Integrative Cancer Therapies
2018, Vol. 17(4) 1109–1114

DOI: 10.1177/1534735418801532
journals.sagepub.com/home/ict
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# Banxia Xiexin Decoction Is Effective to Prevent and Control Irinotecan-Induced Delayed Diarrhea in Recurrent Small Cell Lung Cancer

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## Abstract

**Background:** Irinotecan (CPT-11) can be used as a first-line therapeutic drug against extensive-stage small cell lung cancer (SCLC); it can also be used in second-line treatment for SCLC. CPT-11-induced delayed diarrhea restricts its clinical application. This study aimed to confirm whether Banxia Xiexin decoction was effective in preventing and controlling CPT-11-induced delayed diarrhea. **Methods:** A total of 27 patients with recurrent SCLC undergoing chemotherapy regimens including CPT-11 were enrolled for the study. UGT1A1*28, UGTlAl*6, ABCB1*2, and SLCO1B1*15 gene polymorphisms were detected. If delayed diarrhea occurred in the first cycle of chemotherapy, Banxia Xiexin decoction was orally administered for 5 consecutive days starting 1 day before the second cycle of chemotherapy to prevent and control the delayed diarrhea. The objective response, overall survival, and toxicity were recorded. **Results:** Complete response, partial response, and stable disease were observed in none, 6, and 10 patients, respectively. Delayed diarrhea occurred in 6 patients, and 4 of 5 patients were relieved or controlled using Banxia Xiexin decoction. The median overall survival was 6 months. **Conclusion:** Banxia Xiexin decoction appeared to prevent and control delayed diarrhea induced by CPT-11 in this small observational study, and further study with a larger sample size, including potentially randomized trials, is suggested.

## Keywords

Banxia Xiexin decoction, delayed diarrhea, irinotecan, chemotherapy, small cell lung cancer

Submitted May 21, 2018; revised August 12, 2018; accepted August 20, 2018

## Introduction

Irinotecan (CPT-11), a derivative of camptothecin, belongs to the class of topoisomerase I inhibitors. CPT-11, as a precursor drug, can be converted into the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) by carboxylesterase in the liver. About 60% to 70% of SN-38 is excreted through the stool, 25% via the biliary tract, and 10% to 20% through the urine. SN-38 is absorbed in the intestines and produces cytotoxicity.[1,2] Intestinal mucosa can be damaged, manifesting as intestinal mucosal atrophy, which causes intestinal flora imbalance, pseudomembranous colitis, and severe diarrhea.[3] CPT-11 can be used as a first-line therapeutic drug for extensive-stage small cell lung cancer (SCLC); it can also be used in second-line treatment for SCLC.[4-6] CPT-11-induced delayed diarrhea restricts its clinical application. If CPT-11-induced delayed diarrhea is effectively prevented and controlled, the compliance and tolerance of patients receiving the chemotherapy regimen including CPT-11 can be improved. Also, their quality of life can be increased. Loperamide hydrochloride is the symptomatic treatment drug for CPT-11-induced delayed diarrhea; however, it may increase the risk of paralytic intestinal obstruction.

Banxia Xiexin decoction, a famous and representative medical prescription, was formulated by Zhang Zhongjing in the Han Dynasty to treat the cold-heat complex and

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recorded in *Treatise on Febrile Diseases* and *Synopsis of Prescriptions of the Golden Chamber*. Banxia Xiexin decoction consists of Pinelliae Rhizoma, Scutellariae Radix, Zingiberis Rhizoma, Ginseng Radix et Rhizoma, Coptidis Rhizoma, Jujubae Fructus, and Glycyrrhizae Radix et Rhizoma. Banxia Xiexin decoction is used to treat epigastric distention and fullness, vomiting and diarrhea, and greasiness and yellowing of the tongue. The use of the decoction to treat nausea, vomiting, and diarrhea has been confirmed by the studies on various digestive system diseases.[7,8] A total of 27 patients with SCLC receiving chemotherapy regimens including CPT-11 were enrolled for the study. UGT1A1*28, UGTlAl*6, ABCB1*2, and SLCO1B1*15 gene polymorphisms were detected. If the delayed diarrhea occurred in the first cycle of chemotherapy, Banxia Xiexin decoction was orally administered for 5 consecutive days beginning 1 day before the second cycle of chemotherapy to prevent and control the delayed diarrhea.

