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Kanglaite Injection Combined with Transcatheter Arterial Chemoembolization for Advanced Hepatocellular Carcinoma: A Meta-analysis

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Keywords: Hepatocellular carcinoma; Kanglait injection; Systematic review; TACE; Advanced liver cancer.

Abbreviations: KLT: Kanglaite; TACE: Transcatheter Arterial Chemoembolization; HCC: Hepatocellular Carcinoma; US: Ultrasound; OR: Odds Ratio; AFP: Alpha-Fetoprotein.

Abstract

Objective: Objective To evaluate the clinical efficacy and safety of Kanglaite (KLT) injection combined with Transcatheter Arterial Chemoembolization (TACE) in the treatment of advanced liver cancer.

Materials and methods: We searched CNKI, Wanfang Database, VIP database, China biomedical database, PubMed, Cochrane Library, and EMBASE from the establishment of the database to January 2021 to screen the clinical studies on KLT and TACE in the treatment of advanced liver cancer. The experimental group was treated with KLT combined with TACE, and the control group was treated with TACE alone. Revman 5.3 software was used for meta-analysis. Chi-square test was used to judge the heterogeneity among the studies; odds ratio (or) and 95% confidence interval (95% CI) were used to evaluate the outcome indicators; funnel plot was used to evaluate the publication bias.

Results: Eight trials were finally included in this meta-analysis. In 11 kinds of literature, 927 patients were included, 479 in the experimental group and 448 in the control group. Compared with the control group, the experimental group can significantly improve the effectiveness of tumor treatment.

Conclusion: KLT injection combined with hepatic arterial intervention can improve short-term clinical efficacy and quality of life and decrease patients' pain with advanced HCC.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most serious cancers with a high incidence. At present, surgery is still the best clinical treatment of liver cancer, but many patients are in the middle and advanced stage at the time of treatment [1-3]. At this time, the condition progresses from the early basic asymptomatic to the obvious stage of pain aggravation, and at the same time, it is prone to a variety of serious complications and related symptoms with cancer metastasis. Therefore, transcatheter arterial chemoembolization (TACE) was the first non-surgical treatment for advanced primary liver cancer [4,5]. Many researchers believe that traditional Chinese medicine combined with TACE to treat advanced HCC can reduce toxicity and improve efficiency. In recent years, many domestic and foreign institutions have conducted the study of Kanglaite (KLT) combined with TACE to treat advanced hepatocellular carcinoma, indicating that KLT combined with TACE can increase the efficacy, reduce the toxic and side effects of radiotherapy and increase the body's immunity. However, the current clinical study results are unstable and lack persuasion. Therefore, we systematically evaluated the efficacy, safety, adverse reactions of KLT combined with TACE to treat advanced liver cancer to provide a safe, effective, reasonable, and reliable, evidence-based medicine basis for clinical treatment [6-9].

Materials and methods

Literature search

Clinical studies on KLT and TACE treated advanced liver cancer were searched in CNKI, VIP database, PubMed, Wanfang database, Cochrane Library, EMBASE, and China biomedical database, from January 1990 to January 2021. The keywords were "advanced liver cancer, liver cancer, Kanglaite, coix seed oil, TACE."

Inclusion and exclusion criteria

(1) The study subjects are clinically controlled study cases, using random allocation method or concurrent control trial; (2) The study subjects need to be confirmed by pathology, clinical, imaging examination, etc.; (3) The trial KLT combined with TACE, the control group only TACE; (4) The included literature need to meet: the cohort study published in the form of papers and providing original data.

Exclusion criteria

Literature of non-RCTs study; literature of non-outcome measures of this study; treatment or radiotherapy or surgery of other Chinese patent medicines combined with non-Kanglaite injection; literature that cannot be screened out and summarized; review and systematic review; repeatedly published literature; animal experiments and cell experiments; literature that other researchers believe should be excluded.

Intervention

The experimental group was treated with Kanglaite injection combined with TACE, and the control group was treated with TACE only.

Outcome measures

(1) Clinical effective rate (2) Quality of life improvement rate (3) Adverse Reaction: Incidence of hepatalgia (4) Adverse Reaction: incidence of Gastrointestinal reaction (5) Improvement rate of Kamofsky score (6) AFP improvement rate

Data extraction

Two investigators used Excel office software to determine whether to include them, followed by inclusion and exclusion criteria. If the opinions were different, they were discussed and solved. If necessary, the third party decided.

