TREATMENT OF HEPATOCELLULAR CARCINOMA WITH ADRIAMYCIN

Preliminary Communication

CHARLES L. M. OLWENY, MMED,* TOM TOYA, MD†
EDWARD KATONGOLE-MBIDDE, MB, CHB,‡ JOSUA MUGERWA, MD,§
SEBASTIAN K. KYALWAZI, FRCS(Ed),‖ AND HERMAN COHEN, PHD**

In a Phase II clinical trial, 14 patients with histologically proven primary hepatocellular carcinoma were treated with adriamycin administered intravenously at a dose of 75 mg/m² every 3 weeks. All 11 evaluable patients responded with 3 exhibiting complete tumor regression after two, three, and five courses of adriamycin respectively. The remission durations for these 3 were 3, 6, and 7 months, and their survivals were 8, 9, and 13 months, respectively. The median survival of the evaluable patients is 8 months (range 1–13 months). The side effects encountered included myelosuppression, anorexia, nausea, vomiting, and alopecia. Adriamycin seems to be an effective agent in hepatocellular carcinoma. Further trials are underway to test its true efficacy both singly and in combination with other drugs in the management of this tumor.

Cancer 36:1250–1257, 1975.

HEPATOCELLULAR CARCINOMA IS PROBABLY the commonest malignant tumor seen in Uganda.[7] About 150 cases of this disease are diagnosed every year by the Pathology Department of Makerere University Medical School; that figure is thought to represent only 25% of the total number estimated for the entire country.[13] The disease is rapidly and progressively fatal; most untreated patients die within 1–2 months from the time of diagnosis.[2,6,14] Partial hepatectomy is feasible and is recommended for localized disease, but the operative mortality and morbidity are high, and recurrence in the remaining lobe is the rule rather than the exception.[4] Most patients present with inoperable tumor, and since the liver is intolerant even to low-dose radiation,[8] chemotherapy seems to be the only reasonable approach for palliation. Various forms of systemic chemotherapy have been used by many workers, without significant effect.[5] Hepatic artery catheterization and infusion with drugs such as 5-fluorouracil and dichloromethotrexate are fraught with dangers, and the survival data are far from impressive.[1,11,15] Adriamycin†† is an anthracycline derivative which structurally resembles its parent compound daunorubicin.[10] It differs only slightly from daunorubicin in being hydroxylated at the 14th carbon atom; this gives it a broader spectrum of antitumor activity. In this communication we report our preliminary experience with systemic adriamycin in a Phase II clinical trial in Ugandan

Presented in part at the 2nd International Symposium on Adriamycin held at Brussels, and at the Annual Conference of the Association of Physicians of East and Central Africa in Dar-es-Salaam.

From the Uganda Cancer Institute, Department of Pathology, Makerere University Medical School, Kampala, Uganda, and Princeton Laboratories, NJ.

Supported by Contract No. NOI-CM-71343 with the Chemotherapy Branch, National Cancer Institute, Bethesda, MD.

* Associate Professor of Medicine, and Administrative Director, Uganda Cancer Institute. Makerere University Medical School.

† Kilembe Mines Surgical Oncology Fellow, Uganda Cancer Institute, Makerere University Medical School.

‡Oncology Fellow, Uganda Cancer Institute.

§ Associate Professor of Pathology, Department of Pathology, Makerere University Medical School.

‖ Professor of Surgery, Makerere University Medical School.

** Princeton Laboratories.

Address for reprints: Dr. C. L. M. Olweny, Director, Uganda Cancer Institute, P. O. Box 3935, Kampala, Uganda.

The authors are grateful to Dr. Okot Nyormoi for his review of the manuscript and helpful comments, to Mr. George Mpimbaza for performing the qualitative double diffusion estimation of AFP, and to Mr. Andrew Wamala for his secretarial assistance. They also wish to thank the nursing staff of the Solid Tumour Centre for the interest and care provided to the patients throughout the study.

Received for publication September 23, 1974.

†† (NCS 123127, Farmitalia Research Laboratories, Milan, Italy. Supplied by Cancer Therapy Evaluation Branch, NCI.

patients with primary hepatocellular carcinoma.

MATERIALS AND METHODS

All patients suspected of having hepatocellular carcinoma were referred to the Solid Tumour Centre (STC) of the Uganda Cancer Institute. Histologic confirmation of the diagnosis was made from percutaneous needle biopsy specimens obtained by the Menghini technique.[9] Only biopsy-positive patients were entered into the study, which was begun in June, 1973.