## Methods

### Patient Eligibility

Patients with pathologically or cytologically confirmed SCLC having first-line or second-line chemotherapy failure were prospectively enrolled for the study. This study was approved by the Medical Ethical Committee of Zhejiang Cancer Hospital, and all patients signed written informed consent. All of them met the following inclusion criteria: (1) having measurable lesions that could be evaluated; (2) having Eastern Cooperative Oncology Group score: 0 to 1; (3) ethnic Chinese, aged at least 18 years; (4) having peripheral white blood cell count $\geqslant 3.5 \times 10^9$/L, absolute neutrophil count $\geqslant 1.5 \times 10^9$/L, hemoglobin $\geqslant 9.0$ g/L, and platelet count $\geqslant 100 \times 10^9$/L; (5) having serum alanine aminotransferase and aspartate aminotransferase levels equal to or less than the upper limit of normal × 2, total bilirubin level equal to or less than the upper limit of normal × 1.5, and serum creatinine levels at or above the upper limit of normal; and (6) having a normal electrocardiogram. The exclusion criteria were as follows: (1) having severe diarrhea, severe infection, or any other serious systemic diseases; (2) having symptomatic brain metastases; (3) having second primary tumors, except for cervical carcinoma in situ and skin basal cell cancer; (4) having contraindications to chemotherapy; (5) received chemotherapy containing CPT-11; and (6) pregnant and lactating women.

### Treatment Regimen

All the patients received CPT-11-based combination chemotherapy, which was administered as follows: CPT-11 65 mg/$m^2$ intravenous infusion on days 1 and 8, repeated every 3 weeks. Cisplatin or carboplatin was selected based on the patient's general physical condition, tolerance to chemotherapy, and concurrent diseases. Each patient received at most 6 cycles of chemotherapy. Delayed diarrhea higher than grade 3 occurred in the therapeutic process; hence, the CPT-11 dose should be adjusted to 80% of the original dose. If the delayed diarrhea occurred in the first cycle of chemotherapy, Banxia Xiexin decoction was orally administered for 5 consecutive days beginning 1 day before the second cycle of chemotherapy. If diarrhea happened in the first cycle of chemotherapy, other drugs treating diarrhea such as loperamide hydrochloride and symptomatic support could be used without Banxia Xiexin decoction. If diarrhea happened in the second cycle chemotherapy, other drugs treating diarrhea such as loperamide hydrochloride and symptomatic support could be also used together with Banxia Xiexin decoction.

### Evaluation of Treatment Effect and Follow-up Visit

The primary endpoint is the efficacy of Banxia Xiexin decoction to prevent and control delayed diarrhea induced by CPT-11. The second endpoint is the overall survival (OS) of the regimen of CPT-11-based chemotherapy for recurrent of SCLC; another secondary endpoint is the relationship between gene polymorphisms and delayed diarrhea induced by CPT-11. If the degree of delayed diarrhea in the second cycle of chemotherapy is decreased or disappears compared with the first cycle of chemotherapy, Banxia Xiexin decoction was considered effective to prevent and control delayed diarrhea for that patient. The investigators observed and evaluated the grade of diarrhea according to the symptom and main complaint of the patients. Objective tumor response was evaluated every 2 cycles according to the Response Evaluation Criteria in Solid Tumors 1.1 standard. For the patients with progressive disease, the treatment was switched to the best supportive treatment or another chemotherapy scheme. The OS is defined as the time from the start of the CPT-11-based treatment until death caused by any reason. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria Adverse Events version 4.0. The last follow-up visit was done on May 10, 2018.

### Detection of UGT1A1*28, UGTlAl*6, ABCB1*2, and SLCO1B1*15

Genomic DNA was extracted before therapy using TIANamp Blood Genomic DNA Extraction Kit (Tiangen Biotech, Beijing, China) according to the manufacturer's protocol. Primers (as shown in Table 1) were designed using Primer 6.0 software. The 2 rounds of polymerase chain reaction (PCR) were performed as follows: at 95°C for 5 minutes for 1 cycle; and 95°C for 30 seconds, 55°C for 30 seconds, and 72°C for 40 seconds for 35 cycles,