We used the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 to assess the risk of bias, with the following main evaluation points: (1) generation of random sequences; (2) blind implementation bias; (3) blind allocation; (4) selectivity of reported results; (5) measurement and follow-up bias; and (6) other biases. Each indicator is judged by low, high, and uncertain risk of bias, respectively.

Data analysis and processing were performed using Revman 5.3 software. Odds ratio (OR) was used as the efficacy analysis statistic for dichotomous variables (enumeration data), and Standardized Mean Difference (SMD) was used as the statistic for continuous variables (measurement data), both of which were expressed as 95% CI: 95% confidence interval. Statistically, significance was considered as $P < 0.05$. Heterogeneity analysis of the study literature was performed using the $\chi 2$ test, and the magnitude of heterogeneity was quantitatively estimated with I2. When there was no heterogeneity between studies ($I2 < 50\%$, $P > 0.1$), the fixed-effect model was used, and the random-effect model was used in reverse order. Finally, an inverted funnel plot was used to indicate the presence of publication bias **(Table 1).**

Table 1: Basic features of the included study.

Author	Year of publication	TACE+kanglaite group (Number of subjects)	TACE group (Number of subjects)	TACE Medication	Kanglaite Medication	Outcome Measures
Xing-hu Gao	2019	31	31	MMC+5-Fu+ADM+DDP	200ml,qd	1, 3, 4
Jian-bing Hu	2003	31	25	DDp+5-Fu+THP	200ml,qd	1, 6
Lu-peng Li	2020	55	45	Lobapla tin	200ml,qd	1, 4
Su-mei Liang	2006	31	25	Not stated in text	Not stated in text	1, 6
Ling-wu Meng	2020	50	50	DDP+5-Fu+ADM	100ml,qd	1, 4
Peng-Sun	2019	60	60	Lobapla tin+5-Fu	200ml,qd	1, 3, 4
Jin-lu Wu	2015	60	60	Not stated in text	100ml,qd	1, 2
He-ping Xie	2018	32	32	Lobapla tin	200ml,qd	1, 5, 6
Ru-ru Yi	2009	40	32	Not stated in text	100ml,qd	1
Yi-jiang Zhang	2017	49	48	MMC+5-Fu+ADM+DDP	200ml,qd	1, 2, 3, 4, 6
Xiao-feng Zhu	2006	40	40	DDP+5-Fu	200ml,qd	1, 5

MMC: Mitomycin; 5-Fu: 5-Fluorouracil; ADM: Epirubicin; DDP: Epilepsy; THP: Pyrubicin
1. Clinical effective rate 2. Quality of life improvement rate 3. Adverse Reaction: incidence of hepatalgia 4. Adverse Reaction: Incidence of Gastrointestinal reaction 5. Improvement rate of Kamofsky score 6. AFP improvement rate.

Results

By searching the literature conforming to the basic characteristics and general specifications of the study, we retrieved a total of 1662 relevant pieces of literatures and implemented strict exclusion criteria, and finally, 11 articles were included [10-20]. Among the 11 studies, there were 927 liver cancer patients, including 479 patients in the experimental group and 448 patients in the control group. All literature reported the treatment of patients **(Figure 1).**

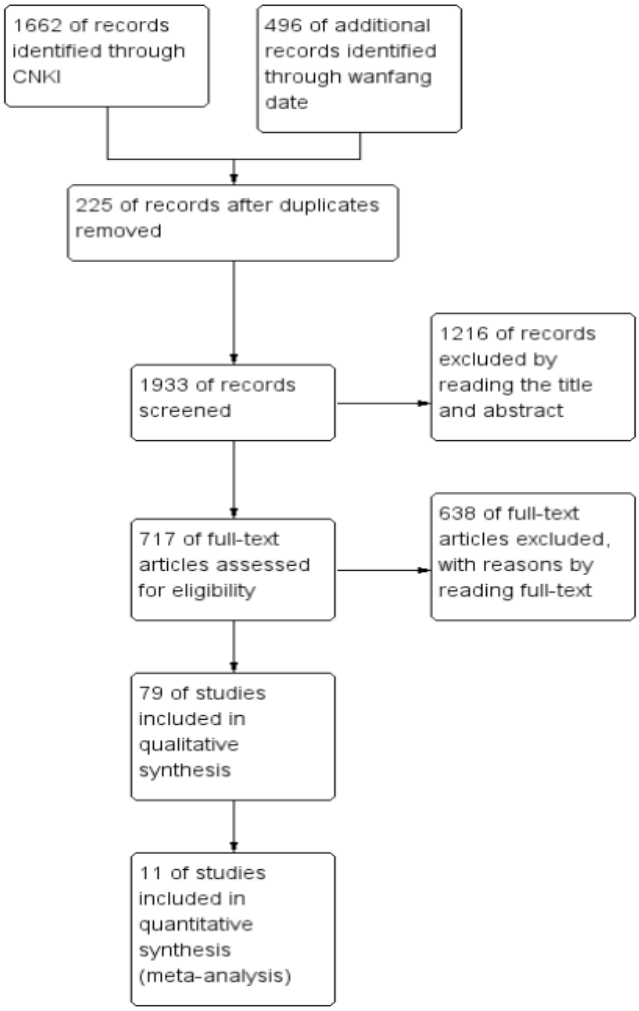

Figure 1: Literature screening procedure and result.

