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Randomised controlled trial of lipiodol transarterial chemoembolisation with or without amiodarone for unresectable hepatocellular carcinoma

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ABSTRACT

Background: There is no consensus about the most effective method for transarterial chemoembolisation of hepatocellular carcinoma.
Aim: The aim of this phase II trial was to compare the efficacy and toxicity of lipiodol transarterial chemoembolisation with amiodarone in association with pirarubicin or doxorubicin versus lipiodol transarterial chemoembolisation with anthracycline alone in a control group.
Methods: Patients with unresectable hepatocellular carcinoma and Child-Pugh A/B7 were considered eligible for the trial. transarterial chemoembolisation was repeated every 6 weeks for a maximum of 4 sessions.
Results: Thirteen patients were randomised in the amiodarone group, and 14 were randomised in the control group. The two groups were comparable with respect to their baseline characteristics. The objective response rate according to the EASL criteria was 62% (95% CI 35–88) in the amiodarone group and 50% (95% CI 24–76) in the control group. At 1 and 2 years, survival rates were 77% (95% CI 44–92) and 52% (95% CI 22–75) in the amiodarone group, and 57% (95% CI 28–78) and 40% (95% CI 15–65) in the control group, respectively. There was no difference between the two groups in terms of toxicity.
Conclusions: The results of this study suggest that lipiodol transarterial chemoembolisation with anthracycline and amiodarone was safe but did not increase survival compared with lipiodol transarterial chemoembolisation with anthracycline alone in patients with hepatocellular carcinoma.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-related death worldwide [1,2]. At diagnosis, only 30% of patients can receive potentially curative treatments such as liver transplantation, resection, or percutaneous ablation [3]. For unresectable intermediate-stage HCC (Child-Pugh A/B, large or multifocal HCC, no vascular invasion or extrahepatic spread), the current standard treatment is transarterial chemoembolisation (TACE) [4]. Two randomised trials and two meta-analyses showed statistically significant survival gains with TACE in patients with unresectable HCC, compared to supportive care or systemic chemotherapy [5–8]. Although TACE has been used worldwide for several years, the procedure varies widely across centres and interventional radiologists, especially regarding anticancer drugs, doses, embolic agents, methods of delivery, and schedules [9]. Overall survival at 3 years remains low (<30%) [8], and there is no consensus about the optimal treatment regimen [9]. There is therefore a need for TACE regimens that improve responses and survival.

Resistance to anticancer drugs in HCC is, like in other malignancies, partly related to multidrug resistance (MDR) [10–12], an intrinsic or acquired cross-resistance to a variety of structurally

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and functionally unrelated drugs [13]. MDR might be caused by an increased ATP-dependent efflux of drugs from within to outside the cells, mediated by MDR proteins such as *P*-glycoprotein (PgP) and multidrug resistance-associated protein 1 (MRP1). Amiodarone, a relatively non-toxic antiarrhythmic drug, is able to inhibit this efflux, and thus restores the sensitivity of MDR cancer cells to anthracyclines [14]. Moreover, the intravenous (i.v.) form of amiodarone contains an excipient (polysorbate 80) which enhances emulsion stability for TACE. When mixed with lipiodol and an aqueous solution of anthracycline (doxorubicin or pirarubicin), i.v. amiodarone increases the stability of the emulsion at 37 °C from <1 h to 4 weeks [15]. It was assumed that a longer emulsion stability would be an advantage as the anticancer drug would be released into the tumour-rich microvascular bed of HCC more slowly [16].

Thus, we conducted a randomised controlled phase II trial to assess the efficacy and toxicity of lipiodol TACE with or without amiodarone in patients with unresectable HCC.

2. Materials and methods

2.1. Patients

Patients aged ≥18 years with HCC unsuitable for curative treatments (resection or percutaneous ablation) were eligible for the study. Eligibility criteria also included a confirmed diagnosis of HCC according to EASL [17], a WHO PS 0, 1 or 2 and preserved liver function (Child-Pugh class A or B7). Exclusion criteria were portosystemic shunts, hepatofugal blood flow, thrombus within the main portal vein, extrahepatic metastases, concomitant malignancy, renal failure (serum creatinine level ≥150 μmol/l), platelet count $\leq 50 \times 10^9$/l, cardiac ejection fraction ≤50%, allergy to iodine-containing agents, and hyperthyroidism.

