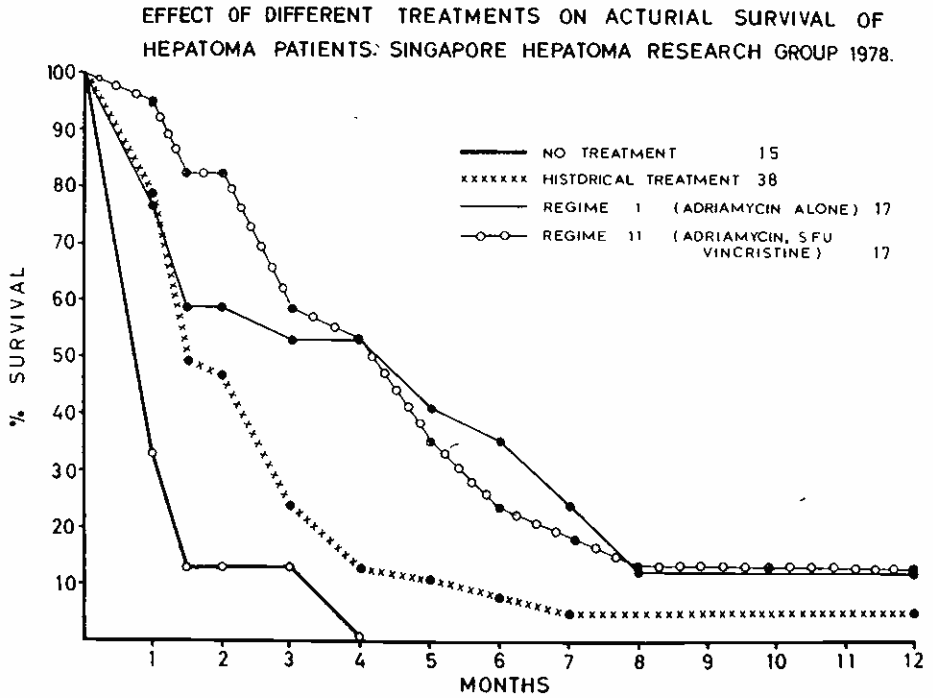
Factors associated with better survival and tissue responses were non cirrhosis and serum Hepatitis B negativity. Functional staging of the disease, morphology, age, sex and racial differences did not alter the overall survival.

The low dose Adriamycin was well tolerated with minimal patient discomfort or side effects. Anaemia (81%) and reversible alopecia (52%) were the two commonest side effects seen. Hepatic tumours responded much better than osseous or pulmonary metastases.

INTRODUCTION

The treatment for irresectible primary hepatocellular carcinoma (PHC) is unsatisfactory with a high mortality rate. The median survival time for untreated patients is less than four weeks despite various established high dose combination treatments, the median survival is not greater than four weeks (see Illustration 1).

Illustration 1 Acturial survival times in patients with irresectible primary hepatocellular carcinoma without treatment, historical treatment, and adriamycin treatment.



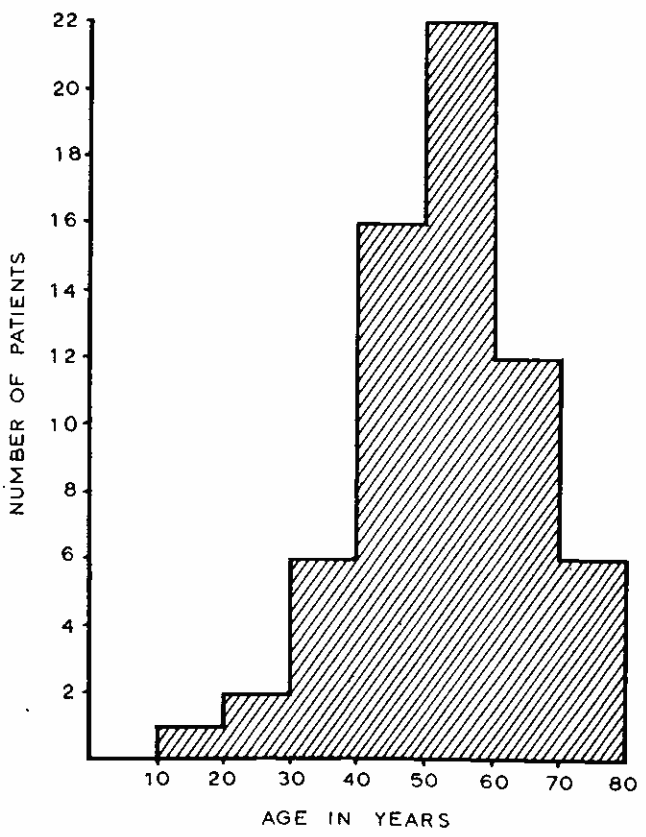
In this region, less than 1% of all patients presenting with primary hepatocellular carcinoma are resectible. This is due to multifocal presentation of the tumour alone, extensive cirrhosis with abnormal liver function, or large unilobular tumours extending beyond the inferior vena cava.

