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REVIEW

Systemic treatment of hepatocellular carcinoma: Past, present and future

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Abstract

Hepatocellular carcinoma (HCC) is a common neoplasia which represents the second leading cause of cancer related death. Most cases occur in developing countries, but its incidence is rising in Western countries due to hepatitis C. Although hepatitis therapies have evolved and the HCC screening has increased in several areas, 40% present with advanced disease which is only amenable for palliative systemic treatment. HCC continues posing a challenge, in part due to the inherent chemoresistance of this neoplasia, the pharmacologic challenges due to an ill liver, difficulty in assessing radiological responses accurately, *etc*. Traditional chemotherapy have shown some responses without clear survival benefit, however, sorafenib demonstrated advantages in survival in advanced HCC when liver function is kept and recently immunotherapy seems to be a promising approach for some patients. This article will briefly expose the most relevant systemic treatment modalities to offer a general view from the past to the future.

Key words: Hepatocellular carcinoma; Alphafetoprotein; Sorafenib; Nivolumab; MEK

Core tip: The incidence of hepatocellular carcinoma (HCC) is rising in Western countries due to hepatitis C. Unfortunately, 40% of patients present with advanced disease which is only amenable for palliative systemic treatment. The development of effective therapies for HCC is a challenge, due partly to its inherent chemoresistance, the pharmacologic challenges due to an ill liver, *etc*. Although some responses to traditional chemotherapy have been reported, the multikinase inhibitor sorafenib has shown survival benefit in advanced HCC with preserved liver function. Recently immunotherapy seems to be a promising approach for some patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a hepatic neoplasia that occupies the second place as cause of cancer related deaths[1]. It appears most frequently in a liver with chronic injury and cirrhosis[2] and it is usually diagnosed as an advanced stage with a poor median survival rate (6-20 mo)[3].

Its incidence varies depending on geographical zones and races. This is mainly related to differences in incidences of hepatitis B and C. The highest rates are seen in Asia (where hepatitis B incidence is very high) and Africa, though increasing in developed areas due to hepatitis C[4]. Other risk factors include steatohepatitis, alcoholic liver disease, aflatoxins and hemochromatosis.

Unfortunately 40% of diagnosis will present with an advanced disease with the only options of systemic therapy in most of them[5]. HCC nowadays continues to pose a significant challenge to the therapy, in part due to poor chemosensitivity (expression of drug resistance genes) and the liver dysfunction which hinders the delivery of these drugs. Moreover, cirrhosis will have an impact on the drug distribution volumes[6].

Although newer treatments have appeared, the survival rates of advanced HCC patients have not yet significantly improved.

HCC is an aggressive tumour whose treatment possibilities will depend on the phase of the tumour, the liver functionality and patient's performance status. There are several staging systems available[7-9] but no consensus on which to use. The Child-Pugh system will assess the patient's hepatic reserve and liver function. Other staging systems, such as Barcelona Clinic Liver Cancer, will consider tumour phase, performance status, hepatic status, symptoms, *etc*. This system may provide the link between disease and treatment strategies. In very early/early stages, curative treatment (liver surgery or hepatic transplantation) and locoregional treatments (such as radiofrequency ablation), have better survival benefits.

Intermediate stage is very heterogeneous and transarterial chemoembolization/radioembolization are the main options if preserved hepatic function (Child-Pugh A) and performance status 0.

Advanced cases have got a short prognosis. For these patients, systemic palliative therapies might be considered.

This article will briefly expose the most relevant systemic treatment modalities to offer a general view from the past to the future.

CYTOTOXIC CHEMOTHERAPY: MONOTHERAPY

HCC is poorly chemosensitive due to the expression of drug resistance genes, and the liver dysfunction which hinders the delivery of drugs. In the past years, no single treatment or regimen have shown superiority to another[10].

Glutathione-S-transferase, topoisomerase Ⅱα, p-glycoprotein, heat shock proteins, and p53[11-17] are related to chemotherapy sensitivity. Most published studies with chemotherapy have shown RRs of less than 25% and there is no evidence of improvement in OS[18-20]. However, chemotherapy may still be an option after progression on sorafenib if good performance status and preserved liver function.

Nagahama *et al*[21] carried out a study in 147 HCC patients in first line. Results showed that those cases affected by severe cirrhosis, tumour involving > 50% of the liver, ECOG performance 2-3 and tumour thrombus in the portal vein do not respond to chemotherapy.

Doxorubicin has been used since the 1970s. A study carried out in Africa enrolled 14 patients and found a 79% of responses[22]. However, posterior trials showed much less RR (10% to 20%)[23,24].

It is not clear whether doxorubicin prolongs survival. A single study with 60 cases randomised to doxorubicin *vs* no treatment and it demonstrated a significant extension in survival (10.6 wk *vs* 7.5 wk, $P = 0.036$) favouring doxorubicin[25]. Later a meta-analysis comparing doxorubicin to no treatment or other treatments did not find a survival benefit[26]. Another randomized study comparing doxorubicin against nolatrexed, found better survival with doxorubicin (32.3 wk *vs* 22.3 wk, $P = 0.007$) but the authors concluded that results could be biased due to more patients failed to continue treatment with nolatrexed due to side-effects[27].

Several phase Ⅱ trials with other anthracyclines did not show any significant benefits over doxorubicin in outcomes or toxicity[28-31] (Table 1).

5-fluorouracil (5-FU) and other fluoropyrimidines have been used in HCC. 5-FU has undergone extensive evaluation in HCC and shown RRs in the range of 10%[32,33]. 5-FU bolus with leucovorin showed higher gastrointestinal adverse effects, and responses of 0%-28%[33,34].

Capecitabine is a prodrug that is converted at the site of the tumour to 5-FU. Its toxicity profile appears to be more manageable[35], but RRs remain relatively low[36]. A retrospective study by Patt *et al*[35] investigated the role capecitabine in 63 patients (37 HCC). Capecitabine in HCC showed a RR of 1% with an OS of around 10 mo. Most frequent adverse events included hand-foot syndrome and thrombocytopenia[35]. Jiang *et al*[37] have reported a high activity of dihydropyrimidine dehydrogenase in liver cancer. This could impact on the chemoresistance to these chemotherapy agents. In the adjuvant setting, Xia *et al*[38] carried out a randomized, controlled trial with capecitabine after HCC operation. Sixty patients were randomized to capecitabine or control. Results favoured the capecitabine arm with a lower recurrence rate (53.3% *vs* 76.7%), longer median time to recurrence (40 mo *vs* 20 mo, $P = 0.046$) and higher 5-year OS (62.5% *vs* 39.8%, $P = 0.216$) with tolerable side effects[38].

Gemcitabine is another chemotherapy drug which appears to be very active *in vitro* (HCC cell lines). However, several clinical studies have shown limited activity[39].

Table 1 Doxorubicin as first line treatment in hepatocellular carcinoma

Ref.	*n*	Line/treatment	Relevant data
Nagahama *et al*[21]	147	First line doxorubicin	Severe cirrhosis, PS 2-3, tumour occupying > 50% liver do not respond to chemo
Olweny *et al*[22]	14	First line doxorubicin	RR 79%
Sciarrino *et al*[23]		First line doxorubicin	RR 10%-20%
Chlebowski *et al*[24]			

RR: Response rate.

Only one small study (28 patients) reported by Yang *et al*[40] showed a RR of 17%. The subsequent trials have only shown RRs of 0%-2%[41,42]. Cisplatin is a platinum analog that has demonstrated a 15% of responses as monotherapy[43].

CYTOTOXIC CHEMOTHERAPY: COMBINATION

In an attempt to increase the rate of clinical benefits, several combinations of chemotherapy have been studied but to date none has proven superiority when compared with single agents. This is very important as combinations are more toxic and thus clinicians should weigh the toxicity against any added palliative benefit they hope to get.

The EACH is a phase Ⅲ, open-label study comparing FOLFOX4 (infusional FU, leucovorin, oxaliplatin) *vs* doxorubicin in 371 patients with advanced HCC. FOLFOX4 showed a higher RR (8.15% *vs* 2.67%, $P = 0.02$), disease control rate (DCR) (52.17% *vs* 31.55%, $P < 0.001$), longer PFS (2.93 mo *vs* 1.7 mo, $P = 0.001$; HR = 0.62) and OS (6.40 mo *vs* 4.97 mo, HR = 0.80; $P = 0.07$)[44].

Shin *et al*[45] reported a trial of cisplatin combined with capecitabine and doxorubicin in 25 patients. They found a RR of 26% and around 1/3 of patients showed a significant reduction in alfa-fetoprotein (AFP) levels, though this reduction is not a reliable marker for clinical benefit. This study mentioned toxicity only briefly with one treatment-related death. Lee *et al*[46] carried out a study with the combination of cisplatin and doxorubicin. This phase Ⅱ trial showed responses in the line of 19%, with around 1/3 of the patients having a significant reduction of AFP. Significant neutropenia was reported in 14.3%.

Combinations of platinum derivatives and gemcitabine seem to be more effective with tolerable adverse events if hepatic function is acceptable. Gemcitabine and oxaliplatin have shown responses of 15%-20% and stabilizations of 48%-58% in small studies[47,48].

A retrospective study in 204 patients with advanced HCC treated with a combination of gemcitabine and oxaliplatin (GEMOX) was reported in 2011 ASCO meeting. Fifty-one percent had Child Pugh A, 20.6% Child Pugh B, and 4.4% Child Pugh C. The results showed a RR of 22% and DCR of 66%. PFS, TTP and OS of 4.5, 8 and 11 mo. Authors found that if an objective response was seen, OS was higher (19.9 mo *vs* 8.5 mo). Grade 3/4 toxicity occurred in 44.1% and most frequent adverse events were diarrhoea, neutropenia, thrombocytopenia and neuropathy[48]. In addition, 8.5% became candidates for curative treatments thanks to responses. Moreover, the response to GEMOX, among other factors, was independently associated to OS.

Patrikidou *et al*[49] carried out a retrospective study of GEMOX as second line. Forty patients were included after failure of one anti-angiogenic treatment minimum. Severe adverse events were found 25% of the cases. Partial response was observed in 20% of patients, while 46% had stable disease.

Median OS was 8.3 mo and survival rate at 6 mo was 59%. Median PFS was 3.1 mo. Performance status, baseline AFP levels and BCLC score were independently associated with OS. Another study has demonstrated RR of 21% with cisplatin and gemcitabine but with 1/3 of the patients suffering from severe neutropenia and 1/4 significant thrombocytopenia[50]. Another trial with cisplatin, 5-FU and mitoxantrone found RR of 27% with 71% patients with severe neutropenia[51].

Docetaxel plus gemcitabine showed a 10% RR and unacceptable hematologic toxicity[52]. Irinotecan has shown minimal effectiveness with significant adverse events, so its use is not advisable[53,54] (Table 2).

HORMONAL THERAPY

As there is a significant male predominance in morbidity and mortality in HCC, it has long been considered that sex hormones play a role in its development. Some HCCs express estrogen receptors (ER) and estrogens have shown some protective effects against HCC.

Tamoxifen, a competitive antagonist of the estrogen receptors, have been studied in several clinical trials to assess its activity against HCC but only a little benefit in response or survival has been found[55,56].

Megestrol acetate blocks wildtype and variant forms of ERs and it has been assessed in HCC with variant ER. Benefits varied according to trials. Whereas some of them showed some benefits, a study of megestrol acetate *vs* placebo as first line of advanced HCC did not prolong OS[57-60].

Octreotide is a somatostatin analogue and around 40% of hepatic carcinomas express these receptors. Octreotide has shown direct antitumor effect in HCC[61,62]. Several studies have shown different benefits but a metaanalysis showed survival rates at 6 and 12 mo higher than those seen in the other arms, though only in Eastern studies[63]. However, these results are still controversial.

Table 2 Clinical trials with chemotherapy agents in hepatocellular carcinoma

Ref.	*n*	Treatment	Results
Lai *et al*[25]	60	Doxorubin *vs* placebo	OS 10.6 wk *vs* 7.5 wk in favour of chemo
Gish *et al*[27]		Doxorubicin *vs* nolatrexed	OS 32.3 wk *vs* 22.3 wk in favour of doxorubicin
Patt *et al*[35]	37	Capecitabine	RR 1%, OS 10.1 mo
Qin *et al*[44]	371	FOLFOX 4 *vs* doxorubicin	RR 8.15% *vs* 2.67% DCR 52.17% *vs* 31.55% PFS 2.93 m *vs* 1.7 m OS 6.4 m *vs* 4.97 m All in favour of FOLFOX 4
Shin *et al*[45]		Cisplatin, Capecitabine and Doxorubicin	RR 26%
Lee *et al*[46]		Cisplatin/doxorubicin	RR 19%
Zaanan *et al*[48]	204	GEMOX	RR 22% DCR 66% PFS 4.5 m OS 11 m
Patrikidou *et al*[49]	40	GEMOX after antiangiogenics failed	Partial responses 20% Stable disease 46% OS 8.3 m
Yang *et al*[50]		Cisplatin/gemcitabine	RR 21%
Kim *et al*[52]		Cisplatin/infusional FU/mitoxantrone	RR 27% but 71% severe neutropenia

RR: Response rate; DCR: Disease control rate; PFS: Progression free survival; OS: Overall survival.

MOLECULARLY TARGETED THERAPY

Carcinogenesis is a complex process involving multiple signalling cascades. Sorafenib is a small inhibitor of several tyrosine protein kinases (TKI), such as VEGFR, platelet derived growth factor receptor (PDGFR) and Raf family kinases. It will inhibit growth of multiple kinases related to angiogenesis, cell proliferation and differentiation[64,65]. In preclinical studies, sorafenib has shown antiproliferative effects in HCC cell lines. It also decreased tumour angiogenesis and tumour-cell signalling, increasing apoptosis in a mouse model[65].

Abou-Alfa *et al*[66] carried out an uncontrolled phase Ⅱ study with sorafenib in advanced HCC and Child-Pugh A or B. Results favoured sorafenib with OS of 9.2 mo and a TTP 5.5 mo.

A large phase Ⅲ, multicenter, randomized, double-blind, placebo controlled trial (SHARP trial) was undertaken in advanced HCC. Six hundred and two patients naïve for treatment, were randomized to sorafenib or placebo. This study showed an OS of 10.7 mo *vs* 7.9 mo in favour of sorafenib, with a hazard ratio of 0.69; 95%CI: 0.55 to 0.87; $P < 0.001$). Both groups were similar in the median time to symptomatic progression (4.1 mo *vs* 4.9 mo, $P = 0.77$).

Two percent of partial responses were seen in patients with sorafenib and 1% in the placebo; overall toxicity was similar between the treatment and placebo arm (52% *vs* 54%), though diarrhoea, hand-foot syndrome, weight loss and hypophosphatemia were more prominent with sorafenib.

Another phase Ⅲ placebo controlled trial was carried out in Asian patients (Oriental study). Two hundred and twenty-six patients with Child-Pugh A cirrhosis and no prior systemic treatment were randomized to sorafenib or placebo. Sorafenib showed significantly longer median OS (6.5 mo *vs* 4.2 mo) and median TTP (2.8 mo *vs* 1.4 mo)[67].

