

Medication Therapy Management of a Rectal Cancer Patient with Multiple Organ Metastasis

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Received: May 06, 2019; **Published:** May 29, 2019

Abstract

Rectal cancer is one of the most common malignant tumors in the digestive tract, which is often accompanied by metastasis in liver, lung, bone and other organs, and its harm is enormous. At present, chemotherapy is still an important therapeutic measure for rectal cancer, especially for those with multi-organ metastasis. But chemotherapy often causes some intolerable adverse reaction such as digestive system reaction, myelosuppression, granulocytopenia and fever. In this case, the patient was given successively neoadjuvant chemotherapy after operation and outpatient chemotherapy in our hospital. He can't tolerate the side effects of chemotherapy, and his disease progressed, therefore he was admitted to hospital by "multiple metastases with pulmonary and bone after rectal cancer surgery and spinal cord compression syndrome". According to the patient's condition, general state and wishes, as well as the clinical guidelines, clinical pharmacist and doctors designed individualized treatment programs for patients, consisting of palliative chemotherapy to alleviate symptom, and treating morphine intoxication, febrile neutropenia and other adverse reactions. During the treatment, clinical pharmacist formulated several key pharmaceutical care measures involved in safety, effectiveness, compliance and standardization of medication such as the initial treatment with large dose of methylprednisolone to alleviate the symptoms of oppression, control of cancer pain, selection, dosage, course and adjustment of therapeutic drugs, and also suggested the patient participated in clinical trials, and provided pharmaceutical care to improve the quality of life of patients. The doctor adopted the clinical pharmacist's suggestion, and the treatment obtained a satisfactory outcome. In conclusion, clinical pharmacists and doctors should make full use of their professional theory, knowledge and skills to design individualized drug therapy regimen, provide medication education and guidance for patients, strengthen medication therapy management and patient care, and improve the safety, effectiveness, economy, compliance and standardization of drug use.

Keywords: Rectal Cancer; Pulmonary Metastasis; Bone Metastases; Acute Spinal Cord Injury; Chemotherapy; Febrile Neutropenia; Medication Therapy Management; Pharmaceutical Care

Introduction

Colorectal cancer includes colon and rectal cancer. It ranks the third in male cancer and the second in female cancer [1], which is estimated to reach 2.2 million cases by 2030 in the world [2]. The morbidity and mortality of colorectal cancer increase all the time in China. According to Chinese cancer statistics in 2015, the incidence and mortality of colorectal cancer ranked 5th among all the malignant tumors in China, and 376,000 new cases and 191,000 dead cases were reported. About 60% of patients were diagnosed at a relatively late stage, and their 5-year survival rate was only about 13% [3], which seriously threatened human physical and mental health.

As an important part of colorectal cancer, rectal cancer is the cancer from the dentate line to the junction between the rectum and sigmoid colon. It is one of the most popular digestive tract malignant tumors in the world. A retrospective study [4] conducted by Beijing Cancer Hospital from 1996 to 2017 showed that pulmonary metastasis of rectal cancer accounted for 32.9% of the patients, which only less than liver metastasis. Although distant metastasis of rectal cancer is mainly in liver and lung, and bone metastasis is relatively rare, the incidence of bone metastasis of rectal cancer has increased year by year [5]. The early rectal cancer is mainly treated by surgical operation, while the middle and advanced rectal cancer are treated by chemotherapy, radiotherapy, biological therapy, and so on [6]. Although targeted drug therapy and immune therapy are increasingly used in cancer treatment, conventional chemotherapy based on cytotoxic drugs remains a cornerstone for the management of early and advanced/metastatic solid and hematological malignancies. Chemotherapy is an independent prognostic factor, which can improve survival time and quality of life of patients with rectal cancer [7], especially the patients with multiple bone metastases or combined with other important viscera metastasis should adopt positive chemotherapy. However, many chemotherapy patients' physical fitness and nutrition status are poor, so they are easy to suffer from adverse reactions, e.g. bone marrow inhibition, febrile neutropenia (FN), anemia and so on. The reported patient suffered from FN during the chemotherapy.

