

Effects of Lamivudine on Outcome after Initial Treatment for Hepatocellular Carcinoma: A Meta-Analysis

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ABSTRACT

AIM: The beneficial effects of lamivudine on hepatitis B virus have been well recognized. After liver resection or radiofrequency ablation for HBV-related hepatocellular carcinoma, the role of lamivudine treatment is still controversial. The purpose of this paper is to assess the effect of lamivudine therapy after initial treatment for HCC on survival rate and HCC recurrence from available Cohort Studies.

METHODS: Articles from PubMed/MEDLINE, EMBASE and the Cochrane database, including the non-English literature identified in these databases, were searched from January 1970 to November 2012. Studies comparing lamivudine treatment with no antiviral therapy after initial treatment for HCC were extracted only. The percentage of graft survival was extracted by “engage digitizer” from survival curve if the data was not display directly. Meta-analysis was performed when at least three provided data.

RESULTS: 10 articles were included in our study. Lamivudine treatment had significant effects on the incidence of HCC recurrence (RR=0.82, $P=0.01$) and 1-yr tumor free survival rates (HR=0.34, $P<0.00001$), but had no significant effect on 1-yr overall survival (HR=0.66, $P=0.05$).

CONCLUSION: The results of this systematic review imply that lamivudine after initial treatment for HCC reduce recurrence rate and promoted tumor free survival rates, but it did not contribute to short-term overall survival.

Key words: Lamivudine; hepatitis B virus; Hepatectomy; HCC; Meta-analysis

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INTRODUCTION

There has been an increasing morbidity of hepatocellular carcinoma (HCC). In recent decades, it becomes the fifth most common malignant neoplasms in the world^[1,2]. Hepatitis B virus (HBV) infections are considered an etiologic factor for HCC. Initial treatment such as surgical lobotomy and radiofrequency ablation can be performed for HCC at the early stages. But patients frequently met decompensated cirrhosis, tumor recurrence and hepatic encephalopathy after operation because of persistent infection for HBV^[3]. Treatment options in patients with cirrhosis are often restricted, and many patients cannot receive optimal curative treatments, as such treatments may lead to severe hepatic decompensation. In order to have optimal treatment options when HCC recurs, it is very important that remnant liver function is improved or well maintained after treatment for initial HCC.

Lamivudine as a potent reverse transcriptase inhibitor has been used for the treatment of chronic hepatitis B and shows to be beneficial for reducing HBV DNA levels and decreases transaminase levels in short-term treatments^[4-7]. In contrast, lamivudine is not routinely performed in HCC related liver resection or radiofrequency ablation in parts of medical center because its importance to increase survival rates is still controversial, with different groups reporting disparate results: although a population of patients acquired benefit from lamivudine treatment after operation, others claim the possibility of more HCC recurrence rate with antiviral therapy. Long time use of lamivudine will increase the risk of HBV mutation and lead to massive replication of HBV DNA^[8-17].

We therefore performed a systematic review and meta-analysis on the efficacy of lamivudine on outcome of initial treatment for HCC in all published controlled clinical trials.

METHODS

Search strategy

Relevant articles were published between January 1970 and November 2012 in PubMed, EMBASE and the Cochrane database. Non-English literatures were identified, too. The search strategy was set up using the following single text words and combinations: lamivudine, liver resection, liver lobectomy (or lobotomy), radiofrequency ablation (or ablation), hepatitis B virus, hepatocellular carcinoma and liver cancer. Reference lists of relevant articles were cross checked for other potentially relevant articles.

Selection of trials and Quality of the studies

Three separate authors (Lan X, L HM and Zeng W) independently reviewed and evaluated all articles for inclusion, which were classified as randomised control trial (RCT), controlled trial (CT), or descriptive study. After the initial article selection, the dataset was reviewed and updated to capture any articles published between the final consensus review and the final data analysis (Chen P).