Sorafenib in combination with chemotherapy has been examined. A study compared doxorubicin with sorafenib *vs* doxorubicin alone[68]. The combination prolonged median TTP (6.4 mo *vs* 2.8 mo, $P = 0.02$), PFS (6.0 mo *vs* 2.7 mo, $P = 0.006$) and median OS (13.7 mo *vs* 6.5 mo, $P = 0.006$)[68]. CALGB80802 study[69] recruited patients with advanced HCC, naïve for palliative treatment and Child-Pugh A. The patients received either doxorubicin 60 mg/m^2 every three weeks plus sorafenib or sorafenib monotherapy. After 346 patients the study was halted. An interim analysis reported that the combination arm produced higher toxicity and did not improve OS[69]. Other studies were designed to evaluate the combination of GEMOX regimen and sorafenib. A randomized, controlled, phase Ⅱ trial (GOTEXT), compared sorafenib and GEMOX combined with sorafenib as first-line treatment. Ninety-four patients were randomized. The results showed that RRs, DCRs, PFS and median OS were 9% *vs* 70%, 16% *vs* 77%, 54% *vs* 61%, and 13 mo *vs* 13.5 mo, respectively, favouring the combination[70].

Sorafenib combined with oxaliplatin has shown good activity in phase Ⅱ trials but requires further investigation in larger randomized clinical trials. Regorafenib is a multi-kinase inhibitor which has shown activity against HCC. Bruix *et al*[71] carried out a study, open-label, phase Ⅱ, multicenter, to assess safety and efficacy of regorafenib in patients diagnosed with advanced HCC after failure with sorafenib. Thirty-six patients were included and disease control was achieved in 26 with one partial response. TTP and OS of 4.3 and 13.8 mo respectively and a tolerable safety profile. Most frequent side effects were fatigue, hand-foot syndrome and diarrhoea.

The phase Ⅲ trial (RESOURCE, NCT01774344) showed a benefit for regorafenib with longer median progression-free survival (3.1 mo *vs* 1.5 mo) compared to placebo. OS (primary end point) was 10.6 mo *vs* 7.8 mo in favour of regorafenib. Overall, authors found that 65.2% of patients on regorafenib showed complete/partial response or stable disease, compared to 36.1% in the placebo group. Side effects were similar to those reported with sorafenib namely hypertension, hand-foot skin reaction, fatigue and

diarrhea[72].

Cabozantinib is a multiple receptor tyrosine kinases inhibitor, including HGF receptor [mesenchymal-epithelial transition (MET)], Ret, and the VEGF receptor. A phase Ⅱ trial which included 41 patients with HCC has shown promising results[73]. These patients had Child-Pugh A and had progressed to a previous systemic therapy. Patients on cabozantinib showed 5% of partial responses, 78% stable disease, and 7% progressive disease, with a median OS of 15.1 mo and median PFS of 4.4 mo, regardless of previous treatment with sorafenib. Most frequent side-effects grade 3 or higher were diarrhea, palmar-plantar erythrodysesthesia, and thrombocytopenia.

A multinational phase Ⅲ clinical trial, CELESTIAL, has been planned to recruit 760 patients with advanced HCC after progression on sorafenib. Patients will receive cabozantinib daily or placebo (randomization 2:1). The trial is expected to show data in 2017[74,75]. The endpoints are OS (primary), RR and PFS.

Lenvatinib is a multitargeted (VEGFR, PDGFR, RET, FGFR and KIT) tyrosine kinase inhibitor. The recommended dose was 12 mg daily in Child-Pugh A (5-6 score) and 8 mg in Child-Pugh B (7-8 score)[76].

A phase Ⅱ clinical trial, multicenter, evaluated lenvatinib in advanced HCC. Patients receive 12 mg once daily in 28-d cycles. The primary endpoint was TTP. Forty-six patients were included in Japan and South Korea showing TTP of 7.4 mo (95 %CI: 5.5-9.4).

Thirty-seven percent had partial response and 41% stable disease (DCR 78%). Median OS was 18.7 mo (95%CI: 12.7-25.1). Frequent adverse events such as hypertension (> 75%), palmo-plantar syndrome (> 60%), reduced appetite (> 60%) and proteinuria (> 60%). Dose reductions in 74% and treatment was stopped in 22%, due to adverse effects. Authors found that median body weight was lower in patients with an early (< 30 d) dose withdrawal or reduction.

This study concluded that lenvatinib shows clinical activity with acceptable toxicity but early dose modification is needed if low body weight. Further studies should consider this[77].

The pivotal Phase Ⅲ REFLECT trial comparing lenvatinib to sorafenib has been completed, and its results will determine whether lenvatinib represents another potential option. A clinical trial of lenvatinib *vs* sorafenib in naïve patients will recruit 1000 patients with unresectable HCC and its completion is estimated for later this year[78].

Tivantinib is a selective small MET tyrosine kinase inhibitor with antitumor activity, especially in MET-high patients. Its activity is due to a disruption of microtubules[79]. An initial study in 20 patients with Child-Pugh A or B[80] found that most relevant side-effects were fatigue (> 1/2), anorexia, alopecia and diarrhoea (15% each). Serious neutropenia (38%) and anaemia (24%) were seen, which implies that a careful haematological monitoring is needed during the treatment.

A phase Ⅱ randomised trial in second line has been carried out. Patients were stratified by circulating levels of MET, hepatocyte growth factor and levels of alpha-fetoprotein. Circulating levels of MET were related to prognosis as OS was 4.6 mo in high levels *vs* 8.9 mo if low (HR = 0.61; P = 0.023). If low MET tumours, TTP, OS or DCR did not show differences.

This trial found relevant toxicities such as grade 3 anemia (9%), neutropenia (6%) and thrombocytopenia (6%). This led to a dose recommendation of 240 mg BID for second-line.

MET expression was also correlated with sorafenib as 40% of biopsies taken prior to sorafenib therapy were MET-high compared with 82% after sorafenib. A significant interaction in OS between tivantinib and MET expression was reported (P = 0.039). The other biomarkers examined were not predictive of tivantinib response[81].

A phase Ⅲ, randomized, double-blind trial in second line, after progression on sorafenib is ongoing in HCC patients with high-expression of MET. The endpoints include OS (primary), PFS and safety. The anticipated study completion date is mid-2017[81-83].

Ramucirumab is a fully human monoclonal anti-VEGFR-2 antibody. It binds to the receptor with high affinity and prevents ligand activation. HCC has got high expression levels of VEGF which entails worse results[84]. REACH is a randomized, double-blind trial, in HCC patients refractory or not amenable to locoregional treatments who had failed to sorafenib. OS, which was the primary endpoint, was not significantly different with ramucirumab or placebo (9.2 mo *vs* 7.6 mo; HR = 0.87; 95%CI: 0.72-1.05; P = 0.14). On the contrary PFS was improved as objective RR. Regarding toxicity, most common side effects grade 3 or above were ascites, hypertension, asthenia, and increased aspartate aminotransferase[85]. When patients were stratified by AFP, OS benefited ramucirumab if AFP > 400 ng/mL (7.8 mo *vs* 4.2 mo; HR = 0.67; 95%CI: 0.51-0.90; P = 0.006). These results suggested that patients with elevated AFP might be more likely to benefit from ramucirumab. A prospective phase Ⅲ trial, REACH 2, whose completion is estimated for late 2017, will assess the safety and efficacy of ramucirumab as second-line in patients with elevated baseline AFP[85].

Apatinib is a small-molecule multi-kinase inhibitor of VEGFR-2. Qin *et al*[86] carried out a phase Ⅱ dose-finding study in naïve patients with HCC Child-Pugh A. These patients were randomised to apatinib 850 mg/qd or 750 mg/qd. Endpoints TTP (primary), OS, RR, DCR, level of AFP and safety. One hundred and twenty-one patients were recruited. The results showed a median TTP of 4.2 and 3.3 mo for the two different dosages respectively. DCR was 48.57% and 37.25% respectively. Median OS was 9.7 and 9.8 mo respectively. The authors concluded that apatinib produced a survival benefit and both doses were recommended for further study[86].

Most frequent adverse effects were elevated levels of bilirubin, aminotransferase, blood pressure, thrombocytopenia, leukocytopenia, palmo-plantar erythrodysesthesia, fatigue, but most of them were easily managed by dose interruptions or reductions.

A phase 1/phase 2 trial of apatinib for advanced HCC

Table 3 Clinical trials with tyrosine kinase inhibitors in hepatocellular carcinoma

Ref.	*n*	Treatment	Results
Abou-Alfa *et al*[66]		Sorafenib	OS 9.2 m TTP 5.5 m
	602	Sorafenib *vs* placebo	
Cheng *et al*[67]	226	Sorafenib *vs* placebo	OS 6.5 m *vs* 4.2 m TTP 2.8 m *vs* 1.4 m
Abou-Alfa *et al*[68]		Sorafenib *vs* doxorubicin	TTP 6.4 m *vs* 2.8 m PFS 6 m *vs* 2.7 m OS 13.7 m *vs* 6.5 m
Assenat *et al*[70]	94	Sorafenib *vs* sorafenib/GEMOX	RR 9% *vs* 70% DCR 16% *vs* 77% PFS 54% *vs* 61% OS 13 m *vs* 13.5 m In favour of the combination
Bruix *et al*[71]	36	Regorafenib second line	DCR in 26/36 patients Partial response 1/36 TTP 4.3 m OS 13.8 m
LBA-03[72]		Regorafenib *vs* placebo	DCR 65.2% *vs* 36.1% PFS 3.1 m *vs* 1.5 m OS 10.6 m *vs* 7.8 m
Verslype *et al*[73]	41	Cabozantinib	Partial response 5% Stable disease 78% PFS 4.4 m OS 15.1 m
Exelixis[74,75]	760	Cabozantinib second line (after sorafenib)	Primary end point OS Expected data in 2017
Koyama *et al*[76]	46	Lenvatinib	DCR 78% TTP 7.4 m OS 18.7 m
Eli Lilly and Company[85]		Ramucirumab *vs* placebo	OS 9.2 m *vs* 7.6 m
Qin *et al*[86]	121	Apatinib *vs* placebo	TTP 4.2 m *vs* 3.3 m DCR 48.57% *vs* 37.25% OS 9.7 m *vs* 9.8 m

RR: Response rate; DCR: Disease control rate; PFS: Progression free survival; OS: Overall survival; TTP: Time to progression.

after first-line treatment failure (NCT02772029) will be soon recruiting patients. A multicenter, randomised, double blind phase Ⅲ trial (NCT02329860) was started in December 2014, aiming to assess its activity and toxicity profile after progression on sorafenib and/or chemotherapy. It has planned to recruit 360 patients (randomized 2:1). Primary endpoint is OS. This trial is still ongoing. See all the results in Table 3.

IMMUNOTHERAPY

Recently tumor immunotherapy has evolved rapidly. As most HCC are driven by inflammation, there is a strong rationale to evaluate immunotherapy in these patients.

Pembrolizumab

The single-arm, multisite, phase 2 KEYNOTE-224 study (ClinicalTrials.gov, NCT02702414) was designed to assess the activity and toxicity pembrolizumab in patients with previously treated advanced HCC. This trial plans to recruit 100 patients. The primary end point will be objective RR.

Another single-arm phase Ⅱ trial of Pembrolizumab in patients with advanced, unresectable HCC is ongoing. Endpoints are DCR (primary), PFS, OS, RR, duration of response and toxicity. Researchers will assess the expression levels of programmed death-ligand 1 (PD-L-1) in tumor tissue, and serum titers of hepatitis B or C in patients with hepatitis B or C, respectively, for whom specimens are available.

Nivolumab

Several tumours express PD-1, among them HCC and this is related with poor prognosis. The union PD-1/PD-L1 block the T cell receptor signal transduction, inhibit proliferation and induce depletion of T cells achieving tumour immune escape. Blocking the PD-1 pathway will promote an antitumoral immune response[87]. Nivolumab is an anti-PD-1 antibody[88].

A phase Ⅰ/Ⅱ study (Interim analysis of the Check-Mate-040 dose escalation study) in advanced HCC was reported at the 2015 ASCO annual meeting.

Patients with advanced HCC, Child-Pugh ⩽ 7, who had failed, declined, or did not tolerate sorafenib were included. Patients had nivolumab 0.1-10 mg/kg every two weeks for a maximum of 2 years. Three parallel cohorts were made depending on hepatitis: No active infection, hepatitis B, hepatitis C. Endpoints were safety (primary), efficacy and RR. Biomarkers assessment was included as an exploratory endpoint.

Fifty-one patients were included. Seventy-three percent of them had prior sorafenib. Twenty-nine percent

Table 4 Clinical trials with immunotherapy in hepatocellular carcinoma

Authors	*n*	Phase	Treatment	Primary end-point
Keynote-224	100	Ⅱ	Pembrolizumab	RR
ongoing		Ⅱ	Pembrolizumab	DCR
CheckMate-040		Ⅰ / Ⅱ	Nivolumab	Safety
CheckMate-459	726	Ⅲ	Nivolumab *vs* Sorafenib	OS TTP

RR: Response rate; DCR: Disease control rate; OS: Overall survival; TTP: Time to progression.

had response or stable disease and most common adverse effects were rash and AST increase. Responses were seen regardless PD-L1 status evaluated by IHC.

Authors concluded that nivolumab showed manageable toxicity with long duration responses or stabilizations regardless dosage or cohorts[89-91]. CheckMate-040 shows that nivolumab is effective with acceptable toxicity in HCC, regardless hepatitis status.

Another phase Ⅲ study, CheckMate-459, (NCT02 576509) has planned to recruit 726 patients to assess nivolumab compared to sorafenib as first line. Endpoints will be OS, TTP (as primary), RR, PFS, expression of PD-L1 and efficacy. The stratification will observe geographical area, etiology, vascular invasion and extrahepatic dissemination. It is planned to be finished by May 2017.

Tremelimumab

It is a humanized anti T-lymphocyte-associated antigen-4 (CTLA-4) IgG2 antibody which has shown good results in the treatment of 21 patients with hepatitis C[92]. RR of 18% and DCR of 76%, with TTP of 6.48 mo[93] were seen.

Transarterial chemoembolization and radiofrequency ablation can also trigger immune activity against HCC and potentiate the anti-CTLA-4 activity[94].

Twenty patients were included and Duffy *et al*[94] presented the results in ASCO 2015. Disease free survival was 16 mo and median PFS 7.4 mo. Forty percent of patients treated with transarterial chemoembolization/radiofrequency ablation showed partial response and 5 out of 7 patients with hepatitis C had a significant reduction in viral load. Most frequent side effect was itching and only 1 patient stopped due to pneumonitis. These authors found evidence of immune cells infiltration in tumour biopsies taken at 6 mo. As clinical activity was encouraging, tremelimumab combined with transarterial chemoembolization/radiofrequency ablation has been considered for further investigation[94] (Table 4).