All patients provided written informed consent before enrolment. Documented approval from the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale and the Agence Française de Sécurité Sanitaire des Produits de Santé was obtained before the start of the study.

2.2. Study design

This was a bicentre (University Hospital of Dijon and the Georges François Leclerc Anticancer Center, Dijon), prospective, randomised phase II study (Lipioamio 051061). Patients were randomised (1:1) to receive either lipiodol TACE (control group) or lipiodol TACE with amiodarone. Randomisation was performed at the data centre of the Fédération Francophone de Cancérologie Digestive (Dijon, France) without stratification, by drawing consecutively numbered sealed envelopes.

Patients underwent lipiodol TACE according a standard protocol. The femoral artery was punctured using the Seldinger technique and a 5-French sheath was inserted. Coil embolisation of the gastroduodenal artery was sometimes required to prevent inadvertent chemoembolisation of the pancreas and duodenum [18]. The therapeutic emulsion contained 50 mg of pirarubicin diluted in 25 ml of 5% glucose (Theprubicine®, Sanofi Aventis, Paris, France), 20 ml of lipiodol (Lipiodol Ultrafluide®, Guerbet, Roissy, France) and 1 mm gelatine sponge pellets (Curaspon®, Curamedical B.V., Amsterdam, Netherlands). When the patient was randomised into the amiodarone group, 150 mg of i.v. amiodarone (Cordarone® 150 mg/3 ml, Sanofi Aventis) was added to the mixture. A homogeneous emulsion was prepared just before injection by passing the mixture from one 50 ml-syringe to another 10 times via a 3-way tap. Under fluoroscopic guidance, the emulsion was injected into the right or left lobar branches according to the tumour location in 10 min. If the tumour involved both lobes, TACE was performed in each lobe alternately. Patients received ceftriaxone (Rocephine®, Roche, Neuilly, France) for 5 days (1 g per day), starting just before TACE.

Treatment was repeated every 6 weeks with a total number of sessions limited to 4. Patients who achieved a partial response (PR) after 4 sessions were eligible to receive 2 additional TACE sessions. Criteria for stopping therapy included: grade ≥3 adverse event according to NCI-CTC AE version 2.0 (except for reversible infection, haematologic and hepatic toxicity); vascular contraindications; disease progression; downstaging for resection; or if the patient so requested.

After inclusion of the first 4 patients, production of pirarubicin was stopped in France. The protocol was modified to replace pirarubicin by doxorubicin (Doxorubicin 2 mg/ml, Teva, Paris, France), at the same dose of 50 mg.

2.3. Assessment of outcome

For both arms, patients were evaluated for tumour response 1-month after each session, and every 4 months thereafter. A complete physical examination, liver function tests, prothrombin activity, serum creatinine level, platelet count, Child Pugh score, electrocardiogram and intercurrent events were performed and the results were recorded. TACE-related AEs were also recorded during the 4 weeks following the procedure. Tumour response was assessed every 4 months through magnetic resonance imaging (MRI) according to the EASL criteria [17]. The definitions of response were complete response (CR): complete disappearance of all known viable tumour (assessed via uptake of contrast in arterial phase of the MRI scan); PR: >50% reduction in viable tumour area of all measurable lesions; progressive disease (PD): >25% increase in the size of one or more measurable lesions or the appearance of new lesions; and stable disease (SD) in all other cases.

We also present tumour response rates according to the modified RECIST criteria [19]; CR: disappearance of any intratumoural arterial enhancement in all target lesions; PR: at least a 30% decrease in the sum of diameters of viable target lesions, taking as the reference the baseline sum of the diameters of target lesions; PD: an increase of at least 20% in the sum of the diameters of viable target lesions, taking as the reference the smallest sum of the diameters of viable target lesions recorded since the treatment started; and SD in all other cases. The objective response (OR) rate was defined as CR plus PR.

2.4. Statistical analysis

The primary endpoint was tumour response. Secondary endpoints included overall survival (OS), progression free survival (PFS) and tolerance.