Neutropenia is the most severe hematologic toxicity of chemotherapy-induced myelosuppression, and FN is the most popular clinical complication. FN will occur in more than 80% of hematopoietic malignancies patients and 10% ~ 50% of solid tumor patients after one course of chemotherapy [8]. Even if significant therapeutic progresses have been achieved in the last decades, FN remains a major life-threatening complication in the course of cancer treatment, associated with considerable morbidity of ADR, mortality and costs of cancer [6]. Among the chemotherapy patients, those without FN treatment had 15% increase of risk of death [9]. The degree and duration of neutropenia are directly related to the risk of infection and even death, which seriously affects the relative dose intensity (RDI) and the established cycle of chemotherapy drugs. In clinical practice, the administered dose has to be reduced, the treatment time has to be delayed, or the treatment plan has to be changed, and the expected outcome cannot be achieved eventually. In this case, the therapeutic program of rectal cancer patients with multiple organ metastases and FN was complicated. It is necessary for clinical pharmacists and doctors to design reasonable chemotherapy protocol, provide patient care so as to improve the quality and level of treatment.

Case Report

The patient, male, 40 years old, visited the hospital 2+ years ago (2016) due to blood stool, was diagnosed as rectal cancer (specific tumor location was unknown) by the colonoscopy and biopsy, and then underwent radical resection for rectal cancer in other hospitals (specific surgery and immunohistochemistry was unknown). After the surgical operation, the patient received XELOX chemotherapy for 8 cycles, and postoperative radiotherapy for rectal cancer. The last treatment time was April 2017. After the treatment, the patient was followed-up regularly, and the re-examination in June 2018 suggested the pulmonary metastasis occurred. FOLFIRI chemotherapy was conducted for 2 cycles in the other hospital, but the follow-up treatment was not given due to diarrhea. The patient received bevacizumab 400 mg ivgtt d1+ retetracete 4 mg ivgtt d1+ Teggio (i.e. tegafur, gimeracil and oteracil porassium) 60 mg Po bid d1-d14 q3w for 4 cycles in the outpatient department of our hospital from the beginning in November 2018. The last treatment time was on March 15, 2019, and the patient did not take orally Teggio capsules due to chest pain. One week after the last treatment, the patient fell down and suffered from fracture of the upper right femur, followed with local swelling, deformity and other manifestations. The orthopaedic doctor implemented symptomatic treatment by external fixation with splint. The bone scan indicated metastasis of multiple vertebrae, multiple ribs, left sacroiliac joint area and right upper femur. Six days ago, the patient developed numbness in the abdomen below umbilicus, lower limbs and urinary retention. He received symptomatic treatment such as urinary tube placement, nutritional nerve, and mannitol dehydration. The patient was admitted to oncology department based on diagnosis of "lung and bone metastasis after rectal cancer surgery, spinal cord compression syndrome" for further treatment. Since the onset of the disease, the patient has been mentally stable, and has poor appetite to only eat a liquid diet. His sleep is well, his urinary retention persists, and has not defecated for the past four days.

Diagnosis and treatment

Admission diagnosis

- (1) Multiple lung and bone metastasis stage IV after postoperative radiotherapy and chemotherapy for rectal cancer (Supplement table 1).
- (2) Polypathic thoracolumbar vertebral fracture with acute spinal cord compression syndrome and double lower limb paralysis.
- (3) Pathological fracture of right proximal femur.
- (4) Acute urinary retention: neurogenic bladder.
- (5) Massive effusion in the right thoracic cavity.
- (6) Cancer pain.

Clinical situations	Classification of lung metastasis			
Whether found in staging inspection	Simultaneity		Heterochrony	
Whether there is extrapulmonary metastasis	Simplicity	Non-simplicity	Simplicity	Non-simplicity
Whether it is primary metastasis		Incipient		Noninitial

Supplementary Table 1: Classification of lung metastases from colorectal cancer.

Medication schedule

On D1 after admission, high-dose methylprednisolone was given to treat acute spinal cord injury, lansoprazole was used to protect the stomach, and oxycodone sustained release tablets were used to control cancer pain. On D3, EP regimen (etoposide 0.1g ivgtt d1-3+ cisplatin 40 mg ivgtt d1-3 q3w) was provided for one cycle of emergency chemotherapy, lansoprazole was used to protect the stomach as before, and tropisetron hydrochloride were used to stop vomiting, and then olanzapine was used to represent them. The patient’s symptoms improved slightly. Thymopentin for injection and liqifuwei oral liquid were used as supportive treatment. On D6, oxycodone sustained-release tablets were added to 50 mg q12h, on D7, 20 mg of morphine was administered to relieve breakthrough pain. The patient developed morphine intoxication and was rescued by emergency treatment. Because of dysphagia, the patient was given compound amino acid injection(18AA-II), ω-3 fish oil fat emulsion injection, medium and long chain fat emulsion injection(C6~24), and alanyl glutamine injection as parenteral nutrition replacement therapy. Rapid-acting insulin was used to treat patient’s transient hyperglycemia. On D10, FN was empirically treated with imipenem-cilastatin sodium for injection. On D11, myelosuppression grade IV was detected, so recombinant human erythropoietin injection, recombinant human granulocyte colony-stimulating Factor injection and recombinant human granulocyte/macrophage colony-stimulating factor for injection were given to raise white blood cells, meanwhile iHuman immunoglobulin (pH4) for intravenous injection was used to enhance immunity. On D12, the patient had severe anemia. AB Rh+ red suspension 2U was injected. On D13, the anemia was corrected. On D16, the patient was generally in good condition, and discharged from hospital. The detailed medication regimen of the patient see table 1.

