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Diagnosis and treatment of coagulopathy following percutaneous cryoablation of liver tumors: Experience in 372 patients ☆

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ABSTRACT

Coagulopathy after liver cryoablation was first reported many years ago; the cause is local platelet trapping and destruction within the margin of the cryolesion. However, the prognosis and therapeutic effects of coagulopathy remain unclear. This study retrospectively reviewed clinical data from 372 patients (525 sessions) who underwent liver cryoablation in our hospital during the past 4.5 years. Small tumors (major diameter < 6 cm) were treated with a single complete ablation; massive tumors (major diameter 6–10 cm or >10 cm) were divided into two or three parts that were dealt with in turn. Platelet counts decreased to an average of $(46.12 \pm 68.13) \times 10^9$/L after each session of cryoablation. The decline was most evident in patients with high pretreatment platelet counts, while those with low pretreatment counts had the highest risk of coagulopathy. Change in platelet count was not correlated with the diameter of the tumor. Slight coagulopathy (platelet count $(70–100) \times 10^9$/L) can resolve without treatment within 1 week and administration of recombinant human interleukin-11 can assist recovery from severe coagulopathy (platelet count $< 70 \times 10^9$/L).

Introduction

During the last decade, cryosurgery has become an interesting alternative in the treatment of nonresectable hepatic tumors, with promising results in terms of patient survival [21,23]. The incidence of complications and side effects of cryoablation may be as high as 40%, however, and they include fracture of the liver parenchyma, cryoshock, biliary fistula, hemorrhage, cold-induced lesions in nearby structures, thrombocytopenia and coagulopathy [19,24]. Theoretically, complications and side effects, with the exception of thrombocytopenia and coagulopathy, can be avoided or reduced by skilled operators and strict patient selection [5,9,22].

Systemic thrombocytopenia is generally defined as a platelet count $\leqslant 150 \times 10^9$/L or a greater than 30–50% decrease [1,26]. Multiple studies have shown that the development of thrombocytopenia is associated with increased length of hospital stay and mortality [11,16,17]. Thrombocytopenia is common in patients after chemotherapy or cryotherapy, which may cause bone marrow suppression [7] or local platelet trapping and destruction within the margin of the cryolesion [10,13,20]. In general, thrombocytopenia is considered to be related to the volume of tissue frozen [5,20], the number of freeze–thaw cycles and the number of cryoprobes used [22]. Systemic thrombocytopenia may be complicated by the development of coagulopathy (platelet count $\leqslant 100 \times 10^9$/L) [10].

In this retrospective study, 372 patients were observed for coagulopathy after cryoablation of liver tumor and the relationship between tumor diameter, ablation protocol, pretreatment platelet count and thrombocytopenia were analyzed. Therapeutic effects for slight and severe coagulopathy after cryosurgeries were analyzed afterwards.

Materials and methods

Ethics

The study protocol received ethical approval from the Regional Ethics Committee of Guangzhou Fuda Cancer Hospital. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

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Patient selection

Between January, 2008 and July, 2012, 372 patients with liver tumor met our inclusion criteria and were enrolled in the study. All patients had a single tumor in the liver and were unwilling to undergo surgery, systemic chemotherapy or transcatheter arterial chemoembolization. Ideal patients for comprehensive cryoablation are those with: only one significant tumor in the liver; Karnofsky performance status score $\geqslant 70$; platelet count $\geqslant 100 \times 10^9$/L; white blood cell count $\geqslant 3 \times 10^9$/L; neutrophil count $\geqslant 2 \times 10^9$/L; hemoglobin $\geqslant 90$ g/L; prothrombin time international normalized ratio $\geqslant 1.5$; hepatic tumor not obviously invading the gallbladder, diaphragm or large vessels; absence of level 3 hypertension, severe coronary disease, myelosuppression, respiratory disease and acute or chronic infection; and adequate hepatic function (bilirubin <30 μM, aminotransferase <60 U/L and Child–Pugh score A or B) and renal function (serum creatinine <130 μM, serum urea <10 mM).

In all patients, the diagnosis of hepatocellular carcinoma (HCC, 241 lesions: 105 advanced and 136 metastatic) or liver metastasis (284 lesions: 64, 61, 87, 51 and 21 with breast, lung, colon, ovarian or pancreatic cancer, respectively) was confirmed by liver pathology; some cases were diagnosed by classical imaging techniques in advance, including computed tomography, magnetic resonance imaging and biochemical markers such as increased alpha-fetoprotein.