MEK inhibitors

A relevant signalling pathway in hepatocarcinogenesis is the MEK cascade. This is involved in cellular adaptation and survival. A key role is played by MEK, with MEK 1/2 as interesting targets for new drugs.

Refametinib is an oral MEK inhibitor which has been combined with sorafenib in a phase Ⅱ trial[95]. The RR 6.2% and DCR 43%, with a median OS of 9.6 mo. The best response was seen in RAS mutated group. Unfortunately, the rate of grades 3 and 4 side-effects was 80% and 4 patients died due to liver failure, hepatic encephalopathy, tumour lysis syndrome and unknown reason.

Another phase Ⅱ[96] of refametinib alone or combined with sorafenib in HCC with mutant RAS was carried out. Patients with HCC, unresectable, Child-Pugh A, no prior systemic therapy for HCC (except prior sorafenib in monotherapy study) were eligible. Patients in the monotherapy trial were treated with refametinib 50 mg bid, while in the combination they were treated with refametinib 50 mg bid and sorafenib 400 mg bid.

Four hundred and ninety-eight patients in the monotherapy and 820 patients in the combination were enrolled. Median PFS was 58 d, median time to radiological progression 84 d, and median OS 177 d. In the combination study no patients achieved a confirmed partial response, median PFS was 46 d, TTP 84 d, and median OS 427 d[96]. Authors concluded that either monotherapy or combination did not show sufficient efficacy to warrant further development in this group of patients.

Some other some small molecule c-MET inhibitors, such as foretinib[97] as first line or tepotinib[98] particularly in C-MET positive tumours, have shown promising activity with high safety profile. The most common side effects were hypertension, fever and anorexia. Capmatinib[99], golvantinib[100], and others are also under study[101].

CONCLUSION

HCC is one of the most frequent worldwide neoplasias and although many efforts have been made to get a prompt detection, many cases are still diagnosed in an advanced stage no amenable to radical treatments. The treatment of an advanced HCC is still challenging and although there are many trials under way to evaluate new drugs targeting different molecular pathways relevant in hepatocarcinogenesis, much knowledge remains still in early stages. Sorafenib improved survival but sorafenib resistance is still a significant issue and several clinical trials assessing other new molecular targeted agents have failed. Regorafenib and lenvatinib showed promising activity in phase Ⅱ clinical trials and are undergoing evaluation in phase Ⅲ. Immunotherapy has recently emerged as a promising therapy for many cancers including HCC. Nivolumab has shown benefits and awaits trials to confirm these positive results. Tremelimumab open the door to combination with locoregional treatments and it has also shown a reduction in tumour viral load in hepatitis C[100].

The efforts will continue and hopefully will soon pay off.

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MINIREVIEWS

Conventional *vs* drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma

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Abstract

Transarterial chemoembolization (TACE) is the current standard of therapy for patients with intermediate-stage hepatocellular carcinoma (HCC) according to the Barcelona Clinic Liver Cancer classification. The concept of conventional TACE (cTACE) is the selective obstruction of tumor-feeding artery by injection of chemotherapeutic agents, leading to ischemic necrosis of the target tumor *via* cytotoxic and ischemic effects. Drug-eluting beads (DEBs) have been imposed as novel drug-delivering agents for TACE, which allows for higher concentrations of drugs within the target tumor and lower systemic concentrations compared with cTACE. Despite the theoretical advantages of DEB-TACE, it is still controversial in clinical practice as to whether DEB-TACE is superior to cTACE in regard to overall survival and treatment response. In this review article, we summarize the clinical efficacy and safety of DEB-TACE for patients with intermediate or advanced stage HCC in comparison with cTACE.

Key words: Hepatocellular carcinoma; Drug-eluting beads transarterial chemoembolization; Transarterial chemoembolization

Core tip: Transarterial chemoembolization (TACE) is the current standard of therapy for patients with intermediate-stage hepatocellular carcinoma. Drug-eluting beads (DEBs) have been introduced as novel drug-delivery agents for TACE, allowing for higher concentrations of drugs to the target tumor and lower systemic concentrations, compared with conventional TACE (cTACE). Despite the theoretical advantages of DEB-TACE, whether DEB-TACE shows superior efficacy to cTACE remains controversial. Reviewing the literature, we found that DEB-TACE shows similar clinical outcomes to and fewer adverse events than cTACE.

Song JE, Kim DY. Conventional *vs* drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma. *World J Hepatol* 2017; 9(18): 808-814 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i18/808.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i18.808

INTRODUCTION

Hepatocellular carcinoma (HCC) is listed as the sixth most common cancer worldwide and the third most frequent cause of cancer-related mortality[1,2]. The majority of HCC cases occur stem from chronic liver disease and cirrhosis. Therefore, the selection of treatment modalities for HCC is determined by tumor size, multiplicity, and liver function status[3].

Transarterial chemoembolization (TACE) has been frequently performed and has become the first-line treatment option for large or multinodular HCC with preserved liver function, no evidence of vascular invasion or extrahepatic spread, and the absence of cancer-related symptoms, which is defined as intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) classification[4,5]. Moreover, in clinical settings, TACE is considered the standard treatment for patients with early stage HCC who are not appropriate candidates for curative therapy[4].

The mechanism of action for conventional TACE (cTACE) is the selective obstruction of tumor-feeding arteries by injection of chemotherapeutic agents (doxorubicin or cisplatin) mixed with lipiodol[6]. This leads to ischemic necrosis of target tumors by cytotoxic and ischemic effects. There are several drawbacks of cTACE that are associated with ineffective treatment responses in many cases: (1) the liquid motility of lipiodol to reduce the effective concentrations of chemotherapeutic agents; (2) the inability to release drugs in a controlled and sustained manner; and (3) heterogeneity in the technique and treatment schedules. To reduce these drawbacks, drug-eluting beads (DEBs) have been introduced as drug-delivering agents for TACE. After delivery of the beads to target tumors, the beads release chemotherapeutic drugs (doxorubicin or epirubicin) in a sustained fashion over a prolonged period of time[7,8]. Figure 1 shows the mechanism of action of DEB-TACE. Treatment with DEB-TACE allows higher concentrations of drugs within the target tumor and lower systemic concentrations compared with cTACE[9,10]. Thus, the use of DEBs can reduce drug-related adverse events such as post-embolization syndrome. As DEB-TACE is widely used interchangeably with cTACE in many hospitals globally, it is necessary to assess the current status of DEB-TACE in comparison with cTACE. Thus, this article aims to evaluate the characteristics of each modality and to compare the clinical outcomes of DEB-TACE with those for cTACE.

cTACE *VS* DEB-TACE: CHARACTERISTICS

cTACE

Typically, cTACE involves the infusion of chemotherapeutic drugs blended with lipiodol and embolic agents into the cancer-feeding artery[6]. Both single chemotherapeutic agents and combination chemotherapy have been used as part of the drug regimen in TACE. However, there is no agreement on the optimal anticancer drug(s) to be used in cTACE. Globally, the most widely used chemotherapeutic agent for TACE of HCC is doxorubicin. The dose of doxorubicin generally ranges from 30 to 75 mg/m^2, at a maximum of 150 mg emulsified in 5 to 20 mL of lipiodol[11].

Lipiodol is a key element in TACE due to its distinctive combination of features as a drug-carrying, tumor-seeking, and embolizing agent[12]. Even though the principle is not concretely comprehended, it seems to be absorbed by a pump in the cancer cell wall and transported to the intracellular space. Then, upon hypoxia within cancer cells, this pump is disabled, such that lipiodol is retained within the cell. Lipiodol is confined to tumors when injected *via* the hepatic artery, and it is generally trapped in HCC for months, even up to a year, whereas it is washed out from non-tumor portions of the liver within 4 wk.

Several embolic agents, such as gelfoam, polyvinyl alcohol (PVA) particles, and tris-acryl gelatin microspheres, have been used over the past three decades in chemoembolization[12]. Among these embolic agents, gelfoam has recently emerged the most commonly used substance worldwide. The intended aim of embolization is as follows: To assist lipiodol to be sustained selectively in the tumor, to inhibit chemotherapeutic agent washout from HCC, and to cause ischemic necrosis.

A significant problem of cTACE is the great inhomogeneity of the technique and treatment schedules used in clinical centers worldwide. Two randomized controlled trials on cTACE used quite different technical approaches. Furthermore, some HCCs do not show lipiodol uptake which may result in lower effectiveness of the treatment[13].

DEB-TACE

The most commonly used DEB, DC Beads (BTG, United Kingdom) are nonbiodegradable PVA microspheres, loaded with calibrated doxorubicin. They can release doxorubicin in a controlled and maintained mode[14]. Through an ion-exchange mechanism, DC Beads actively sequester oppositely charged drugs. In initial *in vitro* studies, doxorubicin could be efficiently loaded into the DC beads up to 45 mg/mL, regardless of the size of beads[15]. Currently, a loading of 37.5 mg doxorubicin/mL beads is recommended, in consideration of a practical therapeutic dose and optimum handling characteristics. According to an animal pharmacokinetic study comparing two sizes of doxorubicin-eluting beads (100-300 μm and 700-900 μm) loaded with same amount of doxorubicin, treatment with the smaller beads (100-300 μm) elicited higher doxorubicin plasma levels[16]. This finding was caused by the increased surface area of the smaller beads, leading to a profuse release of doxorubicin.

In DEB-TACE, the extent of the liver cancer burden should be considered in planning the dose of doxorubicin. As a general rule, for patients within the Milan criteria (defined as single tumor $\leqslant$ 5 cm, or multiple tumors of up to three and < 3 cm each), a planned dose should be up to 75 mg doxorubicin loaded into one vial, including

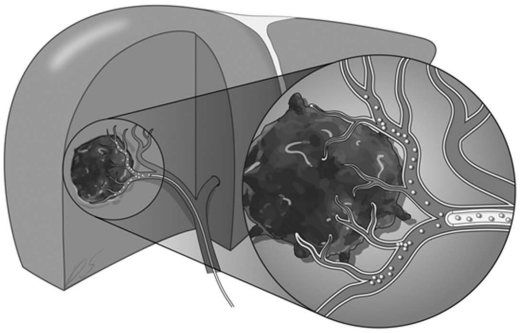

Figure 1 Action mechanism of drug-eluting bead-transarterial chemoembolization in hepatocellular carcinoma. Sustained release of chemotherapeutic agents from microbeads of uniform size, which embolize supplying vessels more distally, enables local concentration of cytotoxic agents to be higher within tumor.

2 mL of DC beads in each single treatment. Meanwhile, for patients beyond the Milan criteria, each treatment should involve a dose up to 150 mg loaded into two vials of DC beads[17]. Generally, the recommended size of beads is 100-300 μm for standard DEB-TACE procedures. This choice is based on the fact that small particles can be transported inside the tumor or in nearness to the tumor margin, and thus they are ideal for drug delivery or accurate embolization.

cTACE *VS* DEB-TACE: OVERALL EFFICACY AND SAFETY IN INTERMEDIATE AND ADVANCED STAGE HCC

The survival benefit of cTACE has been the issue of a finite number of randomized controlled trials (RCTs) that have provided controversial results[18]. Among seven RCTs[19-25] all published between 1988 and 2002, only two trials showed favorable results in respect of overall survival[19,20]. However, a systematic review based on these seven RCTs showed that cTACE has been found to improve 2-year survival (OR = 0.53; 95%CI: 0.32-0.89; *P* = 0.017) of patients with unresectable HCC, compared with best supportive care[26]. Subsequent sensitivity analysis in this study showed a significant survival benefit for chemoembolization with cisplatin or doxorubicin by analyzing 323 patients in four studies (OR = 0.42; 95%CI: 0.20-0.88), but not for embolization alone by assessing 215 patients in three studies (OR = 0.59; 95%CI: 0.29-1.20)[26]. In a current Cochrane review, the evidence based survival benefits of cTACE was challenged[27]. This meta-analysis involved RCTs published after 2002 and showed no solid evidence to support TACE or transarterial embolization (TAE) compared with conservative management, in patients with unresectable HCC. However, some experts have doubted such conclusions, because this review involved RCTs with inappropriate selection of patients and control arms, which likely biased the results of the analysis.

Primarily, DEB-TACE has been introduced to enhance the ability of drug-delivery to target tumor while reducing systemic toxicity and to provide a standardized embolic effect. The role of doxorubicin in embolic microspheres was evaluated in a randomized, cancer-size adjusted trial assessing DEB-TACE *vs* TAE with similar characteristics (BeadBlock-TAE)[28]. Although no survival benefit was reported in the study, the value of doxorubicin was favorable in the setting of TACE with microspheres, because DEB-TACE showed higher local response, less recurrence at 12 mo, and a longer time-to-progression than BeadBloc-TAE. Another trial assessed the rate of tumor necrosis after chemoembolization with epirubicin-loaded beads *vs* TAE with unloaded microspheres (Embosphere particles), which was pathologically proved in explanted livers of HCC patients undergoing liver transplantation: Epirubicin-loaded beads TACE showed complete necrosis in 77% of lesions, while TAE showed complete necrosis in only 27% of lesions (*P* = 0.043)[29]. A recently reported prospective clinical trial of DEB-TACE in a large Korean HCC population showed an overall 6-mo survival rate was 97.4%, although more than half of patients had early stage HCC (BCLC-A, *n* = 77, 50.7%)[30]. Varela *et al*[7] firstly reported that systemic concentrations of doxorubicin were significantly lower in patients treated with DEB-TACE than patients treated with cTACE. This result was verified by Poon *et al*[14], who performed DEB-TACE with possibly the highest dose of doxorubicin (150 mg). Both studies showed that none of treated patients exhibited doxorubicin-related systemic toxicity (alopecia, bone marrow suppression, or dyspnea)[7,14].

Despite the aforementioned theoretical advantages of DEB-TACE, previous studies comparing DEB-TACE with cTACE in HCC of intermediate stage have shown rather conflicting results. Recently reported meta-analysis showed that the two modalities represent comparable results, suggesting an absence of difference in tumor response between DEB-TACE and cTACE[31]. On the contrary, three other meta-analyses, assessing the efficacy of DEB-TACE *vs* cTACE in HCC patients, showed different results[32-34]. Huang *et al*[32] (seven studies, *n* = 700) and Xie *et al*[33] (six studies, *n* = 652) demonstrated that significantly better objective tumor response was found for DEB-TACE than for cTACE. In another meta-analysis of nine studies (866 patients) conducted in 2016, DEB-TACE presented significantly higher complete response rate and better overall survival, although similar objective tumor responses compared with cTACE. Regarding adverse events in these meta-analyses[32-34], overall and severe adverse events were similar or slightly lower in patients receiving DBE-TACE than patients receiving cTACE. Tables 1 and 2 summarize the clinical outcomes and adverse events of the studies that were included in these meta-analyses comparing DEB-TACE and cTACE.