Scoring system was adapted from Stahl, Cochrane Collaboration and others^[18-21]. This system suits not only RCT but CT or other studies well: (1) Was the trial design clearly stated? (2) Selection bias questions: Was the Patient selection process clearly stated? If the trial was an RCT, were patient randomly allocated to the therapeutic intervention? Were patients and clinicians blinded to the intervention? If the trial was not an RCT, were confounders controlled for? If the trial design was case control were matching procedures clearly described and implemented? Were patient recruitment procedures clearly described? Were the intervention and control groups selected for similarly? (3) Performance bias questions: Was the intervention clearly described? Was intervention clearly measured? (4) Attrition bias questions: Were patients followed up? Were they followed up for 2 or more explicitly defined intervals? If patients were lost/dropped out other than due to death were they accounted for? Were all outcome measures captured at the declared follow up intervals? (5) Detection bias questions: Were the outcome measures clearly described? Was measurement of the outcome measures blinded? (6) Were appropriate statistical methods used? Were P values clearly states, was life table analysis provided, etc. (7) Was the presentation of data adequate, for example, in the article were endpoints clearly defined i.e. graft survival, patient survival, duration of follow up, re-transplantation rate, etc? Were survival curves provided or were sufficient data to construct survival curves provided, were donor and recipient variables clearly defined and presented. These questions were placed on a 3 point scale: Unclear/inadequate (0), adequate (1), good (2). Articles were considered for inclusion if their summary score exceeded 30^[18].

Data extraction

Overall survival rates and tumor-free survival rates were measured by hazard ratio (HR) and tumor recurrence was measured by relative risk (RR) at 1- and 2-year in every study by three independent reviewers, reconciling any differences by consensus or when in doubt referring it for arbitration by a forth reviewer (Chen P). Survival rate was extracted for calculating corresponding HR using the formula recommended by Parmar *et al*^[22] Data was extracted by software "Engauge 4.0" from survival curve if it was not shown in articles directly. Patients in the treatment group received lamivudine with or without adefovir dipivoxil, while the control group received no antiviral treatment.

Meta analysis

Both HR and RR were compared between lamivudine treatment group and no antiviral treatment group. Comparability of the studies included in each pooled analysis was confirmed by examination of the chi-square Q (expressed as a *P* value) and *I*² statistics of heterogeneity. Statistical heterogeneity was defined as $P \leq 0.10$ or $I^2 > 50\%$ and $P < 0.05$ was considered statistically significant. Lack of over-influence of 1 individual study to pooled estimates was confirmed by serial omission of each study and examination of the resulting estimate. To account for potential differences that were evident clinically but not identified by statistical tests, random effects models were used for each outcome measure. All statistical analyses were performed using Review Manager 5.0 which was added to a new function for synthesizing HR.

RESULTS

Results of the article selection are described in figure 1. 322 potential relevant articles were searched. The abstracts of all studies identified by the above search strategy were reviewed by 3 independent investigators. Of these studies 45 attend to be duplicates in different date base. Only 11 had something to do with lamivudine and HCC and 1 could not meet inclusion cause of their summary score not exceeding 30. Publications eligible for analysis included 3 prospective cohort studies and 7 retrospective cohort studies. Non RCTs were included in our studies.

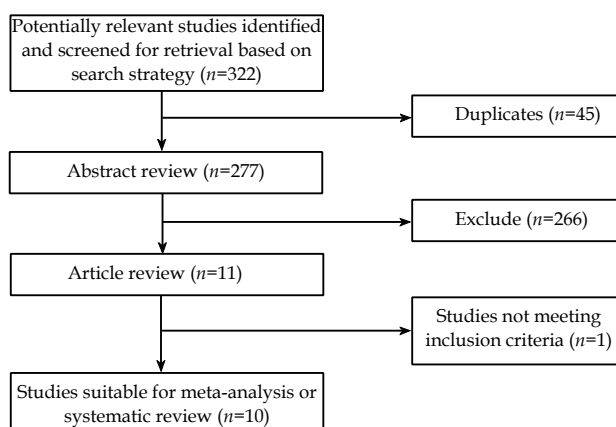


Figure 1 Selection of studies.