All patients were staged according to the classification devised by the International Symposium on Liver Cancer held in Kampala in July, 1971[14] (Table 1). Pretreatment studies included complete blood counts, bilirubin, alkaline phosphatase, transaminases, blood urea, uric acid, and roentgenograms of the chest, skull, pelvis, long bones, and lumbar spine.

A qualitative estimation of alpha fetoprotein (AFP) by the modified Ouchterlony double diffusion technique was performed using a monospecific horse antiserum on agarose media. The central well was filled with the antiserum, while the surrounding wells 3 mm from the central well were filled with the test sera. The wells were examined 24 hours later for precipitin bands. In addition, serial quantitative measurements of AFP using radioimmunoassay were carried out in some patients by one of us (H. C.) Sera were also tested for hepatitis associated antigen (HAA) by immunoelectrophoresis on agarose. Electrocardiography was done on admission and thereafter before each course of adriamycin. Colloidal gold liver scan was done wherever possible in some patients, while urinalysis and stool examination for parasites were routine on admission.

Following completion of these studies, all patients were treated with adriamycin given at a dose of 75 mg/m^2 i.v. every 3 weeks. Although the study design called for dose de-escalation in patients with bilirubin levels above 3 mg/100 ml, in the single patient (case report 2, STC 522) where de-escalation ought to have been done, the full calculated dose was given in error. After each course of therapy, patients were closely observed, and blood and platelet transfusions, as well as antibiotics were administered whenever indicated.

In this communication, complete response is defined as complete regression of all clinical evidence of tumor and qualitative return to negative of previously positive AFP. Partial response is defined as reduction of greater than 50% of measurable tumor. No response is regarded as less than 50% reduction of measurable tumor, or progressive disease.

RESULTS

Fourteen male patients have so far entered the study. Their mean age was 44.8 years (range 34–68 years). Only two patients had functional Stage I tumor, and both presented with metastatic disease. Three patients were Stage II, and the remaining 9 had Stage III disease. Ten of 14 patients (71%) had underlying macronodular cirrhosis (Table 2), and 3 of these (21%) were positive for HAA. In the 11 patients tested for AFP, 8 (73%) were positive by the double diffusion method. The most frequent presenting symptoms were abdominal pain and a right upper quadrant mass. The mean duration of symptoms was 2.3 months (range 0.5–4 months). The signs most commonly encountered were, in order of frequency, hepatomegaly, ascites, jaundice, wasting, and splenomegaly. Table 3 shows the histologic classification of the 14 cases treated

TABLE 1. Functional-Anatomical Staging System for Hepatocellular Carcinoma (International Symposium on Liver Cancer—Kampala, July, 1971)

Stage	Functional	Anatomical	Cirrhosis
I	GOOD No clinical or laboratory evidence of liver dysfunction; no constitutional signs attributable to liver disease	A, one lobe B, both lobes C, metastatic	present (+) absent (−) uncertain (?)
II	MODERATE Mild liver dysfunction; mild, not bloody ascites; mild cachexia		
III	POOR Marked and/or bloody ascites; oesophageal varices; liver failure (actual or impending); marked cachexia		

TABLE 2. Clinical Staging of 14 Ugandan Patients with Hepatocellular Carcinoma

Functional	No.	Anatomical A	B	C	Cirrhosis present
I	2	–	–	2	2
II	3	1	2	–	1
III	9	–	8	1	7
TOTAL	14	1	10	3	10

and compares them with the retrospective analysis of 200 biopsy proven cases from the Kampala Cancer Registry. As expected, the trabecular pattern was the most frequently encountered histologic type, accounting for 50% of the 14 cases.

The results of treatment are depicted in Table 4. Of the 14 patients treated, 3 did not have an adequate drug trial (early deaths) and were considered not evaluable. The remaining 11 who received at least two courses of adriamycin all showed good tumor response, with 3 exhibiting complete tumor regression after two, three, and five courses of adriamycin, respectively. The remission durations of these 3 are 3, 6, and 7 months. One of them developed clinical and biochemical evidence of recurrent disease after 6 months. The second patient died after 7 months following a "second look" operation to ascertain remission. The third is still alive and free of tumor. Case reports of the first two who attained complete responses are given below. The remaining 8 of the 11 patients have achieved good partial tumor regression (>50% tumor reduction).