Among randomized controlled trials reported until recently, the largest trial is the PRECISION V phase-2 trial assessing DEB-TACE *vs* cTACE in 212 patients with mostly HCC of intermediate stage[10]. The primary

Table 1 Clinical outcomes from studies comparing drug-eluting bead-transarterial chemoembolization and conventional transarterial chemoembolization in patients with intermediate-stage hepatocellular carcinoma

Ref.	Study design	Arm	BCLC stage *n* (A/B/C)	Clinical outcomes in intermediate-stage (BCLC-B) (DEB-TACE/cTACE)					
				OS rate	*P* value	TTP	*P* value	Response rate	*P* value
Lammer *et al*[10]	RCT	DEB-TACE	24/69/0	NR		NR		OR 52.4%/34.7%[2]	0.038
		cTACE	29/79/0					DC 63.5%/44.4%[2]	0.026
Wiggermann *et al*[46][1]	Retrospective	DEB-TACE	1/17/3	70%/55% (1-yr	0.01	NR		OR 22.7%/22.7%[3]	
		cTACE	4/15/2	survival rate)				DC 90.9%/68.2%[3]	0.066
Song *et al*[9]	Retrospective	DEB-TACE	27/33/0	DEB > cTACE	0.020	DEB > cTACE	0.038	OR 75.6%/34.1%[4]	< 0.001
		cTACE	28/41/0	(log-rank test)		(log-rank test)			
Golfieri *et al*[35]	RCT	DEB-TACE	41/26/22	NR		NR		CR 19.2%/26.1%[5]	0.734
		cTACE	41/23/24					CR 42.1%/22.2%[6]	0.295

[1]In this study, subgroup analysis according to BCLC stage was not performed. However, majority of patients was BCLC-B (DEB-TACE, 81%; cTACE, 71%); [2]The 6-mo tumor response rate, according to the European Association for the Study of the Liver response criteria; [3]The average 8-mo tumor response rate, according to the EASL response criteria; [4]The 3-mo tumor response rate, according to the mRECIST; [5]The 1-mo; [6]The 6-mo tumor response rate, according to the EASL criteria and mRECIST. RCT: Randomized controlled trial; OS: Overall survival; TTP: Time to progression; NR: Not reported; OR: Objective response; DC: Disease control; CR: Complete response; mRECIST: Modified Response Evaluation Criteria in Solid Tumors; BCLC: Barcelona Clinic Liver Cancer; TACE: Transarterial chemoembolization; DEB: Drug-eluting bead.

Table 2 The incidence of adverse events from studies comparing drug-eluting bead-transarterial chemoembolization and conventional transarterial chemoembolization in patients with unresectable hepatocellular carcinoma

Adverse event	Lammer *et al*[10]	Wiggermann *et al*[46]	Song *et al*[9]	Golfieri *et al*[35]
Nausea	Post-embolization syndrome	Post-embolization syndrome	Post-embolization syndrome	2.2%/3.4%, *P* = 0.682
Pain	24.7%/25.9%	21.7%/16.3%, *P* = 0.52	22.2%/20.6%, *P* = 0.850	24.7%/71.6%, *P* = 0.01
Fever				7.9%/11.4%, *P* = 0.457
Fatigue				0%/4.5%, *P* = 0.059
Marrow suppression	5.4%/5.6%	NR	NR	NR
Cholecystitis	NR	NR	4.7%/3.3%, *P* = 0.692	2.2%/1.1%, *P* = 0.999
Abscess	NR	[2]	NR	1.1%/1.1%, *P* = 0.999
Alopecia	1.1%/20.4%	NR	NR	NR
Liver function worsening	Significant reduction in DEB[1]	NR	AST, 36%/52%, *P* = 0.259	1.1%/5.7%[3], *P* = 0.118
			ALT, 31%/20%, *P* = 0.280	
Hematoma	NR	NR	NR	1.1%/3.4%, *P* = 0.368
Infection	NR	NR	NR	0%/1.1%, *P* = 0.497

[1]The mean maximum ALT elevation in the DEB-TACE group was 50% less than in the cTACE group (95%CI: 39%-65%; *P* < 0.001) and 41% less with regard to AST (95%CI: 46%-76%; *P* ⩽ 0.001); [2]Major complications was defined hospitalization > 24 h, greater therapy and unplanned added costs in treatment, permanent persisting sequelae and death of the patient. DEB-TACE *vs* cTACE, 13.0% (*n* = 6, including 2 liver abscesses) *vs* 2.3% (*n* = 1), *P* = 0.06; [3]Increase in Child-Push score of ⩾ 2 points. DEB-TACE: Drug-eluting bead-transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization; ALT: Alanine aminotransferase; AST: Aspartate transaminase; NR: Not reported.

efficacy endpoint (response at 6 mo, *P* = 0.11) and primary safety endpoint (incidence of severe adverse events within 30 d, *P* = 0.86) were comparable in both two groups. After performing a post hoc comparison, the DEB-TACE group indicated a significant decrease in chemotherapeutic agent-related systemic and liver toxicity compared to the cTACE group. Furthermore, in subgroup analysis, the objective response rate and disease control rate were significantly better (*P* = 0.038 and *P* = 0.026, respectively) with DEB-TACE than with cTACE in 67% of patients with more advanced disease (Child-Pugh B, bilobular or recurrent disease, ECOG 1). Another RCT for evaluating the potential effect of DEB-TACE on overall survival, compared to cTACE using epirubicin, showed no statistical differences between both modalities in terms of survival, treatment response, or adverse episodes[35]. However, it should be considered that the maximally used dose of doxorubicin/epirubicin was limited to only 75 mg for both procedures in this trial. Furthermore, the trial mainly recruited patients with low tumor burden (46% of patients with early HCC, only 20% patients with bilobar disease). Thus, this restricted one of the significant advantages of DEB-TACE, which is the ability to use higher doxorubicin doses without rising drug-related systemic toxicity in patients with larger tumor burden as mentioned in the PRECISION V study. This trial indicated that DEB-TACE did not show better clinical outcomes, compared with cTACE in patients with relatively well preserved liver function and low tumor burden. A retrospective study by Song *et al*[9] reported that overall survival and treatment responses for DEB-TACE were significantly better than those for cTACE. Performing subgroup analysis in accordance with BCLC stage, treatment efficacy was shown in intermediate stage HCC (BCLC B) but not in early stage HCC (BCLC A). Regarding adverse events, there was no statistically significant difference between DEB-TACE and cTACE. On the contrary, a recently published retrospective study

showed that overall survival, time to progression, and disease control rate were not significantly different between DEB-TACE and cTACE groups, even when subgrouped by BCLC stage[36]. However, the incidence of adverse events was significantly lower, particularly in HCC larger than 5 cm in BCLC-B patients receiving DEB-TACE[36]. Considering the results from these studies, there is still controversy regarding clinical outcomes. However, it seems that DEB-TACE shows at least similar efficacy and less adverse events than cTACE. DEB-TACE might be favorable to cTACE for large HCC especially in patients with decreased liver function, even though there is lack of evidence that DEB-TACE is superior to cTACE in term of efficacy.

For advanced HCC (BCLC C), the role of chemoembolization has not been fully established. In accordance with the BCLC staging system, it recommends systemic treatment or palliative therapy to patients with advanced stage. In a small retrospective study comparing cTACE and sorafenib in patients with advanced HCC, overall survival in the cTACE group was higher than the sorafenib group (9.2 mo *vs* 7.4 mo, $P = 0.377$)[37]. Recently, two studies on DEB-TACE for patients with advanced HCC were reported: Kalva *et al*[38] conducted a retrospective trial recruiting 80 patients with advanced HCC treated with DEB-TACE. This study reported median progression free survival of 5.1 mo (95%CI: 4.1-7.7) and overall survival of 13.3 mo (95%CI: 10.1-18.6). Subgroup analysis showed that median survival was better in patients with ECOG performance status (PS) $\leqslant$ 1 than ECOG PS > 1 (17.7 mo *vs* 5.6 mo, $P = 0.025$, respectively). Another retrospective study by Prajapati *et al*[39] reported median survival of 13.5 mo (range, 8.2-18.7 mo) without severe adverse episodes. Subgroup analyses showed that the median survival of Child-Pugh class A patients was 17.8 mo (range, 9.0-26.7 mo). In comparison with median survivals of 10.7 mo and 6.5 mo for sorafenib in the SHARP and Asia-Pacific trials[40,41], it appears that cTACE as well as DEB-TACE shows better or at least comparable efficacy in patients with advanced stage HCC, Child-Pugh class A and good performance status.

A major limitation of TACE is a high rate of cancer recurrence. In two RCTs, a sustained response lasting for 3 to 6 mo was reported in only 28% to 35% of patients treated with cTACE[19,20]. Recently, several trials made an attempt to analyze the potential benefit of combined strategies with chemoembolization and other treatment options for overcoming this limitation. Several RCTs have sought to determine the benefit of an addition of sorafenib to cTACE or DEB-TACE in patients with more advanced HCC. The rationale for this concept is grounded in the demonstration that TACE causes hypoxia and induce angiogenesis by activating angiogenic factors and that the use of sorafenib could decrease angiogenesis. However, these RCTs have not proved definite improvement of clinical outcomes in combination therapy of sorafenib and chemoembolization, compared with chemoembolization alone[42,43]. Recently, trials have been conducted on combination of TACE with other molecular target agents, such as brivanib, sunitinib, and thalidomide. It is hoped that these ongoing trials will contribute to the determination of optimal combinations.

CONTROVERSIAL ISSUES ON cTACE *VS* DEB-TACE

Apart from the overall comparison of clinical outcomes between conventional and DEB-TACE, it is still controversial as to whether DEB-TACE is superior to cTACE in large HCC ($\geqslant$ 5 cm), which frequently suffers from incomplete response or recurrence after cTACE[44] Considering that liver damage given by DEB-TACE is less than that by cTACE, it might be assumed that DEB-TACE offers more therapeutic advantages over cTACE in large HCC. However, regarding response to procedures, complete response rates at 1 and 6 mo were lower in HCC larger than 5 cm, compared with HCC less than 2 cm or 2-5 cm in size[30]. Moreover, in a Korean retrospective study, there was no significant difference in survival between cTACE and DBE-TACE in HCC larger than 5 cm (36.3 mo *vs* 33.4 mo, $P = 0.702$)[36]. Therefore, the notion that a big tumor is more appropriate for DEB-TACE than for cTACE is not currently accepted. Paradoxically, small HCC (less than 2 cm) is sometimes difficult to achieve complete response to both cTACE and DEB-TACE, because the tumor vascularity is fine. In particular, unlike lipiodol in cTACE, the diameter of microspheres in DEB-TACE is still too wide to block peripheral hepatic arteries. Accordingly, the outcomes of small HCC (< 2 cm) treated with DEB-TACE, compared to cTACE are controversial. Indeed, the time to progression after DEB-TACE was shorter that after cTACE in HCC < 2 cm (10.3 mo *vs* 13.8 mo, $P = 0.023$), although there was no difference in overall survival between the two modalities[36]. Lastly, repeated sessions of a procedure could be another distinguishing advantage or disadvantage between cTACE and DEB-TACE. The severity of hepatic arterial damage has been compared between cTACE and DEB-TACE in a retrospective study. After a single session of cTACE or DEB-TACE, the incidence of hepatic arterial damage was significantly higher for DEB-TACE group than cTACE, with doxorubicin dose being a possible risk factor for such damage[45].

CONCLUSION

In comparison with cTACE, DEB-TACE facilitates higher concentrations of drugs within the target tumor and lower systemic concentrations. Despite the theoretical advantages of DEB-TACE, it is still controversial in several clinical studies as to whether DEB-TACE is superior to cTACE in terms of efficacy. However, it seems that DEB-TACE shows at least similar clinical outcomes and less adverse events than cTACE. In order to gain better results for these treatment modalities, selecting proper candidate patients for DEB-TACE or cTACE is needed. Moreover, further well-defined studies are required to identify combination strategies and to develop better

treatment approaches for patients with advanced HCC.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors for acute kidney injury after partial hepatectomy

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Abstract

AIM

To identify risk factors for the occurrence of acute kidney injury (AKI) in the postoperative period of partial hepatectomies.

METHODS

Retrospective analysis of 446 consecutive resections in 405 patients, analyzing clinical characteristics, preoperative laboratory data, intraoperative data, and postoperative laboratory data and clinical evolution. Adopting the International Club of Ascites criteria for the definition of AKI, potential predictors of AKI by logistic regression were identified.

RESULTS

Of the total 446 partial liver resections, postoperative AKI occurred in 80 cases (17.9%). Identified predictors of AKI were: Non-dialytic chronic kidney injury (CKI), biliary obstruction, the Model for End-Stage Liver Disease (MELD) score, the extent of hepatic resection, the occurrence of intraoperative hemodynamic instability, post-hepatectomy haemorrhage, and postoperative sepsis.

CONCLUSION

The MELD score, the presence of non-dialytic CKI

and biliary obstruction in the preoperative period, and perioperative hemodynamics instability, bleeding, and sepsis are risk factors for the occurrence of AKI in patients that underwent partial hepatectomy.

Key words: Kidney injury; Hepatectomy; Postoperative; Liver; Resection

Core tip: Acute kidney injury (AKI) is a serious complication after partial hepatectomy. This research aims to identify risk factors for the occurrence of AKI in the postoperative period of partial hepatectomies. The Model for End-Stage Liver Disease score, the presence of non-dialytic chronic kidney injury and biliary obstruction in the preoperative period, and perioperative hemodynamics instability, bleeding, and sepsis are risk factors for the occurrence of AKI in patients that underwent partial hepatectomy.

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INTRODUCTION

Despite of the limited data regarding the occurrence of acute kidney injury (AKI) after partial hepatectomy, the reported incidence ranges from 0.9% to 15.1%[1-4]. A comprehensive analysis of the scarce data[5] is also hampered by the lack of consensus in the exact definition of AKI after liver resection.

Candidates for liver resections often present with multiple potential risk factors regarding postoperative AKI, such as excessive bleeding during the hepatectomy, and the occurrence of post-hepatectomy liver failure (PLF)[2,3,5-7]. Eventually, patients can have a combination of insults, that can be aggravated by distributive circulatory derangements by sepsis[2,3,5-8] or exposure to nephrotoxic drugs[9].

The hemodynamic changes in patients after major liver resections, mainly in patients with underlying chronic liver injury, may simulate those of patients with acute liver failure or cirrhosis[10]. Thus, the current criteria suggested by the International Club of Ascites (ICA) for definition of AKI would be the most appropriate criteria for these patients[11], since urine output measurement and static serum creatinine (sCr) levels are not included in ICA criteria.

Assuming post-operative AKI as primary endpoint, the aim of the present report was to identify the risk factors for the occurrence of this serious complication after partial hepatectomies.

