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Original Paper

Intra-arterial Chemotherapy Followed by Chemo-embolisation in Unresectable Hepatocellular Carcinoma

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Unresectable hepatocellular carcinoma is related to a poor prognosis. Encouraging response rates and survival have been reported with intra-arterial (i.a.) chemotherapy and chemo-embolisation, but limited data are available on the association of the two treatment modalities. We therefore started a new programme combining i.a. chemotherapy with chemo-embolisation. The treatment regimen consisted of L-leucovorin (100 mg/m^2 i.v.), 5-fluorouracil (800 mg/m^2 i.a.), and carboplatin (250 mg/m^2 i.a.). Chemo-embolisation with mitoxantrone (10 mg/m^2) plus ethiodized oil followed immediately. The same treatment plus gelatin sponge was given after 28 days. 26 patients entered the study and were evaluable for response and side-effects. Main patient characteristics were: males 21, females 5: median age 68 years (range 42–76 years); stage TNM II–III 17, IVA 9; Child's A 12, Child's B 14; elevated baseline α-fetoprotein 17; cirrhosis 25. 14 patients had a partial response (54%; 95% confidence interval 33–73%), 3 had stabilisation and 9 had progressive disease. Median survival was 11 months (range 2–20+). 16 patients had grade I–II pain and 15 grade I–II fever. Our results indicate that the regimen is safe, well tolerated and capable of inducing objective remissions in a high percentage of patients with hepatocellular carcinoma. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: chemo-embolisation, intra-arterial chemotherapy, hepatocellular

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INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is relatively rare in Europe and the United States, but still represents one of the most common cancers worldwide, with an annual death rate of around 250 000 patients [1–3]. The low resectability rate and the high recurrence rate, together with the fact that HCC tends to be fatal because of local hepatic progression rather than widespread metastasis, stimulated the development of several local-regional therapeutic approaches including intra-arterial chemotherapy and transcatheter arterial chemo-embolisation (TAE). Intra-arterial chemotherapy has been considered a promising approach in past years since it makes it possible to increase selectively drug administrations to the tumour with less exposure to other organs [4–6]. Agents are generally chosen because of their pharmacological advantage when administered intra-arterially and include fluoropyrimidines, anthracyclines and platinum derivatives [7–11]. Responses in the range of 30–50% have been observed, but most of the treatment protocols were associated with significant side-effects [4, 7, 11]. Hepatic toxicity has been observed in up to 50% of patients and resulted in toxic deaths in 10–20% of the cases [7, 11]. TAE with various materials such as ethiodized oil [12–19], absorbable gelatin powder plus ethiodized oil [20–25], microspheres [26 and 27], in combination with chemotherapeutic agents, including cisplatin and anthracyclines, has been attempted. Responses ranged from 20 to 60%, with a median survival often not exceeding 10–12 months [1–3, 28]. One of the major problems with conventional TAE is that it seems effective in the main tumour, but has limited efficacy on small intrahepatic metastases and extracapsular or intracapsular invasion [27]. Another major consideration

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is that the role of chemotherapeutic agents in TAE is still undefined, since they are often administered at suboptimal dosages and with long-term recycle in current protocols.

Based on these considerations, the aim of our study was to evaluate the feasibility and activity of a combination of the two treatment modalities with adequate recycling time (every 28 days) and dosage of chemotherapeutic agents. The combination of agents was chosen because of the pharmacological advantage with arterial administration. Carboplatin was selected with the aim of reducing side-effects associated with cisplatin [4, 9]. Mitoxantrone has been reported to be active when administered intra-arterially [10] and is known to be related to limited non-haematological side-effects [29]. Intravenous leucovorin was added to improve the clinical activity of 5-fluorouracil (5-FU), as reported in the literature [30].

PATIENTS AND METHODS

Patients with biopsy-proven unresectable or untransplantable HCC were considered eligible for the study. Other inclusion criteria were: Child's A or B disease; TNM stage II–IVA; age <75 years; bilirubin <3 mg/dl; aspartate and alanine aminotransferase <2.5 the upper limit; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; WBC (white blood cell) count >3000 mm^3 and platelet count >60 000/mm^3; serum creatinine <1.2 mg/dl. Patients with evidence of cardiac disease (congestive heart failure, history of myocardial infarction within the previous 3 months), severe vascular disease or uncontrolled concomitant infections were excluded. Patients with monolobar portal vein obstruction and adequate liver function were included in the study. Informed written consent was required.

