Case Report

A fatal myelosuppression, diarrhea and neurotoxicity induced by combination of irinotecan and tegafur-gimeracil-oteracil potassium in the treatment of colon cancer: a case report

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Abstract: Chemical treatment is the vital pattern for colon cancer patients after surgery. Irinotecan and tegafur-gimeracil-oteracil potassium (S-1) combined chemotherapy is effective on metastatic colorectal cancer (mCRC). Nevertheless, patients receiving this combined chemotherapy might suffer the adverse drug reaction (ADR), such as myelosuppression and/or diarrhea, which could lead to poor prognosis. Here, we report a 76-year-old Chinese female who died due to the toxicity of combined therapy with irinotecan and S-1. This patient received irinotecan and S-1 combined therapy for 6 sessions after laparoscopic radical operation on colon cancer. After 6 sessions of chemotherapy, myelosuppression and severe diarrhea appeared with delirious accompanied. Antineoplastic agents were stopped immediately due to the appearance of III grade myelosuppression and IV grade diarrhea. Loperamide and octreotide were used to stop diarrhea, while granulocyte colony-stimulating factor (G-CSF) and recombinant human IL (IL-11) were used to improve blood cell count. Meanwhile, intravenous fluid replacement was continuously transfused to maintain water electrolyte balance. The patient remained continuous insanity and died 4 days after admission because of multiple organ failure, cardiac insufficiency, sever myelosuppression and ascending colon cancer. Myelosuppression is the principal toxicity associated with chemotherapy. And delayed-onset diarrhea is most frequently reported ADR of irinotecan, which could also be induced by S-1. Moreover, neurotoxicity is rarely reported as ADR for both irinotecan and S-1. Postoperative adjuvant chemotherapy should be carefully selected according to specific condition of patient. Blood routine examination should be monitored, and clinical manifestations should be carefully observed to ensure the safety and effectiveness of chemotherapy during the treatment.

Keywords: Adverse drug reaction (ADR); irinotecan; tegafur-gimeracil-oteracil potassium (S-1); case report; neurotoxicity

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Introduction

Chemotherapy after laparoscopic radical operation varies from different neoplasm stage of patients with colon cancer. Currently, irinotecan combined S-1 therapy shows efficacy on metastatic colorectal cancer (mCRC) (1). However, substantial adverse effects, such as gastrointestinal toxicity and hematological toxicity, decrease the efficacy of the treatment. Meanwhile, increased concern for living quality of cancer patients also limits its usage.

Irinotecan, a water-soluble camptothecin analogue, has been approved for the treatment of patients with advanced CRC through inhibition of the nuclear enzyme

Table 1 The changes of laboratory indexes during hospitalization

Laboratory indexes	Before chemotherapy	D1	D2	D3	D4	D5	D6
WBC ($\times10^9$/L)	7.7	0.2	0.43	0.97	2.76	6.78	13.08
N (%)	59.4	10	13.9	48.9	64	73.9	71.6
RBC ($\times10^{12}$/L)	3.93	2.01	1.62	2.35	2.87	2.53	2.2
Hb (g/dL)	9	5.6	4.5	6.3	8.3	7.2	6.4
PLT ($\times10^9$/L)	186	24	13	32	48	43	1.1

WBC, white blood cell count; N, neutrophil granulocyte; RBC, red blood cell count; Hb, hemoglobin; PLT, blood platelet count.

topoisomerase I (2). The principle adverse effects of irinotecan are diarrhea and neutropenia. It is reported that the adverse events were dose-depended when combined with fluorouracil/folinic acid (3). Fluoropyrimidine S-1 is active in wide range of solid tumors by reversibly inhibiting the rate-limiting enzyme in 5-fluorouracil (5-FU) degradation (4). Currently, few articles reported the adverse events of S-1 and the combination therapy. The combination chemotherapy with irinotecan and S-1 has been approved for second-line therapy of mCRC. This is a case report on severe myelosuppression, diarrhea and neurotoxicity induced by combination of irinotecan and S-1.

Case presentation

A 76-year-old Chinese female with a 1-month history of bleeding in stool has been diagnosed ascending colon cancer. The patient received laparoscopic radical operation on colon cancer, and was defined as T3N0M0 by clinical characteristic and cell pathology examination. The patient recovered well during her 11-day stay in hospital. Fifteen days after discharge, she returned to hospital for chemotherapy treatment. Laboratory data on admission before first chemotherapy presented as follows: white blood cell count 7.7×10^9/L [reference, $(3.97–9.15)\times10^9$/L]; neutrophil granulocyte 59.4% (reference, 50–70%); red blood cell count 3.93×10^{12}/L [reference, $(3.68–5.13)\times10^9$/L]; hemoglobin 119 g/dL (reference, 113–151 g/dL); blood platelet count 186×10^9/L [reference, $(101–320)\times10^9$/L]. Physical examination showed the patient has a clear conscious and absence of gastrointestinal abnormalities, meanwhile the patient had no family history of psychosis and was mentally stable.

