Chemotherapy: Open Access
ISSN: 2167-7700

Wang, et al., Chemo Open Access 2016, 5:2
DOI: 10.4172/2167-7700.1000192

Research Article Open Access

Raltitrexed based Transcatheter Arterial Chemoembolization (TACE) for Unresectable Hepatocellular Carcinoma: A Single-center Randomized Controlled Study

Yu Wang*, Wei Cui*,Jia Wen, Wenzhe Fan, Yingqiang Zhang, Wang Yao, Kunbo Huang and Jiaping Li*

Department of Interventional Oncology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, PR China

**Corresponding authors: Jiaping Li, Department of Interventional Oncology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, China, Tel: +86-20-13352890908; E-mail:* jpli3s@126.com

Yu Wang, Department of Interventional Oncology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, China

Wei Cui, Department of Interventional Oncology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, China

Received date: January 07, 2016; **Accepted date:** February 15, 2016; **Published date:** February 20, 2016

Copyright: © 2016 Jia ping Li, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, andreproduction in any medium, provided the original author and source are credited.

Abstract

Background: We aimed to evaluate the efficacy and safety of transcatheter arterial chemoembolization (TACE), a combination of raltitrexed, oxaliplatin, and epirubicin, for unresectable hepatocellular carcinoma (HCC).

Methods: We enrolled 163 patients in this single-center, randomized, controlled trial comparing TACE with epirubicin and oxaliplatin (control group; 83 patients) to TACE with raltitrexed, epirubicin, and oxaliplatin (raltitrexed group; 80 patients).The primary endpoint was overall survival(OS);secondary endpoints included progression-free survival(PFS),tumor response and adverse events.

Results: The median progression-free survival (mPFS) and overall survival (mOS) were similar (mPFS: 4.3 vs. 4.6 months, P = 0.201; mOS: 9.6 vs. 9.8 months, P = 0.698, respectively). The disease control rates for the control and raltitrexed groups were 57.8% and 63.8%, respectively, and did not reach statistical significance (P = 0.439). Adverse events were also similar in both the groups (P > 0.05).

Conclusion: Although the study did not meet its primary endpoint, the treatment induced a high response rate and promising PFS and OS rates in patients, suggests that the use of raltitrexed as an alternative for TACE may confer some benefit to patients with unresectable HCC.

Keywords: Hepatocellular carcinoma; TACE; raltitrexed; epirubicin; oxaliplatin

Introduction

Transcatheter arterial chemoembolization (TACE) is the gold-standard palliative treatment for unresectable hepatocellular carcinoma (HCC) [1]. This treatment involves catheterizing the tumor-feeding artery and then injecting an emulsion through the catheter. TACE improves survival in HCC patients who are not candidates for resection or transplantation [2]. However, embolization is not always complete; the tumor typically recurs when it is incomplete. Postoperative recurrence and metastasis are common causes for treatment failure. In addition, HCC is often aggressive and resistant to chemotherapy, and any therapeutic effect is constrained by both resistance and liver dysfunction. No standard therapeutic agents or treatment regimens have resulted in any obvious survival benefit for these patients. Doxorubicin, epirubicin, cisplatin, and mitomycin C have been used as anticancer drugs for TACE [3,4]. However, these agents have demonstrated unsatisfactory efficacy. Previous studies have found that the combination of two or more anticancer drugs with embolization may enhance efficacy against HCC, reducing recurrence and increasing survival times. The collective activity of the drugs is believed to have a synergistic effect greater than that of each of the individual drugs alone. However, a recent trial has reported that TACE with multiple anti-cancer drugs (epirubicin, cisplatin, mitomycin C, 5-fluorouracil) was tolerable but appeared not to contribute to an increase in radiographic response or progression-free survival (PFS), and caused significantly more hepatic arterial abnormalities compared with TACE with epirubicin alone [5-7]. Therefore, whether chemotherapy improves patient survival remains controversial in TACE. A common goal for many interventional therapeutic studies is exploring effective and targeted drugs with fewer side effects and therapeutic chemotherapy combinations. We performed this prospective study in consecutive patients with unresectable HCC to compare the safety and efficiency of inpatients who underwent TACE with combination regimen epirubicin and oxaliplatin with or without raltitrexed.

