Clinical and Translational Science

ARTICLE OPEN ACCESS

Transarterial Chemoembolization for Patients With Hepatocellular Carcinoma Using Miriplatin Without the Need for Hydration

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Received: 19 December 2024 | **Revised:** 12 February 2025 | **Accepted:** 18 February 2025

Funding: The authors received no specific funding for this work.

Keywords: cisplatin | hydration | propensity score matching

ABSTRACT

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with a rising incidence. The most common therapeutic choice for HCC is transarterial chemoembolization (TACE). While the standard protocol of TACE adopts cisplatin, the application of cisplatin needs hydration before and after the procedure to alleviate adverse effects on kidney function. Miriplatin, a lipophilic platinum complex, enables the omission of periprocedural hydration compared to cisplatin-based TACE. This study aimed to compare the survival benefit between miriplatin-based TACE and cisplatin-based TACE. Briefly, a retrospective cohort study in a single hospital was designed. Patients with HCC complicated by vascular invasion or distant metastasis were excluded. Background variability was adjusted using a propensity score matching; then, overall survival rates were compared using the Gehan-Breslow-Wilcoxon test. As a result, cisplatin and miriplatin were administered to 166 and 120 patients in TACE procedures. After adjusting baseline characteristics using a propensity score including age, sex, tumor burden, functional hepatic reserve, baseline year, and HbA1c, a pair of 99-patient cohorts was generated. Overall survivals did not differ significantly, despite poorer serum creatinine at baseline (0.89 vs. 0.74 mg/dL, $p < 0.0001$) and fewer patients being prepared for TACE through prehydration (18 patients vs. 38 ones, $p = 0.0025$) in the miriplatin group than in the cisplatin group. The median survival time was 1490 days for the miriplatin group and 1,830 days for the cisplatin group ($p = 0.4022$; ratio = 0.814; 95% confidence interval 0.546–1.215). In conclusion, miriplatin will benefit patients with HCC who cannot tolerate perioperative hydration.

1 | Introduction

Transarterial chemoembolization (TACE) is the third choice of therapeutic strategy for patients with hepatocellular carcinoma (HCC), the first two choices being surgical resection and radiofrequency ablation [1, 2].

TACE is divided into ethiodized oil (Lipiodol) TACE and drug-eluting beads TACE [3]. For ethiodized oil TACE, the emulsion of anticancer agent with ethiodized oil is injected into tumor-feeding arterial vessels. The frequently used drugs for this emulsion are epirubicin, cisplatin, and miriplatin in Japan.

Abbreviations: 95% CI, 95% confidence interval; AIH, Autoimmune hepatitis; ALBI score, Albumin bilirubin score; CACAE, Common Terminology Criteria for Adverse Events; DACH, Diaminocyclohexane; DEB-TACE, drug-eluting beads TACE; DPC, diaminocyclohexanedichloroplatinum; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; ICG-R15, Indocyanine green retention rate at 15 min test; IQR, Interquartile range; MELD score, Model for end-stage liver disease score; NASH, Nonalcoholic steatohepatitis; PBC, Primary biliary cholangitis; TACE, Transarterial chemoembolization; TAE, Transcatheter arterial embolization; TAI, Transcatheter arterial infusion.

Summary

- What Is the current knowledge on the topic?
  - Miriplatin is a lipophilic platinum complex developed specifically for application in ethiodized oil-based transarterial chemoembolization (TACE). Patients with hepatocellular carcinoma (HCC) treated using miriplatin are able to omit perioperative hydration to prevent cisplatin-induced kidney injury.
- What question did this study address?
  - Long-term prognosis after treatment with miriplatin-based ethiodized oil TACE has not been adequately established.
- What does this study add to our knowledge?
  - The median survival time of the patients after miriplatin-based TACE was not inferior to the case of cisplatin-based TACE, even after the baseline characteristics were adjusted using propensity score matching.
- How might this change clinical pharmacology or translational science?
  - Miriplatin benefits patients with HCC who cannot tolerate perioperative hydration.

Miriplatin is a lipophilic platinum complex developed specifically for application in ethiodized oil-based TACE [4]. While the short and intermediate terms of prognosis after ethiodized oil TACE for cisplatin and miriplatin have been compared [5–7], the median survival time based on long-term observation after treatment with miriplatin-based ethiodized oil TACE has not been adequately established. The aim of the current study is to compare the median survival time of patients treated with miriplatin-based ethiodized oil TACE with that of patients treated with cisplatin-based TACE.

2 | Methods

2.1 | Ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki [8], the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (https://www.hhs.gov/hipaa/index.html), and was approved by the Institutional Review Board of Kagawa University, Faculty of Medicine (Serial number: 2024-014). Opt-out methods were adopted to guarantee patients or their relatives the opportunity to refuse enrollment in the current study [9].

2.2 | Study Design

This retrospective cohort study was conducted in a single university hospital. Patient death was defined as the primary endpoint. The sample size of the cohort was limited because of clinical practices in a single center. Propensity score matching was performed to control for potential biases in the original cohort [10]. The study was performed according to the STROBE statement [11].