**Table 1.** Primers Used in Polymerase Chain Reaction Assays.

| Name | Site | Sequence |
|---|---|---|
| C1236T_AF | ABCB1*2 | TTCACTTCAGTTACCCATCTCG |
| C1236T_AR | ABCB1*2 | GGTCCTAATATCCTGTCCATCAA |
| G2677TA_AF | ABCB1*2 | TTTGTTTTGTTTTGCAGGCTA |
| G2677TA_AR | ABCB1*2 | AAGTGGGGAGGAAGGAAGAA |
| C3435T_AF | ABCB1*2 | TTGGCAGTTTCAGTGTAAGAAA |
| C3435T_AR | ABCB1*2 | AGGAGGGTCAGGTGATCAGG |
| T521C_AF | SLCO1B1*15 | AATTACCCAGTCTCAGGTATGTATTT |
| T521C_AR | SLCO1B1*15 | GAATGCATGGTTCTTATTCACC |
| A388G_AF | SLCO1B1*15 | TTGTTAATGGGCGAACTGTG |
| A388G_AR | SLCO1B1*15 | CCACTTAGCCTGGGGTGTAT |
| UGT1A1**6AF | UGT1A1*6 | AAGTAGGAGAGGGCGAACCT |
| UGT1A1*6AR | UGT1A1*6 | ACAGGTACTGGGCCACGAT |

followed by 1 cycle of 72°C for 10 minutes. ABCB1, SLCO1B1, and UGT1A1 genotypes were determined by allelic discrimination assays based on the use of fluorogenic oligonucleotide probes (TaqMan 2120; Applied Biosystems, Foster City, CA) and direct sequencing analysis performed on ABI Prism 3130 Genetic Analyzer (Applied Biosystems).

Short tandem repeat typing was performed by PCR amplification using Toyobo high-fidelity KOD enzyme. Forward and reverse primers (Forward: 5′-TCGTCCTTCTTCCTCTC TGG-3′, and Reverse: 5′-ATTTCATGTCCCCTCTGCTG-3′) were used for PCR amplification. The total volume of the reaction mixture was 25 μL containing 2.5 μL of KOD 10× buffer, 0.5 μL of KOD (Toyobo, Osaka, Japan), 2.5 μL of KOD dNTP, 1 μL of $MgCl_2$, 1 μL of forward and reverse primers, 7.5 μL of $H_2O$, and 10 μL of DNA template. Thermal cycling parameters were as follows: pre-denaturation at 94°C for 2 minutes; thermal denaturation at 94°C for 15 seconds, annealing at 60°C for 30 seconds, and extension at 68°C for 25 seconds, for a total of 35 cycles. Then, the PCR product was diluted 400 times and 10 μL HIDI-ROX was added to 1 μL of PCR-diluted product capillary electrophoresis analysis performed with an ABI3730XL sequencer (Applied Biosystems).

### *Statistical Analysis*

The data were analyzed using the Statistical Package for the Social Sciences version 18.0 software (SPSS Inc, Chicago, IL). The OS curves were plotted using the Kaplan-Meier method.

## Results

### *Patient Population*

A total of 27 patients were enrolled between June 2014 and May 2017. The baseline clinical characteristics for all the patients are shown in Table 2. One patient with limited-stage disease received thoracic radiation and chemotherapy in the first-line treatment; 26 patients had advanced-stage disease. The median number of cycles of chemotherapy was 3. Objective tumor responses were evaluated in 19 patients.

**Table 2.** Patient Characteristics (n = 27).

| Characteristics | Number of Patients |
|---|---|
| Gender | |
| Female | 2 |
| Male | 25 |
| Age, years | |
| Median | 62 |
| Range | 45-72 |
| Smoking history | |
| Nonsmoker | 3 |
| Light smoker | 2 |
| Moderate smoker | 8 |
| High smoker | 14 |
| Stage of disease | |
| LD | 1 |
| ED | 26 |
| Line of chemotherapy | |
| Second-line | 25 |
| Third-line | 2 |
| Regime of chemotherapy | |
| IP | 3 |
| IC | 24 |
| Cycle of chemotherapy | |
| Total (range) | 79 (1-6) |
| Median | 3 |

Abbreviations: LD, limited-stage; ED, extensive-stage; IP, irinotecan plus cisplatin; IC, irinotecan plus carboplatin.

