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Adverse reaction of a combined treatment for unresectable liver cancer

Research Article

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Abstract: To investigate the adverse reactions of transcatheter arterial chemoembolization (TACE) combined with trastuzumab in the treatment of unresectable live cancer, 85 unresectable liver cancer patients were treated with 35 mg epirubicin, with lipiodol and gelatin sponge granule as the embolic agent, and trastuzumab (4mg/kg) was administered intravenously. All the adverse reactions were investigated by blood routine examination and the checking of liver, renal and thyroid functions on the postoperative 2nd and 30th day. No patients died of direct medication. The main adverse reactions included haematological toxicity, liver function lesion and postoperative syndromes such as nausea, vomiting, fever and liver area aching. Two days after the treatment, the amount of the serum total bilirubin (TB) and white blood cell (WBC) increased dramatically, while platelet (PLT) changed a little, and creatinine (Cr) and blood urea nitrogen (BUN) did not change at all. Thirty days after the treatment, blood routine, liver and renal functions were examined, demonstrating that the liver function remained unchanged, PLT decreased apparently, WBC was lower, and Cr and BUN changed slightly compared to those before the treatment. The combined treatment is safe for unresectable liver cancer and thus can be used as a routine intervention method.

Keywords: *Adverse effect • Hepatoma cell • Radioimmunotherapy • Transcatheter arterial chemoembolization • Trastuzumab*

1. Introduction

Trastuzumab (trade name Herceptin) is a monoclonal antibody that interferes with Her 2. By binding with Her 2, trastuzumab prevents it from interacting with the human epidermal growth factors, which inhibits the growth of cancer cells and also stimulates the immune cells to destroy cancer cells. Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody which selectively acts on the extracellular sites of the human epidermal growth factor receptor -2 (HER2). This antibody is IgG1 type, with the human framework region and HER-2 can be combined with mouse anti-p 185 HER2 antibody complementarity-determining regions [1,2].

The humanized anti-HER2 antibody is raised by suspension in a sterile medium of mammalian cells (Chinese hamster ovary cells CHO) and then purified by affinity chromatography and ion exchange, including the specific removal procedures for viral inactivation [3].

HER2 proto-oncogene or C-erbB2 encodes a single receptor-like transmembrane protein with the molecular weight of 185kDa, the structure of which is associated with the epidermal growth factor receptor. It is observed that 20%-30% of the patients with primary breast cancer exhibit the symptom of HER2 overexpression. HER2 gene amplification promotes HER2 protein expression on the surface of tumor cells, resulting in the activation of HER2 receptor [4,5].

Previous research has demonstrated that the disease-free survival of the cancer patients with HER2

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overexpression is shorter than those without HER2 overexpression. HER2 overexpression can be diagnosed through the following methods: evaluating the tumor tissue on the basis of immunohistochemistry and investigating the tissue and the plasma samples by ELISA and fluorescence in situ hybridization (FISH) [6,7].

Trastuzumab is a potential matrix for the antibody-dependent cell-mediated cytotoxic (ADCC) reaction. In vitro studies have verified that trastuzumab-mediated ADCC shows more priority in the cancer cells with HER2 overexpression than those without HER2 overexpression [8].

This drug has been used in clinical trials as a single agent for the treatment of HER2 overexpression in metastatic breast cancer. More than one chemotherapy cases for patients with metastases have failed.

In the clinical tests, combined with paclitaxel, anthracyclines (doxorubicin or epirubicin) and cyclophosphamide, trastuzumab has been used as the main drug to treat metastatic breast cancer in which HER2 is overexpressed [9].

For the cases of metastatic breast cancer without chemotherapy, anthracyclines (doxorubicin 60 mg/m^2 or epirubicin 75mg/m^2), cyclophosphamide (600 mg/m^2) with (trastuzumab +AC) or without (single AC) have been used for the treatment [10]. For the cases of metastatic breast cancer with chemotherapy based on anthracyclines, the treatment has been performed using paclitaxel (175 mg/m^2, 3 hours injection) with (trastuzumab+P) or without trastuzumab (single P). The drugs can be continuously used until patient status improves.