Data of HCC recurrence rates were extracted or compared directly in 9 articles^[8,10-17]. In 6 studies, 1-year overall survival rates were compared^[8,10-12,15,17]. In 6 articles, 1-year tumor free survival rates were extracted^[8-10,12,15,17]. The HR of 2-year overall survival and tumor free survival were excluded in our discussion because the results of statistical heterogeneity were $P < 0.05$ and $I^2 > 50\%$ in Meta analysis. Details of these studies are described in table 1. Methodological quality of the CTs was assessed using a validated tool as described above (Table 2).

Meta-analysis of lamivudine on outcome of initial treatment for hepatocellular carcinoma

1-year overall survival rate: Results of these studies included in the meta-analysis, a total of 488 patients were included in 6 articles (1-year overall survival). No differences between lamivudine treatment group and control group were seen in terms of 1-year overall survival (HR=0.66, 95% confidence interval (CI): 0.43-1.01, $Z=1.93$, $P=0.05$) (Figure 2).

Table 1 Contents of included studies.

First author	Year	Location	Contents	Number of patients	Antivirus	Operation
Nan Li ^[8]	2010	China	Tumor recurrence, 1-yr and 2-yr overall survival and tumor free survival	79	Lamivudine with or without adefovir dipivoxil	Hepatectomy
Shoji Kubo ^[9]	2007	Japan	1-, 2- and 5-yr tumor free survival	24	Lamivudine with or without adefovir dipivoxil	Hepatectomy
Teiji Kuzuya ^[10]	2006	Japan	Tumor recurrence, 1-, 2- and 5-yr overall survival and tumor free survival	49	Lamivudine	Radiofrequency ablation and Hepatectomy
Hideo Yoshida ^[11]	2008	Japan	1-, 2- yr overall survival tumor free survival	104	Lamivudine	Radiofrequency ablation
Chen-Yu Piao ^[12]	2005	Japan	Tumor recurrence, 1-yr and 2-yr overall survival and tumor free survival	70	Lamivudine	Hepatectomy
Chuma ^[13]	2009	Japan	Tumor recurrence	84	Lamivudine	Hepatectomy
Hung ^[14]	2008	Hong Kong	Tumor recurrence	72	Lamivudine	Hepatectomy
Koda ^[15]	2009	Japan	Tumor recurrence 1-yr overall survival and tumor free survival	50	Nucleotide analogue (lamivudine)	Hepatectomy
Shunqun ^[16]	2006	China	Tumor recurrence	33	Lamivudine	Hepatectomy
Chan AC ^[17]	2011	Hong Kong	1-yr, 3-yr and 5-yr overall survival and tumor free survival	136	Lamivudine	Hepatectomy

Table 2 Methodological quality of the CTs.

Study	Selection criteria specified	Study design	Score	Other causing of death report	Dropouts explained	Funding
Nan Li	Yes	PCS	33	Yes	Yes	NS
Shoji Kubo	Yes	PCS	30	No	Ns	NS
Teiji Kuzuya	Yes	PCS	31	No	Ns	NS
Chen-Yu Piao	Yes	RCS	32	Yes	Ns	NS
Hideo Yoshida	Yes	RCS	30	No	Ns	NS
Chuma	Yes	RCS	32	No	Ns	NS
Hung	Yes	RCS	30	No	Ns	NS
Koda	Yes	RCS	31	No	Ns	NS
Shunqun	Yes	RCS	30	Yes	Ns	NS
Chan AC	Yes	RCS	33	Yes	Ns	NS

NS: not specified; RCS: retrospective cohort studies; PCS: prospective cohort studies; RCS: retrospective cohort studies.

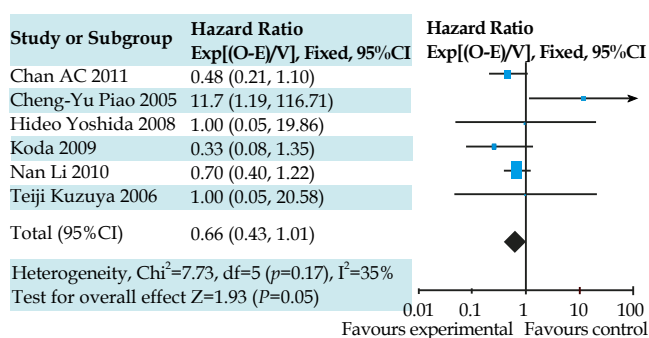


Figure 2 Meta analysis of cohort trials comparing the effect of Lamivudine with or without adefovir treatment on 1-yr overall survival (HR=0.66, 95% CI 0.43-1.01, Z=0.1.93 P=0.05). Heterogeneity was tested and was not statistically significant (P=0.17, I²=35%).