Drug	Dosage	Usage	Start	End	Effect
Oxycodone hydrochloride sustained-release tablets	40 mg	po q12h	D1	D6	Relieve pain
Methylprednisolone sodium succinate for injection	40 mg	ivgtt qd	D1	D6	Anti-inflammatory
Lansoprazole for injection	30 mg	ivgtt qd	D1	D1	Protect the stomach
Tropisetron Hydrochloride Injection	5 mg	ivgtt qd	D3	D6	Stop vomiting
Lansoprazole for injection	30 mg	ivgtt qd	D3	D3	Protect the stomach
Etoposide injection	0.1g	ivgtt qd	D3	D6	Chemotherapy
Cisplatin injection	40 mg	ivgtt qd	D3	D6	Chemotherapy

Thymopentin for injection	20 mg	sc biw1	D6	D6	Support
Olanzapine tablets	5 mg	po hs	D6	D6	Stop vomiting
Liqifuwei oral liquid	10 ml	po ti	D6	D6	Supportive treatment
Oxycodone hydrochloride prolonged-release tablets	50 mg	po q12h	D6	D8	Relieve pain
Compound amino acid injection(I8aa-II)	500 ml	ivgtt qd	D7	D8	Parenteral nutrition
Verapamil hydrochloride tablets	1co	ivgtt qd	D7	D8	Parenteral nutrition
Ω-3 fish oil fat emulsion injection	100 ml	ivgtt qd	D7	D8	Parenteral nutrition
Medium and long chain fat emulsion injection (C6~24)	250 ml	ivgtt qd	D7	D8	Parenteral nutrition
Alanyl glutamine injection	50 ml	ivgtt qd	D7	D8	Parenteral nutrition
Rapid-acting insulin	4u	ivgtt qd	D7	D8	Hypoglycemic
Fentanyl transdermal patches	8.4 mg	Stick in the chest q72h	D8	D16	Relieve pain
Imipenem and cilastatin sodium for injection	2g	po q8h	D11	D14	Anti-infection
Recombinant human erythropoietin injection	10000iu	sc biw	D12	D16	Anti-anemia
Recombinant human granulocyte colony-stimulating factor injection	150 ug	sc qd	D12	D16	Rise white blood cell
Recombinant human granulocyte/macrophage colony-stimulating factor for injection	151 ug	sc qd	D12	D16	Rise white blood cell

Table 1: Medication regimen of the patient.

Results of drug treatment

Doctors and clinical pharmacists designed an individualized medication program for the patient according to his conditions, general state and wishes, and adjusted and optimized it in the light of the treatment effect. After a series of symptomatic, causative and supportive treatment, e.g. relieve pain, anti-inflammatory, stomach protection, antiemetic, parenteral nutrition, hypoglycemia, anti-tumor, anti-infection, anti-anemia, leukocyte elevation, and immunity enhancement, the patient's pain and infection were controlled, and blood cell count, temperature and other indicators returned to normal. The patient discharged in a good condition.

Pharmaceutical care

The patient suffered from advanced rectal cancer with multiple organ metastasis, severe tumor compression symptoms, and poor cancer pain control, high dosage, toxic chemotherapeutic drugs and other serious adverse reactions. Therefore, clinical pharmacists should actively monitor the efficacy, safety, compliance and standardization of drug treatment for patients, provide medication education and guidance, improve the effect of drug treatment, monitor the possible ADR, and formulate preventive measures in advance.

Care for effectiveness

Tumor: Those suspected colorectal cancer patient must be examined by routine digital examination of the anus and rectum. An individualized tumor marker monitoring program need to be designed, e.g. CEA and CA19-9 must be detected in patients with rectal cancer if his tumor markers elevate. AFP is recommended for patients with liver metastasis. Patients with suspected peritoneal and ovarian metastasis are recommended to be detected for CA125. CT reexamination after chemotherapy is performed to observe the size and morphology of pulmonary metastatic lesions and to evaluate the growth rate of pulmonary lymph nodes. Colonoscopy is suitable for colorectal lesions with low lesion position. Total colonoscopy is recommended for all these suspected colorectal cancer patients except

for the exceptional cases. PET-CT is not recommended for routine use, but it can be used as an effective auxiliary examination for patients with complex conditions that cannot be clearly diagnosed by routine examination. Preoperative examination prompt for \geq III period tumors, it is recommended to use.

