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Short communication

Treatment of inoperable hepatocellular carcinoma by intra-arterial Lipiodol and 4′-epidoxorubicin

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Summary. A total of 30 patients presenting with inoperable hepatocellular carcinoma (HCC) were treated with intrahepatic arterial Lipiodol (5 ml) and 4′-epidoxorubicin (90 mg/m^2) once every 4 weeks. The treatment results included no complete response, 2 partial responses, 6 cases of static disease and 19 cases of progressive disease. The median survival was 18.9 weeks. All patients had died by the time of this writing, with survival duration ranging from 4.1 to 87.3 weeks. Toxicities were minimal and included anaemia and alopecia. As compared with a historic control group that had received the same dose of intravenous 4′-epidoxorubicin, the treatment group showed similar response rates but developed fewer toxicities. There was no significant survival benefit over the control group. We concluded that although this form of treatment had comparable activity and produced fewer side effects, it provided no survival benefit over intravenous treatment. The slight prolongation of survival achieved in the treatment group as compared with the control arm might have been due to case selection.

Introduction

Hepatocellular carcinoma (HCC) is a common cancer in Hong Kong. In 1987, about 1,100 new cases were registered at an incidence of 37.5/100,000. It is also the second commonest and most frequent cause of cancer death in Hong Kong [1]. This is a devastating disease for which the overall median survival is only 8 weeks [12]. At present, surgical resection is the only treatment modality based on a curative intent. However, most patients exhibit inoperable disease at presentation due to advanced local disease associated with bi-lobar involvement, poor liver function or systemic metastasis. The overall operative rate is about 10% and about half of the patients are not considered to be suitable for any form of treatment [12]. Among the rest, other forms of palliative treatment have been attempted, including systemic chemotherapy, intra-arterial chemotherapy, immunotherapy and embolisation, with little success.

In 1986, we started phase II trials using intravenous 4′-epidoxorubicin to treat inoperable HCC and found it to be active against the disease [10, 11], as had been demonstrated in other trials [16]. Lipiodol (Lipiodol Ultra-fluide, Laboratoire Guerbet, France) is an iodised-oil contrast medium that is preferentially taken up and retained by HCC after its injection into the feeding hepatic artery [6, 17]. In a pilot study conducted from 1986 to 1987, we mixed and delivered the two substances intra-arterially for the treatment of inoperable HCC. Escalating doses of from 50 to 90 mg/m^2 4′-epidoxorubicin were used [5]. After the pilot study, we returned to the intravenous administration of 90 mg/m^2 4′-epidoxorubicin while waiting for the results, which later proved to be promising [5]. Thereafter, we initiated the present trial using a uniform dose of 90 mg/m^2 intra-arterial 4′-epidoxorubicin (the same as the intravenous dose) and compared the results in terms of tumour response, toxicities and survival with those previously obtained using intravenous treatment.

Patients and methods

Patients aged ≤ 75 years who presented with inoperable HCC as demonstrated either by histology or by a serum alpha-fetal protein (AFP) level of >500 ng/ml along with diagnostic angiographic features were entered into the trial. Subjects exhibiting extrahepatic disease, inadequate bone marrow function (a WBC of $<3 \times 10^9$/l or a platelet count of 100×10^9/l), poor liver function (total bilirubin, >50 μmol/l; prothrombin time, >18 s), previous chemotherapy or surgery, severe concomitant illness, or a Karnofsky performance score of <70 were excluded. Patients who failed angiography due to anatomical or technical reasons were also excluded from the study. Other pre-treatment investigations included determinations of serum AFP levels and of the hepatitis B surface-antigen status, electrocardiography, chest radiography and measurements of tumour size by ultrasound examination (US) and computed tomography (CT) scan.

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Table 1. Comparison of patients' characteristics

	Intra-arterial	Intravenous
Patients (*n*)	30	28
Sex (F/M)	2/28	3/25
Median age (years)	52 (range, 27–75)	47.5 (range, 30–75)
Median KPS	90 (range, 70–100)	90 (range, 70–100)
AFP >500 ng/ml (*n*)	19	21
Median Hb (g/dl)	14.2	12.5
Median PT (s)	13.8	14.0
Median APTT (sec)	34.6	34.1
Median Albumin (g/l)	37	33
Median total bilirubin (μmol/l)	13	15
Median ALT (IU/l)	68.5	50
Median courses/patient (*n*)	3 (range, 1–8)	3 (range, 2–8)

Hb, Hemoglobin; PT, prothrombin time; APTT, ALT, alanine aminotransferase

Table 2. Comparison of response rates

Treatment	CR		PR		SD		PD	
	n	%	*n*	%	*n*	%	*n*	%
Intra-arterial	0		2	6.7%	6	20%	22	73.3%
Intravenous	2	7.1%	2	7.1%	5	17.9%	19	67.9%