Materials and Methods

Study Design

We conducted a prospective trial that enrolled 163 consecutive patients with advanced HCC who were admitted to our department (the Department of Interventional Oncology, the First Affiliated Hospital, Sun Yat-Sen University) from March 2013 to March 2015.All of them were diagnosed with hepatitis B virus (HBV)-related HCC. The patients were divided into two groups: one group received TACE

with epirubicin and oxaliplatin (the control group), and the other received TACE with raltitrexed, epirubicin and oxaliplatin (the raltitrexed group).The Institutional Review Board of our hospital approved this study. The duration of patient survival was calculated from the date of the first TACE to death or study closure. Follow-up was terminated for all patients on death or May 28, 2015.

Evaluation of Outcomes

The primary endpoint was overall survival (OS), defined as the time from the first TACE treatment to death from any cause or to the last follow-up in censored patients. Secondary endpoints were progression-free survival (PFS), tumor response based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines, and treatment-related adverse events (AEs). Treatment-related AEs were assessed using the Common Terminology Criteria for AE (CTCAE) version 4.0.

Patient Selection Criteria

The inclusion and exclusion criteria are presented in Table 1. HCC was diagnosed by distinctive findings from clinical data, computed tomography (CT) or magnetic resonance imaging (MRI) findings, and elevated alpha-fetoprotein (AFP) levels. Diagnosis was confirmed histologically in some patients by CT-guided fine-needle biopsy. TACE procedures for all patients were determined by a multidisciplinary team of interventional oncologists, radiologists, and surgeons.

Inclusion criteria	Exclusion criteria
Unresectable disease by surgery or other local therapies	Severe underlying cardiac or renal diseases
Age between 18 and 75 years	
Adequate hematologic, hepatic and renal function	Secondary malignancy Pregnant or lactating women
BCLC system classifications B and C	
ECOG performance status 0-2	

Table1: Inclusion and exclusion criteria TACE Procedure.

TACE Procedure

Angiography was performed using a 5-Fr catheter inserted through the right femoral artery with selection for the hepatic or superior mesenteric artery based on tumor-feeding arteries, confirmed using arteriography. Guided by digital subtraction angiography (DSA), the tip of the catheter was super-selected into the tumor-feeding branches (a micro-catheter was used if necessary). After identification of the target artery in the tumor, chemoembolization was achieved as selectively as possible for all targeted lesions in the left and/or right lobes of the liver, with 1–15 mL of an emulsion consisting of 10 mL of lipiodol (Guerbet, Paris, France) with 20 mg of epirubicin (Actavis, Nerviano, Italy) depending on liver function and tumor size. Gelatin sponge or polyvinyl alcohol particles were injected to embolize tumor-feeding arterioles if necessary until there was no longer any tumor staining after repeat angiography. After thrombosis with chemolipiodolization, procedures for the two groups were performed as follows: 1) Control group: Patients were prescribed 200 mg oxaliplatin (Qilu Pharmaceutical (Hainan), Haikou, China) via hepatic artery infusion (HAI), followed by 20 mg epirubicin in the tumor-feeding artery. 2) Raltitrexed group: Patients were prescribed 4 mg raltitrexed (NANJING ChIA TAI TIANQING, Nanjing, China) via HAI, followed by 200 mg oxaliplatin (Qilu Pharmaceutical) and 20 mg epirubicin in the tumor-feeding artery. Hematological, hepatic, and renal functions were monitored on the next day and 1-week post-TACE administration. Contrast-enhanced CT or MRI of the liver was performed 6–8 weeks after the procedure, to detect lipiodol retention within the tumor and residual viable tumor tissue. When residual viable tumors were confirmed or new lesions developed in patients with adequate liver function, repeated TACE procedures were performed.