MATERIALS AND METHODS

This report is based on a historical cohort study of patients who underwent partial hepatectomy from January 2008 to July 2016 at the Hepatobiliary Surgery Department of Cancer Hospital-UOPECCAN. Patients with evidence of dialytic chronic renal dialysis at the time of surgery, the need of emergency hepatectomy or patients who died at the intraoperative or immediate postoperative period (within the first 24 h after the procedure) were excluded. The study was approved by the Research Ethics Board at West Parana University (No. 1.665.135; July 2016), and the need for informed written consent was waived. The study was conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Preoperative data

The data collected included: Patient demographic data, preoperative use of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme and inhibitors, the presence of comorbidities including: Non-dialytic chronic kidney disease (CKI), defined as estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m^2[12], liver cirrhosis with Model End- Liver Disease (MELD) score calculation[13], biliary obstruction and prior exposure to chemotherapy.

Preoperative baseline laboratory tests values were obtained from the patient electronic charts in the previous 3 mo, and in patients with more than one value, the value closest to the hospitalar admission date were selected. Laboratory tests included: Serum dosages of urea, creatinine, sodium, potassium, bilirubin, and albumin, International Normalized Ratio value, serum platelet count and eGFR value calculation according to the formula[14]:

eGFR: mL/min per 1.73 m^2 = k × 186 × $(sCr)^{-1.15}$ × $(age)^{-0.203}$;

K = 1 (if male) or 0.72 (if female)

Intraoperative and surgical data

The surgical and anesthesic covariates recorded were: Open or laparoscopic resection, extent of liver resection (major hepatectomy was defined as resection of at least three Couinaud liver segments), resection modalities according to Brisbane nomenclature[15], type of vascular clamping of the liver (intermittent Pringle maneuver[16], continuous Pringle maneuver[17] or total vascular exclusion[18]), segment I resection, two-stage resection[19], associated extrahepatic resection, complex vascular reconstruction (portal vein, hepatic artery or hepatic veins, with or without protesis), regional lymphadenectomy (hepatic pedicle lymph nodes[20]), intraoperative transfusions of red blood cells, and intraoperative hemodynamic instability, defined as a sustained systolic blood pressure less than 90 mmHg or more than 40 mmHg below the patient's usual systolic blood pressure during 30 min.

Postoperative data and complications

Similarly to the preoperative laboratory blood tests, we retrieved its values in the postoperative period, including the most altered values in the first 30 postoperative days.

Postoperative complications the first 30 postoperative

Table 1 Postoperative overall complications and acute kidney injury staging according to International Club of Ascites[11], risk, injury, failure, loss, end-stage[27] and Acute Kidney Injury Network[28] criteria (*n* = 446) *n* (%)

Overall complications	113 (25.3)
Overall complications (Clavien-Dindo classification)	
I	46 (10.3)
II	25 (5.6)
III a/b	18 (4.0)
IV a/b	7 (1.6)
V (death)	17 (3.8)
AKI (ICA)	80 (17.9)
I	26 (5.8)
II	21 (4.7)
III	33 (7.4)
AKI (RIFLE)	70 (15.7)
Risk	16 (3.6)
Injury	21 (4.7)
Failure	33 (7.4)
AKI (AKIN)	80 (17.9)
I	26 (5.8)
II	21 (4.7)
III	32 (7.2)
HRS	11 (2.5)
RRT (hemodyalises)	9 (2.0)

AKI: Acute kidney injury; ICA: International Club of Ascites; RIFLE: Risk, injury, failure, loss, end-stage; AKIN: Acute Kidney Injury Network; HRS: Hepatorenal syndrome; RRT: Renal replacement therapy.

days recorded were: Post-hepatectomy haemorrhage (PHH)[21], post-hepatectomy liver failure (PHLF)[22], biliary fistula[23], postoperative ascites, wound infection[24], pulmonary complications, including pulmonary infection[25], acute respiratory distress syndrome and acute lung injury[26], cardiovascular complications, including coronary insufficiency, cardiac arrhythmias, peripheral thrombosis, thromboembolism, and stroke[5].

The occurrence and staging of AKI were defined according to the ICA[11] criteria, although the RIFLE[27] and AKIN[28] criteria were used for comparative purposes (Table 1). The use of aminoglycosides, renal replacement therapy (hemodyalisis), the occurrence of hepatorenal syndrome (HRS)[11] and hospitalization time in days were recorded. The overall complications were classified according do Clavien-Dindo classification for postoperative complications[29].

Statistical analysis

To ensure the stability of our multivariate model, the sample size of the study was determined based on the results of a historical cohort not published in our Hepatobiliary Surgery Department, with an incidence of ARF after partial hepatectomies fixed at 18%, ensuring the adequate number of events per variable[30]. Categorical variables were expressed in absolute numbers and percentages were compared by the χ^2 test or Fisher's exact test when indicated. Continuous variables were expressed as absolute and mean ± SD, and the comparison by the Student's *t*-test or non-parametric Mann-Whitney test after checking the normality assumptions by the Shapiro-Wilk test. The variables selected in the univariate model ($P < 0.05$) were tested in the multiple logistic regression model to identify independent binary predictors on the occurrence of postoperative AKI. The results of the model were expressed by means of the odds ratio, together with the corresponding 95%CIs and the p values of the Wald test. A value of $P < 0.05$ (two-tailed) was considered significant. Statistical calculations were made with the software GPower 3.0.10 and SPSS 16.0 package for Windows.

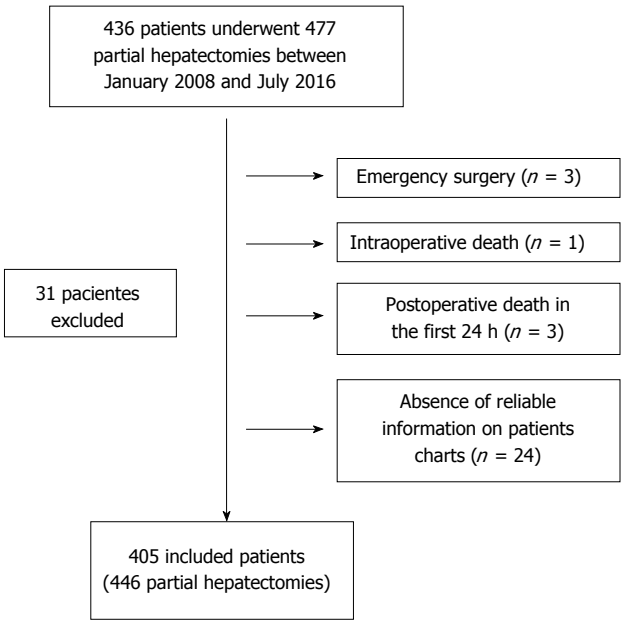

Figure 1 Flow chart outlining the included and excluded patients in the study.

RESULTS

During the period from January 2008 to July 2016, 436 patients underwent liver resection surgery, of which 31 patients were excluded, with 405 included patients in the study for the final analysis (Figure 1).

Of the total of included patients, 271 underwent minor partial hepatectomies (60.7%) and 175 patients (39,3%) underwent major resections, and the most common resection modalities according to Brisbane nomenclature[14] were bisegmentectomy in 105 patients, segmentectomy in 103 patients, right hepatectomy in 85 patients, non-anatomical resections in 63 patients and left hepatectomy in 45 patients. The segment I were resected in 31 patients.

The most common indications for partial hepatectomy in patients with malignant tumors were colorectal cancer metastases 183 patients (41%) and hepatocellular carcinoma in 75 patients (16.8%), and patients with benign tumors were hepatic adenoma in 35 patients (7.8%) and hepatic hemangioma in 15 patients (3.4%).

Table 2 shows the clinical data of the patients prior the 466 partial hepatectomies according to the occurrence of AKI. It is observed that in the AKI group the prevalence

Table 2 Preoperative patient characteristics according to the occurrence of postoperative acute kidney injury in 466 partial hepatectomies *n* (%)

	No AKI (*n* = 366)	AKI (*n* = 80)	*P*
Gender, male	180 (49.2)	43 (53.8)	0.269
Age (years), mean (SD)	54.6 (16.57)	57.4 (16.10)	0.842
ACE inhibitors	19 (5.2)	10 (12.5)	0.210
NSAIDs	26 (7.1)	10 (12.5)	0.082
Non-dialytic CKI	1 (0.27)	8 (10.0)	< 0.001
Diabetes mellitus	44 (12.0)	14 (17.5)	0.121
Systemic arterial hypertension	70 (19.1)	15 (18.8)	0.467
Preoperative chemotherapy	85 (23.2)	24 (30.0)	0.402
Cirrhosis	23 (6.3)	10 (12.5)	0.042
MELD score, mean (SD)	7.67 (1.15)	8.05 (1.05)	0.020
Biliary obstruction	6 (1.6)	13 (16.2)	< 0.001
Baseline laboratory tests			
Serum urea (mg/dL), mean ± SD	31.45 ± 10.71	35.63 ± 23.77	0.021
Serum creatinine (mg/dL), mean ± SD	0.90 ± 0.71	0.98 ± 0.62	0.229
eGFR (mL/min per square meter), mean ± SD	98.38 ± 51.32	89.86 ± 35.46	0.944
Sodium (mEq/L), mean ± SD	135.67 ± 3.25	134.25 ± 3.00	0.350
Potassium (mEq/L), mean ± SD	4.44 ± 0.63	4.34 ± 0.75	0.697
INR, mean ± SD	1.13 ± 0.45	1.14 ± 0.20	0.912
Bilirrubin (mg/dL), mean ± SD	1.63 ± 3.05	2.84 ± 3.95	0.002
Albumin (g/dL), mean ± SD	3.61 ± 0.87	3.41 ± 0.92	0.505
Platelets (mm^3), mean ± SD	211869.55 ± 103744.67	215522.81 ± 115186.57	0.129

AKI: Acute kidney injury; ACE: Angiotensin conversion enzyme; NSAIDs: Non-steroidal anti-inflamatory drugs; CKI: Chronic kidney injury; MELD: Model for End-Stage Liver Disease; INR: International normalized ratio.

Table 3 Intraoperative characteristics of the 446 liver resections according to the occurrence of postoperative acute kidney injury *n* (%)

	No AKI (*n* = 366)	AKI (*n* = 80)	*P*
Surgical approach			0.071
Open	343 (93.7)	79 (98.8)	
Laparoscopic	23 (6.3)	1 (1.2)	
Extention of resection			0.002
Major resection	128 (35.2)	45 (56.2)	
Minor resection	238 (64.8)	35 (43.8)	
Tumoral histology			0.134
Benign	70 (19.1)	6 (7.5)	
Malignant	296 (80.9)	74 (92.5)	
Segment I resection	23 (6.3)	8 (10.0)	0.098
Two-stage hepatectomy	26 (7.1)	6 (7.5)	0.439
Intermitent Pringle maneuver (15'\5')	124 (33.9)	31 (38.8)	0.438
Continuous Pringle maneuver	26 (7.1)	10 (12.5)	0.254
Total vascular exclusion	6 (1.6)	2 (2.5)	0.212
Complex vascular reconstruction	6 (1.6)	1 (1.2)	0.634
Regional lymphadenectomy	86 (23.5)	25 (31.2)	0.155
Associated extrahepatic resection	27 (7.4)	10 (12.5)	0.103
Intraoperative instability	26 (7.1)	25 (31.2)	< 0.001
Red blood cell transfusion	31(8.5)	23 (28.8)	< 0.001

AKI: Acute kidney injury.

of non-dialytic CKI and cirrhosis were higher, as well as higher MELD scores and biliary obstruction prior to partial hepatectomy. Regarding preoperative laboratory tests, the AKI group had higher bilirubin levels than non-AKI group, 2.84 ± 3.95 mg/dL *vs* 1.63 ± 3.05 mg/dL, respectively.

Overall and renal postoperative complications rates are shown in Table 1. A total of 113 patients (25.3%) presented some type of complication, and according to the Dindo-Clavien scale, the complications grade I were the most common, occurring in 46 patients (10.3%). According to ICA criteria, AKI occurred in 80 patients (17.9%), as well as by the AKIN criteria. A slight difference in the incidence of AKI was observed according to RIFLE criteria (15.7%).

Regarding surgical and intraoperative information, patients with AKI underwent more extensive surgical procedures (major hepatectomies), and especially, had significantly higher rates of hemodynamic instability and red blood cell transfusion during liver resections than non-AKI patients, 31.2% *vs* 7.1% and 28.8% *vs* 8.5%, respectively, with $P < 0.001$ for both variables (Table 3).

According to the postoperative laboratory tests (Table 4), patients with AKI had significantly higher levels of urea and creatinine after surgery, with a significant lower eGFR, 53.73 ± 34.38 mL/min per square meter *vs* 83.24 ± 60.04 mL/min per square meter ($P < 0.001$).

In the postoperative evolution, patients with AKI had higher rates of IHPH (25%), PHH (11.2%), sepsis (16.2%) and longer hospital stay (12.20 ± 9.41 d) (Table 4). According to the univariate model (Table 5), six covariates were statistically more frequent in the AKI group and the six were confirmed in the multiple logistic regression model as predictors: MELD score, the presence of biliary obstruction and non-dialytic CKI in the preoperative period, intraoperative hemodynamic instability, and finally PHH and sepsis in the postoperative period.

DISCUSSION

This study aimed to identify the main risk factors for AKI in the postoperative period of partial hepatectomies.

Table 4 Postoperative laboratory tests values and complications after 466 partial hepatectomies according to the occurrence of postoperative acute kidney injury *n* (%)

	No AKI (*n* = 366)	AKI (*n* = 80)	*P*
Laboratoty tests			
Serum urea (mg/dL), mean ± SD	47.61 ± 49.36	82.19 ± 77.45	< 0.001
Serum creatinine (mg/dL), mean ± SD	1.29 ± 1.16	2.29 ± 2.21	< 0.001
eGFR (ml/min/m^2), mean ± SD	83.24 ± 60.04	53.73 ± 34.38	< 0.001
Sodium (mEq/L), mean ± SD	132.88 ± 4.27	132.29 ± 5.55	0.385
Potassium (mEq/L), mean ± SD	4.86 ± 0.81	5.16 ± 0.94	0.013
INR, mean ± SD	1.82 ± 2.46	2.08 ± 1.161	0.438
Bilirrubin (mg/dL), mean ± SD	3.46 ± 4.54	4.54 ± 6.84	0.001
Albumin (g/dL), mean ± SD	2.58 ± 0.62	2.36 ± 0.59	0.069
Platelets (mm^3), mean ± SD	144101.93 ± 120446.829	132906.89 ± 113193.18	0.518
Aminoglycosides	7 (1.9)	3 (3.8)	0.341
PHLF	7 (1.9)	21 (26.3)	< 0.001
A	4 (1.1)	3 (3.8)	
B	3 (0.8)	10 (12.5)	
C	0 (0)	8 (10.0)	
PHH	1 (0.3)	9 (11.3)	< 0.001
A	0 (0)	2 (2.5)	
B	0 (0)	4 (5.0)	
C	1 (0.3)	3 (3.8)	
Biliary fistula	25 (6.8)	10 (12.5)	0.086
A	15 (4.1)	6 (7.5)	
B	7 (1.9)	3 (3.8)	
C	3 (0.8)	1 (1.2)	
Postoperative ascites	58 (15.9)	23 (28.8)	0.059
Wound infection	13 (3.6)	7 (8.8)	0.062
Pulmonary complications	15 (4.1)	6 (7.5)	0.177
Cardiovascular complications	7 (1.9)	2 (2.5)	0.501
Sepsis	2 (0.5)	13 (16.2)	< 0.001
Hospital stay (d), mean ± SD	6.68 ± 3.65	12.20 ± 9.41	0.008

AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate; PHLF: Post-hepatectomy liver failure; PHH: Post-hepatectomy haemorrhage.