All 3 patients who did not receive an adequate drug trial have died. Eight of the 11 evaluable patients have also died. The median survival period of the 11 patients is 8 months (range 1–13 months). Of the 8 deaths, 4 died at home and no autopsy was performed. Among the 4 with available autopsy data, 2 had wide-spread nodular hepatocellular carcinoma, macronodular cirrhosis, portal vein thrombosis, and pulmonary metastasis. One patient died of pyelonephritis and had minimal liver tumor (single nodule), and the fourth had advanced cirrhosis, portal vein thrombosis, and minimal tumor.

TABLE 3. Histopathologic Classification of 14 Patients with Hepatocellular Carcinoma

Histopathology	KCR %* 200 biopsies	Present series No.	%
Trabecular	66	7	50.0
Pleomorphic	12	1	7.2
Adenoid	10	3	21.4
Clear cell	5	3	21.4
Other	7	0	0
TOTAL	100	14	100

* Kampala Cancer Registry.

TABLE 4. Results of Treatment with Adriamycin of 14 Ugandan Patients with Hepatocellular Carcinoma

No. achieving "complete" tumor regression	3
No. achieving partial tumor regression	8
Total responding to treatment	11
No. not responding	3
TOTAL treated	14

The side effects encountered included anorexia, vomiting, stomatitis, myelosuppression, which was severe in 3 (WBC nadir 1000/mm^3), and alopecia. One patient (F.M. STC 522) developed marrow hypoplasia after three courses of adriamycin, but recovered good function 3 months later and subsequently received two further courses.

An attempt was made to correlate the degree of liver dysfunction with the magnitude of myelosuppression. The majoriy of the patients had at least one abnormal liver function test. The most commonly recorded abnormality was elevation of the serum alkaline

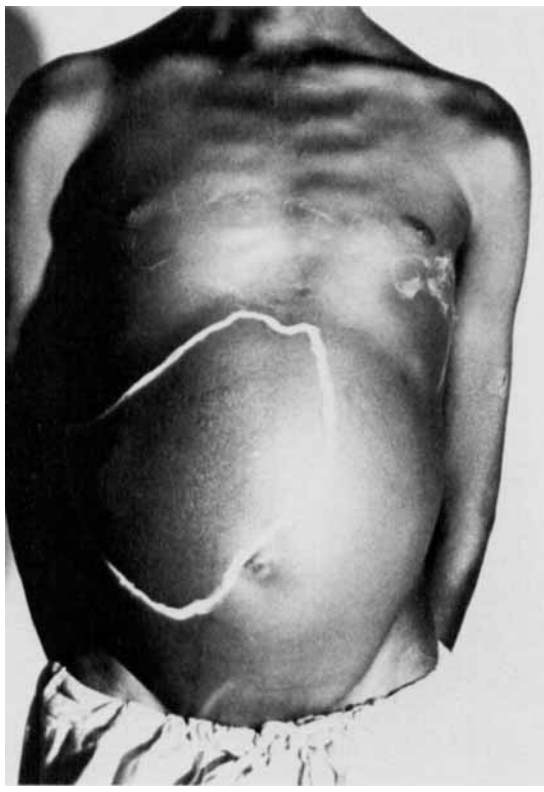

FIG. 1. Patient A.B. on admission. Note the wasting, liver size, and abdominal distention due to ascites.