Patients had baseline liver and renal function tests, electrolyte studies, complete blood count, prothrombin and partial thromboplastin times carried out within 2 weeks of the procedure. Also, chest X-ray, abdominal CT scan plus ultrasound, alpha-fetoprotein and electrocardiography were performed within 2 weeks of chemo-embolisation.

On day 1 of treatment, patients were premedicated with dexamethasone (4 mg) and ondansteron (8 mg). Chemo-embolisation was performed via standard hepatic angiography. At each treatment, a catheter was inserted percutaneously into the femoral artery and directed into the main hepatic artery. After localisation of the neoplastic lesions, arteries were selectively catheterised. L-Leucovorin (100 mg/m^2 dissolved in 250 ml of normal saline solution) was administered intravenously. Carboplatin (250 mg/m^2 dissolved in 50 ml of normal saline solution) followed by fluorouracil (800 mg/m^2 dissolved in 50 ml of normal saline solution) were given intra-arterially. The infusion time was 15 min for carboplatin and 1 h for 5-fluorouracil.

Mitoxantrone (10 mg/m^2) was mixed with 10–15 ml of ethiodized oil using a mechanical agitator for 5 min and administered immediately under fluoroscopic guidance. The same treatment plus gelfoam powder (40–50 μm microfibrillar collagen) dissolved in ethanol was performed on day 28. The powder was injected until stagnation of blood flow was noted. Patients were followed closely for 24 h in the oncology unit.

Anti-emetics and narcotics were administered if needed. Patients had a complete blood count 7 days after treatment. Liver and renal function tests, electrolyte studies and complete blood count were performed 2 weeks after treatment. Dose modifications were made for granulocyte and platelets at the time of recycling in case of no recovery after one week of delay as follows: in case of platelets >50 000 $mm/^3$ but <60 000 mm^3 and/or neutrophils >1000/mm^3 but <1500/mm^3, 50% of the carboplatin and mitoxantrone dose was administered. In case of platelets <50 000/mm^3 and/or neutrophils <1000/mm^3, patients were excluded from the study. The dose of 5-fluorouracil was reduced to 75% of the baseline dose in case of grade III mucositis or diarrhoea and in case of grade III neutropenia.

Responses were evaluated using serial CT scans at 1 month, 3 months and every 2 months thereafter. Patients who responded and had a time to progression >6 months were offered a repeat treatment at the time of liver progression if they still met trial inclusion criteria. Responses were graded according to the standard UICC criteria. Alpha-fetoprotein was monitored every 4 weeks, but was not considered as a response criterion. A complete response was defined as the disappearance of all parameters of disease by two observations not less than 4 weeks apart. A partial response was defined as a 50% or more reduction in the sum of the products of the perpendicular diameters of all lesions for at least 4 weeks without any evidence of new lesions. Stabilisation of disease was defined as a less than 50% reduction or less than 25% increase in the sum of the products of the perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease was defined as a <25% increase in one or more lesions or the appearance of new lesions. Side-effects were scored according to World Health Organisation (WHO) criteria.

Statistical analysis

The aim of the study was to obtain at least 30% objective remissions. Therefore, according to the Gehan two-step statistical approach [31], a total of 9 patients in the first step had to be studied and, if one response was seen, then a total of 25 patients had to be studied. Estimated curves total of 9 patients in the first step had to be studied and, if one response was seen, then a total of 25 patients had to be studied. Estimated curves of survival and time to progression were plotted from the first day of treatment by the method of Kaplan and Meier [32].

RESULTS

Patient characteristics

26 patients were enrolled in the study from December 1993 to January 1995 and were evaluable for response and side-effects. Major patient characteristics are shown in Table 1. 3 patients had tumour relapse after surgical treatment of the initial lesion. Portal vein obstruction was not considered as a major exclusion criteria if only one lobe was involved. Tumour thrombus in the portal vein or external compression of the portal vein was present in 4 cases. Two patients had previous history of heavy alcohol intake. The median age was 68 years, with 9 patients older than 70 years. The median pretreatment alpha-fetoprotein level was 360 ng/dl, with 8 patients presenting with a baseline value >1000 ng/dl.