Cryoablation

Each procedure comprised two freeze–thaw cycles accomplished using an argon gas-based cryosurgical unit (Endocare, Irvine, CA, USA). Cryoprobes (3 or 5 mm in diameter) were inserted into the center of the tumor mass under ultrasonographic guidance, each reaching a temperature of −180 °C at the tip of the probe. The duration of freezing was dependent on the achievement of an ice ball that extended 1 cm beyond the boundary of the tumor and was visible as a hypoechoic region on ultrasonography. Generally, the maximal freezing time was 15 min, followed by thawing for 5 min; this cycle was then repeated. For masses smaller than 5 cm in long diameter, two or three cryoprobes were placed within the center of the tumor, to ensure freezing of the entire mass; for masses with a long diameter of 5–10 cm, the tumor was divided into two parts that were treated in turn, usually at an interval of 1 week; for masses with a long diameter of 10–18 cm, the tumor was divided into three parts treated at intervals of usually 1 week. The tracts formed were sealed with fibrin glue immediately after removal of the cryoprobes to ensure hemostasis.

Measurement of thrombocytopenia and treatment of coagulopathy

Blood platelet counts were measured daily for 1 week post-cryosurgery to detect the occurrence of thrombocytopenia and coagulopathy. Patients with counts less than 100×10^9/L were watched closely. In those with counts lower than 70×10^9/L (i.e. severe coagulopathy), recombinant human IL-11 (rhIL-11) (25 μg/kg/day; Northland Biotech, Beijing, China) [29] was administered, usually for 3–5 days, to enhance the ability of the bone marrow to produce platelets.

Evaluation and statistical analysis

All cases of thrombocytopenia in this study were unambiguous; the influence of heparin, immune factors, drugs, sepsis, acute leukemia and internal or external irradiation was excluded [18]. Complications were recorded and classified in accordance with the Common Terminology Criteria of Adverse Events v4.0. Radiographic local tumor control was assessed using image-guided tumor ablation criteria [8]. Abdominal ultrasonography was performed both 1 day and 1 week after treatment. Follow-up ultrasonography was performed at 1 month and then at 3 month intervals. The revised Response Evaluation Criteria in Solid Tumors v1.1 were used to assess the response of the hepatic tumors [6]. The incidences of coagulopathy after ablation of primary and metastatic tumors were compared using the chi square test. Correlations between the incidence of coagulopathy, tumor diameter, pretreatment platelet count and maximal platelet loss were analyzed by linear regression. Differences in maximal platelet loss according to pretreatment platelet count were analyzed by Tukey's multiple comparison test. The statistical significance of correlations and differences was indicated by $P < 0.05$, $P < 0.01$ or $P < 0.001$. All analyses were conducted using GraphPad software (San Diego, CA, USA).

Results

Clinical data

Three hundred and seventy-two patients underwent 525 sessions of hepatic cryoablation; tumor long diameters were <6 cm in 256 patients, 6–10 cm in 79 and >10 cm in 37. One hundred and ninety-seven patients were male and 175 were female and their ages ranged from 29 to 75 years, with a mean of 53 years. Two hundred and forty-five patients were from China and 127 patients were from Southeast Asia. Of these patients, 116 had initially been treated surgically and 194 had been treated with systemic chemotherapy in other centers; 84 patients had thrombocytopenia.

Perioperative outcomes

All percutaneous cryoablations of primary and metastatic hepatic lesions were performed successfully. No severe complications (such as liver rupture or failure, myoglobinuria or acute renal failure) were discovered post-cryoablation. Many mild side effects occurred after cryosurgery, but the affected patients recovered with or without symptomatic treatment. Slight liver hemorrhage occurred after 105 sessions (20%), all cases of which were healed within 5 days by injection of hemostatic agents. Liver capsular rupture was found in 21 patients (4%) but resolved after blood transfusion. In the 84 patients (104 sessions) who had thrombocytopenia before liver cryoablation, the thrombocytopenia had disappeared after 11 sessions and coagulopathy occurred within 4 days after 50 sessions. Transient coagulopathy occurred within 4 days after 96 sessions (18%); 24 patients with severe disease received rhIL-11 and all patients recovered within 1 week. Liver abscess was observed after 32 sessions (6%) at the site of cryoablation, but the patients recovered within 2 weeks with antibiotic and drainage treatment.

Prediction of coagulopathy after liver cryoablation

Coagulopathy occurred after 41 of 241 sessions of cryoablation of primary HCC and 55 of 284 sessions of cryoablation of liver metastasis. According to the chi square test, this difference was not significant ($P = 0.4966$); thus, the 525 sessions could be combined for further analysis. In our therapeutic protocol, the tumor size was comparable between metastatic cancers and HCCs; smaller hepatic tumors (long diameter <6 cm) were treated with a single cryoablation and larger tumors (long diameter 6–10 cm or 10–18 cm) with two or three cryoablations, usually at intervals of 1 week. After each session, the incidence of coagulopathy was 14–22% (long diameter 1–2 cm, 7 of 34 sessions, 20.6%; long diameter