Suitable patients who had given their informed consent to participate were subjected to selective hepatic arterial cannulation under fluoroscopic control using the Seldinger technique. A mixture of 5 ml Lipiodol and 90 mg/m^2 4′-epidoxorubicin (dissolved in 3 ml water and mixed with Lipiodol using a vortex machine) was slowly injected over 10 min into the arterial catheter, after which the catheter was removed. Patients were observed for 2 days in the ward and were discharged afterwards if they showed no acute side effects. The treatment was repeated every 4 weeks in the absence of undue toxicity. Response was assessed by US, CT scan and serum AFP levels after two courses of treatment. A maximum of eight treatments were given to subjects who showed a favourable response after two cycles in the absence of severe toxicity. A complete blood picture, a clotting profile, liver-function tests and electrocardiography were performed before each course of treatment. In cases of bone marrow suppression, treatment was delayed weekly until the leucocyte count had returned to 3 × 10^9/l and the platelet count, to 100 × 10^9/l. Toxicities were documented according to WHO criteria [15]. Complications arising from angiography were also recorded.

Response was assessed by liver US, CT scan, selective hepatic angiography and determinations of serum AFP levels. A complete remission (CR) was defined as the total disappearance of disease as judged by clinical examination, CT scan, angiography and a normalized AFP level (<20 ng/ml). A partial response (PR) was defined as a reduction of ⩾50% in the product of the two greatest perpendicular diameters of the largest tumour nodule measured radiologically by CT scan, US or angiography. Stable disease (SD) was defined as either no change or a response amounting to less than a PR. The remaining patients were classified as having progressive disease (PD). Survival duration was calculated from the day on which the first course of treatment was initiated until the time of death or of the last event.

A matched group of patients who presented with inoperable HCC in the absence of extrahepatic disease and had not undergone prior treatment were given 90 mg/m^2 intravenous 4′-epidoxorubicin (the protocol used prior to this trial). The resulting response rate, toxicities and survival were compared with those obtained for the present treatment group. Actuarial survival curves were plotted according to the Kaplan-Meier method and compared using log-rank tests.

Table 3. Comparison of toxicities

	Treatment		
	WHO grade	Intra-arterial	Intravenous
Anaemia	0	14	21
	1	5	7
	2	8	2
	3	1	0
	4	0	0
Leucopenia	0	21	28
	1	2	2
	2	4	0
	3	1	0
	4	3	0
Thrombocytopenia	0	27	30
	1	0	0
	2	1	0
	3	0	0
	4	0	0
Alopecia	0	0	2
	1	7	10
	2	11	15
	3	10	3
	4	0	0
Nausea and vomiting	0	5	26
	1	15	4
	2	4	0
	3	4	0
	4	0	0

Data represent numbers of evaluable patients

Results

A total of 30 eligible patients were entered into the trial, including 28 men and 2 women whose median age was 52 (range, 27–75) years. The median Karnofsky performance score (KPS) was 90 (range, 70–100). In all 28 individuals who were treated with 90 mg/m^2 intravenous 4′-epidoxorubicin served as controls. A comparison of the characteristics of the present treatment group vs the control group is shown in Table 1.

A total of 89 courses of treatment were given, with the median value being 3 (range, 1–8) courses/patient. In all, 27 patients were successfully evaluated for response and 3 subjects exhibiting PD represented early deaths. The response evaluation indicated that no patient achieved a CR, 2 attained a PR (6.7%), 6 showed SD (20%) and 22 exhibited PD (73.3%). In only 3 of 19 patients whose initial AFP value had been high (>500 ng/ml) was a subsequent decrease of >50% recorded; however, these individuals failed to achieve even a PR. A comparison of these response rates with those found for the control group is shown in Table 2.

Toxicities mainly involved mild anaemia and alopecia; vomiting and leucopenia were uncommon. No life-threatening complication attributable to chemotherapy or angiography was encountered. Two patients experienced mild right-upper-quadrant pain that was transient and easily controllable with simple analgesics. Transient low-grade pyrexia was also common, usually starting on day 1