Table 5 Univariate and logistic regression analyses of risk factors for acute kidney injury

Univariate analyses	Multiple logistic regression			
	P	OR	95%CI	*P*
Extent of resection	0.002	2.249	1.217	4.156	0.010
Biliary obstruction	< 0.001	10.240	3.094	33.891	< 0.001
Hemodynamics instability	< 0.001	5.244	1.337	20.568	0.017
Red blood cell transfusion	< 0.001				0.244
Cirrhosis	0.042				0.241
MELD score	0.020	4.342	1.347	15.654	0.046
Sepsis	< 0.001	11.609	3.185	39.911	< 0.001
Posthepatectomy haemorrhage	< 0.001	12.652	7.769	53.612	< 0.001
CKI	< 0.001	8.975	1.533	44.675	0.022

AKI: Acute kidney injury; OR: Odds ratio; MELD: Model for End-Stage Liver Disease; CKI: Chronic kidney injury.

There is a certain disparity of the available criteria for postoperative AKI definition in these situations, thus, we adopted the current criteria suggested by the ICA[11] for definition of AKI in cirrhotic patients. In patients eligible for partial hepatectomy with underlying liver diseases or who underwent major liver resections, often the both, the ICA criteria[11] do not include unreal measurements for these patients, such as static sCr measurements and urine output.

The incidence of AKI in the present study according to ICA and AKIN criteria was 17.9%, and according to RIFLE criteria was 15.7%. These AKI incidence were higher than other publications on the subject[1-5]. The AKIN and RIFLE criteria were applied for comparison, and this slight underestimation of AKI by RIFLE criteria can be probably explained by the fact that the ICA and AKIN criteria consider as stage I AKI a small increase of 0.3 mg/dL in sCr.

Including AKI, the overall complication rate in this study was 25.3%, and the mortality rate was 3.8%, that is comparable to the results of two large retrospective studies evaluating morbidity and mortality of partial hepatectomies[31,32].

The present study did not neglect the analysis of the two main AKI risk factors after partial hepatectomies, which would be perioperative bleeding and PHLF[6]. Peri-

operative haemorrhage with renal hypoperfusion[6], with or without the deleterious effects of blood transfusion[3], was a strong predictor of postoperative AKI in this study, reflected by intraoperative hemodynamic instability and posthepatectomy haemorrhage. An increased renal susceptibility to the perioperative renal ischemia[22-25], such as in CKI, was a predictor in the authors' series.

Additionally, it is expected that major resections may have larger blood losses during operation and higher incidence of PHLF as well, it was corroborated by the significant influence of major resections on AKI occurrence, according to our logistic regression model. In a recent report of a large series of liver resections for hepatocellular carcinoma, major liver resection was a predictor for postoperative AKI[4].

For prevention of intraoperative bleeding, there are intraoperative maneuvers that may be crucial, such as vascular control of the liver[2] and LCVP anesthesia[1,33,34], preventing the back bleeding from hepatic veins,. The Pringle maneuver (intermittent[16] or continuous[17]) is routinely applied in liver resections at the authors' Department, thus there was no difference between the groups, and LCVP anesthesia parameters were not evaluated.

Second factor relates to the occurrence of PLF with its distributive circulatory changes, which is a major cause of death after hepatic resection, and eventually can progress to HRS[11]. Similar to the results from a previous report[4], the MELD score[13], a usefully and extensively validated tool for predicting liver failure progression, was a predictor of postoperative AKI, and the most important, it can be applied in the preoperative period.

The presence of biliary obstruction was an independent predictor of postoperative AKI according to the authors' results, and the mechanism by which bilirubin may be toxic to the kidneys seems to be inflammatory as well as obstructive[35], and hemodynamic changes may also play a role in biliary cast nephropathy[36]. In addition to the aforementioned effects, patients who are candidates for surgery in the presence of biliary obstruction with congestive cholestasis in the liver[37,38] may undergo major hepatic resections, with consequent decrease in the volume of a functionally deficient liver parenchyma, predisposing for PHLF.

Eventually, patients can have combinations of renal insults that can be aggravated by sepsis[2,3,5,6], which was an independent predictor in the authors' analysis. The septicemia and its hemodynamic and systemic repercussions may eventually coexist with liver failure, often being the final event of PHLF[5].

The shortcomings of the current study, besides its retrospective nature, were the non-inclusion of anesthesic maneuvers among covariates, such was LCVP anesthesia, and the non-inclusion of hepatic steatosis, since it is a determinant of the functional quality of the parenchyma[39,40]. As mentioned, the retrospective nature of the study did not allow the authors to include non-standardized non-reliable data.

In order to reduce the incidence of postoperative AKI after partial hepatectomy, a careful patient selection and preoperative resection planning are mandatory, specially in the case of predisposing CKI, biliary obstruction and underlying cirrhosis, in which MELD score calculation can be extremely worthfull[41-43]. Measures for preventing sustained intraoperative hypotension and postoperative bleeding must be undertaken, as well as prevention and prompt treatment of sepsis. In the case of high risk patients for postoperative AKI, the nephrologist must be promptly involved in multidisciplinary discussions.

COMMENTS

Background

Acute kidney injury (AKI) is an serious complication after partial hepatectomy, however, there are limited published data regarding this subject, in addition, there is no concensus about the definition of AKI in these patients.

Research frontiers

The present study did not neglect the analysis of the two main AKI risk factors after partial hepatectomies, which would be perioperative bleeding, with or without the deleterious effects of blood transfusion, and post-hepatectomy liver failure.

Innovations and breakthroughs

The hemodynamic changes in patients after major liver resections may simulate those of patients with acute liver failure or cirrhosis. Thus, the current criteria suggested by the International Club of Ascites (ICA) for definition of AKI would be the most appropriate criteria for these patients.

Applications

In order to reduce the incidence of postoperative AKI after partial hepatectomy, a careful patient selection and preoperative resection planning are mandatory, specially in the case of predisposing CKI, biliary obstruction and underlying cirrhosis, in which Model for End-Stage Liver Disease score calculation can be extremely worthfull.

Terminology

Candidates for liver resections often present with multiple potential risk factors regarding postoperative AKI, such as excessive bleeding during the hepatectomy, and the occurrence of post-hepatectomy liver failure (PLF). The current criteria suggested by theICA for definition of AKI would be the most appropriate criteria for these patients. For prevention of intraoperative bleeding, there are intraoperative maneuvers that may be crucial, such as vascular control of the liver and low central venous pressure anesthesia. Second factor relates to the occurrence of PLF with its distributive circulatory changes, that eventually can progress to hepatorenal syndrome.

Peer-review

This paper was retrospectively analyzed the clinical data, and found some risk factors of acute kidney injury. The material was rich, the result was reasonable, and the discussion did have some valuable information.

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ORIGINAL ARTICLE

Retrospective Study

Early acute kidney injury after liver transplantation: Predisposing factors and clinical implications

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Abstract

AIM

To investigate the additional clinical impact of hepatic ischaemia reperfusion injury (HIRI) on patients sustaining acute kidney injury (AKI) following liver transplantation.

METHODS

This was a single-centre retrospective study of consecutive adult patients undergoing orthotopic liver transplantation (OLT) between January 2013 and June 2014. Early AKI was identified by measuring serum creatinine at 24 h post OLT (> 1.5 × baseline) or by the use of continuous veno-venous haemofiltration (CVVHF) during the early post-operative period. Patients with and without AKI were compared to identify risk factors associated with this complication. Peak serum aspartate aminotransferase (AST) within 24 h post-OLT was used as a surrogate marker for HIRI and severity was classified as minor (< 1000 IU/L), moderate (1000-5000 IU/L) or severe (> 5000 IU/L). The impact on time to extubation, intensive care length of stay, incidence of chronic renal failure and 90-d mortality were examined firstly for each of the two complications (AKI and HIRI) alone and then as a combined outcome.

RESULTS

Out of the 116 patients included in the study, 50% developed AKI, 24% required CVVHF and 70% sustained

moderate or severe HIRI. Median peak AST levels were 1248 IU/L and 2059 IU/L in the No AKI and AKI groups respectively (P = 0.0003). Furthermore, peak serum AST was the only consistent predictor of AKI on multivariate analysis P = 0.02. AKI and HIRI were individually associated with a longer time to extubation, increased length of intensive care unit stay and reduced survival. However, the patients who sustained both AKI and moderate or severe HIRI had a longer median time to extubation (P < 0.001) and intensive care length of stay (P = 0.001) than those with either complication alone. Ninety-day survival in the group sustaining both AKI and moderate or severe HIRI was 89%, compared to 100% in the groups with either or neither complication (P = 0.049).

CONCLUSION

HIRI has an important role in the development of AKI post-OLT and has a negative impact on patient outcomes, especially when occurring alongside AKI.

Key words: Hepatic ischaemia reperfusion injury; Liver transplantation; Perioperative care; Acute kidney injury; Marginal grafts

Core tip: Acute kidney injury (AKI) is common after liver transplantation (LT), and has a significant impact on patient outcomes. It is multifactorial in aetiology and has been shown to correlate with the use of higher risk grafts, due to an increased risk of hepatic ischaemia reperfusion injury. In context of the growing use of marginal grafts to meet demands, this study has demonstrated that hepatic ischaemia reperfusion injury was the only variable that predicted early AKI post-LT and that the presence of both HIRI and AKI led to worse clinical outcomes and higher mortality than either complication alone.

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INTRODUCTION

Acute kidney injury (AKI) developing immediately after orthotopic liver transplantation (OLT) is common, and is associated with increased morbidity, mortality and resource utilisation[1]. It affects between 25% and 60% of recipients[2-4], the variation being largely related to the definition of AKI utilised[5,6]. The incidence of AKI following OLT is much higher than with other non-cardiac major surgery, in patients with previously normal renal function[7]. This reflects the additional risks facing the liver transplant recipient during the intra and post-operative course.

Multiple factors predisposing liver transplant patients to post operative AKI have been identified. Pre-operatively, existing renal impairment, increasing Model for End stage Liver Disease Score, diabetes mellitus, hypertension[4] and obesity have all been associated with post OLT renal dysfunction. Intraoperative mean arterial pressure, vasopressor requirements, blood loss and transfusion of blood products are additional risk factors[8,9]. Post-operatively, graft dysfunction and immunosuppression therapy have been regarded as the main renal insults.

More recently, the growing demand for organs in LT has led to the use of increasingly higher risk grafts, in order to reduce the waiting list mortality[10-12]. These include grafts from older donors, prolonged preservation period, graft steatosis, split or partial liver allografts and donation after cardiac death (DCD). In the United Kingdom, DCD organs in particular have been increasingly used over the last decade, accounting for 20% of all liver transplants in 2014/15 (compared to 17% in 2012 and 5% in 2005)[13-15]. This group have been shown to be at a higher risk of both hepatic and extra-hepatic complications, including AKI, which is the most common complication encountered following the transplantation of marginal grafts. The post-operative systemic inflammatory response that occurs as a result of the hepatic ischaemia reperfusion injury (HIRI) following warm ischaemia at retrieval is thought to play a critical role in the pathogenesis of renal injury in these patients[16]. In keeping with this, peak peri-operative serum aspartate aminotransferase (AST), which is a surrogate marker for HIRI[17,18], has been found to be a significant variable related to renal outcomes[19-21].

The additional impact of HIRI on early post-operative renal dysfunction of liver transplant recipients has not been widely investigated. Previous studies, especially those based on large national databases do not usually have sufficient clinical information to analyse the predisposing factors. Early identification of those at risk, followed by prevention and management of HIRI may have important implications on the outcomes of these patients.

The aims of this study were firstly to identify the incidence, risk factors and clinical outcomes of early AKI in our cohort of patients, and secondly to investigate the incidence of HIRI, its correlation with AKI and its additional impact on patient outcomes.

MATERIALS AND METHODS

Single-centre retrospective observational study of consecutive adults (≥ 18 years of age) undergoing OLT between January 2013 and June 2014 at the Royal Free London NHS Foundation Trust, one of the 8 Liver Transplant centres in the United Kingdom and Ireland. Exclusion criteria were those requiring urgent transplantation for acute liver failure and those receiving a combined liver-kidney transplant.

To analyse possible factors associated with post OLT AKI we included recipient age, gender, weight, aetiology of liver disease, Model for End-Stage Liver Disease (MELD) score, presence of anaemia (haemoglobin) and the presence of diabetes mellitus, hypertension and pre-existing renal dysfunction [serum creatinine > 100 μmol/L on the day of admission prior to OLT (baseline)]. Donor data was taken from a prospectively compiled database and included donor age, donor status [DCD or donation after brain death (DBD)] and cold ischaemic time.

Intraoperative factors assessed included surgical technique (piggy back or caval replacement), blood products transfused during OLT (packed red cell units, fresh frozen plasma and platelets), transfused cell salvage blood (as a reflection of blood loss) and noradrenaline infusion rate on admission to intensive care (as a reflection of possible ischaemia reperfusion injury).

Post-operative AKI was determined from serum creatinine at midnight on Day 1 and the need for continuous veno-venous haemofiltration (CVVHF) during the post-operative stay on intensive care unit (ICU). Peak serum AST within the first 24 h post-OLT was used as a measure of ischaemia reperfusion injury.

Clinical outcomes measured aside from the presence of AKI included time to extubation, intensive care length of stay, the incidence of chronic renal failure (CRF), as demonstrated by an estimated glomerular filtration rate of < 60 mL/min per 1.73 m^2 at 6 mo post transplantation and 90-d patient survival.

Extent of AKI was assessed using the AKIN criteria[22], with the multiple rise in creatinine at 24 h post OLT compared to baseline, categorising the post-operative renal status into: No AKI (< 1.5-fold rise in creatinine); Stage 1 (1.5-2 fold rise); Stage 2 (2-3 fold rise) and Stage 3 (> 3 fold rise or the commencement of renal replacement therapy). This time frame was chosen to ensure that the renal complication was not due to post-operative factors such as nephrotoxicity secondary to immunosuppression.

The incidence of AKI at 24 h post OLT was determined and patients with no AKI *vs* those with any grade of AKI were compared in terms of baseline recipient characteristics, donor graft characteristics and intraoperative variables. The two groups were then compared with respect to time taken until extubation, intensive care length of stay (ICU LOS), incidence of CRF and 90 d patient survival. Risk factors for early AKI were then determined including the variables outlined above.