A two-stage Gehan design was adopted for this study [20], enrolling 14 patients in each group in the initial stage. Treatments would be rejected as insufficiently active if no response was observed in this first stage. If 1, 2, 3, 4 or more responses were observed amongst the 14 patients in each group, 1, 6, 9, or 11 additional patients, respectively, would be enrolled in the second stage. Thus, at least 14 patients and at most 25 patients were required for each group. This design has a less than 5% probability of rejecting a treatment with a true response rate of 20%, and provides an estimate of the response rate with a standard error of approximately 10%. The trial was stopped before reaching its recruitment goal. Recruitment for the trial fell when doxorubicin-eluting microspheres became available and the investigators decided to close the trial for analysis.

All analyses were performed on the intention-to-treat principle, which included all randomised patients. Qualitative and continuous variables are described using frequency, percentage, and mean

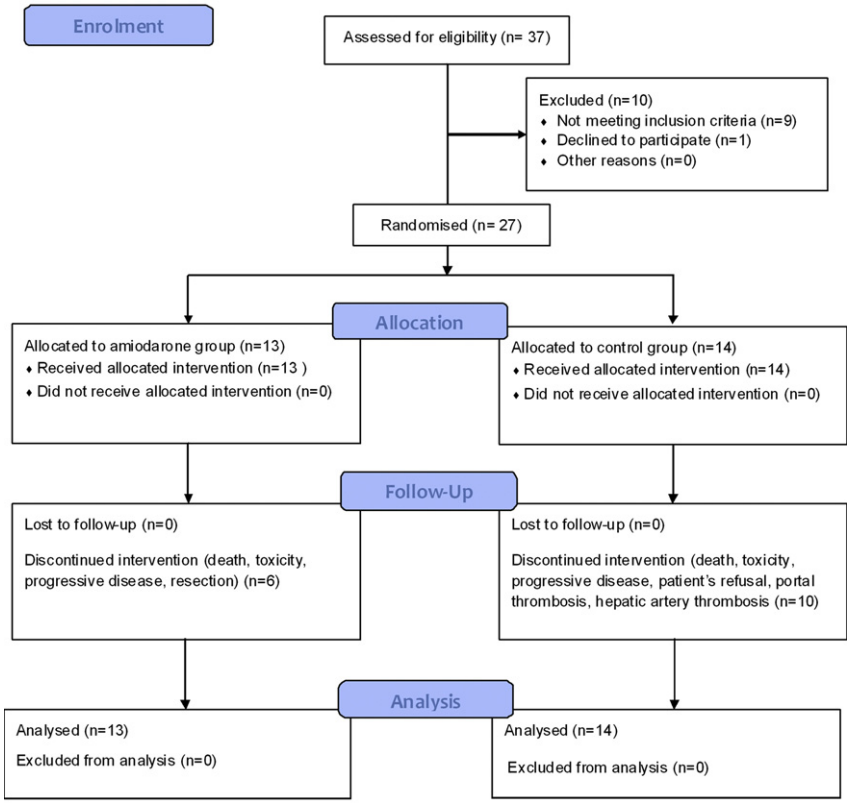

Fig. 1. Flowchart of patients in the Lipioamio study.

(± standard deviation), respectively. The two groups were compared using the Chi2 or Fischer exact test for qualitative variables and the Wilcoxon test for continuous variables.

OS was defined as the time between diagnosis and death (all causes). Surviving patients were censored at the last follow-up. PFS was defined as the time between diagnosis and progression (defined by EASL criteria) or death (all causes). Surviving patients without progression were censored at the last follow-up.

Median follow-up was calculated according to reverse Kaplan Meier estimates. Survival curves were plotted using the Kaplan–Meier method [21] and described using medians with 95% confidence intervals (95% CIs). Data analyses were performed using SAS software 9.1 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

Between August 2006 and March 2009, 13 patients (48%) were assigned to receive TACE with amiodarone and 14 (52%) to receive TACE without amiodarone (Fig. 1).

The median age was 65.8 years (range 43–77 years). Most of the patients were male (85%) and had alcohol-induced cirrhosis (78%). Eight patients (38%) amongst those presenting alcohol-induced cirrhosis were teetotal before treatment. Four patients had received previous curative treatment: surgical resection ($n = 2$), radiofrequency ablation ($n = 1$), and percutaneous ethanol injection ($n = 1$). Median serum α-fetoprotein (AFP) was 13 ng/ml (range 2–17,500 ng/ml). The two groups were well balanced with regard to baseline characteristics (Table 1).