Acute spinal cord injury: Functional activity examination was performed to determine whether paresthesia and numbness in the abdomen below the umbilicus and lower limbs were alleviated or not. Whether the muscle strength of both lower limbs was improved from level 0 or not. Was the muscle tension of both lower limbs increase or not?

Cancer pain: The patient had paroxysmal chest wall pain. According to the NCCN clinical practice guidelines in oncology: Adult Cancer Pain (Version 2.2019) [10] and the Numerical Rating Scale (NRS), cancer pain score of the patient kept 4 since admission, which was evaluated as moderate pain. According to the world health organization (WHO) guidelines for the three-step analgesic treatment of cancer pain, the following treatment measures were taken for the patients: oxycodone hydrochloride sustained-release tablets 40 mg, po q12h. Because the cancer pain score cannot be controlled at 0 - 3 scores, the dosage was adjusted from 40 mg to 50 mg. The patient was given short-acting opioids, e.g. morphine tablet 20 mg in the event of an outbreak of pain. After that, the patient had difficulty in swallowing, so the potent narcotic analgesic fentanyl transdermal patch (8.4 mg, q72h, chest wall pasting) was applied to replace oxycodone hydrochloride sustained-release tablet. The patient's pain is under control.

Febrile Neutropenia (FN): Daily blood routine was examined, blood cell analysis was carried out. Neutrophil count should be followed with interest. Urine routine test, bacterial culture, sputum culture, blood culture, and pleural effusion bacterial culture were conducted.

Care for safety

Allergic reactions: Allergic reactions of cisplatin, such as rash, urticaria, erythema, purpura, rare bronchospasm and hypotension, are similar to other platinum drugs. These reactions generally occur within a few minutes after cisplatin injection, but the incidence will increase after 5 - 6 courses of treatment, and there are cross-allergic reactions with other platinum drugs. Desensitization treatment should be taken if necessary. Pharmaceutical care should be conducted on the first day of cisplatin use.

Myelosuppression: Myelosuppression is a common ADR of chemotherapeutic drugs. Patients may suffer from granulocytopenia, thrombocytopenia, anemia and other symptoms. Cisplatin can lead to myelosuppression, which is mainly manifested as the decrease of white blood cells and/or platelets and is generally related to the drug dose. Myelosuppression generally peaks at about 3 weeks and recovers at 4 - 6 weeks. Resistance of the patients with myelosuppression is often poor, so timely ward ventilation, and ultraviolet disinfection should be carried out. Patients should be strictly aseptic during the invasive operation. Nutrition support should be conducted to enhance immune function of patients. The patient is instructed to keep warm, avoid raw and cold food during medication. Hemogram should be monitored. The patient whose white blood cell decreases apparently, should take nourishing food, take drugs (e.g. herb products diyushengbai tablet or shengxiening tablets) or inject G-CSF and rhGM-CSF. Generally, it is recommended to use injection when the myelosuppression reaches level 3 - 4.

Nephrotoxicity: Nephrotoxicity of cisplatin is related to drug accumulation and administered dose. Generally, the dose exceeding 90 mg/m² per day is a risk factor for nephrotoxicity. It mainly manifests as renal tubular injury. Acute damage generally occurs in 10 - 15 days after medication. It manifests as increase of blood urea nitrogen and creatinine, and decrease of creatinine clearance, which is mostly reversible. Repeated high-dose treatment can cause persistent mild to moderate renal damage. At present, there is no effective measure except hydration, so it is necessary to keep fully hydration during chemotherapy. The patient should be told to drink more water to promote drug excretion. Daily urine volume should be monitored to reach > 2000 ml.

Ototoxicity: Cisplatin has toxic effects on cochlear canal and vestibule, which may lead to tinnitus, hypoacusis (especially high frequency hearing) and even hearing loss and vertigo, and so on. Most of them are reversible and don't need special treatment. Once tinnitus, hypoacusis appears, the patient should inform doctor in time.