Incidence and severity of HIRI were determined using peak serum AST within 24 h of OLT, putting recipients into the groups: Mild HIRI (AST < 1000 IU/L); moderate HIRI (AST 1000-5000 IU/L) and severe HIRI (AST > 5000 IU/L). These groups were compared in terms of time taken until extubation, ICU LOS, incidence of CRF and 90 d patient survival. Peak AST levels within 24 h post OLT were correlated with the presence of early AKI and organ status.

Clinical outcomes (time taken until extubation, ICU LOS, CRF and 90 d patient survival) were then compared between those with neither AKI nor HIRI, either complication or both AKI and HIRI. In this context, HIRI was identified as those with moderate or severe HIRI.

Statistical analysis

Continuous parametric variables were expressed as means with SDs, and compared using student's *t* test and ANOVA analysis of variance. Continuous non-parametric variables were expressed as medians with interquartile ranges, and compared using the Mann Whitney *U* test and Kruskal Wallis analysis of variance. Normality of data was confirmed using both Shapiro Wilk test and histogram analysis. Categorical variables were analysed using χ^2 test or Fisher's exact test and correlations between variables were analysed using Spearman's or Pearson's rank correlation for non-parametric and parametric data respectively. Kaplan Meier plots were used to analyse survival with log rank tests for differences and logistic regression analysis was performed to identify variables associated with AKI. A *P* value of < 0.05 was considered statistically significant unless otherwise stated. Statistical analysis was carried out using Microsoft Excel and IBM SPSS Statistics Version 24.

RESULTS

One hundred and forty OLTs were performed in adult recipients over the study period, using either the caval replacement technique or the piggyback technique, with or without a temporary porto-caval shunt. Veno-venous bypass was not used in any of these cases. Twenty patients underwent urgent transplantation, 3 received a combined liver-kidney transplant and 1 patient died intra-operatively. These patients were excluded from further analysis. The remaining 116 patients were then grouped according to the absence or presence of post-operative AKI and compared with regards to demographics, aetiology, severity of liver disease and relevant co-morbidity (Table 1). These groups were further compared in context of the donor graft and intraoperative characteristics (Tables 2 and 3 respectively).

Incidence of AKI

Out of the 116 patients included in the study, 58 (50%) developed early AKI post OLT using the AKIN criteria[22]. In those sustaining this post-operative complication, 19 were classified as stage 1, 7 as stage 2 and 32 as stage 3 acute kidney injuries. Twenty-eight/116 (24%) patients required CVVHF during the post-operative admission on ICU. The indication for commencement of renal replacement therapy was AKI in all these cases.

Ninety/116 (77.6%) patients had a baseline serum creatinine < 100 μmol/L and 26/116 (22.4%) had a baseline serum creatinine > 100 μmol/L. The incidence of AKI post OLT was 48/90 (53%) in the former group, compared to 10/26 (38%) in the latter group, this difference not being statistically significant (χ^2 = 1.78, *P* = 0.182). However, a greater proportion of those with pre-existing renal impairment (baseline creatinine > 100 μmol/L)

Table 1 Patient demographics

Variables	No AKI (n = 58)	Any grade of AKI (n = 58)	P value
Patient characteristics			
Age (yr)	54 (18)	56 (6)	0.197
Female	17 (29%)	16 (28%)	0.837
Weight (kg)	75 (13)	79 (15)	0.163
Aetiology			
Alcohol	13	14	
Viral hepatitis	20	25	
NASH	2	7	
Autoimmune	16	7	
Hepatocellular carcinoma	10	13	
Other	7	6	
MELD score	16 (7)	16 (5.75)	0.421
Hypertension	8 (14%)	9 (16%)	0.733
Diabetes mellitus	12 (21%)	20 (34%)	0.074
Pre-operative Haemoglobin (g/L)	114 (20)	107 (26)	0.072
Baseline creatinine	76 (39)	75 (26)	0.932

Values expressed as mean (SD), median (interquartile range) and number (percentage) where appropriate. AKI: Acute kidney injury; NASH: Non-alcoholic steato-hepatitis; MELD: Model for End-Stage Liver Disease.

developed stage 3 AKI (35% *vs* 26%) P = 0.081 and required CVVHF (35% *vs* 21%) P = 0.156 during the post-operative admission to ICU, compared to the group with a normal baseline creatinine although again this was not statistically significant.

AKI and clinical outcomes

The median time to extubation was 37 h in the group sustaining AKI compared to 16 h in those without AKI (P < 0.0001) (Figure 1). Additionally, median intensive care length of stay was 5 d in the AKI group compared to 2.5 d in the no AKI group (P < 0.0001) (Figure 1). At the 6-mo follow-up period 39% of those with early post OLT AKI had developed CRF compared to 25% of those without AKI, although this did not reach statistical significance (P = 0.142).

Risk factors for AKI

Variables associated with AKI on regression analysis are described in Table 4. On univariate analysis surgical technique, transfusion of red cell concentrate, fresh frozen plasma, platelets and cell salvage blood and peak AST within 24 h after OLT were all associated with an increased risk of the development of AKI. In a multivariate model that included all clinically relevant variables, only peak AST within the first 24 h post OLT remained statistically significant in predicting early AKI (P = 0.020).

Incidence and severity and of HIRI

To assess the severity of HIRI, patients were divided into groups based on peak AST levels within the first 24 h after OLT: AST < 1000 IU/L (minor HIRI); AST 1000-5000 IU/L (moderate HIRI); AST > 5000 IU/L (severe HIRI)[23]. Thirty-five/116 (30%) of patients developed mild HIRI, 68/116 (59%) developed moderate HIRI and 13/116 (11%) developed severe HIRI. The effect of organ status

Table 2 Donor graft characteristics

Variables	No AKI (n = 58)	Any AKI (n = 58)	P value
Graft characteristics			
Donor age (yr)	50 (14)	47 (15)	0.219
Organ status			
DCD (%)	7 (12%)	10 (17%)	0.454
Cold Ischaemic time (min)	493 (133)	493 (106)	0.502

Values expressed as mean (SD), median (interquartile range) and number (percent) where appropriate. DCD: Donation after cardiac death; AKI: Acute kidney injury.

Table 3 Intraoperative variables

Variable	No AKI (n = 58)	Any AKI (n = 58)	P value
Intraoperative variables			
Surgical technique			
Piggyback	33 (57%)	22 (38%)	0.041
Intraoperative blood products			
RCC transfusion (units)	1 (3)	4 (5)	0.001
FFP transfusion (units)	0 (2)	2 (6)	0.001
Platelet transfusion (units)	0 (1)	0 (2)	0.024
Cell salvage (mL)	281 (550)	764 (929)	0.001
Noradrenaline infusion rate on arrival to ICU (μg/kg per minute)	0.16 (0.10)	0.18 (0.13)	0.343

Values expressed as mean (SD), median (interquartile range) and number (percent) where appropriate. AKI: Acute kidney injury; RCC: Red cell concentrate; FFP: Fresh frozen plasma; ICU: Intensive care unit.

and surgical technique on HIRI severity and the renal implications of increasing ischaemia reperfusion injury are summarised in Table 5.

Correlation of renal dysfunction and HIRI

Median peak AST levels within the first 24 h post OLT were 1248 IU/L and 2059 IU/L in the No AKI and AKI groups respectively (P = 0.0003). Furthermore, increasing levels of peak AST correlated well with increasing severity of AKI (Spearman's r = 0.334, P = 0.0003). Finally, increasing severity of HIRI was associated with both a higher incidence of AKI (P = 0.002) and more frequent use of CVVHF (P = 0.003) (Figure 2).

Correlation of organ status and HIRI

Median peak AST levels within the first post-operative day were 1307 IU/L and 2060 IU/L in those who underwent DBD and DCD transplantation respectively (P = 0.001). A spearman's rank-order correlation was run to examine the relationship between organ status and HIRI, which revealed a positive correlation between the two (spearman's r = 0.322, P = 0.0005). Five thirteenths (38.5%) of those with severe HIRI had received a DCD graft, compared to only 1/35 (3%) of those with mild HIRI, P = 0.007 (Table 5).

HIRI and clinical outcomes

Increasing severity of HIRI was associated with a trend

Table 4 Logistic regression analysis of variables associated with early acute kidney injury after liver transplantation

Variables	Univariate analysis		Multivariate model	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Male gender	1.088 (0.49-2.44)	0.837	0.430 (0.07-2.55)	0.352
Weight	1.020 (0.99-1.05)	0.164	1.026 (0.96-1.10)	0.455
Age	1.034 (0.999-1.07)	0.058	1.121 (1.02-1.23)	0.019
Pre-transplant				
Diabetes mellitus	2.130 (0.92-4.92)	0.077	2.429 (0.48-12.41)	0.286
Hypertension	1.197 (0.43-3.36)	0.733	0.593 (0.04-8.04)	0.694
Serum creatinine	1.000 (0.99-1.01)	0.937	0.979 (0.96-1.002)	0.078
MELD	1.010 (0.97-1.05)	0.639	0.992 (0.91-1.08)	0.845
Haemoglobin	0.985 (0.97-1.002)	0.076	0.977 (0.93-1.02)	0.311
Graft characteristics				
DCD organ	1.488 (0.52-4.23)	0.455	2.638 (0.30-23.12)	0.381
Donor age	0.984 (0.96-1.01)	0.218	0.964 (0.92-1.01)	0.160
Cold ischaemic time	1.001 (0.99-1.004)	0.498	1.000 (0.99-1.01)	0.984
Peak serum AST < 24 h post OLT	1.001 (1.00-1.001)	0.001	1.001 (1.00-1.001)	0.020
Perioperative course				
Caval replacement surgical technique	2.160 (1.03-4.54)	0.042	3.289 (0.71-15-25)	0.128
Noradrenaline infusion rate on ICU arrival	4.830 (0.19-125.48)	0.343	47.468 (0.12-1836.27)	0.204
RCC transfusion	1.137 (1.03-1.26)	0.014	0.917 (0.64-1.32)	0.645
FFP transfusion	1.201 (1.07-1.35)	0.003	1.118 (0.84-1.48)	0.440
Platelet transfusion	1.499 (1.04-2.16)	0.030	1.948 (0.871-4.36)	0.104
Cell salvage volume	1.001 (1.00-1.001)	0.025	1.00 (0.999-1.002)	0.808

CI: Confidence interval; MELD: Model for End-Stage Liver Disease; DCD: Donation after Cardiac death; ICU: Intensive care unit; RCC: Red cell concentrate; FFP: Fresh frozen plasma; AST: Aspartate aminotransferase; OLT; Orthotopic liver transplantation.

Table 5 The effect of organ status and surgical technique on hepatic ischaemia reperfusion injury severity and the renal implications of increasing ischaemia reperfusion injury *n* (%)

	Severity of HIRI			
	Mild (*n* = 35)	Moderate (*n* = 68)	Severe (*n* = 13)	*P* value
DCD organs	1/35 (2.9)	11/68 (16.2)	5/13 (38.5)	0.007
Caval replacement	16/35 (45.7)	36/68 (52.9)	9/13 (69.2)	0.348
Incidence of AKI	12/35 (34.3)	34/68 (50.0)	12/13 (92.3)	0.002
Need for CVVHF	5/35 (14.3)	15/68 (22.1)	8/13 (61.5)	0.003
Development of CRF	6/30 (20.0)	19/53 (35.8)	5/11 (45.5)	0.195

HIRI: Hepatic ischaemia reperfusion injury; DCD: Donation after Cardiac death; AKI: Acute kidney injury; CVVHF: Continuous veno-venous haemofiltration; CRF: Chronic renal failure.

towards longer median time to extubation (Figure 3) *P* = 0.07, longer median ICU length of stay (Figure 3) *P* = 0.01, and a trend towards a higher incidence of CRF at 6 mo (Table 5) *P* = 0.195.

The combined impact on clinical outcomes of AKI and HIRI

To examine the clinical impact of having both the complications of AKI and HIRI, the cohort was divided into 4 groups: Those with neither AKI nor HIRI (group 1); HIRI but no AKI (group 2); AKI but no HIRI (group 3) and those with both complications (group 4). The presence of HIRI included any patient that sustained either moderate or severe HIRI (peak AST within 24 h post OLT > 1000 IU/L). These groups were then compared for median time to extubation, median ICU length of stay and the incidence of CRF.

The median time to extubation (hours) differed between the groups (*P* < 0.001) with the lowest time observed in group 1 and the highest observed in group 4 (Figure 4). Pairwise comparisons revealed statistically significant differences between groups 1 and 4 (*P* = 0.001) and groups 2 and 4 (*P* = 0.003).

Similarly, the median ICU length of stay (days) increased between the groups (*P* = 0.001), with the highest value observed in the patients sustaining both AKI and HIRI (Figure 4). Pairwise comparisons revealed statistically significant differences between groups 1 and 3 (*P* = 0.04), groups 1 and 4 (*P* < 0.0001) and groups 2 and 4 (*P* = 0.005). Finally, there was a trend towards a higher incidence of CRF in those with any one of, or both AKI and HIRI compared to those with neither, with an incidence of only 15% in group 1 and 45% in group 4 (*P* = 0.238).

Survival

Kaplan Meier analysis revealed a reduction in 90-d patient survival associated with the presence of early AKI compared to no AKI (91.4% *vs* 100% respectively, *P* = 0.024) and increasing severity of HIRI (severe 84.6%;

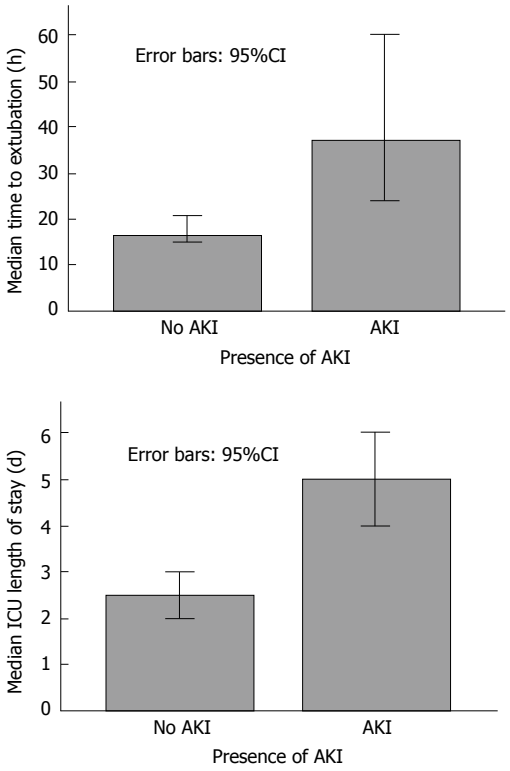

Figure 1 Bar graphs demonstrating median time to extubation and intensive care unit length of stay in the absence or presence of acute kidney injury. ICU: Intensive care unit; AKI: Acute kidney injury.