Table 1. Patient characteristics

Entered/evaluable	26/26
Male/female	21/5
Median age (years) (range)	68 (42–76)
Performance status: 0–1/2	21/5
Stage (TNM)	
II	10
III	7
IVA	9
Child's A/B	12/14
Hepatitis exposure	
HbsAg-positive	4
HbsAb-positive	5
Hcv-positive	14
Cirrhosis	25
Altered alpha-fetoprotein (>400 ng/ml)	17 (11)
Bilirubin, median mg/ml (>1 mg/ml)	1.1 (13)
Platelets, median no./mm^3 (<100 000)	130 000 (10)

HbsAg, hepatitis B surface antigen; HbsAb, hepatitis B surface antibody; Hcv, hepatitis C virus.

Toxicity

Table 2 summarises the side-effects observed. Most of the patients had fever up to 38°C and rarely as high as 40°C. There was no evidence of infection in such cases, and it appeared attributable to intrahepatic tumour necrosis. Median duration of fever was 4 days (range 1–8). Pain was, in general, well controlled by intramuscular ketorolac (30 mg) and had a median duration of 36 h (range 24–72). 2 patients had gastro-intestinal bleeding due to the presence of bleeding varices. No catheter-related complications were observed. The median hospital stay was 24 h after chemo-embolisation, with 6 patients requiring hospitalisation between the cycles because of worsening of liver function (4 patients) and gastro-intestinal bleeding (2 patients). 8 patients presented with worsening of hepatic function on day 28, but they still met baseline inclusion criteria so that the second part of the treatment was performed. No patient had evidence of encephalopathy and 4 patients developed transient ascites. Early mortality (within 30 days of chemo-embolisation) was minimal. Only one patient died within this period due to irreversible hepatic failure, possibly a direct consequence of chemo-embolisation.

51 cycles were administered at the full doses (day 1 plus 28), and nine cycles were delivered at reduced doses. Overall, 21 patients had therapy at the prescribed dose, and 5 patients received cycles at reduced doses. 5 patients had a reduction in the dose of intra-arterial carboplatin, 5 patients had a reduction in the dose of mitoxantrone, and 2 patients had a reduction in the dose of 5-FU. Reasons for dose reduction were mainly thrombocytopenia and neutropenia.

Responses

There were 14 responses among 26 evaluable patients (54%; 95% confidence interval 33–73%), 3 cases of disease stabilisation, and 9 cases of progressive disease. Characteristics of responding patients are shown in Table 3. Responses were obtained in patients with Child's A or B disease and inpatients with both limited and advanced disease stage, although most patients with stage II disease responded (7 out of 10) and only a few patients with stage IVA disease responded (4 out of 9). The median serum alpha-fetoprotein value among responding patients decreased from 563 to 58 at the peak of the response. The median time to progression of the whole group of patients was 6 months. Median duration of response was 5 months (range 2–12+) with 4 patients still responding after 9, 10, 10 and 12 months. One patient, who attained a partial remission, underwent surgery and is now free of disease after 10 months.

Retreatment was offered at the time of progression in 4 cases. Two of these patients achieved a partial remission. Retreatment was not offered in the remaining patients due to extrahepatic progression (1 case), technical limitations (2 cases), worsening of liver functions (3 cases), absence of progression (4 cases) or failure to respond in the liver (12 cases). Median survival of the patients was 11 months (range 2–20+) (Figure 1).

DISCUSSION

The optimal treatment for unresectable HCC still remains a challenge. Numerous studies on chemo-embolisation in HCC have been reported in the past year, but due to the large variation of chemotherapeutic protocols, the real impact of the treatment modality on patient survival is still unassessable. In fact, although encouraging survival rates have been claimed for reported phase II studies with up to 50% of the patients alive at 3 years [19, 28, 33], the difference in the characteristics of patients selected for these trials and the various number of chemotherapeutic agents and embolic materials employed makes any comparison difficult. Two small phase III studies comparing chemo-embolisation with best supportive care failed to observe any significant improvement of survival [20, 22]. However, there was a trend toward increased survival in the chemo-embolisation group in the study by Trinchet and associates [20]. In the current study, intra-arterial chemotherapy was added to chemo-embolisation in a 28-day recycle schedule with the aim of improving clinical results without increasing the rate