Bias risk evaluation results of the included studies One study used a random number table for randomization, one study used random parallel grouping method for randomization, one study used treatment number method for randomization, and the other studies only mentioned randomization, and the specific randomization method was unclear; the data results of 11 studies were complete, the study results were not selectively reported, and whether there were other sources of bias was unclear, and various biases were assessed by reading the literature one by one **(Figure 2).**

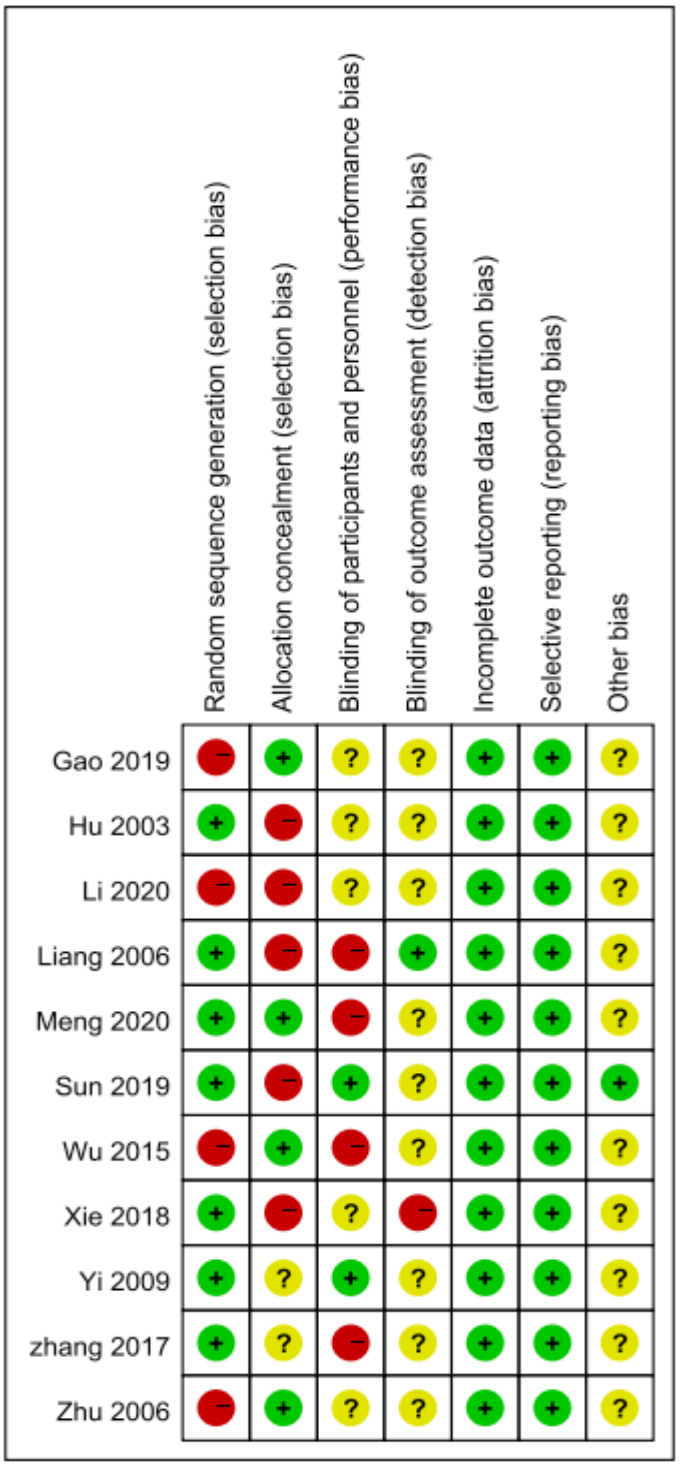

Figure 2: Quality evaluation of included studies.

