RESEARCH ARTICLE

Trans-arterial Chemo-Embolization in Treating Elderly Patients with Hepatocellular Carcinoma

Jian-Feng Zhang, Jun-Mao Liu, Nin Zhang, Chao Du, Qin Zheng*

Abstract

Background: This analysis was conducted to evaluate the efficacy and safety of Trans-arterial Chemo-Embolization (TACE) in treating Elderly patients with Hepatocellular Carcinoma (EHPC). Methods: Clinical studies evaluating the efficacy and safety of TACE on response and safety for patients with EHPC were identified by using a predefined search strategy. Pooled response rate of treatment were calculated. Results: In TACE based regimen, clinical studies which including patients with EHPC were considered eligible for the evaluation of response. And, in these TACE based treatments, pooled analysis suggested that, in all 288 patients whose response could be assessed, the pooled reponse rate was 29.5%(85/288) in TACE based treatment. The most commonly encountered TACE-related morbidity was liver function impairment. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in EHPC patients with TACE based treatments. Conclusion: This evidence based analysis suggests that TACE based treatments are associated with mild response rate and accepted toxicities for treating patients with EHPC.

Keywords: TACE - elderly patients with Hepatocellular Carcinoma

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Introduction

Hepatocellular Carcinoma (HPC) is the most common liver cancer. Most patients with HPC in China are secondary to viral hepatitis infection (hepatitis B, HBV) (Kumar et al., 2003). The prospective HBV study indicated that HBV is the primary driver of the high HPC incidence rates in regions of high HBV endemicity (Seeff et al., 2006). Using these data, it was estimated that the annual incidence rate of HPC in HBsAg carriers was 494 per 100, 000.With the application of HBV vaccination in China for decades, HBV infection in young generation is decreasing and infected people is aging. Thus, it is resonable that HPC in elderly people (EHPC) would be a main target. In fact, the incidence of most sites of cancer increases with age, and it is estimated that more than 60% of these patients diagnosed with cancer in their age of 65 years or more (Ries et al., 2000). In this setting, the risk of developing HPC has been confirmed to be increasing in elderly patients (Cho et al., 2007).

However, among all age groups of patients with HPC, only a small portion of patients are eligible for curative treatments, e.g., tumor resection, liver transplantation or radiofrequency ablation. Most patients will receive palliative medications including transarterial chemoembolization (TACE), selective internal radiation therapy, sorafenib or supportive care. Among these treatment modalities, TACE is also a commonly used one for treating patients with advanced HPC. It was found to prolong the overall survival of patients with unresectable HPC compared with conservative treatment in previous randomized trials (Dhanasekaran et al., 2010; Lammer et al., 2010). A meta-analysis of published randomized trials also concluded that TACE is an effective palliative treatment for HPC (Cohen et al., 2014). Compared with young patients, elderly patients with HPC are associated with more comorbidity during treatment, particularly from pulmonary and cardiovascular diseases. Previously, advanced age was regarded by some clinicians as a contraindication for TACE (Dohmen et al., 2004), and few data are available in the literature regarding the efficacy and tolerability of TACE in treating patients with EHPC (Yau et al., 2009; Mirici-Cappa et al., 2010). Therefore, investigations on the approach to EHPC patients are urgently warranted. International guidelines do not specifically address whether the management and outcomes of EHPC patients are different from those observed in their younger counterpart (Bruix et al., 2005; Makuuchi et al., 2008; Omata et al., 2010; Bruix et al., 2011; European Association et al., 2012), due to not meet study criteria or fear of potential toxicities and poor survival advantage (Hutchins et al., 1999; Earle et al., 2000).

According to this background, we hypothesize that TACE could be established as a choice in treating elderly patients with EHPC.