3.2. Chemoembolisation treatment

All patients underwent at least one TACE session. The number of patients who received 2, 3 and 4 TACE sessions was 17 (63%), 14 (52%) and 11 (41%), respectively. The mean number of sessions was 2.6 (range 1–4). Treatment was discontinued before end of the 4 sessions because of severe adverse events (5 patients), PD (5 patients), death (2 patients), decision to resect (1 patient), patient's refusal (1 patient), portal thrombosis (1 patient), and hepatic artery thrombosis (1 patient). Four patients received TACE with pirarubicin (2 in each group), and the 23 other patients received TACE with doxorubicin.

3.3. Response and survival

Tumour response was assessed in 25 patients; one patient in each group had died before the first evaluation. According to the EASL criteria, the best response achieved in patients was as follows: in the amiodarone group, there were 3 (23%) CRs, 5 (38%) PRs, 3 (23%) SDs and 1 (8%) PD; in the control group, there were 1 (7%) CR, 6 (43%) PRs, 3 (21%) SDs and 3 (21%) PDs. The OR rate according to the EASL criteria was 62% (95% CI 35–88) in the amiodarone group and 50% (95% CI 24–76) in the control group. According to the modified RECIST criteria, the best response achieved in patients was as follows: in the amiodarone group, there were 3 (23%) CRs, 6 (46%) PRs, 2 (15%) SDs and 1 (8%) PD; in the control group, there were 1 (7%) CR, 7 (50%) PRs, 2 (14%) SDs and 3 (21%) PDs. The OR rate according to the modified RECIST criteria was 69% (95% CI 39–91) in the amiodarone group and 57% (95% CI 29–82) in the control group.

As of September 2010, after a median follow-up of 31.6 months (95% CI 27.0–35.3), no patients were lost to follow-up and 15 patients had died: 6 in the amiodarone group (46%) and 9 in the control group (64%). Thirteen patients had died from HCC, one from stroke, and one from TACE-related complications. The median OS was not reached (95% CI 18.6–NA months) in the amiodarone group and it was 18.5 months (95% CI 5.3–40.6) in the control group (Fig. 2). At 1 and 2 years, the OS rates were 77% (95% CI 44–92) and 52% (95% CI 22–75) in the amiodarone group, and 57% (95% CI

Table 1
Baseline characteristics of the 27 patients according to TACE group.

Variable	Control group ($n = 14$)		Amiodarone group ($n = 13$)		p-Value
	No.	%	No.	%	
Sex					1.00
Male	12	86	11	85	
Female	2	14	2	15	
Age					0.58
<65 years	5	36	6	46	
≥65 years	9	64	7	54	
Aetiology					0.38
Alcohol	9	64	6	46	
NASH	2	14	2	15	
Alcohol + HVC	0	0	3	23	
Alcohol + NASH	1	7	1	8	
Alcohol + haemochromatosis	1	7	0	0	
Haemochromatosis	1	7	0	0	
Not determined	0	0	1	8	
Previous curative treatment					0.33
No	13	93	10	77	
Yes	1	7	3	23	
WHO PS					1.00
0	11	79	10	77	
1	3	21	3	23	
Child-Pugh class					1.00
A	13	93	12	92	
B7	1	7	1	8	
BCLC classification					0.33
A4	1	7	3	23	
B	13	93	10	77	
CLIP score					0.65
0	2	14	0	0	
1	6	43	5	38	
2	5	36	6	46	
3	1	7	2	15	
Tumour distribution					0.57
Unilateral	6	43	7	54	
Bilateral	8	57	6	46	
Sum of diameters of nodules, mm					0.38
Mean ± SD	88 ± 40	–	112 ± 55	–	
Median	68	–	108	–	
Diameter of largest nodule, mm					0.40
Mean ± SD	59 ± 49	–	59 ± 30	–	
Median	50	–	40	–	
Diameter of largest nodule					0.57
<5 cm	6	43	7	54	
≥5 cm	8	57	6	46	
Diameter of largest nodule					0.38
<7.5 cm	9	64	11	85	
≥7.5 cm	5	36	2	15	
Number of nodules					0.21
<3	6	43	2	15	
≥3	8	57	11	85	
Segmental portal vein thrombosis					1.00
Absent	13	93	12	92	
Present	1	7	1	8	
AFP					0.33
<400 ng/ml	10	71	12	92	
≥400 ng/ml	4	29	1	8	