Liver cancer is now the third commonest cause of cancer deaths in this country (Registry of Births, Marriages, Deaths, 1975) and the frequency of the disease is 27.1 and 6.9 per 100,000 population per year in males and females respectively. The disease is commonly seen in the fifth and sixth decade of life (see Illustration 2) and is becoming more common in the twenty and thirty-year age groups. There is thus an urgent need for effective chemotherapeutic agent(s) for the treatment of this high grade malignancy.

Olweny et al (1975) reported the efficacy of Adriamycin alone in the treatment of Ugandan patients and these were followed by further reports of tumour regression rates of 14-60% (Falkson et al, Vogel et al, Kane et al, Baker et al) from America. PHC is an uncommon malignancy in the western world when compared with Afro-Asian and Pacific countries.

This report describes the responses in a selected group of hepatoma patients treated by Adriamycin and Prednisolone alone, or in combination with 5-Fluorouracil, Vincristine and Prednisolone in a multi-national Asian population,

Illustration 2
Age distribution of all Hepatoma patients seen over the period of the trial.



using a low dose regime of Adriamycin and 5-F.U. The latter being given at 10% of the usual standard dose for the treatment of PHC.

In this study, analyses have been made on factors which adversely effect the response to these chemotherapeutic regime(s) and a new practical functional classification of PHC is described. Vincristine was added for its known effectiveness in the treatment of solid tumours involving the Liver (Golding, Bagshawe, Priestman) and Prednisolone was used to prevent undesirable marrow depression from the cytotoxic drugs as well as for its anti-inflammatory reaction.

MATERIAL AND METHODS

1. Selection of Patients

All patients with histology-confirmed primary hepatocellular carcinoma were considered for admission into the study if they fulfilled the following criteria.

(a) Surgically irresectible, confirmed by selective hepatic angiography, Indium liver scan, laparoscopy or laparotomy.

(b) No serious medical illness whereby the life-span was reduced to less than 3 months. The following patients who did not fulfill these requirements were rejected.
   i) terminal or moribund states
   ii) respiratory failure with FEV_1 less than 1 litre
   iii) recent acute myocardial infarction or heart failure
   iv) renal failure with creatinine clearance less than 10 mls per minute
   v) hepatic encephalopathy
   vi) psychiatric or suicidal cases
   vii) recent cerebral thrombosis, embolism or haemorrhage
   viii) those unlikely to take treatment regularly

Only "prognostically better" patients were then entered into the study by balanced randomisation. Distribution of these patients into the treatment regimes were unknown to the clinician-in-charge of the case. Informed consent was obtained from all patients.

2. Chemotherapy Regime

Regime I : Adriamycin Day 1 & 2
Prednisolone 40 mg per day, Day 1 to 7

Regime II : Adriamycin Day 1 & 2
5-F.U. 250 mg Day 1 & 2
(given slowly on a fast flowing intravenous solution of 5% Dextrose)
Vincristine 1mg/m² Day 1
Prednisolone 40mg per day, Day 1 to 7

Adriamycin was given (40mg/m²) per course every 28 days. Prednisolone was omitted if there was evidence of gastric erosion(s), ulceration(s), active tuberculosis or any other important medical contra-indication.

Criteria for reduction of dosage

Adriamycin was reduced to one dose of 10 mg if serum bilirubin was greater than 3mg/DL or bromosulphathalein clearance was greater than 15%. 5-F.U. (250mg) was given in one dose if any of the following occurred:

(i) Hb 10 Gm/DL
(ii) Platelet count less than 80,000/mm³ but greater than 50,000/mm³
(iii) Total polymorphonuclear leucocyte count not less than 2,500/mm³

In the presence of severe pancytopenia (Hb $<$ 10 Gm/DL, Total Polymorph count $<$ 2,500/mm³, Platelets $<$ 50,000/mm³) bleeding or obvious deterioration or deleterious effect, all drugs were withdrawn. Once bleeding had stopped and/or the blood counts had been restored to normal, chemotherapy was resumed. Adriamycin was discontinued when a total dose of 550mg/m² was given.

3. Assessment of Progress

(a) Patients follow-up

All patients were assessed with the trial co-ordinator and were followed up fortnightly as out-patients. Patients who had deteriorated and had not come up for their visit, were traced immediately by the medical social welfare worker. No patients were lost to such follow-up.