Gastrointestinal reaction: Chemotherapy-induced nausea and vomiting (CINV) is one of the most common ADR of platinum drugs. When these reactions appear, the patient should eat little but more frequently, avoid to take spicy, excitant food, and do not eat food in the process of infusion chemotherapy. Nk-1 receptor antagonists (e.g. aprepitant), 5-HT₃ receptor antagonists (e.g. tropisetron), and adrenocortical hormone (e.g., dexamethasone) can be used to prevent CINV. Currently, the patient have been treated with glucocorticoid and tropisetron for preventing CINV. If constipation occurs in the process, it can be treated with Maren pills or lactulose oral solution, and dimethicone emulsion can be used to relieve abdominal distension.

ADR caused by opioids

Common ADR: Constipation, nausea, vomiting, drowsiness, pruritus, dizziness, urinary retention, delirium, cognitive impairment, respiratory depression, and so on are common ADR of opioids. Nausea, vomiting, drowsiness, dizziness appears in the first few days of the treatment for the patients who have not ever used opioids. The present patient has passed the initial stage of treatment. These ADR have disappeared. In addition to constipation, ADR of opioids are mostly temporary or tolerable. Symptoms of constipation usually occur continuously in the whole process of analgesic treatment using opioid, and most patients need to prevent constipation by laxatives. An analgesic treatment plan should include the prevention and management of ADR of opioids. Within a few days of the initial treatment with opioids, antiemetic drugs such as metoclopramide may be considered. Antiemetic drugs may be discontinued if there is no nausea.

Morphine poisoning rescue: Opioids such as morphine are commonly used in patients with advanced cancer pain due to their powerful analgesic effects. Dosage of morphine used in patients with severe cancer pain often exceeds the normal dose, and overdose can cause serious consequences. On D7, the patient took orally oxycodone hydrochloride sustained-release tablets 50 mg q12h, he suffered an outbreak of pain at 13:00, so he took another 10 mg by himself, then an outbreak of pain appeared again before radiotherapy at 14:00. The doctor immediately let the patient took orally 20 mg of morphine. In this point, the patient developed the following symptoms, i.e. poor consciousness, drowsiness, response to exhalation, pupil constriction like needle. Morphine intoxication was considered, and the patient was immediately given intensive care. Oxygen inhalation, electrocardiogram monitoring and the other poisoning rescue measures were conducted immediately. The measures included: (1) Potassium permanganate solution (1:4000) was used for gastric lavage to prevent absorption of morphine; (2) 12g sodium sulfate was used to induce diarrhea after gastric lavage, so that the unabsorbed morphine was discharged from the body; (3) Hypertonic glucose fluid was intravenous infusion so as to promote excretion of the absorbed morphine; (4) A total of 3000 ml electrolyte solution including 0.9% sodium chloride solution and 5% glucose solution was input to correct the disorder of water and electrolyte metabolism, maintain acid-base balance and prevent dehydration; (5) Specific antidotes were used to treat morphine poisoning, i.e. 0.8 mg of naloxone (a specific opioid receptor antagonist) was injected intravenously, and the drug was given again after 15 minutes. In order to avoid restlessness and irritation of the patient due to rapid recovery of consciousness, naloxone should not be injected too quickly. After the above measures, the poisoning symptoms of the patient were corrected, his consciousness gradually improved, and at the same time morphine analgesia was suspended.

Care for compliance

Pain caused by infusion: Most platinum drugs belong to vascular irritants, which can cause pain during infusion. The doctor or clinical pharmacist should tell the patient about the discomfort, e.g. local pain in the injection area caused by platinum drugs in advance. The patient should tell the medical staff if he feels discomfort in time. In case of exosmosis, the drug must be stopped at once, 5% lidocaine and 2 ml of dexamethasone was administrated as the annular closure of the swelling area, and analgesia, ice compress, and elevate the limb were carried out at the same time.

Proper use of sustained-release tablets: Clinical pharmacist need to tell the patient that oxycodone hydrochloride sustained-release tablets must be swallowed as a whole and can't be broken, chewed or ground, otherwise, it will result in rapid release and absorption of oxycodone, possibly lead to death of patient.

Proper use of transdermal patch: Clinical pharmacist should tell the patient that fentanyl transdermal patches should be applied on a flat skin surface on the trunk or upper arm that is not stimulated or irradiated. If there is hair, it should be cut off before use (do not shave with razor). The paste area should be cleaned with water. Do not use soap, oil, lotion or other products that may irritate or change skin's properties. The skin should be completely dry before applying this patch. This product should be used immediately after opening the sealed bag. Press hard with the palm of your hand for 30 seconds to make sure the patch is in full contact with the skin, especially at the edges. This product can last for 72 hours. When changing the patch, the adhesive should be changed.