2.3 | Patients

Patients were recruited from two cohorts (Figure S1); one cohort had 426 patients and was based on the previous study cohort [12], who received the indocyanine green retention rate at 15 min before therapeutic intervention for HCC [13]. The other 677-patient cohort was sorted according to angiography between 2010 and 2020 in medical records. Duplication of 269 patients between the two cohorts was eliminated. Excluding patients with distant metastasis or vascular invasion, 286 patients were determined as a study cohort who were administered ethiodized oil TACE using cisplatin or miriplatin; 166 patients for the cisplatin group and 120 for the miriplatin group.

2.4 | Clinical Data

The following clinical data were extracted from the medical records of the participants: age, sex, serum total protein, albumin, AST, ALT, total bilirubin (T-Bil), platelet count, creatinine, prothrombin time (PT), PT-INR, HbA1c, etiology of the liver diseases, ascites, and clinical stage of HCC. HbA1c was assumed to be within normal limits in patients who were not evaluated for HbA1c.

Albumin bilirubin score (ALBI score) was calculated according to its original report: Log 10 T-Bil (μmol/l) × 0.66 + Alb (g/l) × (−0.085) [14]. T-Bil (mg/dl) was converted to T-Bil (μmol/l) according to the equation: T-Bil (mg/dl) × 17.2. Model for end-stage liver disease (MELD) score was derived according to the equation: 9.57 × ln (serum creatinine, mg/dl) + 3.78 × ln (total bilirubin, mg/dl) + 11.20 × ln (PT-INR) + 6.43 [15].

2.5 | Procedure of TACE

TACE was indicated in patients with four or more intrahepatic HCC nodules based on Child A or B cirrhosis according to clinical practice guidelines for hepatocellular carcinoma in Japan [1].

The protocols of ethiodized oil TACE consisted of (1) super selection of each tumor's feeding blood vessel branches in segment or subsegment using microcatheter systems, (2) injection of emulsified cisplatin or miriplatin with ethiodized oil, and (3) embolization of the blood vessel branches by gelatin sponge particles. The choice of cisplatin (Nippon Kayaku, Japan) or miriplatin (Sumitomo Pharma, Japan) was determined through discussion between an attending doctor and a chief operator. Miriplatin was preferred when patients had chronic kidney dysfunction. The glass membrane pumping emulsification device was not employed in the procedures [16].

One of alternative drug in ethiodized oil-based TACE, epirubicin, was basically the first choice in DEB-TACE in our hospital. Cisplatin was preferred to epirubicin based on the past reports showing superior efficacy of cisplatin to epirubicin [17, 18].

2.6 | Hydration Before and After TACE

When cisplatin was adopted for a TACE protocol, hydration was performed before and after TACE administration to prevent acute and chronic nephrotoxicity [19]. Ultimately, at discretion of the doctors-in-charge, the hydration protocol was applied during a perioperative period in accordance with a conventional hydration method [20]. On the day before the TACE procedure, 1 L of extracellular or maintenance fluid was infused for preoperational hydration. In total, 2 L of fluid was infused on the day of operation, followed by 1.5–2 L of fluid infusion on the day after TACE administration. Intravenous magnesium injection, a bolus 20 mEq per patient just before a TACE procedure, was routinely performed from April, 2017 [21].

In the case of a miriplatin-based TACE protocol, prehydration before the day of operation was optional. On the day of the procedure, 1 L of extracellular or maintenance fluid was planned as a standard, followed by 1 L of fluid infusion on the day after TACE.

2.7 | Adverse Events

Adverse events were evaluated using laboratory measures of liver, kidney, and platelet function. The peak values of blood exams within 1 week just after the day of the TACE procedure were referred to, including the maximal values of total bilirubin, AST, ALT, and creatinine, and the minimal values of serum albumin, eGFR, and platelet count. The severity of adverse events was described in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5 available online (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50).

2.8 | Statistical Analyses

Continuous variables are presented as the median and interquartile range and were analyzed using the Mann–Whitney U test or Spearman's rank correlation coefficient. Categorical variables were analyzed using the Mann–Whitney U test, Fisher's exact test, or Chi-squared test. Propensity score matching was performed to match the background variables between the cisplatin and miriplatin groups [10]. Prognosis was compared using the Gehan-Breslow-Wilcoxon because about half of the patients were censored in the current cohort [22, 23]. Based on the nature of a university hospital, patients were transferred to community hospitals for palliative care when treatment was no longer indicated. JMP Pro 15 software (SAS Institute Inc., Cary, NC) was adopted to calculate the propensity score. Statistical significance was set at $p < 0.05$.

3 | Results

3.1 | Baseline Characteristics of Patients

The characteristics of two cohorts were significantly different in the baseline year when TACE was performed. Serum ALT, serum creatinine, estimated glomerular filtration rate (eGFR), MELD score, and observation period were significant ($p < 0.05$, Table 1). Ascites were identified in six and two patients in the two cohorts ($p = 0.3006$).

3.2 | Gehan-Breslow-Wilcoxon Test for Overall Survival

The overall survival of the miriplatin group was significantly lower than that of the cisplatin group (p value = 0.0443), as shown in Figure 1. The median survival time was 1,348 days for the miriplatin group, which had a poorer tendency than that for the cisplatin group, 1,796 days (ratio = 0.751 with 95% CI 0.542–1.039).