(b) Parameters of tumour growth

The size of the tumour was assessed:

(i) by clinical measurements of liver size
(ii) selective hepatic angiography
(iii) alphafoetoprotein levels (AFP) where applicable
(iv) alpha$_1$ antitrypsin (α_1 AT) and alpha$_1$ acid glycoprotein I levels (α_1 AG)

Liver scan (Indium) and selective hepatic angiography were done at 2 monthly intervals initially, then 3 monthly later. AFP (Dianabolt), α_1 AT and α_1 AG were assessed at fortnightly intervals. Hepatitis B surface antigen (HBsAg) was determined by counter-immunoelectrophoresis monthly (W.H.O. Immunology & Training Centre, Singapore). Liver size was assessed by measuring the R. lobe from the upper border to the lowest border in the mid-clavicular line. The L. lobe was measured from the xiphysternum at maximum inspiration to the lower border.

(c) **Criteria for tumour regression is seen in Table I.**

(d) **Monitoring for adverse effects**

Full blood counts, liver function, urea, electrolytes, creatinine, urinary analysis, ECG and a full clinical assessment was done at every visit. Chest X-rays and other investigations were done as indicated.

4. **Staging of Primary Hepatocellular Carcinoma** (Table II a & b)

For practical purposes, an anatomical and functional staging of Hepatocellular carcinoma was done. This was a modification of the International Staging (Kampala, 1971)[7], to give more accuracy in determining the extent and the functional severity of the disease. Cirrhosis was diagnosed histologically.

5. **Selection of "control" groups**

(a) **No treatment group**

The no treatment group consisted of patients who had refused all forms of treatment during the period of this study. Such patients were managed symptomatically. No radiological studies of the gastrointestinal tract were done on these patients.

(b) **Historical group**

This consisted of patients who had similar practical procedures done and who received other chemotherapy (e.g. 5-Fluorouracial (intravenous and oral), Mitomycin C, Vincristine, Futraful, Cyclophosphamide, Methotrexate, Chlorambucil, high dose oral urea and BCG, in adequate therapeutic doses given in the year preceeding this study.

Table I

SINGAPORE ADRIAMYCIN CLINICAL STUDY
PRIMARY HEPATOCELLULAR CARCINOMA
CRITERIA OF RESPONSE

1. **Deterioration:**
   Continued growth of tumour detected clinically, biochemically, radiologically or by immunoassay for AFP. Presence of new distant metastases.
2. **Stasis:**
   No evidence of further growth of tumour clinically, or of new distant metastases. Hepatic mass still present. AFP levels and other laboratory parameters still abnormal. Continued well being.
3. **Regression or Improvement:**
   Partial and/or complete disappearance of tumour without further growth of tumour elsewhere. Partial response is present if there is more than a 50% reduction of tumour mass detected clinically, radio-logically, biochemically and by fall in AFP levels (where measureable).
   Clinically, where bilobe involvement is present, the sum of the perpendiculars is taken. Where one lobe is involved, that perpendicular measurement of that lobe is taken.
   Biochemical regression is present if there is a 50% fall in AFP levels without clinical evidence of tumour progression.
   Radiological regression is the reduction in size on repeat selective hepatic angiography by 50% of the tumour mass as measured by the sum of the perpendicular measurements.
4. **Complete Remission:**
   Total disappearance of all observable tumour masses, for a minimum period of 3 months.

Table II(a)

STAGING-PRIMARY HEPATOCELLULAR CARCINOMA

(SINGAPORE HEPATOMA RESEARCH GROUP 1977)

(I) **Functional Staging**

Stage 1: *Good* — The patient may have one or more of the following features:—

- — Asymptomatic or symptomatic
- — Serum albumin>3.5 gm/DL

— Normal prothrombin and partial thromboplastin times
— No ascites, oedema, jaundice
— ± hepatomegaly

Stage 2: *Moderate* — The patient may have one or more of the following features:-

— Jaundice with Bilirubin < 3.5 mg/DL
— No ascites or varices
— Serum albumin > 3.5 gm/DL
— Normal prothrombin and partial thromboplastin times
— Hepatomegaly
— Dependent oedema

Stage 3: *Poor* — The patient may have one or more of the following features:-

— Jaundice with Bilirubin > 3.5 mg/DL
— Ascites, bloody or non-bloody
— Serum albumin < 3.5 gm/DL
— Oesophageal varices
— Liver failure (impending or actual)
— Marked cachexia
— Metastases
— Thrombopenia: Platelet count $<80{,}000/mm^3$
— Neutropenia: Neutrophil count $<1{,}000/mm^3$
— Prolonged prothrombin and partial thromboplastin times

Table II(b)

PRIMARY HEPATOCELLULAR CARCINOMA

(II) **Anatomical Staging**

A — one lobe involvement
B — both lobes involvement
C — metastatic

Diagnosed by: Liver scan, hepatic angiography, peritoneoscopy or laparotomy.

(III) **Cirrhosis**

Cirrhosis associated with hepatocellular carcinoma is to be diagnosed histologically.