In the immunogenicity tests, only 2 patients did not accept the detection of antibodies. Only 1 patient had the antibody trastuzumab in vivo and did not experience concomitant allergy.

89 patients with unresectable liver cancer have accepted the combined treatment of TACE and trastuzumab from Feb 12 to Nov 15 in 2011 in our hospital, adverse reactions and the safety report on the clinical applications are listed as follows.

2. Materials and methods

2.1. Clinical information

Patients who exhibited the following symptoms were included: 1. hepatocellular carcinoma confirmed by clinical and image detection, alpha-fetoprotein (AFP) test and pathological examination; 2. unresectable liver tumor diagnosed by surgeons; 3. expected survival time for more than three months; 4. physical status Karnofsky score (KPS) more than 60; 5. without serious renal and liver dysfunctions (Child A or B Class liver function); 6. tumor occupy rate less than 70%. The patients who showed the following symptoms were not considered: 1. with poor physical conditions and serious liver function impairment (Child C class); 2. with serious heart, kidney and blood system diseases; 3. with other treatments within 4 weeks; 4. with a record of being allergic to biological agent, anaphylaxis or being in the allergic state; 5. pregnant and lactating women [11,12].

89 patients with liver cancer received the combined treatment of TACE and trastuzumab in total, 57 cases were male and 32 cases were female. Ages of the patients ranged among 42~86, and the average age was 50. 69 and 20 cases were Child A class (77.53%) and Child B class (22.47%) respectively according to the Child-Pugh classification of liver function. In the clinical TNM stage, 7 cases were I-II (7.86%), 22 cases IIIA (24.72%) and 31 cases IIIB (34.83%), and 29 cases IV (32.58%). 25 cases were massive HCC, 45 cases were nodular HCC and 19 cases were diffuse HCC, respectively. 71 cases were AFP positive (>30 μg/L) and 16 cases were negative. KPS scores of 69 cases were higher than 70 and those of 20 cases ranged among 60~70.

2.2. Therapeutic methods

In addition to the preoperative preparation for the conventional TACE, skin tests for Metuximab were performed 3 days before the surgery operation. If the test results were negative, the patients had to take a compound iodine solution (Lugo, iodine solution) orally 3 times a day and 0.5 mL each time until 7 days after the treatment. Seldinger technique was used, and 5FYashiro or RH catheter was inserted to common hepatic artery through femoral artery for angiography with the total contrast agent of 30~40 mL and a flow rate of 3~5 mL/s [13]. Exploring the hepatic artery and the collateral feeding vessels with the ectopic origin ensured that the location, the size and the number of the tumors and the situation of the feeding arteries were known. The hepatic artery or liver lobe artery were then selectively catheterized, and micro-catheter was used if catheterization was not possible. The recommended dose of trastuzumab (Shanghai Roche Pharmaceutical Co., Ltd., 440 mg/bottle, S20100076) was injected through venae in 90 min, and the initial loading dose was 4 mg/kg. Weekly Herceptin consumption was 2 mg/kg. If the initial loading dose of trastuzumab was tolerated, the dose could be injected in 30 min. This intravenous injection method could be performed until the conditions improved. The

catheter was flushed with 10 mL 0.9% NaCl to ensure that all the therapeutic drugs were injected into human body. 40 mg epirubicin and suitable amount of lipiodol emulsion were used for chemotherapy embolization 25 min after the circulation. Lipiodol dosage depending on the tumor size and the blood supply normally ranged among 5~20 mL. If the tumor was large and the blood supply was abundant, gelatin sponge granule could be used to strengthen embolism. The patients were transferred to the medical ward for isolation for 48~72 h with routine liver protection, acid suppression and supporting symptomatic treatments [14].

2.3. Evaluation criteria

According to the new guidelines evaluating the objective treatment effects in solid tumors by World Health Organization (WHO), short term cancer treatments are graded into complete remission (CR), partial remission (PR), minor remission (MR), stable disease (SD) and progressive disease (PD). Clinical remission rate is defined as CR+PR, clinical effective rate is defined as CR+PR+MR, and clinical response rate is defined as CR+PR+MR+SD. Adverse reactions are evaluated on the basis of WHO grading criteria for acute and subacute toxicity of antitumor agents [15,16].