Abbreviations: NASH: non alcoholic steatohepatitis; HCV: hepatitis C virus; WHO PS: World Health Organization performance status; BCLC: Barcelona clinic liver cancer; CLIP: cancer of the liver italian programme; SD: standard deviation.

28–78) and 40% (95% CI 15–65) in the control group. Median PFS was 17.1 months (95% CI 9.0–30.9) in the amiodarone group and 9.0 months (95% CI 4.1–12.3) in the control group (Fig. 3). At 1 year, the PFS rate was 54% (95% CI 25–76) in the amiodarone group and 29% (95% CI 9–52) in the control group.

3.4. Tolerance

For the 69 TACE sessions performed in the study, there was one treatment-related death (Table 2). A 77 year-old man with Child Pugh B7 class and PS 1 rapidly developed acute liver failure and died 27 days after the 1st TACE session without amiodarone. Five patients, 3 in the amiodarone group, and 2 in the control group experienced toxicity that caused discontinuation of the treatment. These AEs included one case of encephalopathy, one of oedemato-ascitic decompensation, one of ischaemic cholecystitis, one case of colic subocclusion with hypoxia requiring assisted ventilation, and one case of hypoxia with 88% O_2 saturation with an indication for continuous oxygen for 24 h. No grade 4 haematologic toxicity was observed. Except for the 3 patients who developed acute liver failure, encephalopathy and ascites, the elevation of serum total bilirubin, aspartate aminotransferase, alanine aminotransferase and of alkaline phosphatase was mild in both groups. The most commonly clinical TACE-related AEs were fever, abdominal

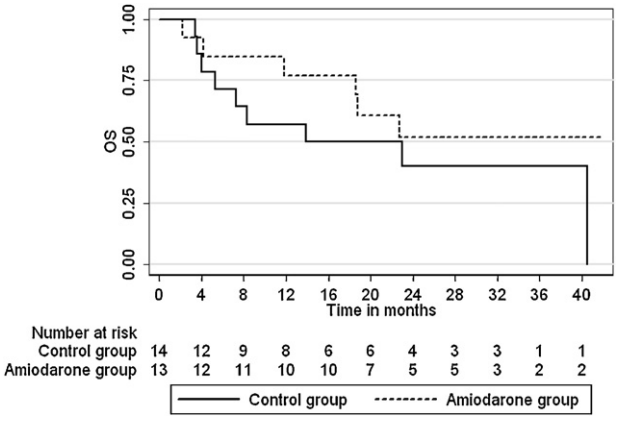

Fig. 2. Kaplan–Meier estimated survival curves by treatment group.

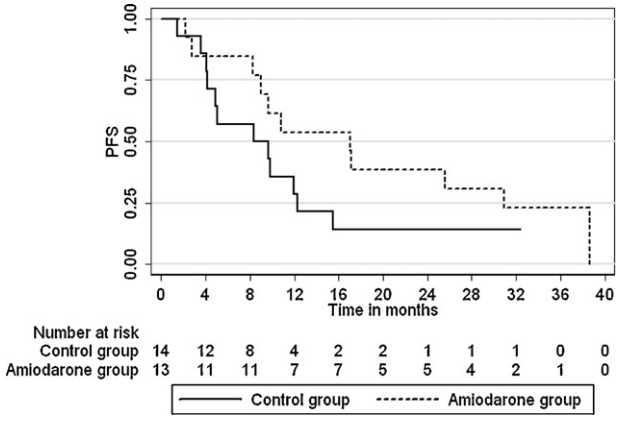

Fig. 3. Kaplan–Meier estimated progression-free survival curves by treatment group.

pain and vomiting; they occurred in 57%, 49%, 19% after TACE with amiodarone, and 59%, 50%, 16% after TACE without amiodarone. One patient treated with amiodarone presented a grade 1 hypotension (intervention not indicated) during TACE. No other cardiac toxicities manifesting as bradycardia were observed in patients treated with amiodarone. Finally, there was no difference between the 2 groups in terms of toxicity.