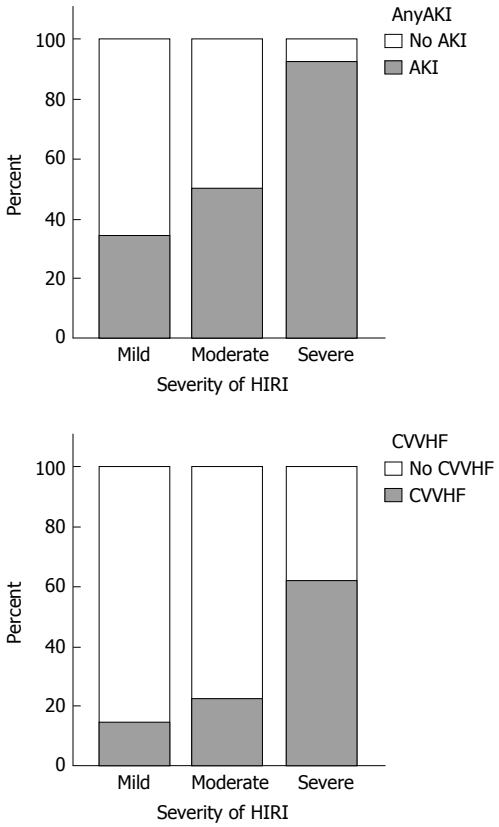

Figure 2 Bar graphs demonstrating the presence of acute kidney injury and use of continuous veno-venous haemofiltration in context of the severity of hepatic ischaemia reperfusion injury. Mild HIRI *n* = 35; moderate HIRI *n* = 68; severe HIRI *n* = 13. AKI: Acute kidney injury; CVVHF: Continuous veno-venous haemofiltation; HIRI: Hepatic ischaemia reperfusion injury.

moderate 95.5%; mild 100.0%, *P* = 0.053) (Figure 5). Furthermore, early AKI and moderate/severe HIRI occurring in combination had a greater impact on 90-d patient survival than either complication when occurring in isolation (89% *vs* 100% respectively, *P* = 0.049) (Figure 6).

DISCUSSION

This single centre study has allowed detailed analysis of factors influencing post-operative AKI in United Kingdom patients undergoing LT, allowing strategies for intervention to be designed. In particular it has investigated the impact of HIRI, which is becoming more prevalent in an era that has seen a steady rise in the use of marginal grafts. The aetiology of AKI following OLT is complex and multifactorial, so our study has benefitted from the analysis of details that are not collected in national databases.

The importance of AKI and HIRI to the outcome of patients undergoing OLT is emphasised by major differences being demonstrated in this small single centre study in important patient centred outcomes. Patients who sustained both AKI and HIRI had a longer time to extubation, longer ICU length of stay and a lower 90-d patient survival. Furthermore, in a multivariate model of all clinically relevant variables, HIRI was shown to be the single most important factor predicting post-operative AKI, suggesting that it plays a critical role in the pathogenesis of renal dysfunction after LT.

The association between HIRI and AKI has previously been reported, with Leithead *et al*[16] demonstrating peak postoperative AST as the main predictor of renal dysfunction after DCD transplantation. Renal outcomes were examined for those undergoing DCD transplantation, but not specifically correlated with the degree of HIRI. Glanemann *et al*[23] examined the clinical implications of increasing severity of hepatic preservation injury, and found it to be associated with initial graft non-function and, as in the current study, to be correlated with an increased duration of post-operative ventilation and haemodialysis. However Glanemann *et al*[23] did not define the cohort that developed AKI. For the first time we have shown that the combination of early AKI and moderate to severe HIRI leads to worse post OLT outcomes than either complication alone.

The aetiology of AKI following LT is thought to be multifactorial, and contributory causes include exposure to high levels of toxic free radicals, renal ischaemia, use of nephrotoxic medications and the effects of end stage liver disease on the kidneys. Perioperative risk factors for the development of AKI post OLT have included pre-existing renal dysfunction, diabetes mellitus, hypertension, previous ascites, MELD score, surgical technique, intraoperative transfusion of blood products, ischaemia time, post-reperfusion syndrome and post OLT immunosuppression[24-26]. In our study, peak serum AST within 24 h of OLT, surgical technique and transfusion of

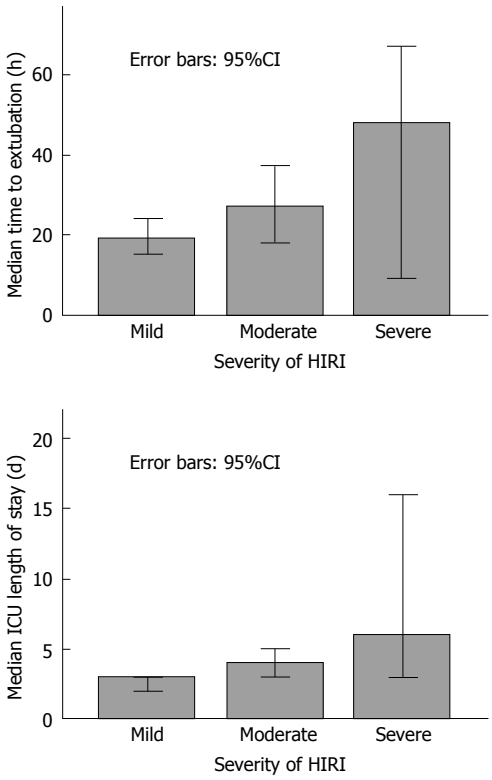

Figure 3 Increasing severity of hepatic ischaemia reperfusion injury compared with median time to extubation and median intensive care unit length of stay. ICU: Intensive care unit; HIRI: Hepatic ischaemia reperfusion injury.

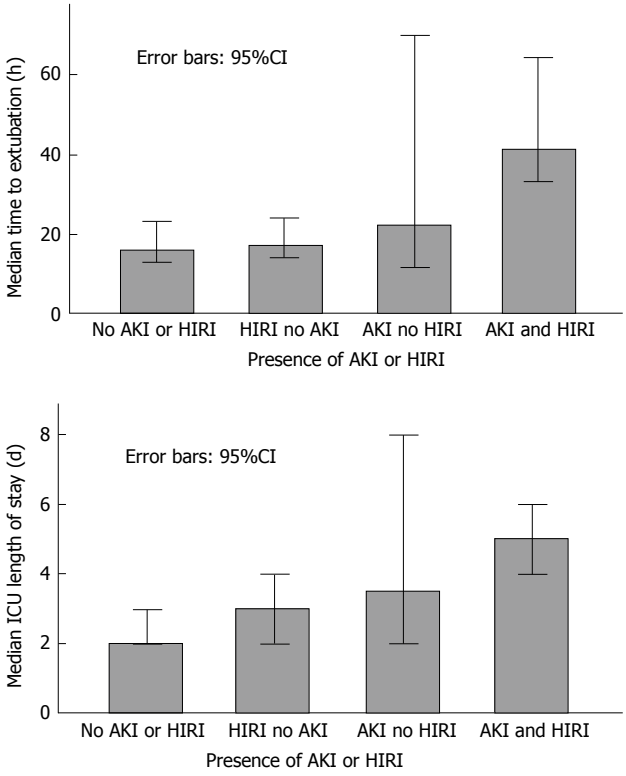

Figure 4 Median time to extubation and median intensive care unit length of stay in groups with the combined absence or presence of acute kidney injury and hepatic ischaemia reperfusion injury. ICU: Intensive care unit; AKI: Acute kidney injury; HIRI: Hepatic ischaemia reperfusion injury.

blood products were all statistically significant in univariate analysis in being predictors of early AKI. However only peak serum AST within 24 h of OLT remained so in the multivariate model.

Previously it has been shown that DCD transplantation is associated with post-operative renal dysfunction[16]. This would be expected as the use of DCD grafts is associated with increased warm ischaemia, incidence of poor and non function of the graft and patient and graft mortality[27]. In our study we were not able to reproduce these results. This perhaps was secondary to the fact that only 15% of our cohort received DCD grafts, or that to compensate for the use of DCD organs the donors may have been younger, had lower cold ischaemia times or were transplanted into younger, fitter patients.

It has been reported that pre-operative renal dysfunction is an independent predictor of post-OLT AKI and the need for CVVHF[28,29]. However, in our study, pre-operative serum creatinine was not a predictor for early post-OLT AKI in logistic regression analysis. In fact, a greater proportion of those with a pre-operative creatinine < 100 μmol/L developed early AKI (53%) than those with a pre-operative creatinine > 100 μmol/L (38%). One possibility to explain this may have been that better quality grafts with a lower donor risk index were matched to the higher risk recipients.

Interestingly though, in those with pre transplant CRF who did develop AKI it was likely to be severe (stage 3 AKI) and require CVVHF suggesting a predisposition to an increased severity of the complication in the setting of pre-operative dysfunction. The difference in outcome of our logistic regression analysis may reflect the discrepancies in the definitions used to categorise AKI. For example, Cabezuelo *et al*[30] categorised post-op AKI as an increase in pre-operative serum creatinine > 50% (compared to our definition of > 150%). In addition, their team defined pre-operative acute renal impairment as an increase in creatinine > 50% from baseline, compared to our pre-operative renal function being defined by the serum creatinine on the day of transplantation alone.

The main limitation of this study lies in its retrospective nature and the inability to control for factors with inter-individual variability, such as the indications and timing in use of CVVHF, which remained reliant on the judgment of the clinician. Also, the variable definitions of AKI mean that interpretation of results needs to be considered in context of the methodologies used.

The frequency of AKI has increased in recent years, and this increase has occurred in parallel with a marked increase in the use of high-risk grafts. In the United Kingdom 29% of donors are over 60 years of age, over 20% are DCD, and clinically obese donors have doubled in the last 10 years. It is known that grafts from these extended criteria donors are more prone to HIRI and poor outcome[31]. HIRI is often more severe when implanting steatotic organs, and it has been reported that the incidence of AKI is significantly higher in patients

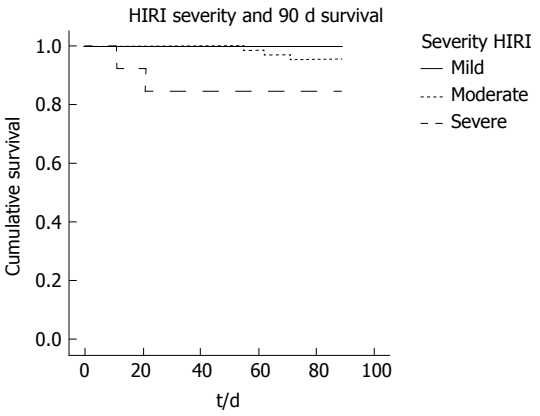

Figure 5 Kaplan Meier plot of 90-d patient survival in those with mild, moderate and severe hepatic ischaemia reperfusion injury. HIRI: Hepatic ischaemia reperfusion injury.

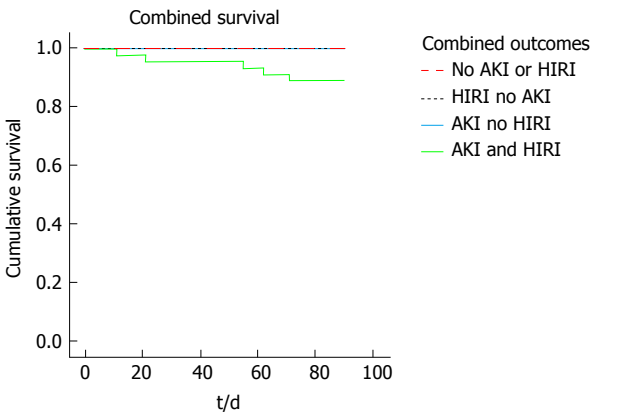

Figure 6 Kaplan Meier plot of 90-d patient survival in those with the combined absence or presence of acute kidney injury and hepatic ischaemia repefusion injury. AKI: Acute kidney injury; HIRI: Hepatic ischaemia reperfusion injury.

receiving grafts from donors with a high BMI, although long term survival was not significantly different when corrected for other variables, such as diabetes[32]. The accelerated search in recent years for methods to expand the organ donor pool has lead to the increasing use of higher risk grafts. This trend in activity has important implications on the recipient population in terms of increased morbidity and mortality post OLT, however, as extended criteria donor grafts are usually allocated to patients with lower MELD scores, this may impact on increased hospital stay, complications and costs but not necessarily poorer graft or patient survival figures.

The role of graft injury and HIRI injury in the pathogenesis of AKI is being increasingly recognised[16,30]. It is one of the most important causes of organ dysfunction, and is a major determinant of successful LT. The deleterious effects are not limited to the liver, but are seen in other organs, including the lungs and kidney[33]. IRI can trigger a systemic inflammatory response and subsequent multi-organ failure, the injury being characterised by intravascular oxidative stress and functional impairment of the mitochondria[34,35]. Peak serum AST is a surrogate marker of the severity of HIRI, and is closely correlated with the development of AKI, as confirmed in this study. Low values of AST following transplantation are associated with superior outcomes[36], and a reduction in AST levels have been used as a primary end point for liver IRI studies in animal models. Preliminary results from a proof of concept study of normothermic machine perfusion compared to a standard cold preservation demonstrated a marked reduction in peak AST levels (417 IU/L *vs* 902 IU/L respectively), indicating that this method of preservation, by "reconditioning" the graft, may reduce HIRI and its attendant consequences, including AKI[37].

Conclusion

In summary, our study has shown that renal dysfunction and use of CVVHF after OLT is common, and rises in proportion to the level of hepatic-ischaemia-reperfusion-injury (as determined by AST levels) and its coexisting systemic inflammatory response. Further work should focus on novel therapies that prevent and treat this graft-related injury to improve recipient outcomes and broaden the donor pool with more extended criteria grafts.

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COMMENTS

Background

Acute kidney injury (AKI) is a common complication following liver transplantation (LT) and has significant clinical implications on patient outcomes. In recent years, the growing demand for organs in transplantation has prompted a search for methods to expand the donor pool, which has included the consideration of use of higher risk grafts, including those from donation after cardiac death donors. This has conferred an increased risk of hepatic ischaemia reperfusion injury (HIRI) to the recipients, of which one of the consequences is AKI.

Research frontiers

It is not fully clear what additional extra-hepatic clinical impact the use of these higher risk grafts have on the recipient in LT. A few reports have addressed the association between HIRI and renal dysfunction post LT but none have explored the clinical impact of having both HIRI and AKI as a combined outcome.

Innovations and breakthroughs

In this study, the authors have shown for the first time that not only do early AKI and moderate to severe HIRI as individual complications, lead to poorer patient outcomes, but combined have a worse impact on time to extubation, intensive care unit length of stay and 90-d survival when compared to each complication alone.

Applications

This study has highlighted the adverse extra-hepatic consequences of HIRI and the subsequent need to develop novel therapies that prevent and treat this graft-related injury to improve recipient outcomes and broaden the donor pool with more extended criteria grafts.

Terminology

AKI: Acute kidney injury, as defined by the AKIN criteria (multiple rise in creatinine from baseline or the need for renal replacement therapy); HIRI: Hepatic ischaemia

reperfusion injury; A graft related injury causing a systemic inflammatory response that has, in this study been categorised according to peak serum aspartate aminotransferase levels on day one post LT.

Peer-review

The study was conducted well in terms of identifying the predictors for and impact of HIRI on early AKIs.

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