META-analysis results

Effective clinical rate

We have included 11 studies with 927 patients, including 448 patients in the control group and 479 patients in the experimental group. We can see that in both groups, the clinical response rate was higher in the KLT combined with the TACE group than in the TACE alone group, with statistical significance [OR = 3.07, 95% CI (2.29, 4.12), P <0.001]], as shown in **(Figure3).**

Quality of life improvement rate

A total of three studies with 279 patients were included, including 139 patients in the control group and 140 patients in the experimental group. Meta-analysis of the fixed-effect model showed that the improvement rate of quality of life in the experimental group was significantly higher than that in the control group, with statistical significance [OR = 2.96, 95% CI (1.60,5.48), P = 0.0006], as shown in **(Figure4).**

Adverse Reaction: incidence of hepatalgia

The pain improvement rate was discussed in 3 studies involving 279 patients, including 140 in the combined group and 139 in the TACE group. The results suggested that the pain improvement rate in the control group was significantly worse than that in the combined group, and the difference was statistically significant [OR = 0.27, 95% CI (0.16, 0.45), P < 0.001], as shown in **(Figure 5).**

Adverse reaction: Incidence of gastrointestinal reaction

Five studies reported liver function impairment, with no significant heterogeneity among the studies (P = 0.93, I2 = 0). The results showed that the incidence of liver injury in the experimental group was lower than that in the control group (OR = 0.25, 95% CI: 0.15 ~ 0.41, P < 0.001) **(Figure 6).**

Improvement rate of Kamofsky score

The Kamofsky improvement rate was recorded in two studies with 144 patients, 72 in both the experimental and control groups. The results showed that the kamofsky improvement rate in the combined group was better than that in the control group [OR =3.53, 95% CI (1.59,7.83), P = 0.002], as shown in **(Figure7).**

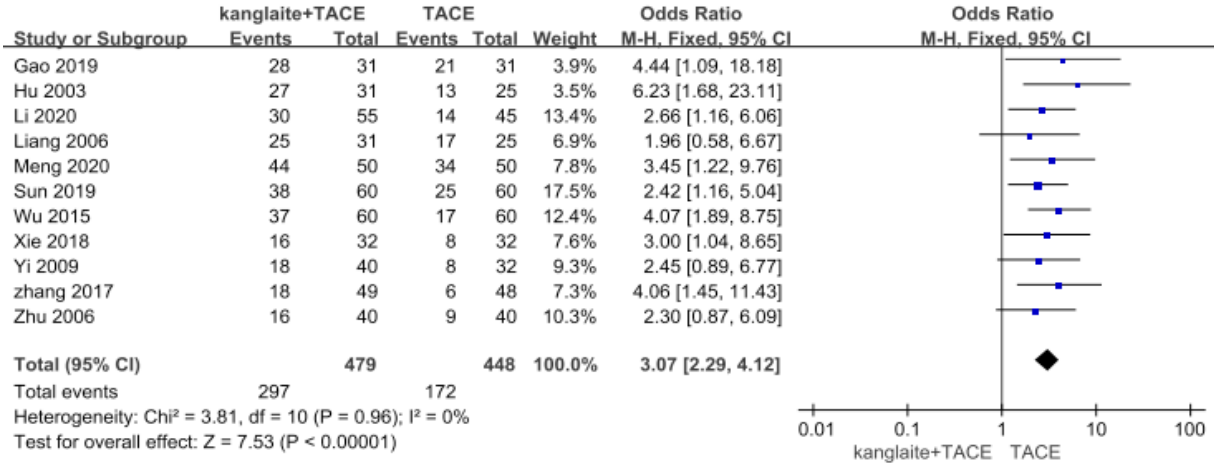

Figure 3: Comparison of effective clinical rate between the two groups META forest map.