### *Objective Tumor Response, Gene Polymorphism, and OS*

Complete response, partial response, stable disease, and progressive disease were observed in none, 6, 10, and 3

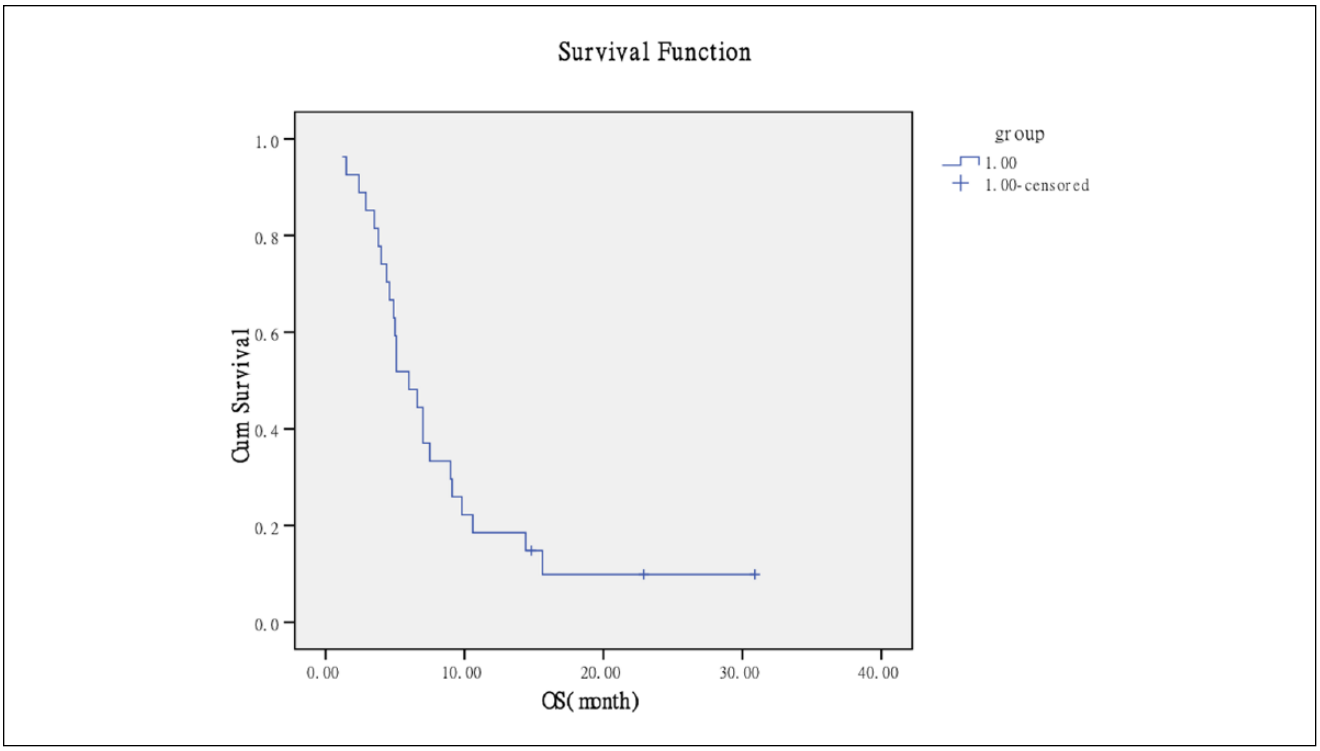


**Figure 1.** Overall survival of the patients (n = 27).

**Table 3.** Summary of Main Adverse Events (AEs).

| AE | Grade 1/2 (n) | Grade 3/4 (n) | Total, n (%) |
|---|---|---|---|
| Leukopenia | 4/10 | 7/0 | 21 (77.78) |
| Neutropenia | 6/7 | 7/1 | 21 (77.78) |
| Anemia | 12/10 | 5/0 | 27 (100) |
| Thrombocytopenia | 10/5 | 1/0 | 16 (59.26) |
| Alanine aminotransferase | 4/1 | 0/0 | 5 (18.52) |
| Aspartate aminotransferase | 7/1 | 0/0 | 8 (29.63) |
| Total bilirubin | 2/2 | 0/0 | 4 (14.81) |

patients, respectively. At the time of data cutoff (May 10, 2018), 3 patients were alive. The median survival time was 6 months in the entire patient group. The OS curve is shown in Figure 1. Toxicity data, including leukopenia, neutropenia, anemia, thrombocytopenia, alanine aminotransferase, aspartate aminotransferase, and total bilirubin, are shown in Table 3. No grade 5 treatment-related toxicity or febrile neutropenia was observed. Grade 2 delayed diarrhea occurred in patient 7. Banxia Xiexin decoction was given in the next cycle of chemotherapy, and grade 1 delayed diarrhea occurred. Grade 2 delayed diarrhea occurred in patient 9. Banxia Xiexin decoction was given in the next cycle of chemotherapy, and grade 4 delayed diarrhea occurred. Loperamide hydrochloride and symptomatic support were given, and delayed diarrhea was controlled. Grade 1 delayed diarrhea occurred in patients 17, 19, and 20. Banxia Xiexin decoction was given in the next cycle of chemotherapy, and no delayed diarrhea occurred. Grade 1 delayed diarrhea occurred in patient 23, and the next cycle of chemotherapy was not administered. Banxia Xiexin decoction was also not given. The associations between delayed diarrhea and gene polymorphisms of UGT1A1*28, UGTlAl*6, ABCB1*2, and SLCO1B1*15 are shown in Table 4. There was no statistical association at all between genotype and incidence of delayed diarrhea ($P > .05$).