RESULTS

Between October 1976 and February 1978, a total of 65 patients with irresectible PHC were evaluated. Only 34 patients were admitted into the study and randomly allocated for treatment. Of the 16 patients who did not fulfill the study criteria:—

(a) 9 had end-stage hepatic failure
(b) 3 had severe chronic respiratory failure
(c) 1 cerebral secondaries and 1 spinal deposits
(d) 1 had recent myocardial infarction
(e) 1 had facial nerve palsy with brain stem involvement

The median survival in this group was less than 4 weeks.

15 other patients in the "no treatment" group were also followed up. These patients were treated symptomatically. Median survival in this group was identical at less than 4 weeks.

(A) Treatment patients

(a) **Pre-treatment peptic ulceration**
During pretreatment assessment 26 of the 34 (76%) treated patients had radiological evidence of chronic peptic ulceration with duodenal ulceration present in 93% of these 26 patients.

(b) **Age** distribution was 17 — 75 (median 50 years).

(c) **Sex** distribution 5 : 1; Male to Female.

(d) **Racial distribution:** All patients were Chinese of whom the majority were local born. Only 8 patients (20%) were China born. However, of the 65 patients evaluated for entry, there were 3 Malays and 3 Indians with P.H.C. No Caucasian or Eurasians were seen.

(e) **Hepatitis Bs antigenaemia** (HBsAg) was present in 9 of the treatment group patients (26%).

(f) **Cirrhosis** was confirmed histologically in 15 (44%), not detected in 4 (12%) and not confirmed in 8 (24%) because of inadequate tissue biopsy.

(g) **Alpha foetoprotein levels** were below 18ng/ml in 3 patients (10%).

(h) **Simultaneous elevations in serum α_1 AT and α_1 AG** were seen in 32 of 34 patients (94%). These elevations were present in all AFP sero-negative patients.

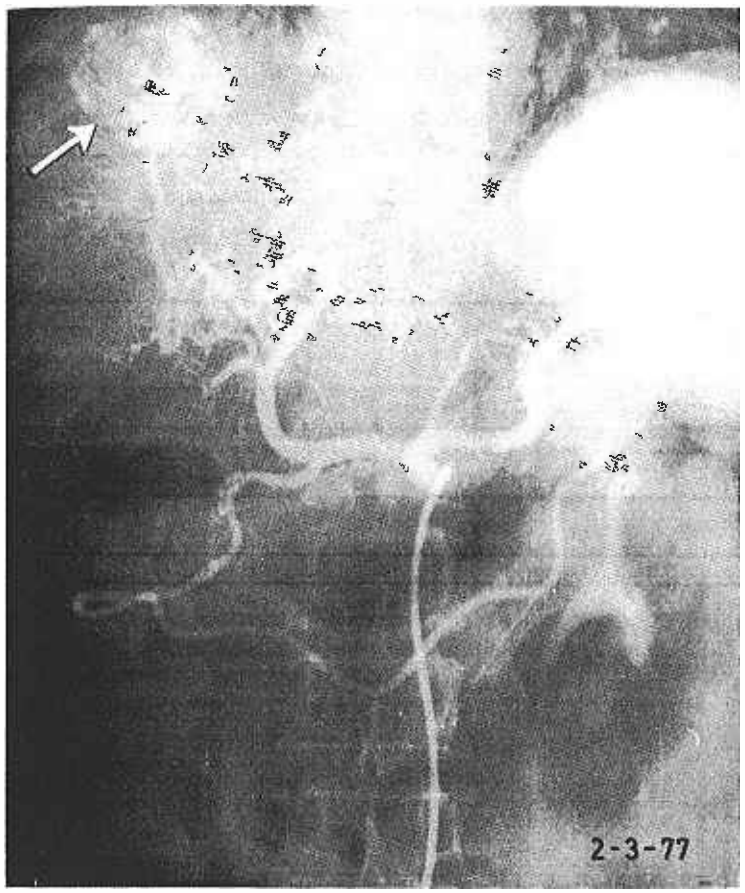
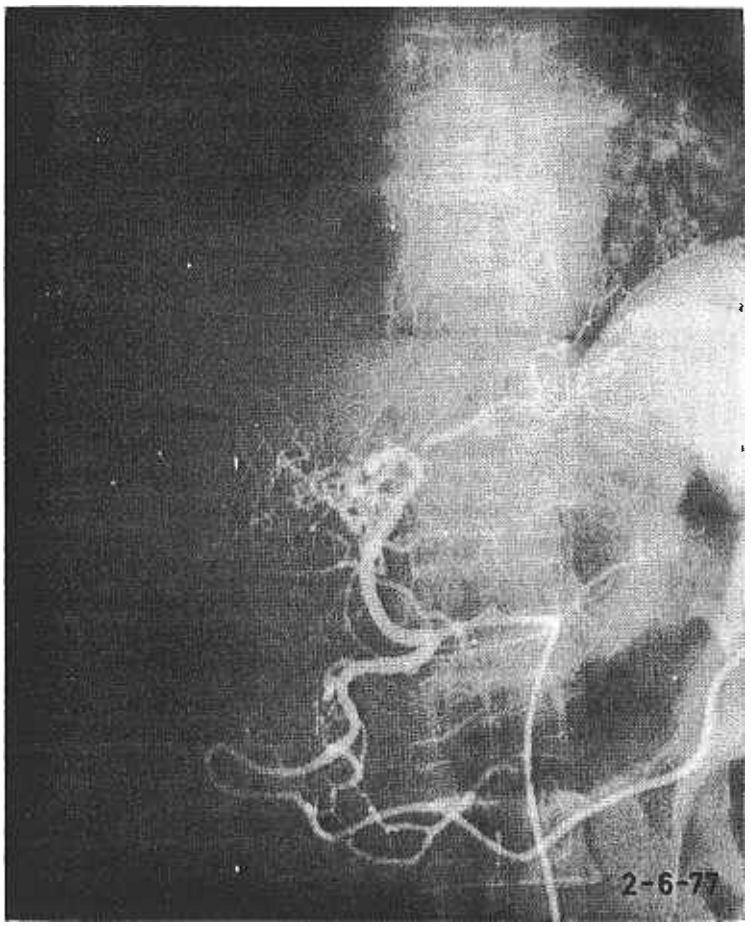