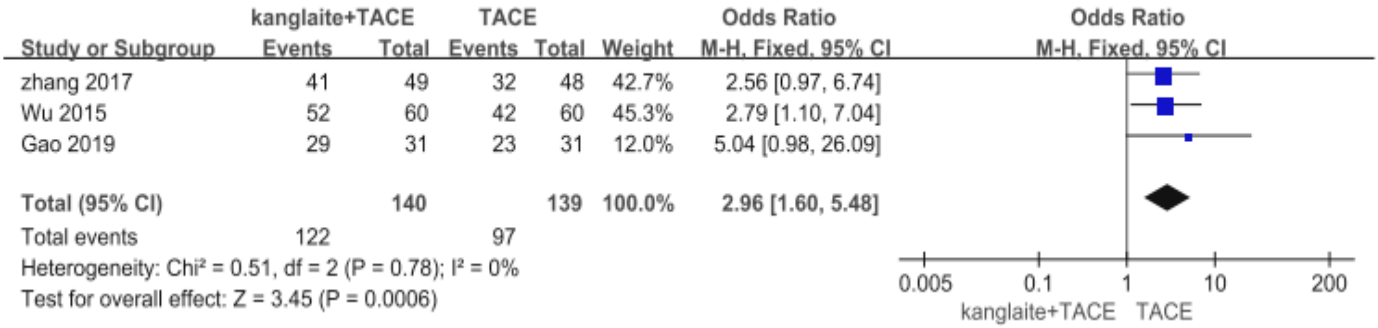

Figure 4: Meta-analysis on the improvement rate of quality of life between KLT combined with chemotherapy and control group.

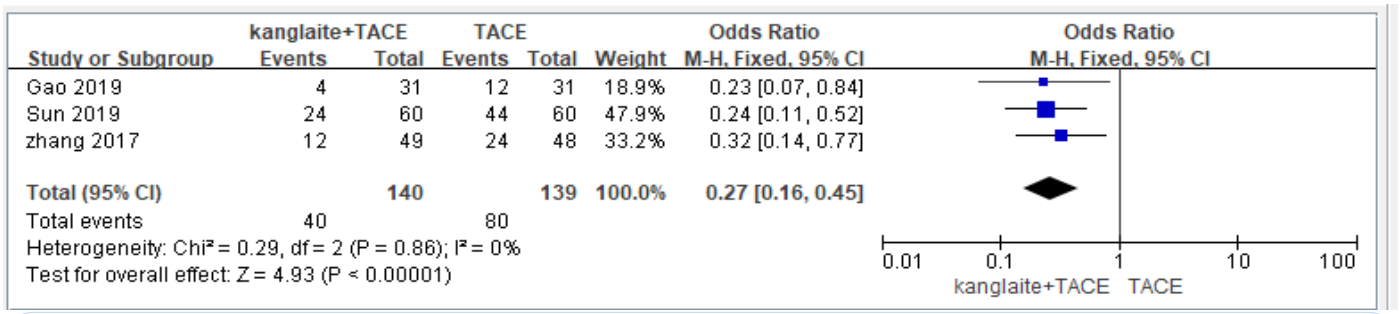

Figure 5: Meta-analysis of incidence of hepatalgia in two groups.

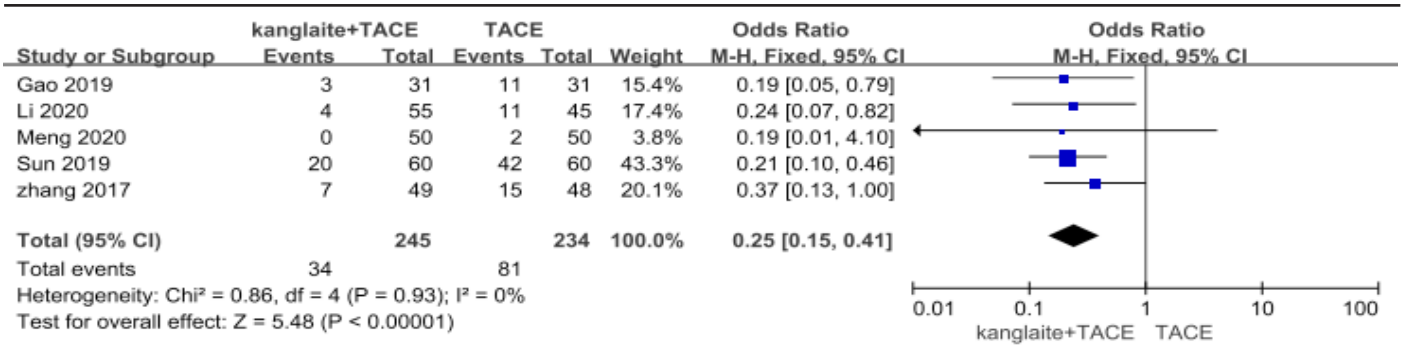

Figure 6: Meta-analysis of incidence of gastrointestinal reaction in two groups.