3.3 | Generating Two Matched Cohorts

To subtract confounding factors at baseline, the propensity score was calculated based on age, sex, maximum tumor diameter, number of tumor nodules, serum albumin, total bilirubin, baseline year, ascites, AFP, HbA1c, and PT-INR. As a result, two 99-patient cohorts were generated, as shown in Table 2. The statistical differences between tumor factors (maximum diameter and number) and functional hepatic reserve (Child Pugh classification, ALBI grade and MELD score) were adjusted between the pair of cohorts. Serum creatinine was significantly higher in the miriplatin group.

3.4 | Prehydration in the Matched-Pair Cohort

Prehydration was more frequently prepared in the cisplatin group compared to the miriplatin one on the day before TACE (38 vs. 18 patients, $p < 0.05$) as shown in Table 2. Volume load per patient was also greater in the cisplatin group compared to the miriplatin group ($p < 0.05$). Kidney dysfunction at baseline was significantly better in the cisplatin group compared to the miriplatin one, as measured by both serum creatinine (0.77 vs. 1.09 mg/dL, $p < 0.05$) and eGFR (72.3 vs. 48.8, $p < 0.05$).

In the case of prehydration on the day of TACE, case number and volume load per patient were also higher in the cisplatin group than in the miriplatin group ($p < 0.05$).

3.5 | Gehan-Breslow-Wilcoxon Test for Overall Survival in the Two Matched Cohorts

The overall survival of the miriplatin group was not lower than that of the cisplatin group ($p = 0.4022$), as shown in Figure 2. The median survival time was 1,830 days for the cisplatin group and 1,490 days for the miriplatin group (ratio = 0.814 with 95% CI 0.546 to 1.215).

3.6 | Adverse Events

Alteration in blood examination data from baseline values were evaluated using the peak values within 1 week subsequent to the day of TACE performance. As shown in Figure 3, the increase

TABLE 1 | Baseline characteristics of patients.

Baseline characteristics	Cisplatin	Miriplatin	*p*
Total cohort	166	120	—
Baseline year (A.D.)	2014 (2011–2017)	2015 (2013–2017)	0.0005
Age	73 (65–78)	75 (67–80)	0.1497
Sex (male/female)	118/48	86/34	1.0000
Total protein (g/dL)	7.3 (6.9– 7.7)	7.3 (6.9–7.9)	0.5036
Albumin (g/dL)	3.8 (3.5–4.2)	3.7 (3.3–4.2)	0.1804
Total bilirubin (mg/dL)	0.8 (0.6–1.2)	0.8 (0.6–1.2)	0.3581
AST (U/L)	40 (29–61)	38 (28–53)	0.3624
ALT (U/L)	34 (20–47)	26 (16–39)	0.0137
γGTP (U/L)	50 (27–91)	50 (29–97)	0.6791
PT (%)	83 (73–93)	83 (71–97)	0.9417
PT-INR	1.10 (1.04–1.19)	1.11 (1.02–1.21)	0.8048
Cr (mg/dL)	0.72 (0.62–0.84)	0.89 (0.70–1.14)	< 0.0001
eGFR	75.4 (64.3–87.2)	60.9 (46.6–74.2)	< 0.0001
Platelet count ($\times 10^4/\mu L$)	11.1 (8.6–15.5)	11.4 (8.1–16.1)	0.9215
HbA1c (%) (< 7/7 ≤)	141/25	100/20	0.7348
Child Turcott Pugh score	5 (5–6)	6 (5–6)	0.1192
Child Turcott Pugh classification (A/B/C)	145/21/0	94/24/2	—
ALBI score	−2.517 (−2.816 to −2.180)	−2.474 (−2.819 to −2.019)	0.3359
MELD score	8 (7–10)	9 (7–13)	0.0025
Maximum tumor diameter (mm)	21 (14–30)	22 (14–28)	0.8738
Tumor number (1/2/3/4 or more)	57/39/18/52	34/27/19/40	0.5228
Alpha-fetoprotein (ng/mL)	11.0 (5.0–57.3)	10.0 (5.0–72.8)	0.7701
Ascites (none/exists)	160/6	118/2	0.3242
Etiology (HCV/HBV/ETOH/NASH/PBC, AIH or unknown)	88/26/26/21/5	63/14/22/17/4	0.8718
Observation period (days)	1079 (630–2022)	750 (357–1453)	0.0010
Death/Censored	90/76	61/59	0.6315

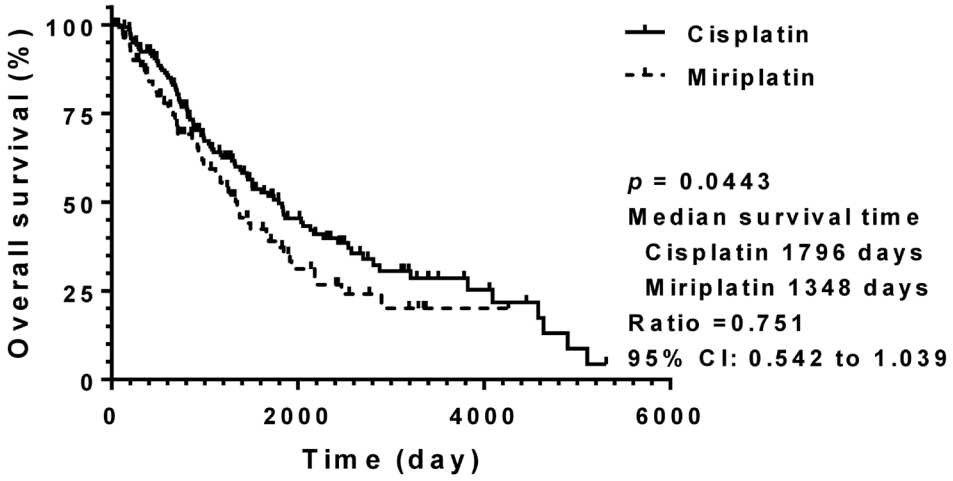
Note: Data are presented as case number or a median with interquartile range. $p < 0.05$ was considered statistically significant.
Abbreviations: AIH, Autoimmune hepatitis; ALBI score, albumin bilirubin score; HBV, Hepatitis B virus; HCV, Hepatitis C virus; MELD score, Model for end-stage liver disease score; NASH, Nonalcoholic steatohepatitis; PBC, Primary biliary cholangitis.