Statistical analysis

All statistical analyses were performed using SPSS software (version 16.0, SPSS, Chicago, IL). For baseline characteristics, continuous variables are described as the median ± standard deviation and categorical variables are expressed as frequencies and percentages. The intergroup differences in categorical variables were analyzed using a chi-squared analysis and a 2-tailed Fisher exact test. The median and range of the continuous variables were calculated. Survival curves were constructed by the Kaplan-Meier method, and the significance of the intergroup differences in OS and PFS were evaluated using the log-rank test. $P < 0.05$ was considered statistically significant in all statistical tests.

Results

Patient Characteristics

From March 2013 to May 2015, 163 patients with unresectable HCC were treated with TACE at our department. The patients consisted of 147 men and 16 women, with a median age of 50 years (range, 25-74 years). The 83 patients in the control group were administered TACE a total of 106 times, and the 80 patients in the raltitrexed group were administered TACE a total of 105 times. The median tumor size was 8.34 cm (range 1.17–24 cm). A comparison of baseline characteristics for all recruited patients is shown in Table 2. There were no differences between the two groups.

Characteristics	Control Group	Raltitrexed Group	P Value
Sex			0.188
Male	72 (86.7)	75 (93.8)	
Female	11 (13.3)	5 (6.2)	
Age, y	49.31±10.43	50.28±8.73	0.525
HBsAg positive	42 (50.6)	58 (72.5)	-
Child-Pugh Classification			0.501
A	65 (78.3)	66 (82.5)	
B	18 (21.7)	14 (17.5)	
ECOG performance status			0.869
0	5 (6.0)	6 (7.5)	
1	70 (84.3)	65 (81.2)	
2	8 (9.7)	9 (11.3)	

Tumor size, cm	8.57±4.37	7.91±4.78	0.297
Tumor number			0.672
Single	8 (9.7)	6 (7.5)	
Two or Three	3 (3.6)	5 (6.3)	
Multiple	72 (86.7)	69 (86.2)	
BCLC stage			0.405
Stage B (intermediate)	30 (36.1)	24 (30)	
Stage C (advanced)	53 (63.9)	56 (70)	
Extrahepatic metastases	33 (39.8)	27 (33.8)	0.516
AFP ≥400 ng/mL	44 (53.0)	40 (50.0)	-
Histologically confirmed	30 (36.1)	35 (43.8)	0.341

Table 2: Comparison of baseline characteristics for all recruited patients. Note- data are numbers of patients, data in parentheses are percentages. HBsAg, hepatitis B surface antigen; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein.

Tumor response

The tumor responses in all patients are shown in Table 3. The disease control rate (DCR) was 57.8% in the control group and 63.8% in the raltitrexed group. There was no significant difference between the groups in terms of radiographic response using mRECIST guidelines (P = 0.439).

	Control Group	Raltitrexed Group	P Value
CR	0	0	-
PR	2(2.4)	4(5)	-
SD	46(55.4)	47(58.8)	-
PD	35(42.2)	29(36.2)	-
ORR	2(2.4)	4(5)	0.380
DCR	48(57.8)	51(63.8)	0.439

Table 3: Radiographic response of HCC patients at 3 months after TACE.Note- data are numbers of patients, data in parentheses are percentages.CR complete response, PR partial response ,SD stable disease, PD progressive response. ORR, objective response rate: CR +PR; DCR disease control rate: CR+PR+SD.

