Observation on paclitaxel intraperitoneal chemotherapy combined with Kanglaite Injection in treating malignant ascites of advanced hepatic carcinoma

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[Abstract] Objective: The aim of this study is to discuss the efficacy and safety of the treatment of malignant ascites in advanced hepatic carcinoma with intraperitoneal paclitaxel combined with Kanglaite Injection. Methods: 24 cases of advanced hepatic carcinoma patients with malignant ascites were enrolled and paclitaxel (60mg/m²) resolved in normal saline (1,500~2,000ml) was administered via intraperitoneal injection weekly for 4 weeks while Kanglaite Injection (100ml/d) was used in the first day of the first chemotherapy cycle for 10 consecutive days. Short-term efficacy, adverse reactions, and the quality of life were evaluated according to WHO criteria. Results: After 4 treatment cycles, complete remission was seen in 9 (37.5%) out of the 24 patients and partial remission was observed in 8 (33.3%) cases, with a total effective rate of 70.8%. Quality of life was improved remarkably in 9 (36.0%) cases and improved in 14 (58.3%) cases. Grade I~II leucopenia was noted in 20 cases, grade I~III abdominal pain was found in 9 cases, and another 3 cases suffered from grade I~II nausea and vomiting. Conclusion: Intraperitoneal chemotherapy of paclitaxel combined with Kanglaite Injection is effective and safe in treating malignant ascites of advanced hepatic carcinoma, which improves therapeutic effects, reduces side effects of chemotherapy, and improves quality of life of patients.

[Keywords] paclitaxel infusion; parenteral; Kanglaite; liver neoplasm; ascites

Refractory tension ascites is often found in advanced liver cancer patients and routine diuretics and albumin supplementary treatment have less effect, which leads to lower life quality and shorter survival time of patient. How to effectively control malignant ascites caused by advanced liver cancer has become an important clinical issue at present. Between October 2009 and July 2010, 24 advanced liver cases with ascites received intraperitoneal paclitaxel perfusion combined with treatment of Kanglaite Injection. Therapeutic effect and safety of the two drugs were observed with the following report.

1. Materials and methods
1.1 General information
All 24 cases were hospitalized with confirmed diagnosis of primary liver cancer based on clinical symptom, α-fetoprotein determination, serum enzymology test, imaging examination (B-ultrasonography, CT) and cancels cells could be detected in ascites. In 24 cases, 14 were primarily treated and 10 once received interventional chemotherapy (paclitaxel perfusion not performed in hepatic artery); male 17 cases, female 7 cases; age between 30~62 years with median age as 46 years. Karnofsky score of 24 cases at admission was high than 60 on average with no abnormality in peripheral blood routine and in heart, liver and renal function.

1.2 Method
Chemotherapeutic regimen for intraperitoneal perfusion: Closed abdominal drainage was adopted to gradually drain cancerous ascites away within 2~3 days. Dexamethasone 5mg, im, 12hr before Paclitaxel. Dexamethasone 5mg, diphenhydramine 20mg, im, and cimetidine, iv drip, 30min before paclitaxel to prevent allergic reaction. Tropisetron 5mg, iv, for preventing vomit. Paclitaxel (manufactured by Bioengineering Co., of Harbin Pharmaceutical Group Co. Ltd.) was added to 1,500~2,000ml 0.9 saline for intraperitoneal administration. Patients were instructed to change position within 1 hr of administration to make even distribution of drug in abdominal cavity. Vital sign of patients was closely monitored during administration. Administration frequency was once per week for 4 weeks. Kanglaite Injection 100ml, iv drip, was given concomitantly for 10 days and no general chemotherapy was conducted during the period. Evaluation was made after every 2 cycles for short-term response rate of 2 cycles and 4 cycles including absorption of ascites, life quality and adverse reaction of chemotherapeutic drugs.