in serum creatinine and decrease in eGFR following the TACE procedure were not significantly different between the two groups ($p > 0.05$). The increase in AST and ALT from baseline was significantly smaller in the miriplatin group compared to the cisplatin group ($p < 0.05$). Changes in serum albumin, total bilirubin, and platelet count were not significantly different between the two groups ($p > 0.05$).

CTCAE grade indicated that severe kidney injuries were more frequently observed in the miriplatin group compared to the cisplatin group ($p < 0.05$), as shown in Table 3. That might be attributed to the fact that CTCAE grade does not consider significantly severe kidney dysfunction at baseline in the miriplatin group compared to the cisplatin group.

3.7 | Unmatched Patients Treated with Miriplatin-Based Ethiodized oil TACE

Among the 120 patients treated using miriplatin-based ethiodized oil TACE, 21 were unmatched in the propensity score matched analysis. Comparative analysis of the 99 matched patients and 21 unmatched patients revealed that the unmatched patients were characterized by significantly poorer ALBI



	0	1000	2000	3000	4000	5000
Cisplatin	166	87	43	19	9	3
Miriplatin	120	49	16	6	2	1

FIGURE 1 | A crude analysis of median survival times. The overall survival rate of miriplatin group was poorer than that of cisplatin group ($p = 0.0443$); the median survival time was 1348 days for the miriplatin group vs. 1,796 days for cisplatin one (ratio = 0.751 with 95% CI 0.542–1.039). MST, median survival time; 95% CI, 95% confidence interval.

grade ($p = 0.0331$) and Child Pugh classification ($p = 0.0468$), as shown in Table 2. Tumor number and AFP were also relatively high in the miriplatin-treated group ($p < 0.05$). Serum creatinine and eGFR did not significantly differ between the two cohorts ($p > 0.05$). The median survival time was significantly shorter in the unmatched cohort compared to that in the matched cohort ($p = 0.0069$; ratio = 0.4577 with 95% CI 0.244–0.861), as shown in Figure 4.

4 | Discussion

The aim of this study was to determine the overall survival of patients with HCC after ethiodized oil TACE treatment using miriplatin, compared to that of patients treated with cisplatin. The data revealed that the overall survival of the miriplatin group equaled that of the cisplatin group despite significantly poorer serum creatinine levels at baseline in the miriplatin group. Furthermore, perioperative changes in kidney function were not severe in the miriplatin group compared to the cisplatin group in spite of fewer patients being prepared for TACE through prehydration.

Miriplatin was developed based on the histological characteristics of hepatocellular carcinoma and customized for conventional TACE [24]. Whereas the blood supply to normal liver tissue is approximately 75% from the portal vein and 25% from the hepatic artery, the blood supply to hepatocellular carcinoma tissue is almost 100% from the hepatic artery [25]. When an oily contrast agent, iodinated poppy oil fatty acid ethyl ester, is administered into the hepatic artery supplying blood to the tumor, the oily contrast agent selectively migrates to the tumor site [26]. If the anticancer drug is dissolved or suspended in a suspension and then gradually released from the suspension lodged in the tumor, the anticancer drug is believed to kill the tumor tissue.

Cisplatin has been reported to show good antitumor effects in hepatocellular carcinoma and hepatic arterial embolization [27]. However, because cisplatin is water-soluble (1.43 mg/mL in saline), the physical stability of the cisplatin suspension is not always excellent [28, 29].

Miriplatin is a lipid-soluble platinum complex with diaminocyclohexane (DACH) as the carrier ligand and myristic acid as the leaving group, as shown in Figure S2A [30]. Miriplatin is virtually insoluble in water (< 0.00260 mg/mL) and no acid–base dissociation constant information is available [31]. In general, platinum-based anticancer drugs with the DACH skeleton as the carrier ligand are effective when DACH-Pt(II) forms a platinum-DNA adduct. The platinum-DNA adduct induces apoptosis, which is an important mechanism of cell death induced by platinum-based anticancer drugs [32].

The active form of miriplatin is 1,2-diaminocyclohexanedichloroplatinum (II) (DPC), which is formed as a result of the substitution of myristic acid with chloride ions (Figure S2B) [30]. DPC is identical to the active form of oxaliplatin (Figure S2C) [33]. The conversion of miriplatin to DPC, like the conversion of oxaliplatin to DPC, is understood as biotransformation based on a nucleophilic substitution not mediated by enzymes [34].

