Title: Prophylactic antibiotic use in transarterial chemoembolization for hepatocellular carcinoma: an open-label, randomised, prospective study

Introduction:

Liver cancer especially hepatocellular carcinoma (HCC) is among the top five most common carcinomas in the world [1]. The treatment options for HCC includes surgery, liver transplantation, and radiofrequency ablation (RFA) with good survival rates. However, most HCC patients have angioinvasion. Furthermore, multiple lesions cannot be treated with such treatment strategies [2]. Image-guided transarterial chemoembolization (TACE) is accepted worldwide as a standard of care treatment for patients with hepatocellular carcinoma (HCC) in intermediate stage and good performance status [3]. TACE procedures, performed by the interventional radiologists, are minimally invasive with excellent outcomes as part of the nonsurgical treatment of HCC [1, 4]. Post-procedure-infection is uncommon but can lead to liver abscess and prolonged hospital stay. [7, 8] The chances of post-procedure-infection are higher in patients taking anticancer drugs due to immunosupression. [5, 6]. Incidence of liver abscess after TACE is 0.1 – 4.5% but carries a mortality rate of up to 50% [7, 8, 9].

TACE was linked to a risk of liver abscess. Prophylactic antibiotics pre-procedure lower this risk and ensuing surgical intervention [6]. Prophylactic antibiotics may not be required in TACE for HCC patients [10, 11, 12]. Moreover, old age, compromised hepatic function, hypoalbuminemia, portal vein cancer embolus, invasive procedures, using broad-spectrum antibiotics, and having diabetes mellitus are the independent risk factors for hospital-acquired infections (HAIs) after TACE in patients with primary liver cancer [1, 13].

According to the latest Cardiovascular and Interventional Radiological Society of Europe (CIRSE) standards of practice guidelines (2021), routine antibiotic prophylaxis is not recommended [14]. However, prophylactic antibiotics are recommended in cases where there is a high risk of developing a liver abscess. These include biliary obstruction or the presence of a bilioenteric anastomosis. The choice of agent is dependent on the suspected path ogens (upper gastrointestinal tract flora) and consideration should be given to potential hepatotoxicity of each agent. In complex cases involving multiple organisms, antibiotic resistance, or allergies, consulting with a microbiologist may be beneficial [14].

To date, it is uncertain whether the use of antibiotics as prophylaxis before TACE is beneficial or not in the prevention of postoperative infection.

Excessive antibiotic use is a global problem and carries risks of adverse drug reactions like allergy or anaphylaxis, increased cost, and contributes to the emergence antimicrobial resistance [15, 16]. Therefore, it is the need of the hour to explore the utility of prophylactic antibiotics in TACE.

This study aims to determine the effectiveness of prophylactic antibiotic use for TACE and occurrence of postoperative liver abscess.

Methods

Inclusion Criteria:

1. Age 18 - 65 years
2. Diagnosis of primary liver cancer or hepatocellular carcinoma
3. Patients receiving TACE in PKLI & RC

Exclusion Criteria:

1. Receiving two or more TACE during the same hospitalization
2. Use of any antibiotics other than the prophylactic antibiotic in 48hours prior to TACE
3. Known hypersensitivity to specified antibiotic used in the study
4. Incomplete or missing laboratory investigations and data
5. Taking Sorafenib before TACE
6. TACE combined with ablation or immunetherapy
7. Tumor size >10 cm
8. Portal vein thrombosis
9. Dilated biliary channels on CT scan / Billiary invasion by tumor

Study Outcomes:

1. Predominantly neutrophilic leukocytosis (> 11 $\times 10^9$/L) with fever (> 38 °C) in upto 48 hours post-TACE
2. Occurrence of liver abscess as diagnosed by imaging within 30 days of the procedure

3. Liver abscess requiring an intervention (e.g., percutaneous transhepatic abscess drainage (PTAD), percutaneous transhepatic abscess puncture or liver abscess incision) within 30 days of TACE

Sampling Technique:

In this study, consecutive sampling technique and randomization by lottery method will be applied. In lottery method the investigator will randomly draw numbers from the box to choose sample until the final sample size reaches. Two numbers will be assigned as '1' for antibiotic group and '2' for no antibiotic group.

Current standard of care treatment at PKLI&RC (as per local guidelines) would be given to all patients receiving TACE for the intervention group or 'antibiotic group' (i.e., Inj. Ceftriaxone 1g, intravenous × stat). While no antibiotic would be given to the 'no antibiotic group'.

Statistical analysis:

1. Data to be recorded on Excel sheet and subsequently exported to SPSS version 24 for further analysis.
2. A univariate analysis will be employed for the comparison of variations in patients' baseline characteristics between the preventive medication group and the nonpreventive medication group. The Student's t-test will be employed to evaluate if the obtained data had a homogeneous variance and a normal distribution. For nonhomogeneous variance, the comparisons were made using a one-way analysis of variance (ANOVA). In order to compare categorical variables, Fisher's exact test or Pearson's 2 test was used as applicable.
3. The univariate analysis included chi-square tests for categorical variables and t-tests for continuous variables. Significant variables ($P < 0.01$) in univariate analysis and covariates considered clinically influential were then analyzed by multivariate stepwise logistic regression (forward stepwise logistic regression) to identify significant variables. We applied univariate and multivariate logistic regression models to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for significant

variables for finding potential risk factors in WBC＞11×10^9/L group or postoperative infection group.

4. *P* value less than 0.05 was considered statistically significant.

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