1.3 Evaluation criteria of therapeutic effect
Patient short-term therapeutic effect i.e. ascites absorption, life quality and adverse reaction of chemotherapeutic drug were monitored during treatment period for 4 cycles. Short-term effect was based on WHO recommended criteria for evaluating therapeutic effect on solid tumors, which is divided into complete remission (CR): complete disappearance of ascites in treatment for more than 2 weeks; partial remission (PR): reduction of ascites by 50% and above for more than 2 consecutive weeks; Total therapeutic effect was based on CR+PR.

Adverse reaction was, based on WHO’s grading criteria on adverse reaction of anticancer drugs, divided into 0~IV grades; Patient changes in Karnofsky score (≥20 scores after treatment compared with that before treatment as remarkable improvement and ≥10 scores as improvement), appetite, and bodyweight were evaluated as patient life quality.
1.4 Statistical method
SPSS 16.0 was used for statistical analysis and data was tested with $X^2$. $P<0.05$ suggested statistical significance.

2. Results
2.1 Short-term effect
In 24 cases after 2 cycles of treatment, CR 5 cases (20.8%), PR 7 cases (29.2%), total effective rate was 50.0%. After 4 cycles, CR 9 cases (37.5%), PR 8 cases (33.3%), total effective rate was 70.8%. In comparison with total effective rate between 4 weeks and 2 weeks the difference had no statistic significance ($X^2=1.389$, $P>0.05$).

2.2 Life quality
Life quality was compared with patient himself before and after treatment in Karnofsky scores and different changes were found. After 2 cycles, 7 cases had remarkable improvement and 10 had improvement with 7 cases having no apparent improvement; After 4 cycles, 9 cases had remarkable improvement, 14 had improvement and 1 had no notable improvement. Comparison of remarkable improvement rate and improvement rate between 4 cycles and 2 cycles had no statistical significance ($P>0.05$). However, case number with improved appetite and increased bodyweight after 4 cycles was higher than those treated with 2 cycles and the difference had statistic significance ($P<0.05$). See Tab. 1.

| Tab. 1 Comparison of patient life quality improvement after treatment [n, (%)] |
|---------------------------------|----------------|----------------|----------------|----------------|
| Cases                          | Karnofsky score increased ≥20 | Karnofsky score increased ≥10 | Appetite improved | Bodyweight increased |
| After 2 cycles treatment        | 24              | 7 (25.9)        | 10 (41.7)       | 9 (37.5)       | 10 (41.7)       |
| After 4 cycles treatment        | 24              | 9 (36.0)        | 14 (58.3)       | 17 (70.8)      | 19 (79.2)       |
| $X^2$ value                    | 1.457           | 1.239           | 3.957           | 4.520          |
| $P$ value                      | > 0.05          | > 0.05          | <0.05           | <0.05          |

2.3 Adverse reaction
Among 24 cases, 20 had bone marrow inhibition at different degrees in administration with majority at I–II degrees, mainly leukopenia. 9 cases had I–III degrees of abdominal distension or abdominal pain, 3 cases had slight nausea or vomit, 2 cases had I degree alopecia. 1 case infused with Kanglaite Injection had slight phlebitis and got improved in symptom after lowering drop speed and fomentation without other apparent side effect.
3. Discussion

Comprehensive treatment is stressed in treating primary hepatic carcinoma. In early stage excision or liver transplantation could be adopted. At middle or late stages, arterial embolism, local ablation, chemotherapy, or biological therapy could be considered to constantly improve cure rate. However patients with advanced liver cancer often have refractory ascites to impair life quality and shorten survival period. At present clinically effective method to treat malignant ascites is mainly intraperitoneal perfusion chemotherapy that is a regional measure to raise drug concentration at location of tumor to reduce systemic toxic adverse reaction caused by chemotherapy. Compared with systemic chemotherapy it has apparent pharmacokinetic advantage and has been clinically applied for many years. Most commonly used drug includes 5-fluorouracil (5-Fu) and cisplatin that have shown certain therapeutic effect in controlling intraperitoneal neoplastic diseases. Literature reported that intraperitoneal peak concentration of cisplatin after perfusion and area under concentration-time were respectively 20 times and 12 times higher than that in plasma with heavier gastrointestinal adverse reaction. Moreover, cisplatin and 5-Fu are water soluble small molecular compounds to be quickly absorbed by blood vessels after perfusion and cannot be locally retained so as to prevent therapeutic effect from further improvement.