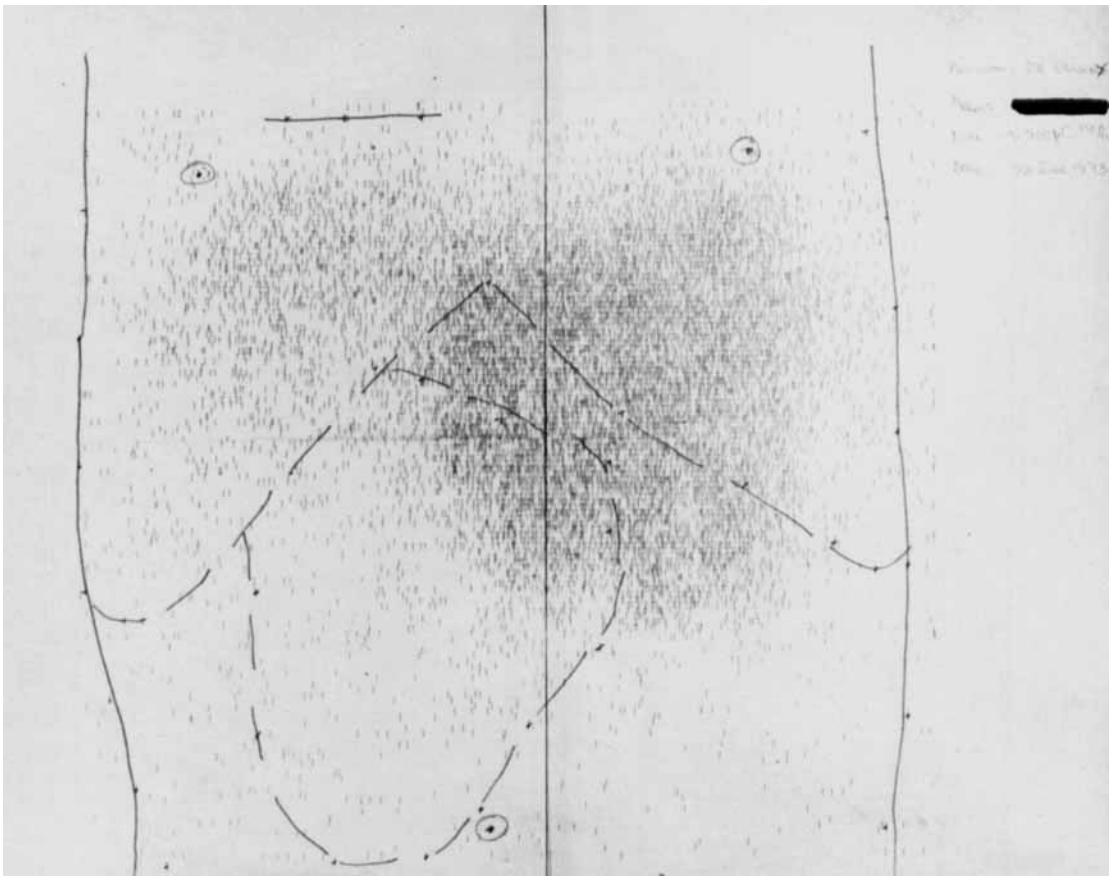

FIG. 2. Liver scan of patient A.B. done on admission, June, 1973. Note the mass outlined.

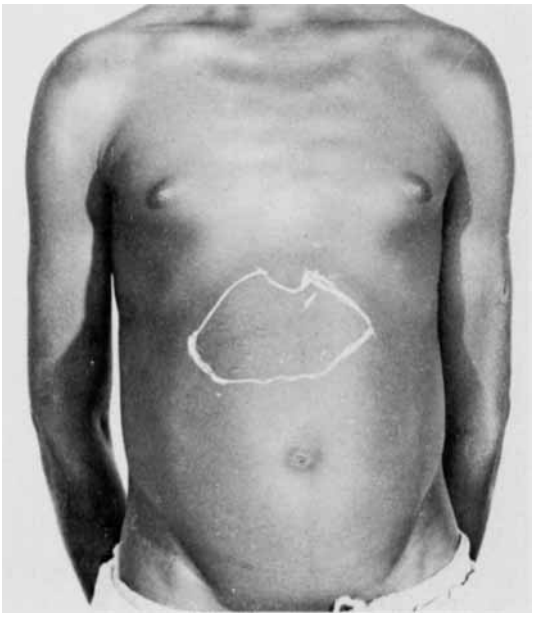

FIG. 3. Patient A.B. a week after first dose of adriamycin. Note the reduction in liver size.

phosphatase. Eleven of the 14 patients had levels well above 100 IU (range 136–510 IU). There was no relationship observed between the degree of alkaline phosphatase elevation and the severity of myelosuppression. No patient has so far developed clinical or electrocardiographic evidence of cardiac toxicity.

CASE REPORTS

Case 1

A.B. (STC 517) was a 37-year-old Munyankole African man who was admitted to the STC on June 21st, 1973 with a history of progressive weakness, right hypochondrial pain, and swelling and abdominal distention of 2 months' duration. Physical examination revealed a slightly wasted man, with distended abdomen and mild icterus. The liver mass was 18.5 cm below the costal margin. He had moderate ascites (Fig. 1). The liver scan showed defective uptake on the lower pole of the right lobe of the liver (Fig. 2). Percutaneous liver biopsy was performed and read as hepatocellular carcinoma of the adenoid type, but there was no normal (nontumor) liver to exclude cirrhosis. He