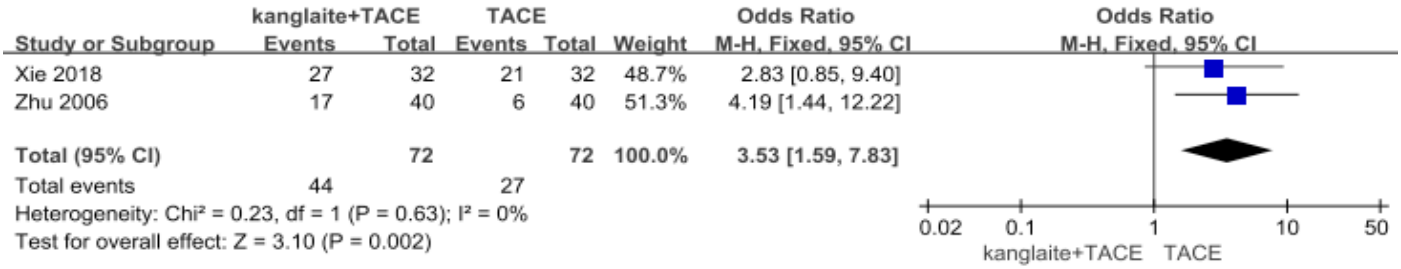

Figure 7: Meta-analysis of Karnofsky performance status in two groups.

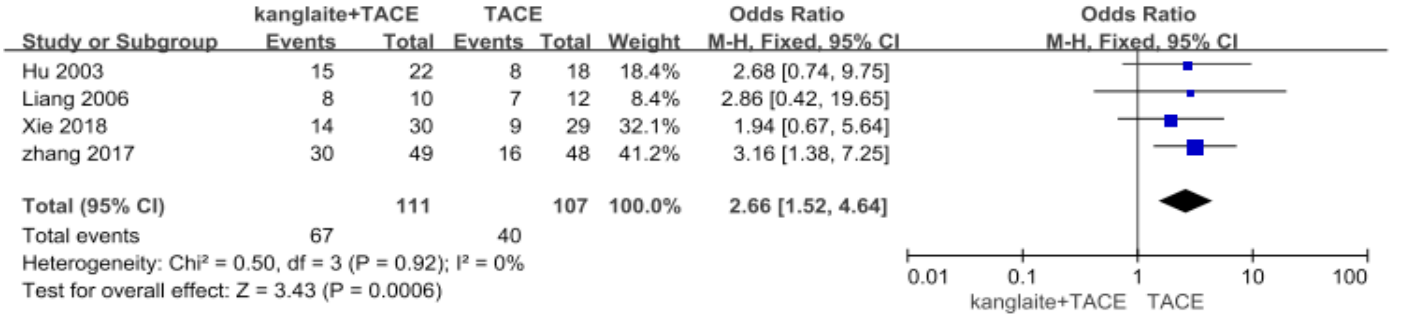

Figure 8: Meta-analysis on the improvement of AFP level in the two groups.

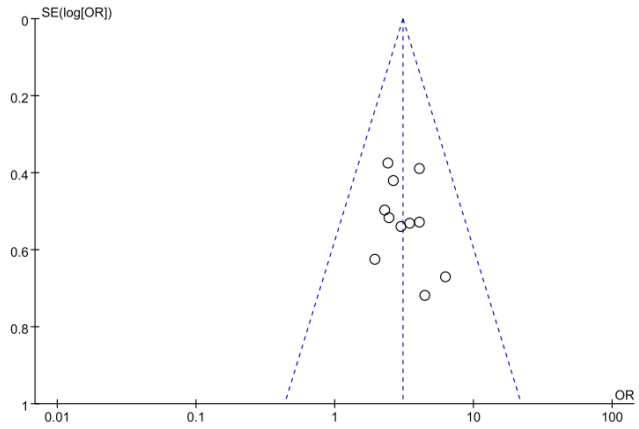

Figure 9: Funnel plot of effective rate of tumor treatment.

AFP improvement rate

A total of five studies recorded the AFP improvement rate. Through Figure 8, we can see that the AFP improvement rate of patients in the experimental group was significantly higher than that in the control group (OR =2.66, 95% CI: (1.52,4.64), P = 0.0006) **(Figure 8).**

Publication bias analysis

Using the effective clinical rate as the evaluation index, 11 articles were presented by funnel plot, and the results showed that the funnel plot showed an asymmetric distribution (Figure9), suggesting that there was a certain publication bias. **(Figure9).**

Sensitivity analysis

In order to evaluate whether the study results are stable and reliable, the investigators eliminated anyone literature and then re-performed meta-analysis on the remaining data. The above-obtained results were not statistically significantly different from those before exclusion (P < 0.05). The reasons for the improvement rate of AFP, with greater sensitivity, may occasionally present with P > 0.05. Secondly, the random-effect model was changed to a fixed-effect model to re-plot and analyze the results of this study, and the analysis results were approximately the same as the actual results. It is suggested that the results of this meta-analysis are relatively stable and have some reference significance.