Table 2. Side-effects of treatment

	WHO grade			
Side-effects	1	2	3	4
Nausea/vomiting	3	—	—	—
Pain	13	3	—	—
Infections	3	—	—	—
Leucopenia	3	2	2	—
Neutropenia	4	1	2	—
Thrombocytopenia	1	3	—	—
Fever	13	2	—	—

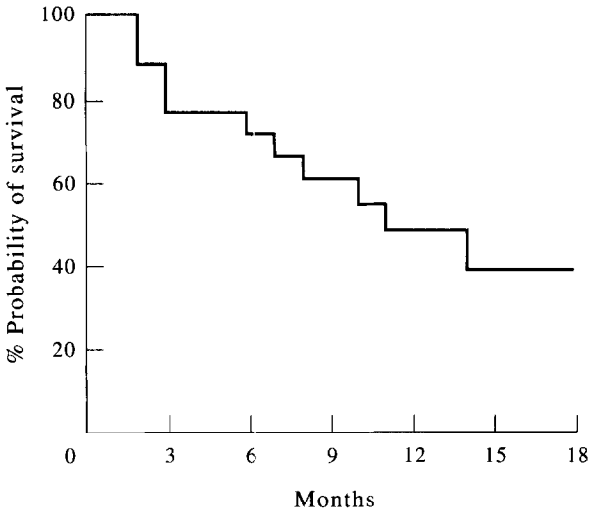

Figure 1. Overall survival of 26 evaluable patients.

of side-effects. Using this approach, we observed only 1 early death and side-effects have been limited, with only 5% grade 3–4 myelotoxicity.

Both intra-arterial chemotherapy and TAE are known to be related to significant morbidity and mortality. In particular, for the former treatment Patt and associates [11] reported 4 toxic deaths among 31 patients submitted to intra-arterial chemotherapy with floxuridine, doxorubicin, cisplatin and leucovorin, and in 13 patients hospitalisation was required due to severe infectious complications. Doci and associates [7] observed 11 hepatic failures among 28 cases submitted to intra-arterial doxorubin in of 5-FU, and 1 patient died of treatment-related sepsis. Both authors concluded that toxicity seems strictly related to patient's characteristics and, in particular, to the presence of previous or concomitant hepatitis virus infection and advanced liver cirrhosis. Similar conclusions have been reported by Stuart and associates [24], who reported 17% early deaths in a group of 47 patients submitted to chemo-embolisation. Although it is difficult to compare different series of patients with unresectable HCC due to the influence of multiple prognostic features in the incidence of side-effects, our results indicate that association of the two treatment modalities does not seem to be correlated with a significant worsening in the incidence of side-effects. Inclusion criteria may have positively influenced side-effects in the present study. Hepatic function was well preserved in most of the patients and no patient had Child's C disease.

A 54% response rate was observed in this study, with a median duration of response of 5 months and a median survival of 11 months. As reported in Table 2, no significant differences in response were observed with respect to baseline alpha-fetoprotein or serology status, as reported by others [11, 34]. A direct comparison of our results with other studies is difficult. Differences in patient selection and methodology are reflected by a response rate that varied from 15 to 75% in patients treated with chemo-embolisation [21, 23, 25, 27] and a response rate ranging from 20 to 60% for patients treated with intra-arterial chemotherapy [10, 11]. Moreover, reported median survival for TAE varies from 7 to 28 months [18, 21, 25] and for intra-arterial chemotherapy from 3 to 15 months [7, 10, 11].

In local-regional therapy of the liver, an essential role is played by the group of physicians involved, in particular, interventional radiologists [28]. Superselective TAE, which can induce effective tumour necrosis with minimal damage of the non-tumorous liver tissue, is needed in patients with HCC with advanced liver cirrhosis. In a previous trial performed with the same clinical team and with the same trial inclusion criteria, we observed only 13% objective remissions in a group of 22 patients treated with chemo-embolisation including epirubicin, lipiodol and gelfoam [21]. Moreover, the median survival observed in these patients with baseline characteristics superimposable on those of the patients herein reported was only 7 months. Therefore, on the basis of these results, a more favourable impact can be attributed by the approach reported here.