The patient received second-line chemotherapy regimen which consists of irinotecan 240 mg through embedded venous transfusion port and S-1 capsule (80 m/day, bid, d1–14) for oral administration because she was allergic to oxaliplatin. The combined chemotherapy repeated every 21 days for each cycle. During the whole treatment of chemotherapy, there was no regular monitoring on blood routine examination, liver function or conventional imaging examination.

Three days after the 6th treatment (124 days after the first chemotherapy), the patient suffered from diarrhea which occurred 2–3 times daily, accompanied by mild abdominal pain, which did not draw the patient's attention. For the next four days, diarrhea gradually worsened and occurred 7–10 times daily. Nine days after the last round of chemotherapy, the patient presented delirium and unclear consciousness, and was admitted to emergency treatment. The temperature was 38.6 ℃ (reference, 36.0–37.4 ℃), heart rate was 126 beats per minute (reference, 60–100 bpm), breathing rate was 26 per minute (reference, 16–20 per minute), and blood pressure was 105/65 mmHg (reference, 90–140/60–90 mmHg). Laboratory data showed as follows: white blood cell count 0.20×10^9/L [reference, $(3.97–9.15)\times10^9$/L]; neutrophil granulocyte 10.0% (reference, 50–70%); red blood cell count 2.01×10^{12}/L (reference, $3.68–5.13\times10^{12}$/L); hemoglobin 5.6g/dL (reference, 11.3–15.1 g/dL); blood platelet count 24×10^9/L [reference, $(101–320)\times10^9$/L].

The patient was diagnosed with grade 3 myelosuppression (anemia, bone marrow hypocellular, and febrile neutropenia) and grade 4 diarrhea according to common terminology criteria for adverse events (CTCAE) toxicity judgment standard (5). granulocyte colony-stimulating factor (G-CSF) and recombinant human IL (IL-11) were immediately given to improve the hemogram, whereas laboratory data showed slow improvement in myelosuppression for the next three days (*Table 1*). Intensive loperamide therapy was given with diarrhea remained uncontrolled. Intravenous hydration therapy was taken to maintain water and

Table 2 Treatment and timeline of the present case

Month	Symptoms and diagnosis	Treatment
1	Bleeding in stool	
2		
Day 1–11	Ascending colon cancer (T3N0M0)	Hospitalization and laparoscopic radical operation
Day 12–27	–	Discharge
Day 28	Good physical and mental condition	6 rounds of chemotherapy treatment: irinotecan 240 mg iv at the first day, S-1 capsule orally from day 1 to day 14 (80 mg/day, 2/d), 21 days for one round
3–6	–	–
7		
Day 1–8	Diarrhea (2–3 times daily till 7–10 times daily)	Discharge
Day 9	Delirium and unclear consciousness, Grade 3 myelosuppression and Grade 4 diarrhea	G-CSF 300 μg sc daily
		IL-11 6 mg sc daily
		Loperamide 4 mg orally 2/d
		NS 500 mL +10% KCl 3 g iv 2/d
		Compound sodium chloride
		Injection 500 mL iv 2/d
		Imipenem 0.5 g iv 3/d
Day 10	Arrhythmia, somnolence, low blood pressure and petechiae	Adrenaline 11 μg/kg/h,
		Norepinephrine 22 μg/kg/h
		Amiodarone 300 mg iv
Day 11	Declared dead	–

iv, intravenous; S-1, tegafur-gimeracil-oteracil potassium; G-CSF, granulocyte colony-stimulating factor; IL-11, recombinant human IL; sc, subcutaneous; 2/d, twice daily; 3/d, three times daily; NS, normal saline.

electrolyte balance, while antibiotics were taken for the fever. On the second day, diarrhea reduced by contrast, and patient's consciousness recovered once. However, arrhythmia developed as well as somnolence companied with chest distress at evening. The patient was then transferred to ICU for further treatment. Positive inotropic support (adrenaline 11 μg/kg/h, norepinephrine 22 μg/kg/h) were needed to maintain blood pressure and heart rate. However, low blood pressure induced by arrhythmia occurred iteratively, and petechiae appeared during the first day at intensive care unit (third day after hospitalization). The patient declared dead the next day. The details of historical and current treatment were showed in *Table 2*.