Illustration 3

Selective Hepatic Angiogram

Patient No. 9 L.F. M/56 yrs. Non cirrhosis, Hepatitis Bs negative, showing a Stage I/C tumour

(a) before combination treatment



(b) three months after 3 courses of treatment. Sustained complete remission is maintained for 20 months in this patient.

(B) **Responses**

I. **Remissions**

Regressions were seen in 11 of 34 patients (32%). Complete remission was seen in one male patient L.F. M/56, who had a 8 cm × 10 cm tumour at laparotomy. This was adherent to diaphragm, and involved both lobes. The liver showed no cirrhosis and hepatitis Bs antigen was negative. Subsequent repeated gallium scans and hepatic angiograms showed complete disappearance of tumour at 3 months and 20 months. (Illustration 3) AFP levels fell from 12,500 ng/ml to less than 10ng/ml (see Illustration 4). Serum α_1 AT and α_1 AG were normal.
Sustained remissions were seen in 2 other patients at 18 months.

II. **Survival** (see Table III)

(a) **At 4 weeks.** Both regimes I & II showed similar survival responses as the historical group. All forms of chemotherapy were better than the no therapy group ($p < 0.001$). There was significantly a better response for regime II than for regime I ($p < 0.001$).

(b) **At 6 and 8 weeks.** Survival between the historical group, Regime I and II were better than the no therapy group ($p < 0.001$). There was no difference between Adriamycin alone, and the historical group but Adriamycin combined with 5-F.U. and Vincristine appeared better at the 6th and 8th week than Adriamycin alone, but this was not statistically significant.

(c) **At 3 months and thereafter.** In both instances, Regime I and II were superior to the historical group. The median survival was 4 months in Regime I and II as compared with the historical group of 2 months ($p < 0.001$) or the no therapy group of 4 weeks ($p < 0.001$).

Illustration 4

L.F. M/56 years showing the fall in AFP levels in relationship to treatment.

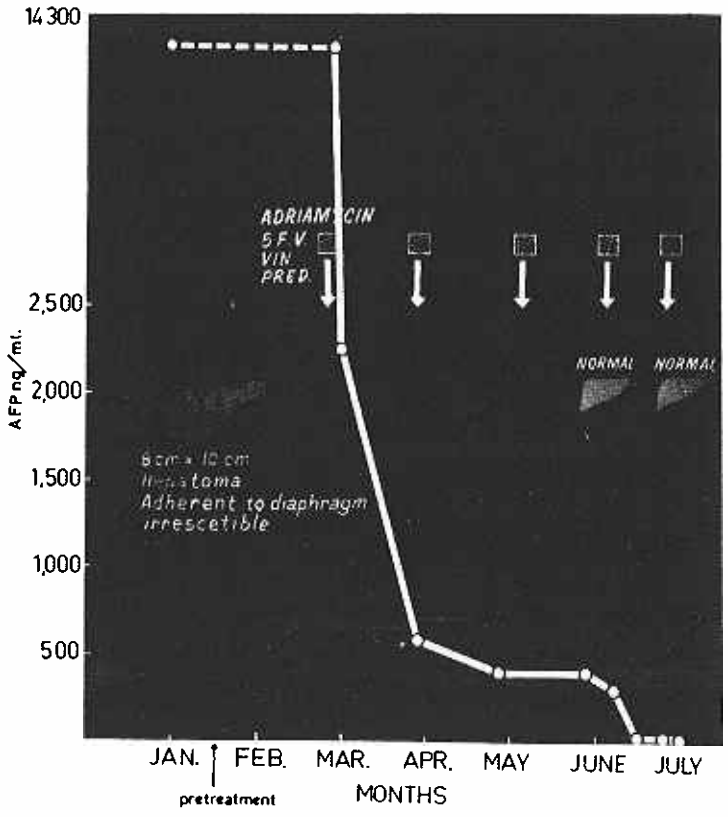


Table III

Survival studies in patients with hepatocellular carcinoma, untreated, treated (historical group) and those in current study.
Regime I: Adriamycin alone. Regime II: Adriamycin, 5-F.U., Vincristine.