## Discussion

Compared with TA6/7 and TA7/7, UGT1 A1*28 wild genotype TA6/6 was significantly associated with reduced toxicity (42.1% vs 15.7%, $P = .027$) in Chinese patients with colorectal cancer. Chinese patients exhibited less CPT-11-related diarrhea due to a higher frequency of UGT1A A1*28 wild genotype TA6/6 compared with American or European patients.[9] No association was observed between UGT1A1*28 and severe diarrhea at low doses of CPT-11 (<125 mg/m$^2$).[10] In this study, the dosage of CPT-11 was 65 mg/m$^2$ intravenous infusion on days 1 and 8, repeated every 3 weeks. Compared with Western populations, Chinese patients had a distinct frequency of UGT1A1*6 or UGT1A1*28 genotypes.[11] The percentage of TA7/TA7

**Table 4.** Gene Polymorphism and Delayed Diarrhea.

| No. | C1236T | G2677TA | C3435T | T521C | A388G | UGT1A1*6 | UGT1A1*28 | Delayed Diarrhea |
|---|---|---|---|---|---|---|---|---|
| 1 | C/T | A/T | C/T | T/T | G/G | G/G | — | No |
| 2 | C/T | A/G | C/T | C/T | G/G | G/G | TA (6/7) | No |
| 3 | T/T | T/T | T/T | T/T | A/G | A/G | TA (6/6) | No |
| 4 | C/T | A/T | C/T | T/T | G/G | G/G | TA (6/7) | No |
| 5 | T/T | A/T | C/T | T/T | G/G | G/G | TA (6/6) | No |
| 6 | C/T | G/T | C/T | T/T | A/G | G/G | TA (6/7) | No |
| 7 | C/T | G/G | C/C | T/T | G/G | G/G | TA (6/6) | Grade 2 |
| 8 | T/T | G/T | C/T | C/T | A/G | A/G | TA (6/7) | No |
| 9 | T/T | T/T | T/T | C/T | G/G | G/G | TA (6/7) | Grade 2 |
| 10 | C/T | G/G | C/C | T/T | A/G | G/G | TA (6/6) | No |
| 11 | T/T | G/T | C/T | T/T | A/G | G/G | TA (6/6) | No |
| 12 | T/T | T/T | T/T | T/T | A/A | G/G | TA (6/6) | No |
| 13 | C/C | G/G | C/C | C/T | A/G | G/G | TA (6/6) | No |
| 14 | C/T | A/T | C/T | T/T | G/G | G/G | TA (6/6) | No |
| 15 | C/T | G/G | C/C | T/T | A/A | A/G | TA (6/6) | No |
| 16 | T/T | G/T | C/T | T/T | A/G | G/G | TA (6/6) | No |
| 17 | C/T | A/T | C/T | T/T | A/A | G/G | TA (6/6) | Grade 1 |
| 18 | T/T | G/T | C/T | T/T | G/G | G/G | TA (6/6) | No |
| 19 | C/T | G/T | C/T | T/T | G/G | G/G | TA (6/6) | Grade 1 |
| 20 | C/C | G/A | C/C | T/T | A/A | G/G | TA (6/6) | Grade 1 |
| 21 | T/T | G/T | C/C | T/T | G/G | A/G | TA (6/6) | No |
| 22 | C/T | T/A | C/T | T/T | A/A | G/G | TA (6/7) | No |
| 23 | T/T | G/T | C/T | T/T | A/A | A/G | TA (6/6) | Grade 1 |
| 24 | T/T | G/T | C/T | T/T | G/G | G/G | TA (6/6) | No |
| 25 | T/T | G/T | C/T | T/T | A/G | G/G | TA (6/6) | No |
| 26 | C/T | G/T | C/T | T/T | G/G | G/G | TA (6/7) | No |
| 27 | C/T | G/G | C/C | T/T | A/G | G/G | TA (6/6) | No |