2.4. Outcome measures

Postoperative clinical manifestations such as nausea, vomiting, fever and pain and the changed nature of the urine and stool were observed for the patients. Enhanced liver CT scan was carried out 4 weeks after the surgery operation to study the varied number and size of intrahepatic tumors. Postoperative AFP levels and human anti-mouse antibody (HAMA) reactions were checked every 4 weeks. 2 and 30 days after the surgery, electrocardiograms, three major routines as well as liver, renal and thyroid functions were examined.

2.5. Statistical analysis

All the data were expressed as absolute values or percentages. SAS6.12 software was used for statistical analysis, and CMH chi-square test was used for toxicity comparison with the statistical differences when $P < 0.05$.

3. Results

3.1. Objective treatment effects

Recent objective treatment effects of 89 cancer patients are listed as follows: CR: 3 cases (3.37%), PR: 19 cases (21.35%), MR: 19 cases (21.35%), SD: 42 cases (47.19%) and PD: 6 cases (6.74%); clinical remission rate (CR+PR): 22 cases (24.72%), clinical effective rate (CR+PR+MR): 41 cases (46.07%), clinical response rate (CR+PR+MR+SD): 83 cases (93.26%); decreased AFP: 40 cases (44.94%).

3.2. Adverse reactions

No patients died of direct medication. The main adverse reactions included fever, nausea and vomiting, liver area pain, reduced blood cells, and increased bilirubin and transaminases. Changed urine and renal functions, abnormal electrocardiogram, constipation and diarrhea were observed in minor patients. The patients with proteinuria, hematuria, cardiac, singultus, hepatoma disruption and thyroidhypo function accounted for 4.49% (4 cases), 12.63% (11 cases), 3.37% (3 cases), 14.61% (13 cases), 7.87% (7 cases) and 6.74% (6 cases), respectively. Toxicity analysis was performed referring to WHO toxicity grading criteria (0-IV), and the results are shown in Table 1. 2 days after the surgery, blood routine, liver and renal functions were checked, exhibiting that serum total bilirubin (TB) and white blood cell (WBC) increased significantly (P=0.007), N (P=0.326), platelet (PLT) changed slightly (P=0.075), creatinine (Cr) and blood urea nitrogen (BUN) did not change at all compared to those before the operation. 30 days after the treatment, liver functions were restored to preoperative levels (P=0.364), PLT decreased apparently (P=0.026), WBC reduced without statistical differences (P=0.142), Cr and BUN changed a little (P=0.068, P=0.171) compared to those before the operation. The results are listed in Table 2 and Table 3.

3.3. HAMA reactions

After Metuximab skin tests, the results were positive if the diameter of the flush was more than 4 mm in the presence of either pseudopodia or blisters. Before the treatment, results of all the skin test were negative. 80 cases of skin tests were then randomly selected, in which 31 cases (34.83%), 65 cases (81.25%) and 7 cases (7.87%) were positive after 4, 12 and 24 weeks, respectively.

Table 1. Adverse reaction grading for 89 cases of liver cancer patients after the combined treatment of trastuzumab and TACE

Parameter	WHO grading criteria				
	0	I	II	III	IV
Gastrointestinal					
Sick and vomit	18(20.22)	36(40.45)	26(29.21)	4(4.49)	5(5.62)
Ulcer or bleeding	82(92.13)	3(3.37)	4(4.49)	0	0
Diarrhea	80(89.89)	4(4.49)	2(2.25)	1(1.12)	2(2.25)
Constipation	58(65.17)	21(23.60)	5(5.62)	3(3.37)	2(2.25)
Urologic					
Proteinuria	85(95.51)	4(4.49)	0	0	0
Hematuria	78(87.64)	9(10.11)	2(2.25)	0	0
Cardiac	86(96.63)	3(3.37)	0	0	0
Bellyache	44(49.44)	23(25.84)	21(23.60)	1(1.12)	
Drug febrile	36(40.45)	22(24.72)	27(30.34)	4(4.49)	0
Singultus	76(85.39)	13(14.61)	0	0	0
Hepatoma disruption	82(92.13)	4(4.49)	3(3.37)	0	0
Thyroidhypo function	83(93.26)	6(6.74)	0	0	0