Education for patients with cancer pain: Understanding and cooperation of patients and their families are crucial in the process of treatment of cancer pain. Doctors and clinical pharmacists should provide targeted publicity and education on pain relief knowledge. Key education contents include: (1) Encourage patients to actively describe the degree of pain to medical staff; (2) Analgesic treatment is an important part of comprehensive tumor treatment, pain tolerance is harmful to patients; (3) Most cancer pain can be effectively controlled by drug treatment. Patients should be treated to relieve pain under the guidance of doctors and take medicine regularly. It is not advisable to adjust the dose of anodyne and pain relief plan by themselves. (4) Morphine and similar drugs are commonly used in the treatment of cancer pain. Addiction caused by morphine is extremely rare in the treatment of cancer pain. (5) Safe placement of drug shall be ensured; (6) During the analgesic treatment, the efficacy and ADR of the drugs should be closely observed, and patients should communicate with the medical staff at any time. If the treatment effect is not significant, the treatment objectives and measures should be adjusted in time; (7) Regular follow-up visits should be carried out.

Discussion

Use of glucocorticoid to treat acute spinal cord injury

Acute spinal cord injury is harmful to patients. Spinal cord injury will lead to paraplegia or incomplete paraplegia with loss of limb movement, urinary and fecal incontinence. Of the current drugs for spinal cord injury, the only effective, convenient and widely used drug is glucocorticoid. methylprednisolone can reduce the number of inflammatory cells in the site of spinal cord injury, and decrease apoptosis, lipid oxidation, and improve vascular permeability of injured tissue, and promote the recovery of nerve function. The most famous randomized controlled trial of clinical application of glucocorticoid is NASCIS II-III study. This study reported that the patients who were hospitalized within 3h after injury were given 30 mg/kg methylprednisolone at 1h, followed by 5.4 mg/kg/h methylprednisolone in the next 23h. The patients who were hospitalized within 3 - 8h after injury were treated with 30 mg/kg methylprednisolone at 1h, followed by 5.4 mg/kg/h methylprednisolone in the next 47h. Clinical function of the patient was improved by the therapeutic method.

The patient was treated for several days after the injury. The initial dose of methylprednisolone was only 40mg, which was not calculated according to the patient's weight, and the dose was not adjusted thereafter. Duration of the drug use was 5 days, greatly exceeded 47 hours. The patient was also treated with methylprednisolone to prevent nausea and vomiting caused by cancer chemotherapy. The current clinical empirical usage is: for patients with incomplete injury, within 8 hours, methylprednisolone 40 mg, qd, ivgtt, plus mannitol 25g, q8h or q12h, ivgtt. At the same time protecting the stomach, rehydration, trophic nerve are conducted, last for 3-5 days, it can indeed alleviate part of the sensory impairment and improve muscle strength.

In recent years, the results of the multiphase clinical trial of NASCIS that established the basic status of glucocorticoid therapy for spinal cord injury have been questioned. Many clinical studies have shown that large dose of methylprednisolone can cause more serious complications. The NASCIS II study also reported that large dose of glucocorticoid can increase wound infection rate by 2 times, pulmonary embolism rate by 3 times, and gastrointestinal bleeding rate by 1.5 times. The foundation of glucocorticoid therapy has been shaken. In

the past few years, many countries have adjusted the recommendations of glucocorticoid use for the treatment of spinal cord injury in their guidelines, the original recommendation has been revised as no recommendation. However, there is no updated evidence to support the change.

At present, most of the studies on the treatment of acute spinal cord injury by methylprednisolone are retrospective, observational studies with different conditions, such as different doses, bias in patient selection and different clinical outcome indicators, which result in low level of evidence provided by these studies. Therefore, more clinical studies are needed to form a consensus on whether shock therapy of high dose glucocorticoid should be used for spinal cord injury, how to use it, and what dose is suitable, *et al.* We think that glucocorticoid should be used because the clinical role of glucocorticoid in relieving edema and reducing the inflammation is exact. Glucocorticoid should be recommended when surgical decompression, nerve nutrition and dehydration are not effective.