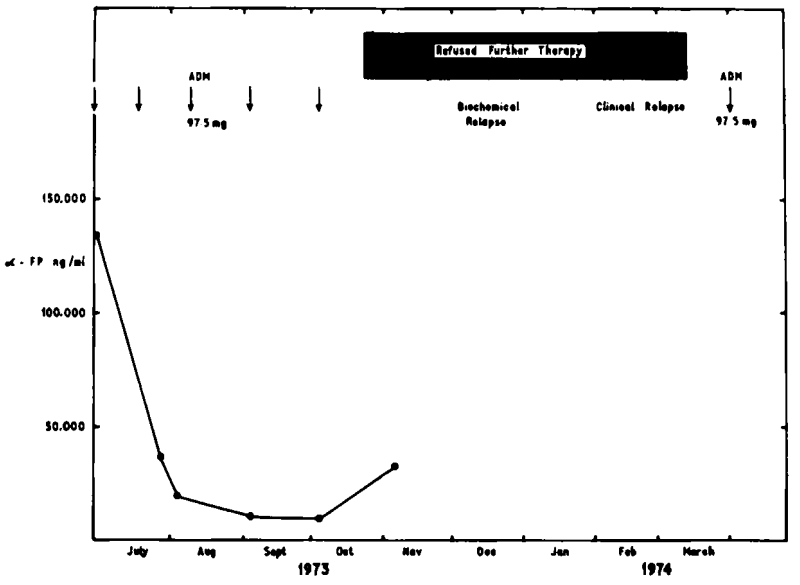

FIG. 4. Graph showing Serial RIA AFP data of patient A.B. (STC 517). Note the rapid drop of AFP following 1st course of adriamycin.

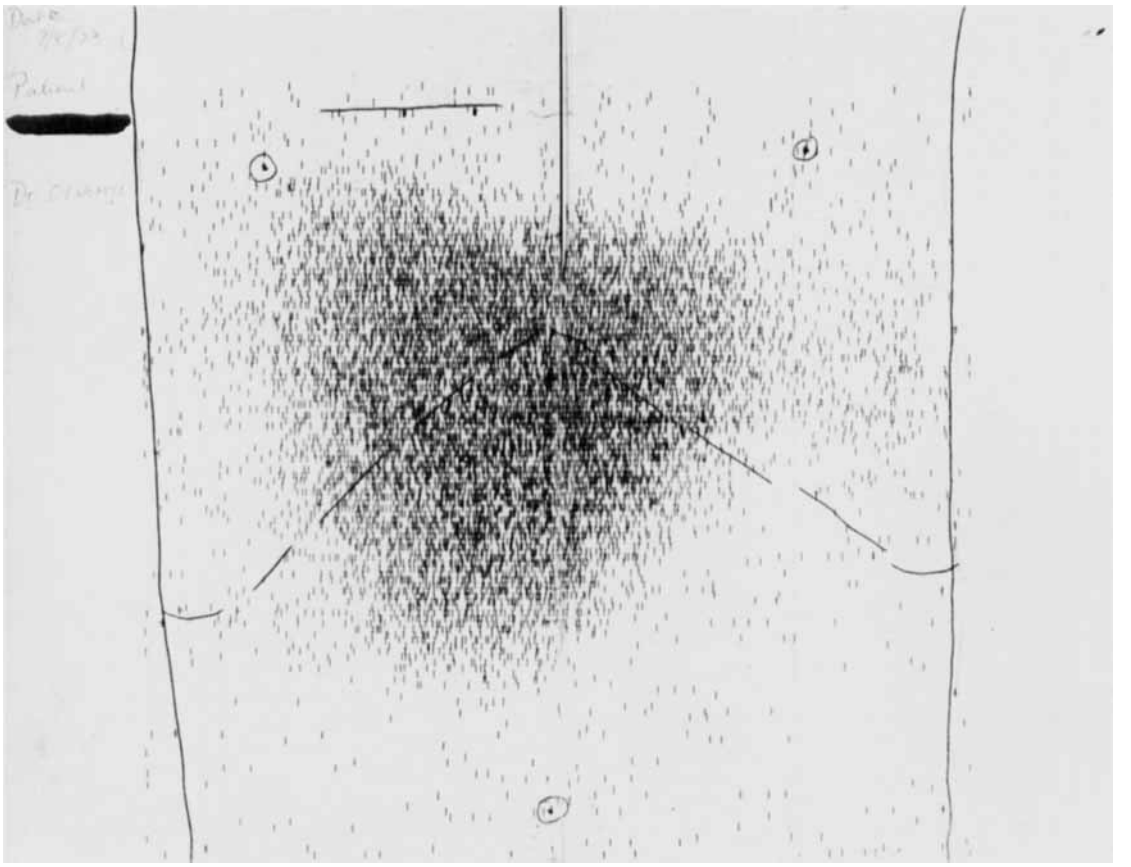

FIG. 5. Liver scan of patient A.B. done after two courses of adriamycin, August, 1973. Note the rapid return to normal.