Discussion

For patients with colon cancer at stage III or higher, adjuvant chemotherapy after surgery is an important way to improve the prognosis. 5-FU based chemotherapy, FOLFOX or CAPOX chemotherapy have been applied widely as the first-line chemotherapy regimens of colorectal carcinoma (6). However, the patient showed allergic reaction to oxaliplatin, which was considered as the regimen of first-line chemotherapy. Irinotecan is a topoisomerase I inhibitor which shows effectiveness as monotherapy in advanced colorectal cancer (CRC), and is more effective in combination with fluorouracil. S-1 is an oral fluoropyrimidine that includes three different agents: tegafur, gimeracil and oteracil. Some researches indicated irinotecan and S-1 combined therapy might have good efficacy on mCRC, and several countries outside the United States used the combined therapy as second-line treatment.

Myelosuppression appears common in combined chemotherapy. And diarrhea could be induced by both

Table 3 Adverse drug reaction probability scale of the present case

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was re−administered?	+2	−1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total score				6

irinotecan and S-1, even though S-1-related hyper enteritis happened less than irinotecan induced delayed-onset diarrhea. Although unconsciousness might be caused by water electrolyte imbalance, the serum electrolytes were normal during the hospitalization. Therefore, neurotoxicity associated with the coadministration of irinotecan and S-1 cannot be excluded according to Naranjo Adverse Drug Reaction Probability Scale score (definite >8 points, probably 4–8 points, possible 1–4 points, doubtful 0 points). The patient's Naranjo score (Adverse Drug Reaction Probability Scale) being 6 indicated that her life-threatening diarrhea, myelosuppression and neurotoxicity were probably caused by both irinotecan and S-1 (*Table 3*).

As far as we concerned, life-threatening diarrhea and myelosuppression is dose-limiting toxicities of irinotecan, which could also appear in S-1 chemotherapy. Therefore, monitoring blood parameters and gastrointestinal adverse effects are normally required during the chemotherapy. Noticeably, this patient did not follow the doctor's advice during 6 rounds of irinotecan and S-1 combined therapy. Once severe diarrhea and myelosuppression occurred, the patient was critically ill. Although medics speeded up the rescue work, the patient still died. Neurotoxicity is first reported at irinotecan and S-1 combined therapy.

Diarrhea and neutropenia are the main dose-limiting toxicities of irinotecan monotherapy (7). It was reported 80% of patients using irinotecan presented diarrhea, and 30–40% of them were grade 3 to 4 (2). Diarrhea caused by irinotecan has two types: cholinergic-like syndrome which is usually occurs acutely during or immediately after infusion, another is delayed-onset diarrhea appears about 5–6 days after its administration on every 3 weeks schedule (8,9). It is reported life-threatening diarrhea maybe related to exposure to SN-38 and UDP-glucuronosyltransferase 1A1 gene (10). S-1 related diarrheas were less reported than irinotecan induced diarrheas, but the incidence rate of S-1 induced diarrhea above grade 3 was still 34.5% during the treatment (11). The patient appeared mild diarrhea after the 6th treatment and developed to grade 4 diarrhea on the 9th day (CTCAE standard), which could eliminate the possibility of cholinergic-like syndrome. But delayed-onset caused irinotecan and S-1 related diarrhea could not be excluded.

Myelosuppression is the most common adverse effect of all cytostatic agents which always lead to chemotherapy failure. A post-marketing surveillance of 13,935 patients treated with irinotecan in Japan reported high incidence of myelosuppression (grade 3 or more) with leukopenia being 23.8% and 38.3%, thrombocytopenia being 6.5% and 14.3% for lone and concomitant use, respectively (12). The incidence of S-1-related blood and lymphatic system disorders is as high as 68.47%, with severity being grade I/II for most cases. It is reported that DPYP gene could

influence the activity of 5-FU metabolic enzyme, which might contribute to the difference in blood concentration of S-1 (13). Therefore, patients with lower enzyme activity on S-1 might suffer higher risk of myelosuppression. In fact, myelosuppression is predictable with blood routine examination, and the use of antimicrobials, RHG-CSF and immunopotentiator could help prevent infection and death. In this case, the patient did not take doctors' advice of regularly monitoring blood indicator.

As a result, the patient was in a critical condition when severe neutropenia and diarrhea were found (8). Neurotoxicity is commonly reported in platinum-based regimens, and rarely happened in irinotecan or S-1 relevant chemotherapy. Despite of this, neurotoxicity could result from water-electrolyte imbalance which induced by diarrhea, abnormal liver or kidney function. However, the patient in this case had normal level of renal function and metabolism of electrolytes. Accordingly, the possibility was large considering that neurotoxicity was induced by chemotherapy.

Conclusions

The combination of chemotherapy with irinotecan and S-1 might cause severe adverse effects such as myelosuppression, diarrhea or even neurotoxicity. Therefore, to ensure the safety and the effectiveness of chemotherapy, it is important to evaluate the variation in biochemical parameters during the course of treatment. In case of severe adverse effects, physicians should immediately make the judgement and give the individualized treatment. And the self-care and self-monitoring of patient is also unneglected an early stage of adverse effects.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.11.39). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient's relatives for publication of this case report.

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