Analysis of chemotherapy regimens

Analysis of the program's rationality

The patient was newly diagnosed as bone metastatic rectal cancer at stage 4 and underwent EP chemotherapy. The NCCN guidelines recommend that 5-Fu+LV, irinotecan, oxaliplatin, and capecitabine are currently used for the treatment of advanced or metastatic colorectal cancer. Targeted drugs include cetuximab (recommended for patients with K-ras, N-ras, and BRAF wild-type genes), bevacizumab, and regorafenib. The recommended drug regimen is as follow (1) Combination chemotherapy should be used as the first and second line treatment for patients with metastatic colorectal cancer who can tolerate chemotherapy. The recommended chemotherapy regimen: FOLFOX or FOLFIRI (combination with cetuximab), which is recommended for patients with wild-type genes of K-ras, N-ras and BRAF; CapeOx or FOLFOX or FOLFIRI (combination with bevacizumab). (2) For patients who fail in the standard systematic treatment of third-line and above, regorafenib is recommended or enroll in clinical trials. (3) For patients who cannot tolerate combination chemotherapy, 5-Fu+LV, or capecitabine monotherapy (combination targeted drugs) regimen is recommended. The patients with advanced colorectal cancer who are not suitable for 5-Fu +LV may consider to be treated with raltitrexed.

According to the expert consensus of multidisciplinary comprehensive therapy for colorectal cancer lung metastasis (version 2018), the patient currently belongs to heterogeneous, non-simple and non-primary metastasis. This patient has received previous drug treatment, and the effect was relatively poor, so the type, dose and treatment cycle of drugs should be adjusted according to the patient's physical conditions. Systemic palliative treatment is recommended for patients with no cure extrapulmonary metastasis.

FOLFIRI was performed in the patient after he was diagnosed as postoperative lung metastasis, which met the first-line protocol recommended by the guidelines, but it was stopped due to intolerance. Subsequently, targeted therapy was adopted in our hospital. The EP regimen is not reasonable. He is a palliative care patient without surgical guidelines for multi-organ metastasis and cannot tolerate the combined chemotherapy because of the digestive tract reaction. So, the clinical pharmacist recommended the patient to participate in the clinical trial of raltitrexed or take regimen of 5-FU+LV, or single drug capecitabine (combination targeted drug).

Analysis of medication of cancer pain

According to the NCCN clinical practice guidelines in oncology: Adult Cancer Pain (Version2.2019) [10] and the Numerical Rating Scale (NRS), cancer pain score of the patient was 4, which is considered as moderate pain. According to the world health organization (WHO) guidelines for the three-step analgesic treatment of cancer pain, the five basic principles are as follows: (1) Oral administration. For patients who are not suitable for oral administration, other administration ways should be used, such as subcutaneous injection of morphine, patient-controlled analgesia and transdermal patch. On D8, the patient got dysphagia, so the application of fentanyl transdermal patch was in line with the principle of analgesia. (2) Administration by the ladder: the patient with moderate pain can be treated with mild opioids (e.g. oxycodone hydrochloride sustained-release tablets) and nonsteroidal anti-inflammatory drugs. (3) Take medicine on time. (4) Individualized administration. (5) Pay attention to specific details.

For patients with relatively stable pain conditions, use of controlled-release opioids as background administration may be considered. The patient has kept maintenance therapy, so oxycodone sustained-release preparation is appropriate. Since the score cannot be controlled at 0 - 3 points, it is reasonable to adjust the dose from 40 mg to 50 mg. The patient was given morphine 20 mg in the event of an outbreak of pain, and the guidelines recommend that short-acting opioid painkillers be used during the use of long-acting opioids. When patients have explosive pain or the dose of long-acting analgesics is insufficient due to illness changes, short-acting opioids should be given immediately for rescue treatment and dose titration. The rescue dose is 10% ~ 20% of the total drug used in the previous 24 hours, $100\text{mg} \times (10\% \sim 20\%) = (10 - 20) \text{ mg}$, so 20 mg morphine is suitable for the rescue dose. After that, the patient had difficulty in swallowing and replaced the painkiller for fentanyl transdermal patch 8.4 mg applied to the chest q72h. For the patient had less than 3 times of rescue medication using short-term opioid in the previous day, it is not necessary to convert the previous 24 hours of rescue medication into long-term opioid. Oxycodone is converted into fentanyl transdermal patch (Supplement table 2), $100 \text{ mg oxycodone orally} = 150 - 200 \text{ mg morphine orally} = 75 - 100 \text{ ug /h, q72h}$, $75 - 100 \text{ ug /h} \times 72\text{h} = 5.4 - 7.2 \text{ mg}$, so it is unreasonable to use 8.4 mg of dosage which is more than the maximum dosage. However, only 8.4mg of fentanyl transdermal patch is available in China, and that the patient suffered from explosion of pain yesterday, an appropriate rise in dosage is also accepted in clinical practice.