Our initial protocol (reported here) included gelfoam only on day 28, with the aim of reducing liver damage resulting from prolonged embolisation. However, reported data on lipiodol and doxorubicin plus or minus gelfoam have suggested that the addition of the latter increases the response rate [13]. Similar data have been reported by other authors, where the addition of gelfoam increased the response rate from 25 to 58% and 1-year survival from 38 to 62% [33]. Based on the limited toxicity observed in the pre-

Table 3. Clinical, serological and histological features of responding patients

Age (year)	Sex	Stage (TNM)	Serology		Baseline AFP (ng/ml)	Child's status
			HCV	HBV		
67	M	II	+	–	4	A
53	M	IVA	–	+	240	B
68	M	II	+	–	746	A
60	F	II	+	+	72	A
71	M	III	–	+	2280	B
71	F	II	+	–	472	B
74	M	III	–	+	1282	A
64	M	IVA	+	–	10	B
65	M	II	–	+	3	A
74	M	IVA	+	–	450	B
72	M	II	+	–	10	A
67	M	IVA	–	–	2180	B
62	F	III	+	–	380	B
74	M	II	+	–	4	A

AFP, alpha-fetoprotein; HCV, hepatitis C virus; HBV, hepatitis B virus.

sent trial and on the interesting activity recorded, we are investigating a more aggressive schedule that includes three treatment performed at intervals of 28 days with inclusion of gelfoam at every treatment.