Discussion

Kanglaite is an active ingredient extracted from coix seed, a biphasic broad-spectrum anticancer drug, which can efficiently inhibit cancer cells and significantly improve the body's immune function. The animal experiments showed that this product had a significant inhibitory effect on various transplanted tumors and human tumor cells transplanted in the tumor strains and had a certain enhancement of immune function. In addition, there is some analgesic effect. Moreover, it has a synergistic and attenuated effect on radiotherapy and chemotherapy. It has certain anti-cachexia and analgesic effects in patients with advanced cancer. At the same time, some studies have also shown that KLT pretreatment may increase the effect of cisplatin on HepG2 cells by showing a synergistic effect on HepG2 cell inhibition.

Moreover, KLT inhibited the expression of MDR1 and MRP1 by inhibiting the expression of PVT1, suggesting a potential mechanism of KLT involvement in multidrug resistance in Alimentary cancer. Domestic scholars try to combine KLT with TACE to reduce the adverse reactions caused by chemotherapy, prolong the survival time of patients, and improve patients' quality of life, but the results are not completely consistent. This study combined and analyzed them [21-24].

A total of 11 literature of KLT combined with TACE versus TACE only for advanced liver cancer were included in this study. Meta-analysis showed that tumor treatment response rate, quality of life, Karnofsky performance status, the improvement rate of clinical symptoms, and AFP decrease level in the experimental group were higher than the control group, and the incidence rate of adverse reactions of liver pain was lower than that in the control group. The differences had statistical significance ($P < 0.05$). These results suggested that KLT combined with TACE to treat advanced liver cancer can improve patients' clinical symptoms while reducing the incidence of some toxic and side effects.

These 11 articles were assessed for risk bias according to the Cochrane criteria, and the bias of the included articles was low. Publication bias was also performed through the funnel plot, and the results showed that the funnel plot was not completely symmetrical, and there was a part of publication bias. Finally, various studies were removed in turn for sensitivity analysis. The results showed that the results of Clinical effective rate, quality of life improvement rate, Adverse Reaction: incidence of hepatalgia, Adverse Reaction: incidence of Gastrointestinal reaction, Improvement rate of Kamofsky score, AFP improvement rate forest plot were the same as before, and the direction did not change, indicating that the meta-analysis results were stable, while AFP improvement rate had some limitations due to the small sample size and the large fluctuation of the results. However, there is no randomized controlled trial with strict design for this study at home and abroad, so there is still some demonstration basis for this result.

Although this meta-analysis defines strict inclusion and exclusion criteria, there are still some limitations: (1). There are relatively few RCTs on KLT combined with TACE in the treatment of advanced liver cancer, while the sample size in the literature is not large, so the power of the test will be reduced; (2). the included studies use different statistics for some outcome indicators. The results of some trials fail to be combined, and no unified conclusion can be drawn, and individual outcome indicators use subjective indicators, which will have a certain impact on the final results; (3). most of the included studies do not describe the randomization method and the concealment of allocation plan in detail, whether the subjects and investigators use the blind method is not clear, and the funnel plot shows incomplete symmetry, suggesting that there may be publication bias (4); the differences in the dosage and course of treatment of kanglaite treatment will also cause the occurrence of clinical heterogeneity (5). The chemotherapy regimens included in the study are not completely uniform. Certain clinical heterogeneity may affect the evaluation of efficacy and safety, suggesting that later studies standardize clinical medication and use core indicators as evaluation outcome indicators to improve the consistency between different clinical studies.

In summary, Kanglaite combined with TACE in treating patients with advanced liver cancer can significantly improve the quality of life and reduce the adverse reactions after TACE. Due to the small number of articles, some publication bias, and other reasons, it is still necessary to carry out a large-sample, multicenter RCT, conduct a longer follow-up observation and describe the endpoint indicators in detail to verify the above conclusions further.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

A copy of this consent to publish is available for review by the editor of the journal.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest

Acknowledgements: Not Applicable

References

1. Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004; 127: S5-s16.

2. Grandhi MS, Kim AK, Ronnekleiv-Kelly SM, Kamel IR, Ghasebeh MA, et al. Hepatocellular carcinoma: From diagnosis to treatment. Surgical oncology. Jun 2016; 25: 74-85.

3. Liu CY, Chen KF, Chen PJ. Treatment of Liver Cancer. Cold Spring Harbor perspectives in medicine. Jul 17 2015; 5: a021535.

4. Han K, Kim JH. Transarterial chemoembolization in hepatocellular carcinoma treatment: Barcelona clinic liver cancer staging system. World journal of gastroenterology. 2015; 21: 10327-35.

5. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. Journal of hepatology. 2015; 62: 1187-95.

6. Huang X, Qin J, Lu S. Kanglaite stimulates anticancer immune responses and inhibits HepG2 cell transplantation-induced tumor growth. Molecular medicine reports. 2014; 10: 2153-9.

7. Lei X, Chen J, Liu CX, Lin J, Lou J, et al. Status and thoughts of Chinese patent medicines seeking approval in the US market. Chinese journal of integrative medicine. 2014; 20: 403-8.

8. Liu J, Liu X, Ma J, Li K, Xu C. The clinical efficacy and safety of kanglaite adjuvant therapy in the treatment of advanced hepatocellular carcinoma: A PRISMA-compliant meta-analysis. Bioscience reports. 2019; 39.

9. Lu Y, Li CS, Dong Q. Chinese herb related molecules of cancer-cell-apoptosis: a minireview of progress between Kanglaite injection and related genes. Journal of experimental & clinical cancer research : CR. 2008; 27: 31.

10. Xinggao HuClinical study of Kanglaite combined with interventional chemotherapy in the treatment of primary liver cancer% J World Compound Medicine. 2019; 5: 166-168.

11. Hu Jianbing, Weng Jie, Liu Songlian, Guan Lili, Zhou Jiang, Li Yongjun. Observation on the efficacy of Kanglaite combined with interventional chemoembolization in the treatment of advanced liver cancer% J Shaanxi Oncology. 2003; (01): 48-49.

12. Li Lupeng, Cao Guangshao, Cao Huicun, Liu Jianwen, Liu Yuyan, et al. Effect of Kanglaite combined with transcatheter arterial chemoembolization in the treatment of liver cancer and its effect on serum MMP-9, Bcl-2 and VEGF levels% J Chinese Practical Medical Journal. 2020; 47: 48-52.

13. Sumei L, Jing W, Song Jian. Kanglaite combined with interventional embolization chemotherapy in the treatment of advanced liver cancer% J Modern application of pharmacy in China. 2006; (S2): 825-826.

14. Lingwu M, Zhibin Li, Jie C. Effect of transcatheter arterial chemoembolization combined with Kanglaite injection on tumor volume and quality of life in patients with primary liver cancer% J World Journal of Integrated Traditional Chinese and Western Medicine. 2020; 15: 727-730.

15. Peng S, Yixin S, Baiqiu Z, Changsheng Z, Shujie Z. Efficacy analysis of Kanglaite injection combined with interventional chemoembolization in the treatment of advanced hepatic malignant tumor% J World Latest Medical Information. 2019; 19: 50+56.

16. Jinlu WU. Clinical observation of Kanglaite injection combined with interventional chemotherapy in the treatment of advanced liver cancer%. J Chinese folk therapy. 2015; 23: 60-61.

17. Heping X, Yue L, Fenglin W, Weikang W, Hongzhi Y. Clinical efficacy of Kanglaite injection combined with transcatheter arterial chemoembolization in the treatment of primary liver cancer% J Chinese patent medicine. 2018; 40: 2821-2823.

18. Iru Ru. Observation on the efficacy of interventional therapy combined with Kanglaite injection in the treatment of advanced liver cancer%. J Chinese and Foreign Medical. 2009; 28: 78.

19. Yijiang Z, Jihua C, Xingdong X, Xiaobo Y. Yin Jianhuai. Clinical study of Kanglaite combined with interventional chemotherapy in the treatment of primary liver cancer% J Oncology Pharmacy. 2017; 7: 104-108.

20. Xiaofeng Z. Kanglaite injection combined with interventional chemoembolization in the treatment of primary advanced liver cancer. J tumor basis and clinical. 2006; (02):132-134.

21. Qi F, Li A, Inagaki Y, et al. Chinese herbal medicines as adjuvant treatment during chemo- or radio-therapy for cancer. Bioscience trends. 2010; 4: 297-307.

22. Shan SJ, Xiao T, Chen J, et al. Kanglaite attenuates UVB-induced down-regulation of aquaporin-3 in cultured human skin keratinocytes. International journal of molecular medicine. 2012; 29: 625-9.

23. Wang Z, Qi F, Cui Y, et al. An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics. *Bioscience trends*. 2018; 12: 220-239.

24. XW Z, Liu L, Zhang XZ, Bo P. Kanglaite inhibits the expression of drug resistance genes through suppressing PVT1 in cisplatin-resistant gastric cancer cells. Experimental and therapeutic medicine. 2017; 14: 1789-1794.