Months (Weeks)	*No treatment group = 15	Historical treatment group = (38)	Regime I = (17)	Regime II = (17)
4 weeks	5 (33%)	30 (79%)	13 (76%)	16 (94%)
6 weeks	2 (13%)	19 (50%)	10 (59%)	14 (82%)
2 months	2 (13%)	18 (47%)	10 (59%)	14 (82%)
3 months	2 (13%)	9 (24%)	9 (53%)	10 (59%)
4 months	0 (0)	5 (13%)	9 (53%)	9 (53%)
5 months	0	4 (11%)	7 (41%)	6 (35%)
6 months	0	3 (8%)	6 (35%)	4 (24%)
7 months	0	2 (5%)	4 (24%)	4 (24%)
8 months	0	2	2 (12%)	3 (18%)
9 months	0	2	2	2
10 months	0	2	2	2
11 months	0	2	2	2
12 months	0	2	2	2
14 months	0	2	— UNKNOWN —	
16 months	0	2		
18 months	0	1		
24 months	0	1		
36 months	0	1		

*This is a concurrent group of patients who had rejected specific treatment during the period of this study.

(C) **Factors affecting survival**

(a) **Staging** (see Table IV and V)
The difference in median survival between Regime I and II was similar at 4 months. However, survival for Stage III patients was better for patients on Regime II than for Regime I ($p < 0.01$). The coexistence of cirrhosis at Stage III did not affect the survival with either treatment.

(b) **Hepatitis Bs antigenaemia**
All antigen-positive patients continued to be HBsAg sero-positive throughout the period of chemotherapy and terminally. 90% of these individuals succumbed to tumour progression and hepatic failure. However, more patients survived who were Hepatitis Bs negative, than positive. Median survival being 5 months and 2 months respectively ($p < 0.01$).

(c) **Survival in relationship to sex and age**
There was no difference in survivals between the sex or age.

(d) **Survival in relationship to cirrhosis**
Coexistent cirrhosis appears to play an important part in the ultimate prognosis. Non-cirrhosis in Stage I, who had functionally "milder" liver derangement had a slightly better outcome — median survival of 4½ months (non-cirrhotics) as compared with two months (cirrhosis). Stage III patients with functionally advanced cirrhosis showed poorer survival when compared with non-cirrhotics (median survival 3 months and 6 months respectively).

Table IV

HEPATOCELLULAR CARCINOMA — ADRIAMYCIN STUDY

Survival in relationship to staging

Stage I **Regime I**

Name/Sex/Age	Status of Responses	Hepatitis B Status	Cirrhosis	Survival Time
6 patients:				
1. LAS/M/48	Partial	Positive	Cirrhosis	8 months
2. NHL/F/45	Nil	Positive	*Unknown	4 months
3. LGK/F/18	Partial	Negative	Nil	15 months (+)
4. LTS/M/63	Partial→Stasis	Negative	*Unknown	1 year (stasis)
5. SET/M/57	Partial	Negative	Cirrhosis	1 year (alive) PR
6. LYY/M/66	Nil	Negative	Cirrhosis	2 months
				Median Survival = 4 months

CR = complete remission
PR = partial remission
* = no histological confirmation of cirrhosis
\+ = dead

Regime II

Name/Sex/Age	Status of Responses	Hepatitis B Status	Cirrhosis	Survival Time
9 patients:				
7. LPH/M/43	Nil	Positive	*Unknown	15 days
8. TCH/M/51	Nil	Positive	*Unknown	5 months
9. LF/M/56	CR	Negative	Negative	18 months (CR)
10. THM/M/38	PR	Negative	*Unknown	8 months
11. CFK/F/61	PR	Negative	Negative	1 year (alive)
12. ABA/M/57	Nil	Negative	Negative	3 months
13. FSS/M/42	Nil	Negative	Cirrhosis	6 weeks
14. NCB/M/43	Nil	Negative	Cirrhosis	6 weeks
15. GKC/M/37	Nil	Negative	Negative	4½ months
				Median survival = 4 months

CR = complete remission
PR = partial remission
* = no histological confirmation of cirrhosis
\+ = dead