The antitumor activity was compared using an in vitro assay, and the IC50 of miriplatin/ethiodized oil suspension (1.3 μg/mL) was lower compared to that of Cisplatin/ethiodized oil suspension (2.5 μg/mL) in HepG2 cells, a human hepatoma cell line

TABLE 2 | Propensity score-matched cohorts.

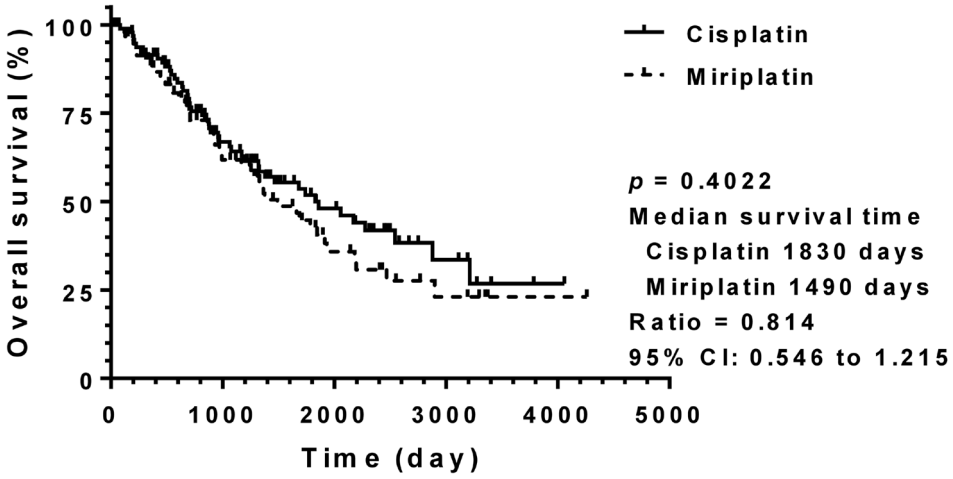
	Cisplatin group in the matched cohort	Miriplatin group in the matched cohort	*p* (cisplatin vs. miriplatin)	Miriplatin group in the unmatched cohort	*p* (matched vs. unmatched in miriplatin)
Baseline characteristics					
Total cohort	99	99	—	21	—
Baseline year (A.D.)[a]	2016 (2014–2018)	2015 (2013–2017)	0.1739	2014 (2013–2016)	0.2141
Age[a]	73 (66–79)	74 (67–81)	0.5913	77 (68–80)	0.5793
Sex (male/female)[a]	75/24	72/27	0.7454	14/7	0.5995
Total protein (g/dL)	7.3 (7.0–7.7)	7.3 (6.9–7.8)	0.8278	7.8 (6.6–8.1)	0.1748
Albumin (g/dL)[a]	4.0 (3.6–4.2)	3.9 (3.4–4.2)	0.1330	3.5 (3.0–4.0)	0.0250
Total bilirubin (mg/dL)[a]	0.8 (0.6–1.1)	0.8 (0.6–1.2)	0.5457	0.9 (0.7–1.4)	0.6135
AST (U/L)	37 (27–53)	38 (28–52)	0.8377	44 (28–70)	0.3895
ALT (U/L)	28 (18–41)	26 (16–39)	0.3836	23 (17–46)	0.9276
γGTP (U/L)	44 (26–90)	54 (29–104)	0.3683	41 (29–66)	0.4657
PT (%)	83 (72–94)	84 (70–98)	0.7415	75 (72–91)	0.3048
PT-INR[a]	1.09 (1.03–1.18)	1.09 (1.01–1.21)	0.8541	1.17 (1.05–1.20)	0.2359
Cr (mg/dL)	0.74 (0.61–0.87)	0.89 (0.72–1.14)	< 0.0001	0.83 (0.67–1.09)	0.4128
eGFR	74.6 (62.6–87.1)	60.4 (46.5–75.0)	< 0.0001	61.9 (44.9–73.2)	0.7826
Platelet count ($\times 10^4/\mu L$)	11.0 (9.0–14.8)	11.8 (8.1–16.5)	0.8146	9.7 (8.0–13.0)	0.2060
HbA1c (%) (< 7/7 ≤)[a]	80/19	82/17	0.8540	18/3	1.0000
Child Turcott Pugh score	5 (5–6)	5 (5–6)	0.1006	6 (5–7)	0.1099
Child Turcott Pugh classification (A/B/C)	86/13/0	80/17/2	0.2528	14/7/0	0.0468
ALBI score	−2.615 (−2.868 to −2.277)	−2.509 (−2.868 to −2.164)	0.1922	−2.275 (−2.608 to −1.676)	0.0331
MELD score	8 (7–11)	9 (7–12)	0.0093	10 (8–14)	0.4297
Maximum tumor diameter (mm)[a]	22 (15–30)	21 (14–28)	0.5624	23 (15–32)	0.5582
Tumor number (1/2/3/4 or more)[a]	38/20/11/30	32/26/12/29	0.7156	2/1/7/11	0.0024
Alpha-fetoprotein (ng/mL)[a]	10.0 (4.0–47.0)	8.0 (4.0–39.0)	0.8646	72.0 (11.5–1071)	0.0003

(Continues)

TABLE 2 | (Continued)