Survival Analysis

Figure 1A shows the PFS curves for the two groups ($\chi 2 = 1.638$, P = 0.201, no significant difference). The median PFS was 4.6 months (95% CI 3.37-5.83) in the raltitrexed group and 4.3 months (95% CI 3.54-5.07) in the control group. Repeat TACE for recurrent HCC was performed in 25 patients in the raltitrexed group and in 23 patients in the control group. Figure 1B shows patient OS curves for the two groups. No deaths occurred within 1 month. The median follow-up time was 7.4 months (range 1.7-18.8 months). At the last follow-up, 68 patients had died. The median OS was not significantly longer in the raltitrexed group compared with the control group (9.8 months vs. 9.6 months, respectively; $\chi 2 = 0.151$, P = 0.698).

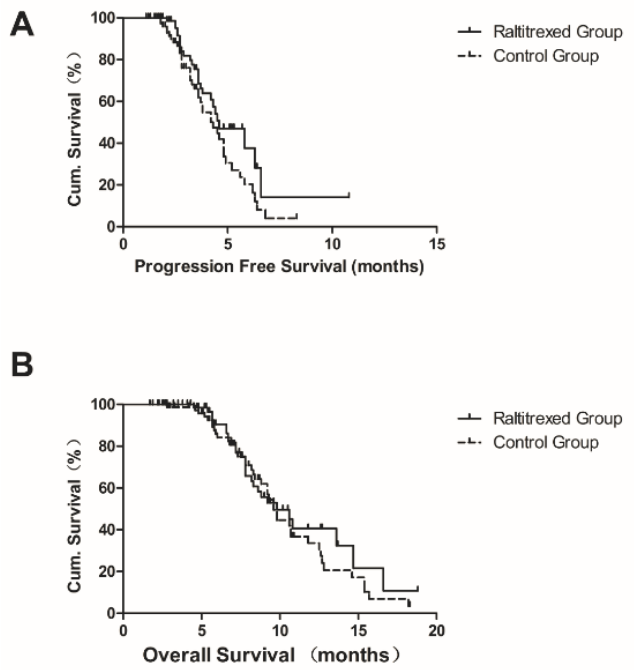

Figure1: Kaplan-Meier survival analysis of two groups, P was calculated using the log-rank test;A: Kaplan-Meier analysis of progression-free survival (PFS) for TACE with control group (epirubicin and oxaliplatin) and that with raltitrexed Group (raltitrexed, epirubicin and oxaliplatin);B: Kaplan-Meier analysis of overall survival (OS) for TACE with control group (epirubicin and oxaliplatin) and that with raltitrexed Group (raltitrexed, epirubicin and oxaliplatin).

Toxicity and Adverse Reactions

The most frequent side effects of the TACE procedure were fever, abdominal pain, vomiting, and liver dysfunction. None of the patients showed serious clinical complications or side effects relevant to the procedure. Toxic effects from the trial according to National Cancer Institute Common Toxicity Criteria are summarized in Table 4 (only grade 3/4 toxicities are presented). Symptoms related to post-embolization syndrome were transient and largely resolved within 1 week, and no significant difference was found between the two groups. Blood and laboratory data are shown in Table 5. Student's t test did not show any significant differences in the serum level changes of prothrombin time, alanine aminotransferase, aspartate aminotransferase, total bilirubin, serum albumin and renal function, and blood counts were normal in patients before and after the procedure between the two groups (P > 0.05).

Adverse Events	Control Group	Raltitrexed Group	P Value
Nausea/vomiting	17 (20.5)	19 (23.8)	0.615
Fever	9 (10.8)	10 (12.5)	0.742
Pain	6 (7.2)	12 (15)	0.114

Diarrhea	7 (8.4)	7 (8.8)	0.943
Allergies	0	0	-

Table 4: Summary of grade 3/4 adverse events by treatment. Note- data are numbers of patients, data in parentheses are percentages.