Meta-analysis of lamivudine on outcome of initial treatment for hepatocellular carcinoma

1-year overall survival rate: Results of these studies included in the meta-analysis, a total of 488 patients were included in 6 articles (1-year overall survival). No differences between lamivudine treat group and control group were seen in terms of 1-year overall survival (HR=0.66, 95% confidence interval (CI): 0.43-1.01, Z=1.93, P=0.05) (Figure 2).

1-year tumor free survival rate: Results of these studies included in the meta-analysis, a total of 394 patients were included in 6 articles (1-year tumor free survival). Significant difference between lamivudine treat group and control group were seen in terms of 1-year tumor free survival (HR=0.34, 95% CI: 0.25-0.46, Z=6.90, P<0.00001) (Figure 3).

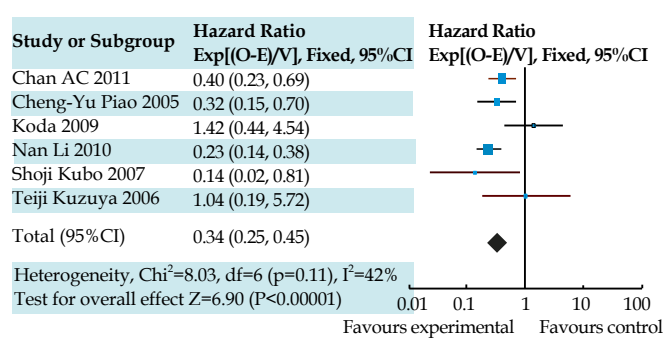


Figure 3 Meta analysis of cohort trials comparing the effect of Lamivudine with or without adefovir treatment on 1-yr tumor free survival (HR=0.34, 95% CI: 0.25-0.46, Z=6.90, P<0.00001). Heterogeneity was tested and was not statistically significant (P=0.11, I²=42%).

Tumor recurrence rate: Results of these studies included in the meta-analysis, a total of 677 patients were included in 9 articles (tumor recurrence rate). Significant difference between lamivudine treat group and control group were seen in terms of tumor recurrence rate (HR=0.82, 95% CI: 0.70-0.95, Z=2.57, P=0.01) (Figure 4).

DISCUSSION

This is the first systematic review and meta-analysis on the efficacy of lamivudine treatment after hepatocellular carcinoma resection on 1-year overall survival, tumor free survival and tumor recurrence. We identified and analyzed 10 unique cohort studies and the results

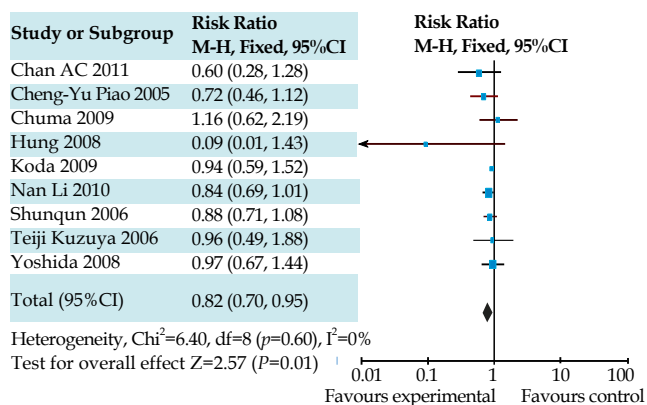


Figure 4 Meta analysis of cohort trials comparing the effect of Lamivudine with or without adefovir treatment on tumor recurrence rate (HR=0.82, 95% CI: 0.70-0.95, Z=2.57, P=0.01). Heterogeneity was tested and was not statistically significant ($P=0.60$, $I^2=0\%$).

clearly showed that lamivudine therapy after initial treatment for hepatocellular carcinoma did reduce the incidence of tumor recurrence. The antiviral treatment after operation had no significant effect on 1-year overall survival rate but was effective for increasing tumor free survival rate.