	Cisplatin group in the matched cohort	Miriplatin group in the matched cohort	*p* (cisplatin vs. miriplatin)	Miriplatin group in the unmatched cohort	*p* (matched vs. unmatched in miriplatin)
Ascites (none/exists)[a]	98/1	97/2	1.0000	21/0	1.0000
Etiology (HCV/HBV/ETOH/NASH/PBC, AIH or unknown)	50/15/20/10/4	52/14/19/11/3	0.9905	11/0/3/6/1	0.1317
Patients with prehydration on the day before TACE	38	18	0.0025	—	—
Volume (500/1000/1500/2000 mL)	2/35/0/1	8/9/0/1	0.0011	—	—
Cr (mg/dL) at baseline	0.77 (0.60–0.94)	1.09 (0.97–1.25)	< 0.0001	—	—
eGFR in patients at baseline	72.3 (61.8–88.7)	48.8 (39.3–54.9)	< 0.0001	—	—
Patients with prehydration on the day of TACE	32	17	0.0206	—	—
Volume (500/1000/1500/2000 mL)	3/26/3/0	7/10/0/0	0.0197	—	—
Follow up					
Observation period (days)	1063 (572–2017)	921 (383–1663)	0.1391	401 (136–828)	0.0021
Death/Censored	52/47	50/49	0.8870	9/12	0.6329

Note: Data are presented as case number or a median with interquartile range. $p < 0.05$ was considered statistically significant.
Abbreviations: ALBI score, albumin bilirubin score; MELD score, Model for end-stage liver disease score; HCV, Hepatitis C virus; HBV, Hepatitis B virus; AIH, Autoimmune hepatitis; NASH, Nonalcoholic steatohepatitis; PBC, Primary biliary cholangitis; TACE, transarterial chemoembolization.
[a]Variables were adjusted using a propensity score-matched analysis.



	0	1000	2000	3000	4000
Cisplatin	99	51	26	8	2
Miriplatin	99	45	16	6	2

FIGURE 2 | An adjusted analysis of median survival times using a propensity score matching. Two 99-patient cohorts were generated after adjusting baseline year (A.D.), age, sex, serum albumin, total bilirubin, PT-INR, ascites, the maximum tumor diameter, tumor number, serum AFP, HbA1c. The overall survival of the miriplatin group was not significantly different from that of cisplatin group ($p = 0.4022$); the median survival time was 1,490 days for the miriplatin group and 1,830 days for cisplatin one (ratio = 0.814 with 95% CI 0.546 to 1.215). MST, median survival time; 95% CI, 95% confidence interval.

[35]. In another experiment using a rabbit liver tumor model, the antitumor effect of arterial infused miriplatin/ethiodized oil suspension was comparable to that of cisplatin/ethiodized oil suspension [36]. Because miriplatin is not designed as an oral drug, its membrane permeability is not evaluated with regard to the Biopharmaceutics Classification System waiver [37].

Miriplatin was released very slowly into the systemic circulation from ethiodized oil, resulting in very low levels of platinum compounds in plasma and other organs. The Cmax of miriplatin was around 10 ng/mL [24, 38], which is 1/100 to 1/500 lower than that of cisplatin [27]. Therefore, for a lower incidence of adverse events, the choice of miriplatin was expected [6].

The therapeutic efficacy of ethiodized oil TACE using miriplatin has been reported using a randomized controlled trial in the past study [39]. In the past study, a pair of 49 patient cohorts was observed for up to 1000 days, concluding that the 2-year survival rate was equal between the miriplatin and cisplatin groups. Another study reported the overall survival rate of 26 patients with HCC treated using miriplatin; however, the study did not yield the median survival time, partly because of the small sample size [5] or a relatively short observation period [39]. In the current study, the median survival time was determined at 1,365 days for a pair of 99-patient cohorts based on a 5,000-day observation, comparable to that of the cisplatin group.

Although the past study canceled selection biases using baseline randomization [39], the current retrospective study adjusted the background variability using a propensity score matched analysis. With regard to variable selection in propensity score matching, functional hepatic reserve was adjusted using serum albumin, total bilirubin, PT-INR, and ascites, instead of Child-Pugh classification or ALBI grade. Controversies for Child Pugh classification lie in that (1) it has not been established based on a statistical method, and (2) the classification is a mixture of objective (ascites, hepatic coma) and semiquantitative factors [40]. The ALBI grade is limited because it does not incorporate ascites into the equation. Tumor burden was matched using the maximum tumor diameter, tumor number, and AFP, instead of TNM staging systems because the current cohort excluded patients with lymph node metastasis or distant metastasis [1, 41].

In addition, patients were included in a 10 year period (2010–2020). Due to advances in procedures the time of inclusion could have changed the outcome. Including year (A.D.) at TACE procedure as a variable in propensity score matching, we controlled two biases; one is any changes in therapeutic strategy caused by development of multikinase inhibitors and immune check point inhibitors, and the second is proficiency of TACE operators.