Variable	Control Group	Raltitrexed Group	P Value
Increased white-cell count (×109/L)	1.62±0.33	2.07±0.24	0.263
Increased neutrophil ratio	0.143±0.013	0.167±0.013	0.187
Decreased platelet (×109/L)	13.98±5.86	19.69±6.33	0.509
Decreased red- cell count (×109/L)	0.87±0.74	0.15±0.04	0.335
Increased PT	0.28±0.13	0.43±0.07	0.294
Increased ALT (U/L)	99.23±23.16	78.69±19.34	0.497
Increased AST (U/L)	168.63±32.83	210.71±41.24	0.425
Increased TB (μmol/L)	12.75±1.51	12.59±1.54	0.940
Increased DB (μmol/L)	6.43±1.03	5.57±0.84	0.515
Decreased ALB (g/L)	2.20±0.40	1.64±0.38	0.313
Decreased CREA (μmol/L)	3.62±1.90	5.32±1.00	0.431
Increased BUN (mmol/L)	-0.37±0.20	0.04±0.16	0.116

Table 5: Blood and laboratory data changed before and after procedure in two groups.Data are expressed as mean ± SD where applicable; PT, prothrombin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; DB, direct bilirubin; ALB, albumin; CREA, serum creatinine; UREA, blood urea nitrogen.

Discussion

Recently, a large, nationwide prospective cohort study involving 8,510 patients revealed TACE to be a safe therapeutic modality with a 5-year survival rate of 26% in unresectable HCC. The degrees of liver damage, TNM stage, HBV status and AFP values were independent prognostic factors for unresectable HCC treated by TACE [8,9]. TACE significantly improves survival and is an effective form of treatment in patients with unresectable HCC [10,11]. Although a number of chemotherapeutic agents have been used in the TACE procedure, the choice of the chemotherapeutic agents and the combination have varied in different countries and areas, and controversy exists about the selection of the most appropriate drug [4]. It remains uncertain whether adding chemotherapy to the embolization agent enhances its anti-tumor effects [12]. TAE is as effective as TACE on a meta-analysis of TACE versus TAE alone (including 3 randomized controlled trials and 412 patients), demonstrating no difference in survival [4]. In 2012, Ming Shi et al. [13] documented that a triple-drug TACE (lobaplatin, epirubicin, and mitomycin C) may contribute to improve survival compared with TACE with epirubicin alone. However, more side effects were observed in the triple-drug group than in the epirubicin groups. Sahara et al. [7] reported that no significant difference was found between the multiple-drug groups (epirubicin, cisplatin, mitomycin C, 5-fluorouracil) and the epirubicin alone group in terms of radiographic response, PFS curves, or patient survival (1-and 2-year survival). However, most of the patients with HCC were not treatment-naive but had received previous treatment, including TACE. Another limitation was that the follow-up term was too short to evaluate patient survival.

Raltitrexed is a novel antifolate that is a direct and specific inhibitor of thymidylate synthase. In preclinical and clinical studies, raltitrexed has shown activity against a variety of tumor types, including colorectal and cervical cancer [14,15]. An early phase II study of raltitrexed in 33 patients with HCC found that raltitrexed appeared to have some activity against this tumor and was generally well tolerated with reversible and manageable toxicities and without evidence of cumulative or renal toxicity [16]. Additionally, a recent retrospective study reported the combination regimen of raltitrexed and oxaliplatin hepatic arterial infusion (HAI) was feasible and promising in patients who presented with isolated hepatic metastases of colorectal cancer after failure of irinotecan and oxaliplatin treatment [17]. Raltitrexed-based chemotherapy regimens have achieved equivalent OS and response rates with acceptable toxicities compared to traditional 5-fluorouracil-based regimen in patients with advanced colorectal cancer [18]. However, no studies have reported on the safety and efficacy of raltitrexed-based TACE for HCC. Our study is the first to test this regimen, and our results clearly show that raltitrexed, oxaliplatin and epirubicin together are tolerable and can produce comparable tumor response and survival times. This study suggests that the TACE combination of raltitrexed, oxaliplatin, and epirubicin produced a higher objective response rate (5%) and DCR (63.8%) than the TACE combination of oxaliplatin and epirubicin (2.4% and 57.8%, respectively). We observed a median OS and PFS of 9.8 and 4.6 months in raltitrexed group vs. 9.6 and 4.3 months in the control group, respectively. Although there was no significant difference between the two groups, we observed that the likelihood of differences increased over time through the survival curves. Therefore, raltitrexed-based TACE is feasible and promising in patients who present with unresectable HCC. These promising results may contribute to the wider use of raltitrexed. The theoretical mechanism of action for raltitrexed is that, as a thymidylate synthase inhibitor, it has a similar anti-cancer effect and fewer side effects compared to fluoropyrimidine and the FOLFOX4 regimen, and has shown some benefit in Asian patients with advanced, inoperable HCC, increasing objective response rates and the DCR, thereby prolonging PFS [19]. However, the OS and PFS in our study were lower than those rates in similar studies [4]. We suspect the reasons for this as follows: 1) the follow-up term was too short to evaluate survival; 2) the number of patients was small, leading to possible bias; 3) the mean tumor diameters in both groups were over 8 cm; 4) most of our patients had a hepatic tumor of BCLC stage C. The follow-up term and the sample sizes were also limitations of our study.