*The Second People's Hospital of Nanjing, Nanjing, China *For correspondence: njzq83626472@sina·com*

Materials and Methods

Search strategy

We searched PUBMED, by using the following search terms: hepatocellular carcinoma, elderly, and transarterial chemoembolization. All clinical studies evaluating the impact of TACE on the response or survival and side effects for elderly patients with EHPC published in English prior to September 2015 were identified. If samples of two studies overlap, only the newest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with supportive care, or others; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included clinically verified HCC, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) of less than 2. Studies were excluded if one of the following existed: (a) duplicate data; (b) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, country of the first or corresponding author, the number of patients. Outcome presented in at least 3 studies were extracted for combined analysis.

Results

There were 51 papers relevant to the search words by the end of September 2015. Via steps of screening the title and reading the abstract, 4 studies were identified (Yau, et al., 2009; Cohen et al., 2013; Poon et al., 1999;Golfieri et al., 2013; Nishikawa et al., 2014). These studies had been carried out in the US, Europe, Japan and Hong Kong China. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities. Characteristics of studies included in this analysis are presented as short-term outcomes: the response rate of Nishikawa et al. was 81.8% (54/66), and of Poon, et al. was 14.0% (31/222). Totally, 288 patients were enrolled for evaluating response rate and 85 patients achieved CR or PR, the pooled response rate thus was 29.5% (85/288). In the study of Cohen et al., 120 patients (22%) older than 75 years and 47 patients (8.6%) older than 80 were recruited. Median survival estimates were 23 , 21 and 19 months (p=0.14) among patients aged younger than 65, 65-75 and older than 75 respectively. An age above 75 years at diagnosis was not associated with worse prognosis, hazard ratio of 1.05 (95% CI 0.75-1.5), after controlled by disease stage, gender, diagnosis year, HBV status and stratifying per database. No differences in complication rates were found between the age groups (Cohen et al., 2013). Yau et al reported a result that included 843 patients who were <or=70 years old and 197 patients who were >70 years old received TACE treatment for advanced HCC (Yau, et al., 2009). They suggested that significantly more comorbid illnesses could be associated with elderly than young patients (64 % vs 33%, p< 0.01). However, overall median survival (14.0 months vs 8.1 months, P < 0.003) and disease-specific survival (15.2 months vs 8.7 months, p<.001) were significantly higher in elderly than in young patients. The most commonly encountered TACE-related morbidity in both age groups was liver function derangement. Young patients had a significantly higher rate of developing liver derangement after TACE than elderly patients (21% vs 11%, p< .01) (Yau, et al., 2009). On the other hand, elderly patients had a significantly higher rate of developing peptic ulcer disease during TACE treatment than young patients (2.5% vs 0.5%, p= .01) (Yau, et al., 2009). Thus in this study, they suggested no significant difference existed in TACE-related mortality between young and elderly patients (3% vs 4%, p= 0.49) (Yau, et al., 2009).

Discussion

Among patients with HPC whose tumor without vascular invasion or extrahepatic spread and tumor characteristics are not appropriate for surgical or ablation therapy, TACE is recommended as a first-line, noncurative treatment option (Cammà et al., 2002). The main mechanism of TACE is to utilize the neoangiogenic properties of HPC, focusing on the hepatic arterial supply from which the tumor receives its blood flow. The treatment process usually involves injection of intra-arterial chemotherapy—frequently suspended in lipiodol, a substance that is selectively retained within the tumor and increases chemotherapy exposure—to the affected hepatic lobe (Cammà et al., 2002; Llovet et al., 2003; Lewandowski et al., 2009). Following intra-arterial chemotherapy, the hepatic artery supply to the tumor is obstructed (Chuang et al., 1982; Carr et al., 1997; Bruix et al., 1994; Gunji et al., 1992;). However, facing with elderly cirrhotic patients with HPC, EHPC patients are becoming a routine work in clinical practice, and clinicians should be aware that EHPC patient may still be expected to experience more adverse effects and less favorable prognosis compared to younger patients. It has been shown that EHPC patient are poorer transplantation candidates (Thuluvath et al., 2010). Similarly, elderly patients are reported to receive less aggressive treatment compared to younger patients with similar disease stages (Collier et al., 1994). Still, there is data to suggest that the outcome and prognosis of hepatic resection is similar among EHPC and younger patients (Huang et al., 2009; Oishi et al., 2009; Portolani et al., 2011; Lee et al., 2012). To date, there have been only a few publications describing the

results of TACE among EHPC patient; these data come from diverse geographical regions (Biselli et al., 1997; Hoshida et al., 1999; Dohmen et al., 2004; Pignata et al., 2006; Tsukioka et al., 2006; Fernandez-Ruiz et al., 2008; Yau et al., 2009; Mirici-Cappa et al., 2010; Cohen et al., 2013). The data from these publications suggested that TACE is safe and effective in selected EHPC patient. Nevertheless, these independent studies were relatively small and heterogeneous.