Table V

HEPATOCELLULAR CARCINOMA — ADRIAMYCIN STUDY

Survival in relationship to staging

Stage III

Regime I

Name/Sex/Age	Status of Responses	Hepatitis B Status	Cirrhosis	Survival Time
10 patients:				
16. LKC/M/55	Nil	Positive	Cirrhosis	2 months
17. LHP/M/65	PR	Negative	Cirrhosis	7 months
18. LLN/F/59	PR	Negative	Negative	7 months
19. TBK/M/42	Nil	Negative	Cirrhosis	11 days
20. CCS/M/61	Nil	Negative	Negative	5 months
21. TCT/M/50	Nil	Negative	Cirrhosis	17 days
22. TWK/F/45	Nil	Negative	Unknown	5 weeks
23. NBL/M/45	Nil	Negative	Unknown	4½ months
24. RM/M/70	Nil	Negative	Cirrhosis	3 days
25. TKW/M/60	Nil	Negative	Unknown	13 days
				Median survival = 2 months

Regime II

Name/Sex/Age	Status of Responses	Hepatitis B Status	Cirrhosis	Survial Time
9 patients:				
26. YNC/M/45	Nil	Positive	Cirrhosis	10 weeks
27. NPW/M/53	PR	Positive	Cirrhosis	6 months
28. FCL/M/45	Nil	Positive	Cirrhosis	10 days
29. KGI/F/60	Nil	Positive	Unknown	6 weeks
30. SLP/M/28	Nil	Negative	Negative	6 months
31. NKP/M/43	PR	Negative	Cirrhosis	9 months
32. NVQ/M/45	Nil	Negative	Cirrhosis	5 months
33. STG/M/30	Nil	Negative	Negative	6 months
34. TSH/M/75	Nil	Negative	Unknown	5 weeks
				Median survival = 5 months

(e) **Relationship to histology**
There was no difference in survival in relationship to the grade of malignancy.

(f) **Response in relationship to other viscera**
3 patients who had pulmonary deposits showed no response to treatment by either Regime II (2 patients) or Regime I (1 patient). Bony deposits in the ribs did not respond to Adriamycin alone in patient 17, whereas the tumour hepatic mass showed clinical regression.

ADVERSE EFFECTS

Anaemia was seen in 17 patients (81%) and was not related to either mode of therapy. In most instances, it was reversible by the 3rd week. Fall in Hb levels in the first 2 weeks ranged between 1-5Gm (mean 2Gm/DL).

Neutropenia was seen in 3 (19%) and thrombocytopenia in 2 (10%) patients. Both were seen in the Regime II group and reversible.

Alopecia was seen in 11 patients (52%) and was complete in 2. Purpura and puritic reactions were seen with Vincristine allergy. Alopecia was reversible in all cases.

Hepatic pain soon after chemotherapy were seen in 6 patients following each course of treatment.

ECG changes such as T wave inversion was seen in one patient soon after the 2nd course of combination therapy. Another patient developed terminal congestive cardiac failure related to progression of tumour. He had received a total of 240mg/m² Adriamycin, 3Gm of 5-F.U. and 6 mg Vincristine.

General myopathy was seen in 7 patients (35%). These changes were compatible with changes caused by progression of the malignancy. No nephrotoxic changes were seen. The rise in blood urea was often seen as a terminal event and/or related to a gastrointestinal bleed.

Nausea, anorexia were mild and seen in 20% patients on Regime II.

CAUSE OF DEATH

(A) **In first six weeks** — 13 patients (38%)
- (a) Sudden death and ruptured liver — 4
- (b) *Bleeding gastrointestinal tract from varices, ulcer — 9
  (*Tumour progression at that time in all).*

(B) **In the following 12 months** — 15 patients
- (a) Ruptured liver — 1
- (b) Tumour progression
  Hepatic Failure
  Gastrointestinal bleeding — 13
- (c) Congestive Cardiac Failure
  Tumour Progression — 1

DISCUSSION

This study has shown that in spite of the low doses of Adriamycin used in this study, this drug is a superior therapeutic agent in the treatment of PHC than other current drugs in use. On the low dosage (40mg/m²), significant remissions were seen in 32% of patients and the median survival was prolonged to over 16 weeks as compared to other modes of previous treatment, where such patients were given established high dose regimes of cytotoxic agents. Remissions although attained in 11 of 34 patients were not sustained in all but 3 patients at 18 months. Subjective improvement such as improvement in well being, mobility, reduction in abdominal discomfort, pain and appetite were synchronous with these objective improvements. Clinical regression when associated with minimal side effects is an advantage when treatment is given to an indigenous Asian population, and Adriamycin used at this low dose regime, has just this advantage. The low dose regime of 5-F.U. introduced in the combination, showed a better response for 4 weeks only. In other studies elsewhere, the median survival rates, using higher doses of Adriamycin (60mg/m² every three weeks) e.g. in American patients was nearly similar (19 weeks) (Falkson et al) but at 75mg/m² given every three weeks Olweny et al, obtained median survival rates of 8 months in the Ugandan patients. This was complicated by both myelo- and gastrointestinal toxicity.