The toxicity profile of the raltitrexed group was comparable with the control group. We observed classical but manageable toxic effects from raltitrexed, oxaliplatin, and epirubicin. There were no significant differences in grade 3/4 adverse events and blood and laboratory data before and after the procedure between the two groups. Although the alanine aminotransferase level and bilirubin were increased, these abnormalities resolved within 5 days and did not show any relevant deterioration. The occurrence of main adverse events including biochemistry level changes and gastrointestinal adverse reactions in our study were consistent with that reported previously [20]. However, Sahara et al. reported that Grade 3 transaminase elevation and hepatic

artery abnormality in TACE with multiple anti-cancer drugs (epirubicin, cisplatin, mitomycin C, and 5-fluorouracil) was significantly greater than that in the epirubicin group among 63 consecutive patients who underwent TACE prospectively [7]. One possible reason was that the concentration of epirubicin per lipiodol for use in our study was prepared as 2 mg/mL, whereas concentrations of 4 mg/mL and 10 mg/mL were used in the multi group and epirubicin group, respectively. Another reason was its small sample size and the lack of adequate blinding, although it was a single center, prospective, randomized controlled trial. Moreover, our figures showed that no patients experienced allergic reactions while HAI with raltitrexed, and no studies have reported allergic reactions to raltitrexed. However, allergic reactions related to oxaliplatin, epirubicin, and other anti-cancer drugs are frequently reported in the literature [17,21,22].

Conclusion

In conclusion, the raltitrexed-based TACE procedure combining epirubicin and oxaliplatin showed similar clinical effects in tumor response and survival, but had no supplementary toxic effects and did not worsen the syndrome related to post-embolization compared with TACE with epirubicin and oxaliplatin. Although the study did not meet its primary endpoint, the treatment induced a high response rate and promising PFS and OS rates in patients, suggests that the use of raltitrexed as an alternative for TACE may confer some benefit to patients with unresectable HCC. However, this study was merely a single-center prospective study with a limited number of patients. The role of raltitrexed in this regimen must be confirmed in future studies by multicenter and randomized controlled trials with a larger number of patients.

Acknowledgments

We thank all of the patients and their families in this study.