Table 2. WHO toxicity grading

Parameter	Post-treatment/n (%)				Day 2 of post-treatment/n (%)				Day 30 of post-treatment/n (%)			
	0	I	II	III/IV	0	I	II	III/IV	0	I	II	III/IV
WBC	42(47.19)	28(31.46)	16(17.98)	3(3.37)	65(73.03)	22(24.72)	2(2.25)	0	44(49.44)	26(29.21)	15(16.85)	4(4.49)
Plt	45(50.56)	26(29.21)	13(14.61)	5(5.62)	59(66.29)	17(19.10)	12(13.48)	1(1.12)	42(47.19)	27(30.34)	12(13.48)	8(8.99)
TB	81(91.01)	6(6.74)	2(2.25)	0	43(48.31)	22(24.72)	18(20.22)	6(6.74)	80(89.89)	5(5.62)	3(3.37)	1(1.12)
DB	75(84.27)	12(13.48)	2(2.25)	0	47(52.81)	25(28.09)	15(16.85)	2(2.25)	73(82.02)	14(15.73)	2(2.25)	0
ALT	74(83.15)	10(11.24)	4(4.49)	1(1.12)	41(46.07)	32(35.96)	15(16.85)	1(1.12)	70(78.65)	11(12.36)	6(6.74)	2(2.25)
AST	68(76.40)	13(14.61)	7(7.87)	1(1.12)	26(29.21)	38(42.70)	20(22.47)	5(5.62)	67(75.28)	15(16.85)	3(3.37)	4(4.49)
Cr	88(98.88)	1(1.12)	0	0	88(98.88)	1(1.12)	0	0	85(95.51)	2(2.25)	2(2.25)	0
BUN	84(94.38)	5(5.62)	0	0	84(94.38)	5(5.62)	0	0	83(93.26)	4(4.49)	2(2.25)	0

Table 3. Effects of combined treatment on hematology, liver and renal functions (mean ± SD)

Parameter	Unit	Before treatment	Day 2 of post-treatment	p1	Day 30 of post-treatment	p2
WBC	($\times10^9$/L)	4.15±0.32	9.23±0.66	0.007	3.67±0.27	0.142
Plt	($\times10^9$/L)	109±19	92±16	0.075	67±12	0.026
TB	×N	1.12±0.25	2.44±0.42	0.001	1.23±0.34	0.436
DB	×N	1.04±0.21	2.54±0.52	0.000	1.10±0.23	0.317
ALT	×N	1.12±0.26	2.75±0.41	0.000	1.19±0.17	0.364
AST	×N	1.22±0.15	2.66±0.47	0.000	1.20±0.12	0.596
Cr	×N	1.03±0.17	1.05±0.16	1.000	1.17±0.09	0.068
BUN	×N	1.08±0.22	1.07±0.16	1.000	1.22±0.15	0.171

p1: statistics of postoperative hematology, liver and renal functions compared to the preoperative ones; p2: statistics of postoperative 30d hematology, liver and renal functions compared to the preoperative ones. N = upper limit of the normal range. $P<0.05$ indicates a significant difference

4. Discussion

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Early stage HCC is often asymptomatic, which cannot be diagnosed until the middle or late stage. Successful resection rate is less than 20%, and the postoperative recurrence rate is extremely high [17]. In the last 30 years, radiology has been used for the treatment, which has proven that TACE based on the blood supply theory of liver cancer has achieved remarkable success in the assessments of tumor shrinkage, AFP declining and the evaluations on the survival time and the quality of life. However, the overall effectiveness of TACE is still not satisfactory hitherto [18]. Therefore, it is of great significance to perform effective comprehensive treatment for numerous unresectable HCC [19].