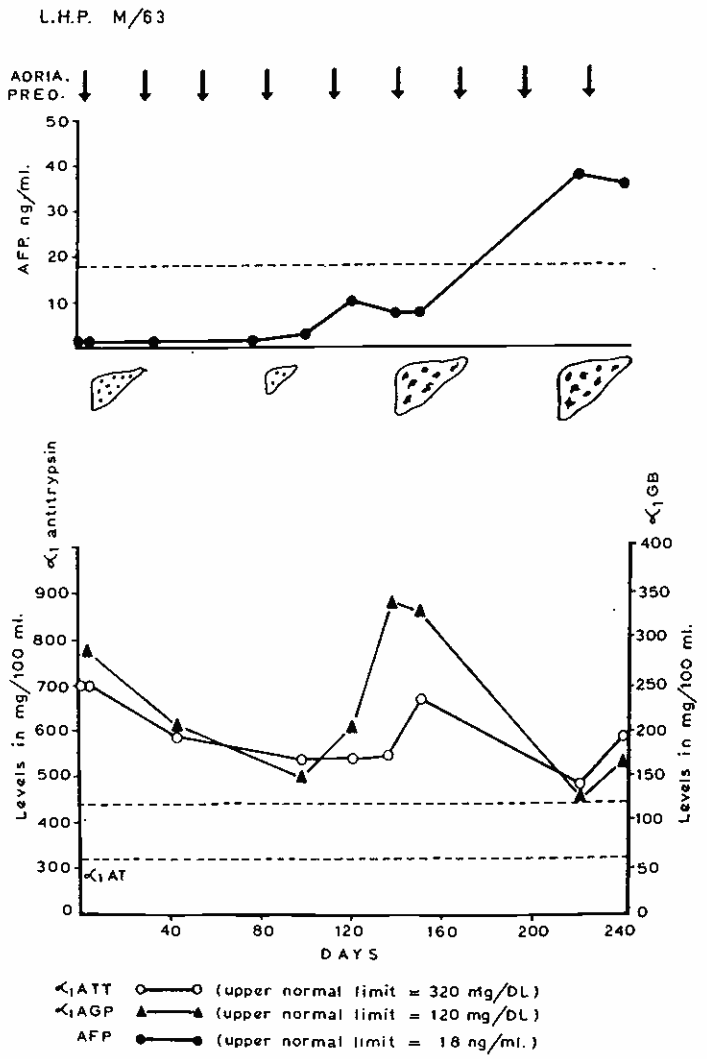
There was no overall advantage of either regime in treating disease in relationship to staging, age, sex or morphology but where the cirrhosis or HBsAg were absent, more patients fared better. Future anti-cancer treatment would therefore have to include the concomittant treatment of coexistent HBsAg infections, since present chemotherapeutic agents do not convert sero-positive HBsAg patients to negativity. Hepatic tumours appear to be more sensitive to this drug, alone or in combination, than other tissues such as pulmonary or osseous deposits. The coexistent early finding of a high incidence of radiological proven

peptic ulceration(s) in 76% of patients with and without cirrhosis may have been responsible for the terminal gastrointestinal bleeding. This may be due to a failure to deaminate histamine and/or the existence of an "ectopic gastrin secreting state" in some of these tumours. However, coexistent oesophagogastric varices, due to cirrhosis or to tumour in non-cirrhosis were other contributing causes for bleeding. 8 patients (25%) of patients who were non-cirrhotics also had evidence of tumour compression of the inferior vena cava and oesophagogastric varices and they show little evidence of improvement on chemotherapy.

Although serum AFP measurement is a useful index for diagnosing and monitoring PHC, it was of no value in 3 (10%) of our patients. Serial measurements in such patients over many months were repeatedly below 15ng/ml and marginal elevations occured terminally. However, gross elevations of α_1 AT and α_1 AG were seen in these 3 patients. Initially these levels fell synchronously with objective incidence of regression (see Illustration 5), but occasional terminal falls in these levels occurred in patients on prolonged chemotherapy[2]. In general, rising levels of AFP or α_1 AT, α_1 AG signified tumour progression although very high levels of AFP (15mg/DL) were seen in a female patient, F/17, who was in stasis for 14 months.

Future anti-hepatoma cancer therapy regimes will need to take into account the management of early and late resistant tumours by incorporating other modalities with and without Adriamycin.

Illustration 5 Patient No. 17. L.H.P. M/65 years. Stage III/C cirrhosis, non Hepatitis Bs antigen. Persistently low levels of AFP inspite of very high levels of α_1 AT and α_1 AG which fell initially during treatment. Note the discordance in AFP, α_1AT, α_1 AG terminally.



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