Paclitaxel is anticancer active compound extracted and separated from bark of mountain mahogany with unique antineoplastic efficacy. It presents anticancer effect mainly through formation of stable polymer with canaliculus to interfere with cell division. Paclitaxel has macromolecular structure and high relative molecular mass that is not easily to be absorbed by blood vessels. Study also found that paclitaxel had high appetency with protein of ascites to make it easily retained in abdominal cavity and not easily to be removed. Prolonged intraperitoneal retention time is able to give full play to its anticancer efficacy. In addition it can induce apoptosis of tumor cells, generate tumor necrosis factor α (TNF-α), and enhance sensitivity of radiotherapy. All these provide theoretical basis for paclitaxel to treat malignant ascites through intraperitoneal perfusion. Small-sample clinical studies showed that intraperitoneal direct injection of paclitaxel to treat gastric cancer with peritoneum metastasis had satisfactory preventive and therapeutic effect. Study of Kobayashi et al showed that 60~80mg/m² of paclitaxel intravenously injected to 2 cases of advanced gastric cancer with intraperitoneal metastasis and ascites could quickly reach plasma peak value. Although the value dropped to 85ng/ml within 24 hrs, intraperitoneal drug concentration got elevated stably to reach plasma level and maintained for more than 72 hrs. Ascites of the 2 patients was quickly eliminated after treatment for 2 therapeutic courses. Paclitaxel, widely used in treating ovarian
cancer with malignant ascites \textsuperscript{[6]}, showed good effect and longer patient surviving period. However, this kind of study on hepatic carcinoma is rarely found. Result from this study showed that 9 cases could reach CR after being treated for 4 cycles and 8 cases for PR with total effective rate of 70.8\%. This not only verified good therapeutic effect of paclitaxel in treating intraperitoneal ascites caused by hepatic cancer, but revealed that paclitaxel in combination with Kanglaite Injection could further improve patient life quality and minimize adverse reaction. Currently, most studies do not support drug with paclitaxel to be applied in treating primary hepatic carcinoma and discord with the result from this study. This is possibly related to that all patients in this study got good response to chemotherapy due to initial treatment or Kanglaite Injection was combined in the treatment.

Kanglaite Injection is a compound with anticancer active substance extracted and separated from traditional TCM herb coix seed \textsuperscript{(7)}. It mainly acts on G2/M phases of tumor cells to induce cell apoptosis, notably kill cancer cells, control tumor growth and resist tumor metastasis so as to reach antineoplastic objective \textsuperscript{[8-9]}. At the same time it presents the effect of synergy and reduction of toxicity. It not only improves result of chemotherapy but also reduce gastrointestinal adverse reaction caused by chemotherapy and incidence of bone marrow inhibition to improve patients’ tolerance to chemotherapy and their life quality. As fat preparation, it can also provide with high energy nutrition to human body so that patients with advanced malignant cancers are willing to accept Kanglaite treatment.

Adverse reaction most commonly occurred in this study was abdominal pain that was compliant with past literature report \textsuperscript{(10)}. This abdominal pain was possibly caused by local stimulation of chemotherapeutic drugs and could be relieved after symptomatic treatment. There was no other apparent adverse reaction to be detected in this study.

In summary, therapeutic effect of intraperitoneal perfusion chemotherapy with paclitaxel in combination with Kanglaite Injection to treat ascites of hepatic carcinoma was acceptable and safety was relatively high. It can be recommended to be an effective clinical method in treating ascites of primary hepatic carcinoma.

[References]


