Cancer cell research 9 (2016) 210-213

www.cancercellresearch.org Article

Clinical study of FOLFIRI treatment for gastric cancer patients with metachronous ovarian metastasis

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Abstract: **To observe the short-term effects and adverse reaction of FOLFIRI for gastric cancer patients with metachronous ovarian metastasis. 30 cases of patients using the Irinotecan for 180 mg/m2, intravenous drip, d1; Leucovorin (CF) 200 mg/m2, intravenous drip, d1~2; 5-FU 400 mg/m2 intravenous drip, d1~2 and 2400mg/m2 using an ambulatory pump continuous infusion for 44-48 hours, repeat every 2 weeks; The therapeutic effects were evaluated after 3 cycles. In the 30 cases, 0 cases were CR, 6 cases were PR, 8 cases were SD, 16 cases were PD. The overall response rate was 20%, disease control rate was 46.7%. The most common adverse reactions was leukopenia, diarrhea, nausea and vomiting. The short term efficiency of FOLFIRI is good, and its adverse reactions are tolerable and can be controlled.**

Keywords: Gastric cancer; Metastatic ovarian tumor; FOLFIRI

Received 9 December 2015, Revised 20 January 2016, Accepted 25 January 2016

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1. Introduction

The Krukenberg tumours is an uncommon variety of metastatic cancer to the ovary, first described by the German gynecologist, pathologist Friedrich Krukenberg' in 1896. The Krukenberg tumours include the synchronous ovarian metastasis and the metachronous ovarian metastasis [1]. Most series report that, where a primary source has been identified, this is the stomach in 60-70 percent of Krukenberg tumours [2]. Other source includes the colon, cervix, bladder, renal pelvis, etc [3-6]. At present, reports on the Krukenberg tumours are growing, but effective treatment methods for ovarian metastasis are lacking. And the prognosis for ovarian metastasis of gastric cancer was poor without curative resection.Our department treated thirty gastric cancer patients who were diagnosed with metachronous ovarian metastasis with FOLFIRI, to study the clinical effects and adverse reaction of FOLFIR.

2. Patients and methods

2.1. Clinical data

The clinical characteristics of all study participants are shown in (Table 1): 30 female gastric cancer patients 30 to 66 years old (mean age: 46.4 years) were diagnosed with metachronous Krukenberg tumours on the basis of corresponding symptoms after primary cancer surgery or imaging tests. The interval to metastasis was 2 months to 20 years after gastric cancer, with an average of 16 months. Among these 30 cases, 20 were premenopausal, and 10 were postmenopausal. The patients showed different histopathologic types of primary gastric cancer: poorly-moderately differentiated adenocarcinoma(8 cases), anaplastic carcinoma(6 cases), mucinous adenocarcinoma (6 cases), and signet ring cell carcinoma (10 cases). These patients were grouped according to primary gastric cancer lesion: gastric sinus (19cases), gastric body (6 cases), cardia (5 cases). They were also classified according to their ovarian metastasis neoplasms: unilateral (8 cases) and bilateral (22 cases). The common sites of metastases were celiac lymph nodes, liver supraclavicular lymph nodes, bone, lung and Peritoneum. Up to 10 patients had more than two metastases. For primary cancer, 14 cases underwent subtotal gastrectomy, 8 underwent total gastrectomy, 8 did not undergo surgery Due to extensive metastasis. All patients of this group received chemotherapy for gastric cancer and ovarian metastasis. The chemotherapy medicine mainly includes fluorouracil, oxaliplatin/cisplatin, calcium folinate, docetaxel, and so on. Currently, all patients: unresectable disease; at least one measurable lesion shown by computed tomography (CT) or magnetic resonance imaging (MRI); Eastern Cooperative Oncology Group (ECOG) score≤2; expected survival time≥3 months; normal results including routine blood, biochemical, ECG; no contraindications for chemotherapy treatment.

2.2. Treatment

Irinotecan 180 mg/m2, intravenous drip, d1; Leucovorin (CF) 200 mg/m2, intravenous drip, d1~2; 5-FU 400 mg/m2 intravenous drip, d1~2 and 2400mg/m2 using an ambulatory pump continuous infusion for 44-48 hours. This treatment regimen was repeated every 14 days and a 14-day treatment period was defined as one chemotherapy cycle. In both groups, palonosetron routinely was administered during the chemotherapy in order to prevent vomiting. Once patients appeared watery diarrhea, they would take Imodium immediately. Imodium was first administered 4mg, and 2mg every two hours, until

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after the last diarrhea continue medication for 12 hours, but total time within 48 hours. If patients had III-IV degree diarrhea, the dose would be reduced by 20% -30% in the next cycle.

2.3. Evaluation criteria for short-term efficacy and safety

After each three complete chemotherapy cycles, the lesion size was monitored using CT or MRI, and reviewed after 4 weeks. The short-term efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines and recorded as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Response rate (RR) = (CR + PR) / total cases × 100%. Disease control rate (DCR) = (CR + PR + SD) / total cases × 100%. Adverse reactions were assessed according to the WHO Cancer Common Toxicity Criteria and graded 0–IV.

3. Results

3.1. Short-term efficacy

All 30 patients were evaluable, no patients had CR, 6 patients had PR, 8 patients had SD, 16 patients had PD, so the RR was 20.0%, and DCR was 46.7%.

3.2. Adverse reactions

There were no treatment-related deaths, no allergic reaction. Bone marrow depression and gastrointestinal reactions were common reactions. Nausea, vomiting symptoms were often1-2 degree. The rate of grade III–IV leucopenia was 20%, and diarrhea was 16.7% (Table 2).

Table 1 General clinical parameters of 30 patients included in this study.