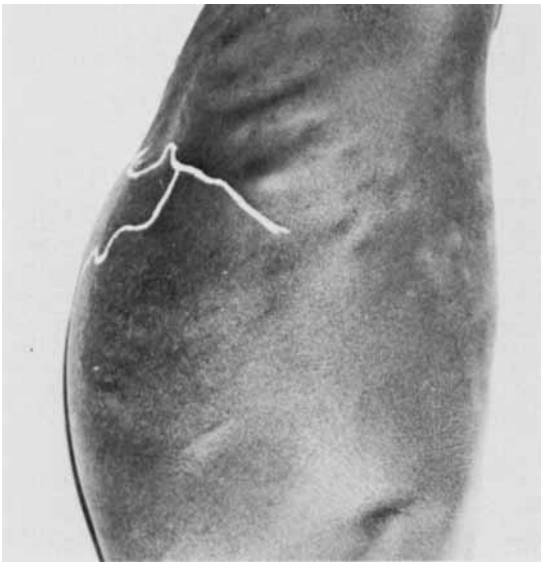

FIG. 6. Patient F.M. (STC 522) after surgery before commencing chemotherapy with adriamycin. Note the tense ascites and the size of the liver.

was regarded as Stage IIB? and therefore unsuitable for surgery. Chemotherapy with adriamycin was started on June 25th, 1973 at a dose of 75 mg/m²; within 3 days he was free of abdominal pain. A week later the liver mass had shrunk to less than half its original size (Fig. 3), the ascites was less marked, and jaundice had cleared. By August 2nd, a few days before the third course of adriamycin he appeared to have achieved complete remission. His liver function tests were normal. His AFP, which was originally strongly positive, was now negative (Fig. 4) and his liver scan was almost normal (Fig. 5). A repeat percutaneous liver biopsy was negative, and the patient was allowed to resume his previous employment. He received three more courses of adriamycin (total dose 485 mg), following which he refused further therapy, thinking he was cured as he no longer felt pain. He was, however, followed at monthly intervals, and in November his AFP, which had been negative after the second course of adriamycin, was again positive; by December, 1973 he had clinical evidence of relapse. He still refused further therapy, but agreed to return for followup. In April, 1974 when he returned he had severe abdominal pain, a rapidly enlarging liver, and re-accumulation of ascites. Repeat liver scan and liver biopsies were performed, and the histology was again interpreted as showing the adenoid type of hepatocellular carcinoma. Although he again showed initially good responses to adriamycin, he became refractory after two further courses and died on July 31st, 1974.

Autopsy revealed primary liver carcinoma with marked tumor necrosis, portal vein thrombosis, cirrhosis of the liver, ascites, and pleural effusion. He had survived for 13 months from the date of diagnosis.

Case 2

F.M. (STC 522) was a 46-year-old Rundi man who was admitted to the Surgical service of New Mulago Hospital on February 15th, 1973 for a badly comminuted compound supracondylar fracture of the left femur. Twelve weeks later, while still in traction he complained of abdominal pain and distention. Physical examination revealed an enlarged, tender liver. Hepatocellular carcinoma was suspected, and the encology service was consulted. The patient gave a history at this stage of heavy ethanol ingestion for many years prior to the accident which caused the fracture, but denied any past history of icterus, hematemesis, or melena. Physical examination revealed a healthy looking male patient on skeletal traction, well oriented, with no evidence of liver failure. The liver mass was 7 cm below the costal margin, along the nipple line. He had mild ascites. The liver function tests and barium swallow were normal, but the colloidal gold scan was interpreted as showing defective uptake, suggestive of a space-occupying lesion in the right lobe of the liver. A percutaneous liver biopsy using the Menghini technique was performed; the histology was interpreted as showing trabecular well-differentiated hepatocellular carcinoma, with underlying macronodular cirrhosis.