4. Discussion

Although two recent randomised trials [5,6] and two meta-analyses [7,8] have established that TACE improved survival in patients with unresectable intermediate HCC, there is no consensus about the best chemotherapeutic agent or the most effective method since survival rates amongst studies vary widely [9]. In a previous pilot study of TACE with lipiodol, pirarubicin and amiodarone in 43 patients with unresectable HCC, the authors concluded that this new TACE procedure was safe and with high median OS at 29 months [22]. Interestingly, one patient showed a sustained biological CR (decrease in AFP from 155,000 ng/ml to <8 ng/ml) with a residual tumour mass that persisted for 5 years after treatment [23]. The rationale for the use of amiodarone was based on two points. First, MDR, the classical mechanism of resistance to anticancer drugs, is mainly attributed to the action of two proteins, the 170-kDa Pgp and the 190-kDa MRP1, which pump drugs out of MDR cells [13]. Amiodarone, an antiarrhythmic drug, is also an MDR-modulator [14,24,25] and it was demonstrated that the drug enhanced the *in vitro* cytotoxicity of the two anthracyclines, doxorubicin and pirarubicin in HCC cell lines [15]. This property of amiodarone may be of major importance, as MDR1 and MRP1 genes and their products Pgp and MRP1 are intrinsically expressed by HCC cells [10–12]. Second, a simple emulsion of doxorubicin or pirarubicin in aqueous solution with lipiodol usually separates into two distinct phases within a few minutes [15]. The authors have shown that after the injection of a doxorubicin-lipiodol emulsion for TACE, the majority of the anticancer drug was released into the bloodstream in 5–40 min [26,27], so that only lipiodol remained in the tumour. In contrast, when i.v. amiodarone is mixed with lipiodol and aqueous solutions of doxorubicin or pirarubicin, the emulsions remain stable for up to 4 weeks at 37 °C [15]. This property is due to the presence of polysorbate 80 in the i.v. formulation of amiodarone. Polysorbate 80 is an emulsifier with a high hydrophilic–lipophilic balance (HLB) which enhances the solubility of water-soluble drugs such as anthracyclines in a

Table 2
TACE sessions: adverse events.

	Control group (n = 14)				Amiodarone group (n = 13)			
	Grade 3–4		Grade 1–4		Grade 3–4		Grade 1–4	
	No.	%	No.	%	No.	%	No.	%
Haematological toxicity								
Leukocytes	3	9	12	38	4	11	13	35
Neutrophils	2	6	6	19	3	8	7	19
Haemoglobin	2	6	9	28	3	8	9	24
Platelets	5	16	20	63	7	19	24	65
Non-haematological toxicity								
Total bilirubin	4	13	20	63	5	14	24	65
Aspartate aminotransferase	8	25	30	94	8	22	31	84
Alanine aminotransferase	7	22	29	91	8	22	30	81
Alkaline phophatase	2	6	17	53	3	8	18	49
Encephalopathy	0	0	0	0	1	3	0	0
Ascites	1	3	0	0	0	0	0	0
Cholecystis	1	3	0	0	0	0	0	0
Hypoxia	1	3	0	0	1	3	0	0
Creatinine	0	0	2	6	0	0	2	5
Fever	0	0	19	59	0	0	21	57
Abdominal pain	0	0	16	50	0	0	18	49
Nausea/vomiting	0	0	5	16	0	0	7	19
Fatigue	0	0	4	13	0	0	6	16
Hypotension	0	0	0	0	0	0	1	3

Note: A 77 year-old man rapidly developed acute liver failure and died 27 days after the 1st TACE session without amiodarone.

lipophilic medium. With this stable emulsion, the anticancer drug should diffuse slowly out of the droplets of lipiodol that had selectively remained in the tumour, thus significantly reducing systemic toxicity. This concept lies behind the rationale for the recent development of drug-eluting microspheres for TACE in HCC.