Characteristics	n
Age	
Premenopausal	20
Postmenopausal	20
Pathological Types	
Poorly-moderately differentiated adenocarcinoma	8
Anaplastic carcinoma	6
Mucinous adenocarcinoma	6
Signet ring cell carcinoma	10
Krukenberg Location	
Bilateral	22
Unilateral	8
Surgical Treatment	
Yes	22
No	8
The site of metastases	
Celiac lymph nodes	19
Peritoneum	9
Liver	3
Supraclavicular lymph nodes	3
Bone	2
Lung	4
Chemotherapy	
DCF	8
ECF	5
XELOX	7
FOLFOX	6
OXA+S1	4

Table 2 Summary of adverse events n (%).

Adverse events	Grade I-II	Grade III-IV
leucopenia	16(53.3)	6(20.0)
neutropenia	18(60.0)	7(23.3)
thrombocytopenia	4(13.3)	3(10.0)
increased AST or ALT	8(26.7)	0(0.00)
diarrhea	9(30.0)	5(16.7)
nausea	21(70.0)	0(0.00)
vomiting	10(33.3)	0(0.00)
oral mucositis	5(16.7)	0(0.00)

4. Discussion

Gastric cancer is the second highest cause of cancer mortality [7], a serious threat to human life. Ovaries are the common metastasis site for many malignant neoplasms. The incidence rate of postoperative ovarian metastasis of female gastric cancer patients ranges from 2.7% to 6.7% [8]. Currently, standard treatment methods for gastric cancer ovarian metastasis are lacking. Many scholars believe that surgery is the preferred method to treat ovarian Krukenberg tumors [9-10]. Foreign researches showed [11-13] that only primary tumor resection, patients who underwent total excision of the metastatic lesion had better prognosis than patients with tumors. In last year's ASCO meeting, Professor Jang Ho Cho from Korea compared the combined modality therapy with chemotherapy alone in patients with Krukenberg tumors. The results showed that, patients with synchronous ovarian metastasis treated with combined modality therapy compared with those who had chemotherapy alone tended to have a better Overall survival (OS: 21.0 vs 12.0 months; $P < 0.001$); Also for patients with

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metachronous ovarian metastasis, combined modality showed a significantly better OS (19.0 vs 8.0 months; P＜0.002). The results also showed that survival was significantly longer in patients who underwent curative resection combined with chemotherapy compared with those who had chemotherapy alone.

Due to the pathogenesis of the Krukenberg tumor is concealed, patients are already at an advanced stage when first diagnosed difficult to cure with surgery. Moreover, Krukenberg tumor is poorly differentiated, with wide seeding metastasis of abdominal and pelvic peritoneum, its progress is rapid, and its prognosis is poor. According to statistics, the median survival period of the patients is less than 1 year. Most patients died within 3 years, and 5-year survival rate is about 0 [14-15].For patients without indications for surgery, appropriate chemotherapy can control the disease to a certain degree, and maintain the quality of life of patients. Sometimes chemotherapy may Alleviates the condition, making it possible for patients to receive surgical treatment. There have been many reports about the use of drugs for the treatment of Krukenberg tumor, such as paclitaxel, docetaxel, irinotecan and oxaliplatin, combined with cisplatin or fluorouracil (5-FU) for advanced gastric cancer.

Irinotecan is a semi-synthetic water-soluble camptothecin derivative, is a specific inhibitor of topoisomerase I. Irinotecan, as the third generation of new anticancer drugs,is effective against gastric, colorectal and lung cancer. Single agent Irinotecan or in combination with other drugs have been widely used in the treatment of colorectal cancer. Currently NCCN guidelines recommend single agent irinotecan as a second-line treatment for patients with advanced gastric cancer, obtaining an overall response rate of 20% [16]. In 2011, a randomized controlled phase III clinical study , reported by AIO from Germany, showed that patients with advanced gastric cancer treated with irinotecan in second-line chemotherapy compared with those who had supportive care tended to extend median survival from 2.4 months to 4.0 months, the risk of death down to 0.48 [17]. The positive results provide with relevant clinical evidence for second-line chemotherapy of advanced gastric cancer.

A randomized phase Ⅲ study shows: to patients with advanced adenocarcinoma of the stomach or esophagogastric junction, some treated with irinotecan combined with 5-FU / leucovorin tended to have a non-inferior progression-free survival compared with those treated with cisplatin combined with 5-FU,and former better tolerated. In some cases, irinotecan may be a suitable replacement for platinum in chemotherapy [18]. Our department treated thirty patients with metachronous ovarian metastasis with FOLFIRI. All Patients had undergone multiple cycles of chemotherapy, and has not used the drug irinotecan, and has no cross-resistance with previous chemotherapy. After three chemotherapy cycles, the FOLFIRI regimen obtaining a RR of 20% and a DCR of 46.7%.Although the FOLFIRI regimen demonstrated passable short-term efficacy in patients with metachronous ovarian metastasis,it along with a common side effect of grade I-II nausea, vomiting, bone marrow suppression, diarrhea, and grade III–IV leucopenia ,diarrhea. To compare with the reports about advanced gastric cancer chemotherapy domestic and international [19-21], There were lighter adverse reactions,and no treatment-related deaths.

In summary, the ovarian metastasis of gastric cancer is in the IV period, with unfavorable prognosis. We should put more emphasis on early detection, the early diagnosis and treatment. Currently, there are no standard treatment methods for patients with gastric cancer ovarian metastasis. Our department treated patients without indications for surgery with the FOLFIRI regimen, achieved an exact efficacy. The FOLFIRI regimen can control some patients' condition effectively, with mild clinical toxicity. In addition, it was affordable medicines for patients. This present preliminary study demonstrated that the FOLFIRI regimen was effective for the treatment of advanced gastric cancer, and it can expand the number of clinical samples for further study.

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