Because of the patient's apparent fit state and localized disease, he was subjected to laparatomy, with the view to performing partial hepatectomy. At operation, inoperable tumor of the massive type involving nearly the whole of the right lobe and the medial aspect of the left lobe was found. The liver showed advanced cirrhosis, and there was some ascites. An open biopsy performed at the time of surgery confirmed the previous findings of hepatocellular carcinoma in a previously cirrhotic liver.

Following this operation, the patient ran a stormy course, characterized by deep jaundice (bilirubin 12.3 mg/100 ml), tense ascites (Fig. 6), and evidence of cholemia (asterexis, fetor hepaticus, and episodes of confusion). Ten days after surgery (August 4th, 1973) he was started on adriamycin at a dose of 75 mg/m² i.v. Three days later his jaundice had worsened, but the AFP level had dropped to less than one-third of its pretreatment level (Fig. 7). The following week he was noted to have made dramatic improvement. The abdominal pain was gone; the liver mass had shrunk; the ascites and jaundice were less marked. Further courses of adriamycin were given at 3-week intervals, and by the third course he appeared to be in complete clinical remission (Fig. 8). This was supported by negative AFP measured by the double diffusion technique, return to normal of liver function tests, and two negative percutaneous liver biopsies. The drug side effects include severe stomatitis, alopecia, and anorexia, but worst of all he developed marrow hypoplasia. The patient took three months to recover from this latter complication; during this time he moved freely on a wheel chair (since he still had a non-united fracture) and was able to go

home for several weeks. Upon recovery from the marrow depression, he was started on further courses of adriamycin; after the fifth course surgery was contemplated to ascertain his remission state. This was performed on April 2nd, 1974. The surgeon (SK) described the liver as shrunken to about half its original size; the area of the right lobe which previously contained massive tumor was scarred and there were many adhesions. There was no tumor seen macroscopically on the dome of the liver. On the under surface of the lateral segment of the left lobe there were four pin-head nodules. Biopsy of the scarred area showed no evidence of tumor, but the histology of one of the under surface nodules was read as showing active trabecullar carcinoma.

Following this operation, the patient again ran a very stormy course, with deep jaundice, gross ascites, and evidence once more of hepatic encephalopathy. He was treated vigorously for this, but he gradually went downhill and died 4 days after the operation. At postmortem the pathologist described the liver as shrunken and showing evidence of advanced cirrhosis. There was minimal tumor, mainly pinpoint nodules on the under surface of the liver. There were portal vein thrombosis (blood) and ascites. The patient had survived 9 months from the time of diagnosis.

DISCUSSION

Primary hepatocellular carcinoma is uniformly fatal and has hitherto defied all forms of systemic drug therapy. The present study adds carcinoma of the liver to the already growing list of malignant neoplasms that respond to adriamycin.[10,12] So far all the patients with adequate drug trial have responded. The earliest observable feature is the rapid disappearance of pain.

The clinical manifestations in this small group of patients are no different from those in patients seen and studied at our Institute prior to the availability of adriamycin. Their mean age of 44.8 years and the histologic pattern are similar to that reported by Hutt and Anthony.[7] Ten of 14 patients (71%) had associated cirrhosis; this too agrees with the figures of 79%[3] and 86%[7] quoted by earlier workers. All patients were poor-risk patients; none was considered suitable for partial hepatectomy.[4] Although the number of patients studied so far is small, to our knowledge it is the first time that systemic drug therapy has caused consistent objective response in this tumor. Because of the small numbers studied so far, no attempt has been made to correlate remission induction, remission duration, or survival with the histologic pattern. Of the three patients who achieved complete tumor regression, two relapsed subsequently with the same histologic tumor type. This might suggest that probably the tumor was not completely eradicated and that further courses of adriamycin were needed to rid the liver completely of this tumor. The patient who died following a "second look" operation