Given the encouraging results of a pilot study [22], we designed this randomised phase II study to evaluate the efficacy of and tolerance to the addition of i.v. amiodarone to an anthracycline-lipiodol emulsion for TACE of HCC. Pirarubicin was first chosen for its higher liposolubility and increased penetration into HCC cells compared with doxorubicin [15]. However, as the production of pirarubicin was stopped in France, the protocol was modified to replace pirarubicin with doxorubicin, the most widely used drug for TACE of HCC [9].

The response rate, 2-year OS and 1-year PFS were 62%, 52%, 54% in the amiodarone group and 50%, 40%, 29% in the control group, respectively. Although the superiority of the addition of amiodarone could not be shown statistically, there was a trend towards better outcomes in all of the criteria for lipiodol TACE with amiodarone compared with lipiodol TACE without amiodarone. It could be argued that the absence of a significant difference in response and survival rates between the two groups may be attributed to the small sample size. However, the 2-year survival rate >50% in the amiodarone group in our study is an encouraging result, as 2-year survival in TACE RCTs rarely exceeds 50% [6,28]. This result is even more interesting given that in half of our patients, the tumour measured >8.5 cm, and that large tumour size is associated with a poor outcome in patients with HCC [5,29,30]. Moreover, a large number of our patients (78%) had alcohol-induced cirrhosis, as was the case in other French TACE RCTs, which reported lower two-year survival rates of 24%, 25%, and 38% in patients in TACE groups [31–33].

One major strength of our study is the absence of cardiovascular toxicity of repeated lipiodol TACE with amiodarone. There were no cases of cardiac failure related to the administration of anthracycline and/or amiodarone, perhaps because we used lower doses than the recommended maximal dose for i.v. use, *i.e.* 550 mg/m^2 for doxorubicin. In our trial, we chose to use a relatively low single dose of 150 mg amiodarone per session for the following reason. It has been demonstrated that a concentration of 700 ng/ml was sufficient to obtain a maximal enhancing effect on anthracycline toxicity on HCC cell lines [15]. After a single 15-min infusion of 2.5 mg/kg of amiodarone in 10 Japanese patients (mean total dose 150 mg), the mean maximum plasma concentration (C(max)) was 7140 ± 1480 ng/ml, which is approximately 10 times higher than that necessary to enhance anthracycline cytotoxicity on HCC cell lines. No significant changes in electrocardiographic parameters, pulse rate or blood pressure in the 77 days following the infusion were observed in the Japanese patients [34]. Moreover, it was recently demonstrated in pigs that amiodarone was sequestered to a great extent by an intravenously administered lipid emulsion in plasma, which completely prevented the decrease in arterial blood pressure caused by amiodarone infusion [35]. Another argument to explain the absence of cardiovascular toxicity in our study is that we injected the amiodarone-containing emulsion slowly, over 10 min, as recommended for amiodarone when infused alone.

TACE is a procedure with a known risk of mortality and morbidity. In a systematic review of 37 TACE trials that included a total of 2858 patients, treatment-related mortality (death within 3 weeks of TACE) was 2.4% (range 0–9.5%) [9]. In the Precision V trial, 14/108 (13%) patients treated in the conventional TACE group (doxorubicin-lipiodol) discontinued the treatment for adverse events [36]. With one patient (3.7%) who died within 30 days after the first TACE session from acute hepatic failure, and with 5/27 patients (19%) who discontinued treatment for adverse events, our data are consistent with the reported toxicity of TACE in the literature.

Our study has two limitations. First, it would have been interesting to measure plasma concentrations of anthracyclines after TACE. These data may have helped us to explain why we did not observe better tolerance in the amiodarone group, even though it was expected, due to stabilisation of the emulsion by amiodarone. Second, we performed lobar TACE in our population of patients, a large majority of whom had multinodular HCCs. As two recent studies have demonstrated that hyperselective TACE was more successful than lobar TACE in achieving complete tumour necrosis [37,38], hyperselective TACE should be performed as often as possible in the future.

In conclusion, our study failed to demonstrate that lipiodol TACE with amiodarone was better than conventional lipiodol TACE. This might be explained by the premature termination of the trial. New formulations of the lipiodol emulsion with amiodarone and anthracycline with faster tumour cell penetration are currently under investigation.

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Conflict of interest statement

None declared.

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