A previous research that retrospectively evaluated the safety and efficacy of TACE in EPHC patients in Israel was conducted at Division of Internal Medicine and Center for Clinical Quality and Safety, Hadassah-Hebrew University Medical Center, Jerusalem (Cohen et al., 2014). In this study, they registered 548 PHC patients, of which 120 were EPHC patients. Median (95% CI) survival were 23 (17-28), 21 (17-26) and 19 (15-23) months (p=0.14) among patients aged younger than 65, 65-75 and older than 75 respectively (Cohen et al., 2014). An age above 75 years at diagnosis was not associated with worse prognosis, hazard ratio of 1.05 (95% CI 0.75-1.5), controlling for disease stage, sex, diagnosis year, HBV status and stratifying per database. No differences in complication rates were found between the age groups (Cohen et al., 2014). In conclusion, Cohen et al.suggested that TACE is safe for patients older than 75 years. (Cohen et al., 2014).

In a retrospective study by Poon et al. conducted in Hong Kong China, they analyzed 222 elderly (> or = 70 yr) and 1116 younger patients with HPC (Poon et al., 1999). In their results they suggested the resection rate in EHPC patients (14%) was lower than in younger patients (27%) ($p < 0.001$) (Poon et al., 1999). Among patients who underwent resection, there were no significant differences in morbidity rate (48% vs 40%, $p = 0.354$), hospital mortality rate (10% vs 6%, $p = 0.431$), or long-term survival (median, 38 vs 42 months, $p = 0.940$) among EHPC and younger patients (Poon et al., 1999) . Sixty-seven elderly and 317 younger patients underwent TACE, with similar morbidity rate (24% vs 26%, $p = 0.775$), mortality rate (7% vs 5%, $p = 0.365$), and long-term survival (median, 12 vs 9 months, $p = 0.277$) (Poon et al., 1999). In conclusion, this study indicated that hepatic resection for HPC is safe in selected elderly patients, and the improved results in recent years indicate that more elderly patients could benefit from surgical management. TACE is well tolerated in EHPC patients and is the treatment of choice for unresectable HCC.

In another study by Nishikawa et al., they enrolled 66 patients with EHPC and 84younger patients aged <75 years with intermediate HPC and all underwent TACE (Nishikawa et al., 2014). In their results, they suggested that The median survival time and the 1- and 3-year cumulative OS rates were 2.90 years and 84.1% and 48.0%, respectively, in the elderly group and 2.44 years and 78.2% and 39.3%, respectively, in the control group (p=0.887) (Nishikawa et al., 2014). The objective response rate in the elderly group was 81.8% (54/66 patients), while that in the control group was 78.6% (66/84 patients) (p=0.227) (Nishikawa et al., 2014). Therefore, in their conclusion, they indicated that EHPC had a prognosis comparable with that of younger patients with similar tumor stage who underwent TACE.

Our current study was conducted to evaluate the efficacy and safety of TACE in treating EHPC patients. Our results demonstrated that in these TACE based treatments, pooled analysis suggested that, in all 288 patients whose response could be assessed, the pooled reponse rate was 29.5% (85/288) in TACE based treatment. The most commonly encountered TACE-related morbidity was liver function impairment. No grade IV renal or liver toxicity were observed. No treatment related death occurred in EHPC patients with TACE based treatments.

In conclusion, our current systemic analysis suggests that TACE based treatments are associated with mild response and accepted toxicities for treating patients with EHPC.

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