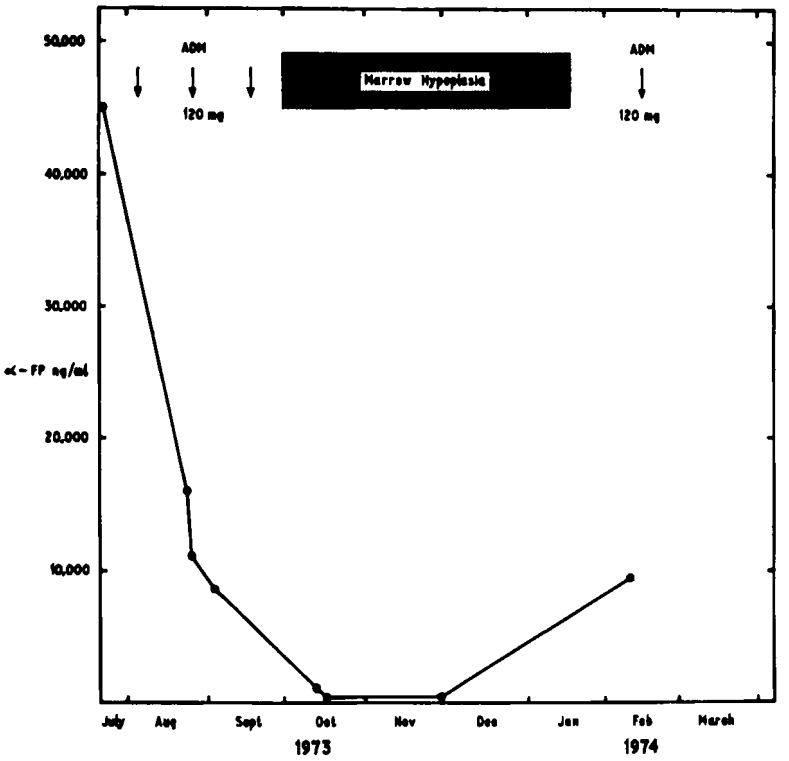

FIG. 7. Graph showing Serial RIA AFP data of patient F.M. (STC 522). Note the rapid drop of AFP following first course of adriamycin.

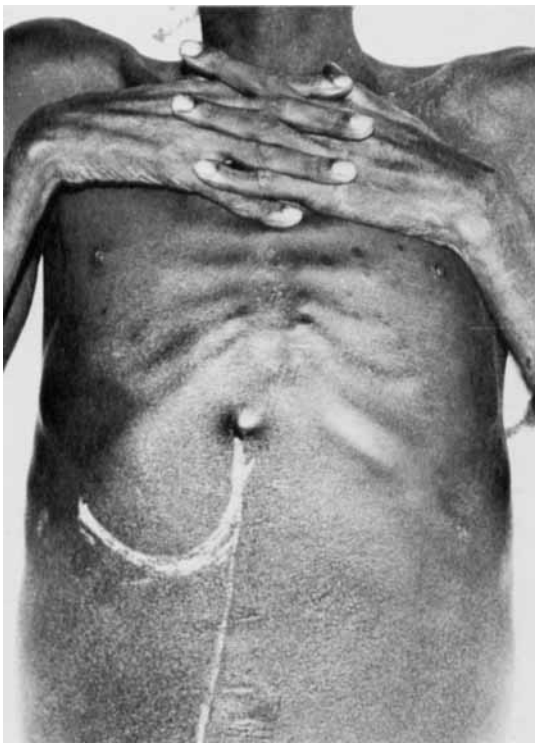

FIG. 8. Patient F.M. (STC 522) after three courses of adriamycin. Note the size of the liver and the disappearance of ascites.

probably developed severe hepatic decompensation following surgical trauma, and the portal vein thrombosis tipped the balance against him. In retrospect the second laparotomy should not have been carried out, since he had severe advanced cirrhosis and had shown signs of decompensation following the first laparotomy.

The remission durations for the three complete responders are 3, 6, and 7 months, while their survival periods are 8, 9, and 13 months, respectively. Although only 3 of the 11 evaluable patients are still living, the median survival of 8 months is to our mind a remarkable achievement in this tumor.

The side effects of adriamycin in this group of patients were tolerable. Three had severe myelosuppression; in one case it contributed to gram-negative sepsis and death. The patient who had severe marrow hypoplasia was deeply jaundiced at the time he received the full calculated dose of adriamycin in error.

It is conceivable that larger than usual doses are needed to induce complete remissions in this tumor. The 75 mg/m^2 dose used in this study is higher than that which some investigators would recommend. Secondly, one of the complete responders who was deeply jaundiced received the full calculated dose and perhaps required such a dose to attain a remission. Although most of the patients had abnormal liver function (mostly elevated alkaline phosphatase) there was no direct correlation between the degree of liver dysfunction and severity of myelosuppression. No patient has to date showed any electrocardiographic changes of cardiac toxicity known to follow therapy with adriamycin, but this is mainly because the cumulative doses so far are well below the cardiac toxic levels.

We believe these preliminary observations indicate a turning point or breakthrough in the management of this tumor, and provide a basis for optimism in further trials in hepatocellular carcinoma with adriamycin, either singly or in combinations.

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