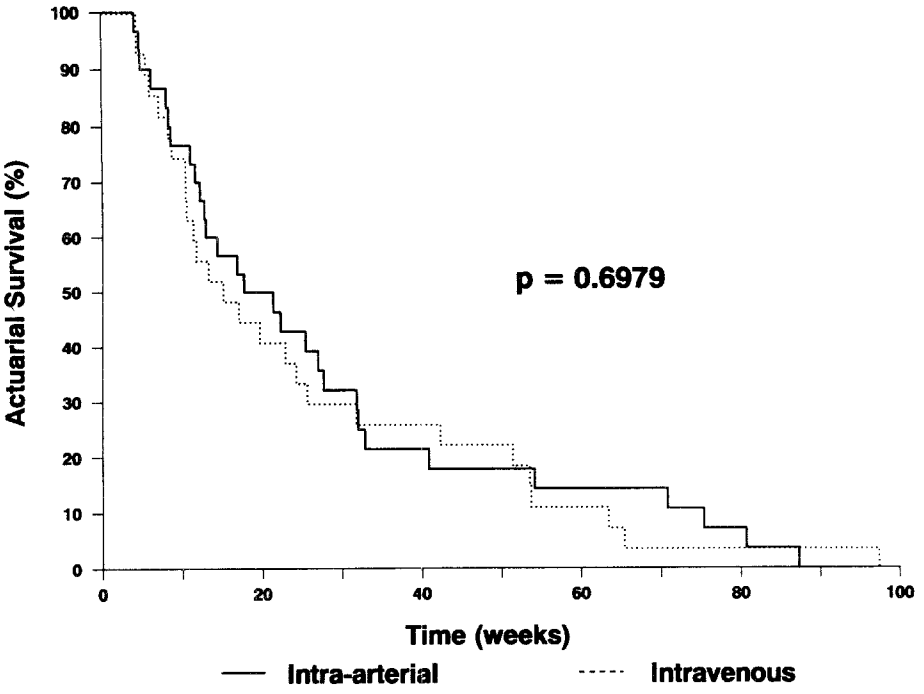

Fig. 1. Actuarial survival curves

and lasting for 2–3 days. The hospital stay per patient was <72 h. Otherwise, no immediate complication was observed. Moreover, no cardiac toxicity was documented and no patient required a delay of treatment because of bone marrow suppression. The incidence of bone marrow toxicities, gastrointestinal symptoms and alopecia was lower in the present treatment group than in the intravenous control arm (Table 3).

All patients had died of PD by the time of this writing. The median survival was only 18.9 (range, 4.1–87.3) weeks. For the historic control arm, the median survival was 14 (range, 4.3–97.3) weeks. The actuarial survival curves for both groups of patients are shown in Fig. 1. Obviously, no survival benefit could be established for either group.

Discussion

The prognosis for inoperable HCC is grave. In our previous clinical study of 340 cases of HCC, the median survival was only 8 weeks [12]. Anthracyclines such as doxorubicin are relatively more active than other drugs in evoking a response, but the survival of individuals receiving these agents is only about 4 months [7]; this small impact on survival is probably attributable to patient selection. To improve the therapeutic index, we attempted to deliver regional chemotherapy via the intra-arterial route.

Since the discovery of the targeting property of Lipiodol for HCC [6, 17], it has been mixed with cytotoxic drugs to treat this disease. Although there is no physical or chemical bonding between anticancer drugs and Lipiodol, the latter can serve as a drug carrier. Lipiodol can also induce a micro-embolisation effect in small arteries supplying the tumour. This may slow down the blood flow and enhance the delivery of cytotoxic drugs to the tumour, thus possibly reducing systemic toxicity as well. The co-distribution of Lipiodol and 4′-epidoxorubicin is difficult to prove. However, from our unpublished data, we have found that the area under the curve in the peripheral blood for 4′-epidoxorubicin following the combination treatment (Lipiodol and 4′-epidoxorubicin) is statistically significantly lower than that resulting from therapy with 4′-epidoxorubicin alone.

Various anti-cancer drugs have been mixed with Lipiodol to treat HCC including doxorubicin, mitomycin C and 4′-epidoxorubicin [2, 3, 5, 8, 13]. Clinical responses in terms of either a decrease in AFP levels or a radiologically proven regression of tumours were reported in these trials. However, the question as to whether this combination treatment has any impact on survival remains unanswered. In a trial conducted by Shibata et al. [9], a prolongation of survival was obtained following the intra-arterial administration of a cisplatin-Lipiodol suspension. In these and other trials, tumour response and survival benefits correlated with the stage of disease (size of the tumour) [3, 4] and the degree of retention of Lipiodol [14].

However, in the present study the response rates and survival duration obtained for the intra-arterial arm were disappointing. These results probably did not reflect a lack of efficacy for 4′-epidoxorubicin, as its activity has been documented both in previous investigations [10, 11] and in the present intravenous control arm. The lower CR rate obtained following intra-arterial treatment may have been due to the more sensitive method of reassessment by angiography. As in most other series, the toxicities encountered after intra-arterial therapy in the present trial occurred less frequently and were less severe than those observed following intravenous treatment. This can be explained by the first-pass effect, whereby the drug is metabolised early in the liver. As the retention of Lipiodol and anti-cancer drugs in the tumour is an important prognosticator, gel-foam embolisation should be added in future trials [14]. Furthermore, survival and toxicities are impor-

tant endpoints in the evaluation of new modalities of treatment for inoperable HCC due to the aggressive nature of the disease.

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