genotype of UGT1A1*28 was lower than that in Whites; in contrast, the prevalence of UGT1A1*6 allele was much higher in Chinese patients compared with Whites.[11] The incidence of grades 3 and 4 delayed diarrhea and neutropenia was higher in the patients harboring UGT1A1*6 G/A mutation than in the wild-type (WT) genotype (36.4% vs 6.6%, $P = .034$; 27.2% vs 4.4%, $P = .026$, respectively) for CPT-11-based regimen in Chinese patients with advanced-stage SCLC.[12] P-glycoprotein encoded by ABCB1/MDR1 in the proximal tubules is crucial in the renal exclusion of CPT-11 and its metabolites.[13] A significant association of the *2 haplotype in Block 2, which included 1236C>T, 2677G>T, and 3435C>T, was found with a reduced renal clearance of the aforementioned compounds.[13] A population-related pharmacogenomics analysis showed that ABCB1 (C3435T)T/T was associated with CPT-11 plus cisplatin (IP)-related diarrhea; UGT1A1 (G-3156A)A/A was associated with IP-related neutropenia.[14] Organic anion transporting polypeptide 1B1 (OATP1B1, gene SLCO1B1) is expressed on the basolateral membrane of hepatocytes and can facilitate the hepatic uptake of anticancer drug SN-38.[15] Patients with OATP1B1*15 haplotype showed a significantly higher area under the curve (SN-38) than those with OATP1B1*1a or OATP1B1*1b haplotypes ($P = .006$).[16] Grade 4 neutropenia was associated with the 521TC or CC genotypes, whereas grade 3 diarrhea was associated with 388GG genotype ($P = .046$).[16]

The incidence rate of grades 3 and 4 delayed diarrhea was 14% for the regimen of IP, as reported by Schmittel et al.[17] The present study showed that the incidence of grade 1 or 2 diarrhea was 22.2%, and no grade 3 or 4 diarrhea was observed in the first cycle of chemotherapy. The incidence and severity of delayed diarrhea were higher in patients with SCLC from the Caucasian population than from the Chinese population. The study by Xiao et al about the influence of CPT-11-based regimen on extensive-stage SCLC showed UGT1A1*28 WT genotype TA6/6 (56, 83.6%) and heterozygous mutant genotype TA6/7 (11, 16.4%); UGT1A1*6 WT genotype G/G (45, 67.2%) and heterozygous mutant genotype G/A (22, 32.8%).[12] The frequency of grades 3 and 4 delayed diarrhea was higher in the study by Xiao et al than in the present study due to the different doses of CPT-11.[12] The dose of this study (CPT-11 65 mg/m$^2$ intravenous infusion on days 1 and 8, repeated every 3 weeks) is lower than the doses in the study by Xiao et al (CPT-11 60 mg/m$^2$ intravenous infusion on days 1, 8, and

15, repeated every 4 weeks; CPT-11 85 mg/m$^2$ intravenous infusion on days 1 and 8, repeated every 3 weeks.).[12] The prediction of the frequency of CPT-11-induced delayed diarrhea for SCLC according to the genetic polymorphisms of UGT1A1*28, UGTlAl*6, ABCB1*2, and SLCO1B1*15 is of limited significance in this study and the dose of CPT-11 used. This is because the incidence of CPT-11-induced delayed diarrhea is low during the treatment of patients with SCLC in China, and most of the patients have grades 1 and 2 delayed diarrhea. In this study, delayed diarrhea occurred in 6 patients, and 4 of 5 patients were relieved or controlled using Banxia Xiexin decoction. Therefore, for patients with SCLC having CPT-11-induced delayed diarrhea, administering Banxia Xiexin decoction for consecutive 5 days starting 1 day before the second cycle of chemotherapy apparently prevented and controlled delayed diarrhea.

This study has a very small sample size of patients with delayed diarrhea. The efficacy of Banxia Xiexin decoction to prevent and control delayed diarrhea induced by CPT-11 need to be further verified with larger sample size trials. The efficacy was assessed by the investigators; an independent review facility to assess efficacy would be needed in further study.

## Conclusions

In conclusion, Banxia Xiexin decoction appeared to prevent and control delayed diarrhea in this small observational study, and further study with a larger sample size, including potentially randomized trials, is suggested.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Zhejiang Province Traditional Medical Science Fund Project of China (No. 2014ZB021).

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