1. Ellis LM, Demers ML, Roh MS. Current strategies for the treatment of hepatocellular carcinoma. *Curr Opin Oncol* 1992, **4**, 741–751.
2. Colleoni M, Gaion F, Liessi G, Mastropasqua G, Nelli P, Manente P. Medical treatment of hepatocellular carcinoma: any progress? *Tumori* 1994, **80**, 315–326.
3. Nerenstone SR, Ihde DC, Friedman MA. Clinical trials in primary hepatocellular carcinoma: current status and future directions. *Cancer Treat Rev* 1988, **15**, 1–31.
4. Carr BI, Iwatsuki S, Barov R, *et al.* Intrahepatic arterial cisplatinum and doxorubicin with or without lipiodol for advanced hepatocellular carcinoma (HCC): a prospective randomized study. *Proc Am Soc Clin Oncol* 1993, **12**, 668.
5. Chen H, Gross J. Intra-arterial infusion of anticancer drugs: theoretical aspects of drug delivery and review responses. *Cancer Treat Rep* 1980, **64**, 31–40.
6. Collins J. Pharmacologic rationale for regional drug delivery. *J Clin Oncol* 1984, **2**, 498–454.
7. Doci R, Bignami P, Bozzetti F, *et al.* Intrahepatic chemotherapy for unresectable hepatocellular carcinoma. *Cancer* 1988, **61**, 1983–1987.
8. Friedman MA, Volderding P, Cassidy M, Resser K, Wasserman T, Philips T. Therapy for hepatocellular cancer with intrahepatic arterial adriamycin and 5-fluorouracil combined with whole-liver irradiation: a Northern California Oncology Group study. *Cancer Treat Rep* 1979, **63**, 1885–1888.
9. Kajanti M, Rissanen P, Virkkunen P, Fransilla R, Mantyla M. Regional intraarterial infusion of cisplatin in primary hepatocellular carcinoma. *Cancer* 1986, **58**, 2386–2388.
10. Shephard FA, Evans WK, Blackstein ME, *et al.* Hepatic arterial infusion of mitoxantrone in the treatment of primary hepatocellular carcinoma. *J Clin Oncol* 1987, **5**, 635–640.
11. Patt YZ, Charnsangavey C, Yoffe B, *et al.* Hepatic arterial infusion of floxuridine, leucovorin, doxorubicin, and cisplatin for hepatocellular carcinoma: effects of hepatitis B and C viral infection on drug toxicity and patient survival. *J Clin Oncol* 1994, **12**, 1204–1211.
12. Shibata J, Fujiyama S, Sato T, Kdrumoto S, Fukushima S. Hepatic arterial injfection chemotherapy with cisplatin suspended in an oily lymphographic agent for hepatocellular carcinoma. *Cancer* 1989, **64**, 1586–1594.
13. Takayasu K, Shima Y, Muratnatsu Y. Hepatocellular carcinoma: treatment with intra-arterial iodized oil with and without a chemotherapeutic agent. *Radiology* 1991, **62**, 345–351.
14. Johnson PJ, Kaayci C, Dobbs N. Pharmacokinetics and toxicity of intraarterial adriamycin for hepatocellular carcinoma: effect of coadministration of lipiodol. *J Hepatol* 1991, **13**, 120–127.
15. Patt YZ, Chuang VP, Wallace S. Hepatic arterial chemotherapy and occlusion for palliation of primary hepatocellular and unknown primary neoplasm in the liver. *Cancer* 1983, **51**, 1359–1363.
16. Patt YZ, Charnsangavej C, Boddie A. Treatment of hepatocellular carcinoma with hepatic arterial floxuridine, doxorubicin, and mitomycin C (Fudram) with or without hepatic arterial embolization: factors associated with longer survival. *Res Cancer Treat* 1989, **2**, 98–104.
17. Kalayci C, Johnson PJ, Raby N. Intraarterial adriamycin and lipiodol for inoperable hepatocellular carcinoma: a comparison with intravenous adriamycin. *J Hepatol* 1990, **11**, 349–353.
18. Kanematsu T, Furuta T, Takenata K, Inokuchi K, Tamura J. A 5-year experience of lipiodolization: selective regional chemotherapy for 200 patients with hepatocellular carcinoma. *Hepatology* 1989, **10**, 89–102.
19. Kasugai H, Kojima J, Tatsuta M, *et al.* Treatment of hepatocellular carcinoma by transcatheter arterial embolization combined with intraarterial infusion of a mixture of cisplatin and ethiodized oil. *Gastroenterology* 1989, **97**, 965–971.
20. Groupe d'etude et de Traitement du carcinoma hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995, **332**, 1256–1261.
21. Colleoni M, Gaion F, Liessi G, Mastrapasqua G, Manente P. Arterial chemoembolization with epirubicin in unresectable hepatocellular carcinoma in cirrhosis. *Oncol Reports* 1994, **1**, 1171–1175.
22. Pelletier G, Roche A, Ink O. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990, **77**, 181–184.
23. Sasaki Y, Imaoka S, Kasugi M, Fusita M, Kawamoto S, Ishiguro S. A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin and gelatinum sponge. *Cancer* 1987, **60**, 1194–1203.
24. Stuart K, Stokes K, Jenkins R, Trey C, Clouse M. Treatment of HCC using doxorubicin/lipiodol/gelfoam. *Cancer* 1993, **72**, 320–329.
25. Vennok AP, Stagg RJ, Lewis BJ, *et al.* Chemoembolization for hepatocellular carcinoma. *J Clin Oncol* 1990, **8**, 1108–1114.
26. Audisio RA, Doci R, Mazzaferro V, *et al.* Hepatic arterial embolization with microencapsulated mitomycin C for unresectable hepatocellular carcinoma in cirrhosis. *Cancer* 1990, **66**, 228–236.
27. Beppu T, Ohara C, Yamaguchu Y, Schihara T, Yamanaka T, Katafuchi S. A new approach to chemoembolization for unresectable HCC using aclarubicin microspheres in combination with cisplatin suspended in iodized oil. *Cancer* 1991, **68**, 2555–2560.
28. Levin B, Amos C. Therapy of unresectable hepatocellular carcinoma. *N Engl J Med* 1995, **332**, 1294–1296.
29. Colleoni M, Buzzoni R, Bajetta E, *et al.* A phase II study of mitoxantrone and beta interferon in unresectable hepatocellular carcinoma. *Cancer* 1993, **72**, 3196–3201.
30. Petors GJ, van Groeningen CJ. Clinical relevance of biochemical modulation of 5-fluorouracil. *Ann Oncol* 1991, **2**, 469–472.
31. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chron Dis* 1961, **20**, 346–353.
32. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
33. Yamashita T, Takahashi M, Koga Y. Prognostic factors in the treatment of HCC with TAE and arterial infusion. *Cancer* 1991, **67**, 385–391.
34. Patt Y, Yoffe B, Charnsangavej C, *et al.* Low serum alpha-fetoprotein levels in patients with hepatocellular carcinoma as a predictor of response to 5-FU and interferon-alpha-2b. *Cancer* 1993, **72**, 2574–2582.