Lamivudine therapy already has been developed as a classical treatment for chronic hepatitis B. And it as the first agent of this category was reported to decrease the incidence of HBV-related HCC. In some randomized controlled trial, continuous treatment with lamivudine has been shown to delay clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and the risk of HCC^[23,24]. These studies demonstrate the potential benefit of lamivudine treatment for patients with HCC. But the role of lamivudine therapy to the incidence of recurrent HCC or (tumor free) survival rate after initial treatment for HCC remains controversial. Usually, tumor recurrence and postoperation survival rate rely on tumor size, the degrees of differentiation and vascular infiltration^[25,26]. Antiviral treatments after operation is usually not taken into account for most surgeons. Literatures which have been published are inconsistent on the role of this parameter, too. There have been very few studies that have documented whether lamivudine therapy is beneficial to the incidence of recurrent HCC or survival after treatment for HCC. Only 10 related high score cohort studies (another 1 was excluded) were included in our systematic review and draw our own opinion through Meta-analysis.

After initial treatment for HCC, a great part of postoperative readmission is caused by recurrent disease and then hepatic decompensation related HBV. Recurrences after surgery include both intrahepatic metastases from the primary HCC and newly developed HCC. If no antiviral intervention, HBV-DNA duplication might be still at a high level after operation, leading to sustained necrosis of hepatocytes. And then regeneration of hepatocytes amid a background of necrosis during active hepatitis may directly induce DNA mutation, as well as chromosomal rearrangement resulting to genetic instability. All of these have been linked closely to the risk factor HCC recurrence^[27-29]. The reliable benefits of lamivudine treatment in patients with decompensated cirrhosis have been proved by several studies^[30-33]. To regret, overall survival rate seemed no significant difference whether the antiviral intervention had been used. Postoperative overall survival rate could be influenced by many factors: tumor recurrence, hepatic decompensation, upper gastrointestinal hemorrhage, operative complication and others.

Although a meta-analysis may provide a high level of scientific evidence, it is important to realize the limitations of interpreting results of meta-analyses. One major limitation to meta-analysis is that inferences are based on aggregate analysis of relatively heterogeneous studies. We acknowledge the potential heterogeneity of combining studies from different centers in different geographic locations with different treatment protocols. In our systematic review, results coming from each study were considered to be homogeneous (heterogeneity test was $P>0.10$ and $I^2<50\%$ in all available studies) in spite of no RCTs in this meta-analysis. Although we didn't confirm through meta-regression that differences in the use of antiviral drug or the differences of study centers, the treatment protocols were nearly the same: Lamivudine was the primary anti-viral therapy in the majority of patients, and lamivudine resistance was treated by adefovir dipivoxil (Table 2).

Additionally, some studies did not report results with the metric that we chose for data extraction. It is the second limitation we must deal with. Survival rate under 1-year was extracted by special software from survival curve if it was not shown in articles directly. We even didn't get any data from some cohort studies. But including or excluding these articles also did not affect our conclusions.

The length of postoperation follow-up was another limitation of many of the trials that we have analyzed. Although most trials reported follow-up of some patients up to 5 years or even longer, a part of these reported follow-up only to 1 year or 6 months. Long-term graft survival, including HBV and hepatocellular carcinoma recurrence, may only become apparent or more pronounced after many years of post-liver transplantation follow-up, and hence we may have under estimated the mortality in our study. So the 2-year overall survival and tumor free survival were dropped in this study because of heterogeneity.

Despite these limitations, our meta-analysis suggests that lamivudine with or without adefovir dipivoxil after initial treatment for HCC reduce short-term recurrence rate and promoted tumor free survival rates. Although it did not contribute to 1-year overall survival, patients will get advantage from postoperative antiviral therapy.

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