Because doctors in charge tended to choose miriplatin for patients with lower eGFR and higher serum creatinine, renal function at baseline was significantly worse in patients treated by miriplatin-based TACE than in those treated using cisplatin-based TACE. Prehydration was less frequently performed in the miriplatin group than in the cisplatin one. However, the magnitude of additional kidney injuries caused by arterially infused anticancer agents was not statistically different between cisplatin and miriplatin. The median survival time was identical in the two patient groups, suggesting that patients will be able to omit preprocedural hydration for cisplatin by alternatively

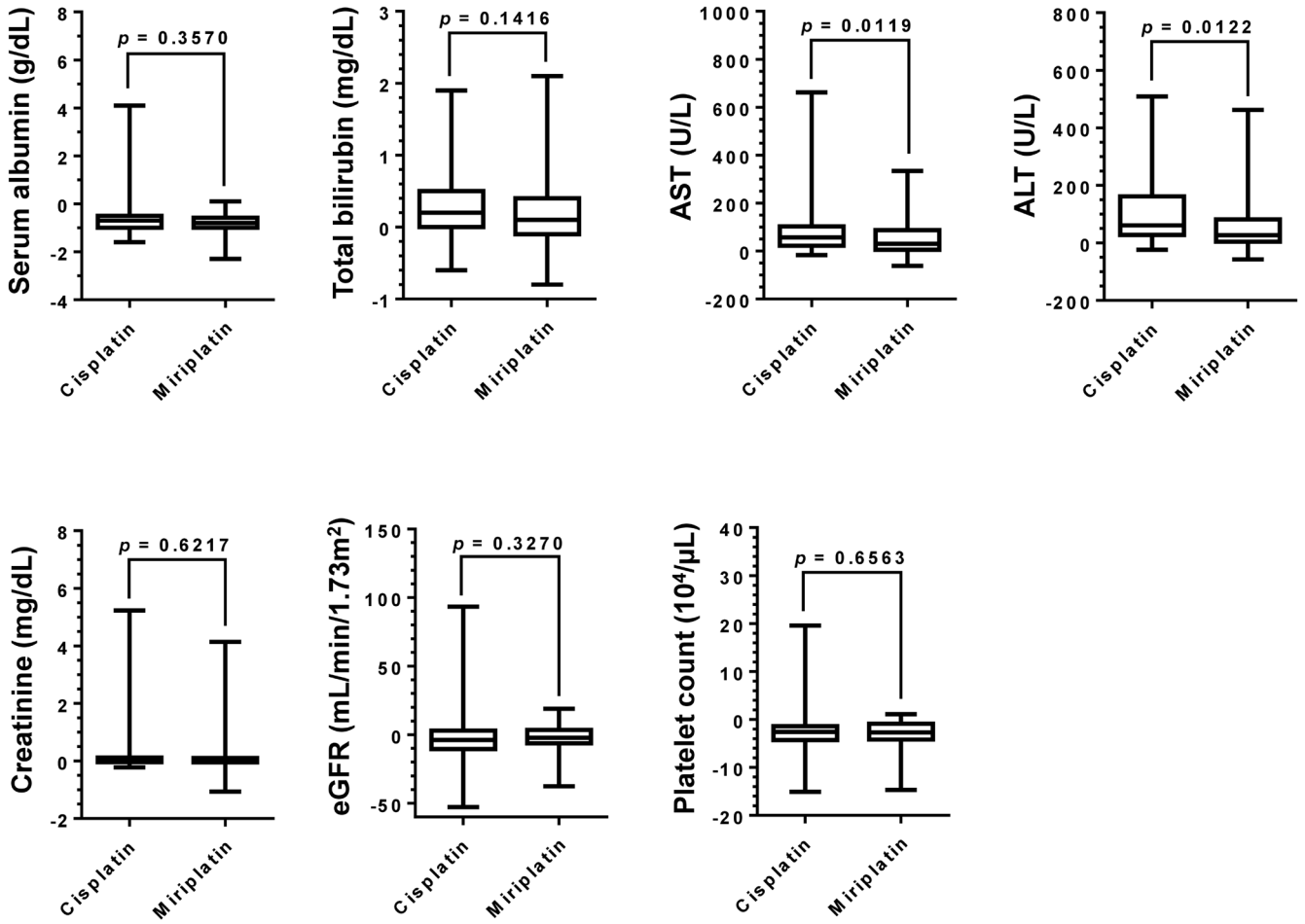


FIGURE 3 | Changes in blood examination data before and after TACE procedure in the matched pair of cohorts. The peak values of blood exams were collected within one week just after the day of TACE procedure. The maximal values were picked up for total bilirubin, AST, ALT, and creatinine; and the minimal values for serum albumin, eGFR, and platelet count. The change in each data was calculated based on the corresponding value at baseline, and compared between the matched pair of cohorts. Alteration in AST and ALT was smaller in miriplatin group compared to cisplatin group ($p < 0.05$). No significant difference was observed in increase in serum albumin or total bilirubin as indicators of functional hepatic reserve, in changes in serum creatinine and eGFR as biomarkers of kidney function including, or in decrease in platelet count as an index of bone marrow function ($p > 0.05$). TACE: Transarterial chemoembolization.