References

1. Maleux G, van Malenstein H, Vandecaveye V, Heye S, Vaninbroukx J, et al. (2009) Transcatheter chemoembolization of unresectable hepatocellular carcinoma: Current knowledge and future directions. Dig Dis 27:157-163.
2. Firouznia K, Ghanaati H, Alavian SM, Azadeh P, Nasiri TM, et al. (2014): Transcatheter arterial chemoembolization therapy for patients with unresectable hepatocellular carcinoma. Hepat Mon 14:e25792.
3. Nishimine K, Uchida H, Matsuo N, Sakaguchi H, Hirohashi S, et al. (1994) Segmental transarterial chemoembolization with Lipiodol mixed with anticancer drugs for nonresectable hepatocellular carcinoma: follow-up CT and therapeutic results. Cancer Chemother Pharmacol 33 Suppl: S60-68.
4. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, et al. (2007) Transarterial therapy for hepatocellular carcinoma: Which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 30:6-25.
5. Brown DB, Pilgram TK, Darcy MD, Fundakowski CE, Lisker-Melman M, et al. (2005) Hepatic arterial chemoembolization for hepatocellular carcinoma: Comparison of survival rates with different embolic agents. J Vasc Interv Radiol 16:1661-1666.
6. Gomes AS, Rosove MH, Rosen PJ, Amado RG, Sayre JW, et al. (2009) Triple-drug transcatheter arterial chemoembolization in unresectable hepatocellular carcinoma: assessment of survival in 124 consecutive patients. AJR Am J Roentgenol 193: 1665-1671.
7. Sahara S, Kawai N, Sato M, Tanaka T, Ikoma A, et al. (2012) Prospective evaluation of transcatheter arterial chemoembolization (TACE) with multiple anti-cancer drugs (epirubicin, cisplatin, mitomycin c, 5-fluorouracil) compared with TACE with epirubicin for treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 35:1363-1371.
8. Takayasu K, Arii S, Ikai I, Omata M, Okita K, et al. (2006) Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 131: 461-469.
9. Shi M, Chen JA, Lin XJ, Guo RP, Yuan YF, et al. (2010) Transarterial chemoembolization as initial treatment for unresectable hepatocellular carcinoma in southern China. World J Gastroenterol 16:264-269.
10. Llovet JM, Real MI, Montaña X, Planas R, Coll S, et al. (2002) Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 359: 1734-1739.
11. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, et al. (2002) Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164-1171.
12. Llovet JM, Bruix J (2003) Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 37:429-442.
13. Shi M, Lu LG, Fang WQ, Guo RP, Chen MS, et al. (2013) Roles played by chemolipiodolization and embolization in chemoembolization for hepatocellular carcinoma: single-blind, randomized trial. J Natl Cancer Inst 105: 59-68.
14. Jackman AL, Farrugia DC, Gibson W, Kimbell R, Harrap KR, et al. (1995) ZD1694 (Tomudex): a new thymidylate synthase inhibitor with activity in colorectal cancer. Eur J Cancer 31A: 1277-1282.
15. Li XY, Liu L, Xie XM, Zhou C (2014) The role of raltitrexed/cisplatin with concurrent radiation therapy in treating advanced cervical cancer. Eur Rev Med Pharmacol Sci 18: 3491-3496.
16. Rougier P, Ducreux M, Kerr D, Carr BI, François E, et al. (1997) A phase II study of raltitrexed ('Tomudex') in patients with hepatocellular carcinoma. Ann Oncol 8: 500-502.
17. Khouri C, Guiu B, Cercueil JP, Chauffert B, Ladoire S, et al. (2010) Raltitrexed and oxaliplatin hepatic arterial infusion for advanced colorectal cancer: a retrospective study. Anticancer Drugs 21: 656-661.
18. Liu Y, Wu W, Hong W, Sun X, Wu J, et al. (2014) Raltitrexed-based chemotherapy for advanced colorectal cancer. Clin Res Hepatol Gastroenterol 38: 219-225.
19. Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, et.al (2013) Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol 31:3501-3508.
20. Barni S, Ghidini A, Coinu A, Borgonovo K, Petrelli F (2014) A systematic review of raltitrexed-based first-line chemotherapy in advanced colorectal cancer. Anticancer Drugs 25: 1122-1128.
21. Oltmans R, van der Vegt SG (2003) Serious allergic reaction to administration of epirubicin. Neth J Med 61: 226-227.
22. Grewal GD, Badrick TC, Gilbar PJ (2015) Immediate and delayed hypersensitivity reactions to a single dose of oxaliplatin. Clin Colorectal Cancer 14: 128-130.