Radioimmunotherapy (RIT) uses a monoclonal antibody with specificity for a tumor-associated antigen to deliver a radionuclide to a tumor cell that leads to the radiation therapy [20]. In addition, Herceptin may induce the immune cells to kill the tumor cells, which does not significantly affect the normal cells and produces scarce adverse reactions. The recurrence rate and mortality rate decreases by 52% and 33% accordingly. The results of CR+PR, CR+PR+MR and CR+PR+MR+SD in the tested 89 tumor patients indicate that trastuzumab and TACE synergistically improved the anticancer effects [21].

Blood tests showed that hematological toxicity increased with increasing dose of trastuzumab, which reached grade III toxicity according to WHO toxicity grading criteria [22]. The toxic effects on liver function also increased with increasing dose of the trastuzumab. 4mg/kg of trastuzumab intravenous infusion did not obviously affect renal functions. Thyroid function was not significantly influenced by sealing the thyroid with Lugo l solution from 3 days before to 7 days after receiving the drug. No dramatic effects of the drug on blood electrolytes and myocardial enzymes were discerned.

After the treatment of TACE with Trastuzumab, various extents of nausea, vomiting, fever, liver area pain were observed for all the patients with scarce diarrhea, constipation, intractable hiccups and abnormal ECG changes. All the symptoms were classified into TACE embolization syndrome [23]. After chemoembolization, the edema of the liver tissue and portal venous drainage were blocked, which led to intestinal congestion, edema of the bowel wall and gas accumulation in the bowel. Then abdominal distension, diarrhea, constipation and intractable hiccup originated from the stimulated phrenic nerve could be observed [24].

After the symptomatic treatment, the adverse reactions could be relieved in a few days to 2 weeks. If the tumor was large and protruded above the liver surface, it was prone to tumor tissue necrosis that induced spontaneous bleeding after embolization. The patients with this symptom were cured by emergent TAE to stop the bleeding and active anti-shock treatment. In addition, the patients with primary liver cancer were often accompanied by liver cirrhosis and portal hypertension. Either stress ulcer or upper gastrointestinal hemorrhage due to esophageal variceal bleeding was induced after TACE treatment [25]. Melena was observed in one case after the treatment, which was diagnosed with severe varicose gastric veins. After the conservative treatment, the bleeding was stopped. Moreover, the continued internal radiation effects of trastuzumab on the damaged gastric mucosa could not be excluded. The treatments with acid suppression and protection for gastric mucosa should be strengthened for postoperative care. No patient died during the treatment.

It has been previously reported that the main side effects of trastuzumab were hematological toxicity and liver function damage. Various extents of impaired liver function and hematological toxicity could be also observed after TACE treatment owing to ischemia and hypoxia in the target liver tissue, reperfusion injury, and toxic side effects of chemotherapy drugs. The toxic side effects from both of the two parts could mutually superimpose, leading to the serious adverse reactions of the combined therapy [26]. The study results show that the PLT was much lower than that before the treatment, and the Cr and BUN did not change significantly, which were probably ascribed to tumor ischemic necrosis, liver aseptic inflammation and persistent fever. Tumor necrosis substances in the bloodstream and the toxicity of the chemotherapy drugs aggravated the damage to the kidneys in the combined therapy. The renal function, Cr and BUN did not change significantly compared to those before the treatment.

In the treatment with trastuzumab, the signs and symptoms of cardiac dysfunction, such as difficult breathing, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, and reduced ejection fraction, were found in the patients [27]. The congestive heart failure related to the treatment with Herceptin may be extremely serious and could lead to fatal heart failure, death, and cerebral embolism with mucus emboli. Especially, moderate and severe heart dysfunction (New York Heart Association (NYHA) class III/IV) were observed in the combination of Herceptin with anthracycline (doxorubicin or epirubicin) and cyclophosphamide for the treatment of metastatic breast cancer [28].

About 2/3 patients with heart dysfunctions were treated until improvement. The therapy usually included diuretics, cardiac glycoside drugs or angiotensin-converting enzyme inhibitor drugs [29]. Most of the patients mentioned above continued to use Herceptin weekly, and no more clinical heart problems were observed as a result.

5. Conclusion

In summary, the combined treatment of TACE and trastuzumab showed a good security for the unresectable live cancer, no serious adverse reactions, which thus can be used as a routine intervention therapy for liver cancer.

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