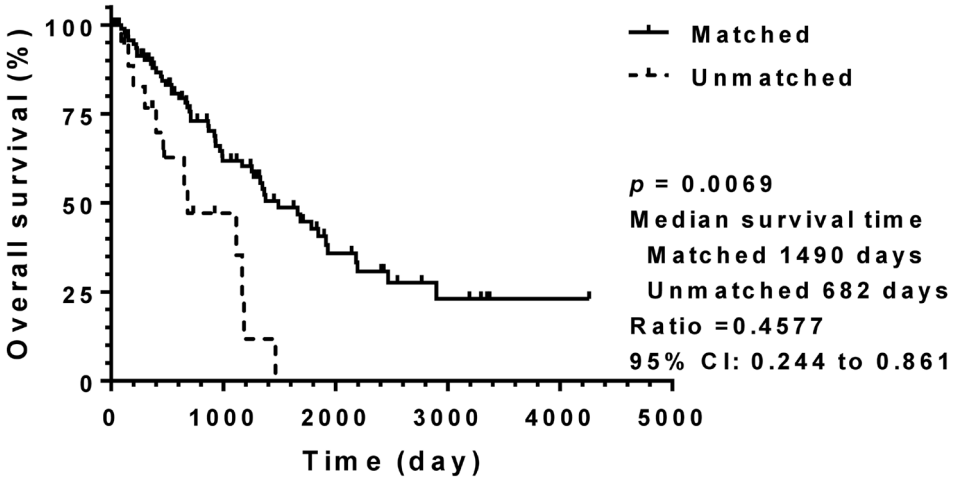
TABLE 3 | Severity of adverse events.

	Cisplatin	Miriplatin	*P*- value
Hypoalbuminemia (None/Grade 1/2/3/4)	3/67/29/0/0	3/51/44/1/0	0.1000
Hyperbilirubinemia (None/Grade 1/2/3/4)	81/16/2/0/0	81/14/4/0/0	0.6703
AST increase (None/Grade 1/2/3/4)	19/47/20/12/1	41/31/18/9/0	0.0119
ALT increase (None/Grade 1/2/3/4)	23/42/14/20/0	45/30/9/15/0	0.0122
Creatinine increase (None/Grade 1/2/3/4)	89/8/1/0/1	60/29/7/0/3	<0.0001
eGFR decrease (None/Grade 1/2/3/4)	53/19/25/1/1	27/20/44/5/3	0.0016
Thrombocytopenia (None/Grade 1/2/3/4)	9/44/36/10/0	13/49/23/11/3	0.1408

Note: Data are presented as case number. Chi-square test was adopted in each calculation. $P < 0.05$ was considered statistically significant.

selecting miriplatin, although it should be noted that less than half of the patients received prehydration. Based on the comparison of prognosis between the matched and unmatched patients, functional hepatic reserve and tumor burden should be considered negative prognostic factors in TACE using miriplatin.

Currently, periprocedural hydration for TACE might involve two questions. The first is that a standard protocol of hydration has not been reported in detail for miriplatin-based TACE. Most clinical studies did not describe specific duration or volume of periprocedural hydration for TACE using miriplatin [5–7, 38,



	0	1000	2000	3000	4000
Matched	99	45	16	6	2
Unmatched	21	5	1	1	1

FIGURE 4 | A median survival of the unmatched patients in miriplatin group in the propensity score matching. In the propensity score matching, 99 patients in miriplatin group were matched with a corresponding one in cisplatin group; the other 21 patients in miriplatin group were not matched in the analysis. The overall survival of the unmatched group was significantly poorer than that of the matched group ($p = 0.0069$); the median survival time of the unmatched 21 patients was 682 days and 1490 days for the matched 99 patients (ratio = 0.4577 with 95% CI 0.244 to 0.861). MST, median survival time; 95% CI, 95% confidence interval.

42–47]. Another clinical trial reported that patients treated with miriplatin-based TACE were not hydrated after the TACE procedure [39] while the report did not mention prehydration.

The second question in periprocedural hydration for TACE lies in that short-hydration methods have the potential to reduce infusion load in patients treated with cisplatin-based chemotherapy [48]. Hydration volume in the short-hydration group ranged from 1.9 to 4.3 L while conventional hydration load resulted in 4.5 to 7.8 L [49]. However, short-hydration protocols have not been established specifically for the TACE procedure, compared to those for the systemic administration of the agent.

This study has the following limitations: (1) the study was designed as a single-center study; (2) the study did not consider progression-free survival or time to progression after the initial TACE; (3) the study did not cover information on additional treatment, including repeat TACE for recurrent lesions; and (4) despite the recommendations in the guidelines, prehydration was not performed in more than half of the patients even in the cisplatin group. Prehydration will be more popular as prehydration is incorporated into chemotherapeutic regimens and clinical paths prepared for the TACE procedure.

In conclusions, the median survival time for patients with HCC treated using miriplatin-based ethiodized oil TACE equaled that of patients with HCC treated using cisplatin-based HCC. Based on an 8999-patent cohort extracted from the Japanese medical claims database, the first choice of the therapy for 44.6% of patients was TACE. Subsequently, 25.8% of patients were treated using TACE as the second choice of therapy [50]. Miriplatin will benefit patients with HCC who cannot tolerate perioperative hydration to prevent kidney injuries caused by cisplatin.

Author Contributions

K.F. wrote the manuscript; K.F. and H.K. designed the research; K.T., K.O., and T.T. performed the research; A.M. and T.H. analyzed the data.

Ethics Statement

This study protocol was reviewed and approved by the Institutional Review Board of Kagawa University, Faculty of Medicine (Serial number: 2024–014).

Consent

Opt-out methods by publishing a summary of this study on our university website were adopted to guarantee patients or their relatives the opportunity to refuse enrollment in the current study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.