Drugs	Non-gastrointestinal administration dose	Oral dose	Equivalent dose
Morphine	10 mg	30 mg	Non-gastrointestinal: oral = 1:3
Codeine	130 mg	200 mg	Non-gastrointestinal: oral = 1:1.2 Morphine (oral): codeine (oral) = 1:6.5
Oxycodone	10 mg		Morphine (oral): oxycodone (oral) = 1.5 ~ 2.1
Transdermal patch of fentanyl	25 $\mu\text{g/h}$ (transdermal absorption)		Transdermal fentanyl patches of fentanyl ug/h, q72h dose = $1/2 \times \text{oral morphine mg/d dose}$

Supplementary Table 2: Dose conversion table of opioids.

Analysis of antibacterial use of febrile neutropenia caused by chemotherapy

Diagnosis of Febrile neutropenia

Neutropenia refers to the absolute neutrophil count (ANC) in peripheral blood $< 0.5 \times 10^9/\text{L}$, or less than $0.5 \times 10^9/\text{L}$ predicted 48 hours later; Severe neutropenia refers to $\text{ANC} < 0.1 \times 10^9/\text{L}$. Fever refers to a single oral temperature is up to $>38.3^\circ\text{C}$ or $> 38^\circ\text{C}$ last 1h. The neutrophil of the patient was less than $0.250 \times 10^9/\text{L}$ and his highest temperature was up to 38.6°C since yesterday. It conformed to the diagnostic criteria in "Guidelines for clinical application of antibiotics in Chinese patients with febrile neutropenia". So, the diagnosis of FN for the patient was correct.

Indications for the use of antibiotics

Stratification of risk in patients with febrile neutropenia is necessary before treatment and is crucial for the subsequent empirical selection of antimicrobial agents. This patient suffered from dysphagia, which met the ISA guidelines [11] for "high-risk standard of stratification of risk in patients with febrile neutropenia" (Supplement table 3) i.e. clinical complications of oral or gastrointestinal mucositis (dysphagia), so the patient must be empirically treated with intravenous antibiotics.

Degree of risk	Definition
High-risk	<p>Any of the following</p> <ul style="list-style-type: none"> • Severe neutropenia (<0.1×10⁹/L) or predicted neutropenia lasting for >7 days • Any of the following clinical complications (including but not limited to): (1) Hemodynamic instability; (2) Oral or gastrointestinal mucositis (dysphagia); (3) Gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea); (4) The new hair of the nervous system's lesions or mental symptoms; (5) Intravascular catheter infection (especially catheter lumen infection); (6) Newly developed lung infiltration or hypoxemia or potential chronic lung disease; (7) Liver insufficiency (transaminase level > 5 times the normal upper limit) or renal insufficiency (creatinine clearance rate < 30 ml/min)
Low-risk	<p>Neutropenia is expected to disappear within 7 days, no active complications, at the same time liver and kidney function is normal or just mild and stable injury.</p>

Supplementary Table 3: Stratification of risk in patients with Febrile Neutropenia.

Antibiotic selection

Along with the problem of antibiotic resistance is increasingly serious, the patient with FN should also receive drug resistance evaluation according to the ECIL - 4 guidelines [12] before the empirical treatment (Supplement table 4). This patient suffered from severe disease (advanced tumor), has been hospitalized repeatedly for a long time and was at risk of drug-resistant bacterial infection. Antimicrobial agents should be used empirically immediately after the assessment of risk of infection and drug resistance. Broad-spectrum antimicrobial agents that can cover *Pseudomonas aeruginosa* and other severe G- bacteria must be used intravenously in high-risk patients. Anti-pseudomonas lactam drugs alone should be recommended, including piperacillin sodium and tazobactam sodium, cefoperazone sodium and sulbactam sodium, carbapenems (imipenem and cilastatin sodium or meropenem or panipenem and betamipron), cefepime, and ceftazidime. The patient was treated with imipenem and cilastatin sodium, which belongs to the carbapenems group and meets the recommendations of guidelines.

1. The patient previously had a resistant pathogen colonization or infection, especially: (1) Enterobacteria producing extended-spectrum beta-Lactamases (ESBL) or carbapenemases; (2) drug-resistant non-fermented bacteria: <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i> , <i>Stenotrophomonas maltophilia</i> ; (3) Methicillin-resistant staphylococcus aureus (MRSA), especially Minimum inhibitory concentration of vancomycin (MIC) > 2 mg/L; (4) Vancomycin resistant enterococcus
2. Previous exposure to broad-spectrum antibiotics (especially first-generation cephalosporins and quinolones)
3. Severe disease (advanced tumor, sepsis, pneumonia)
4. Nosocomial infection
5. Elderly patients
6. Use a catheter
7. Long-term and/or repeated hospitalization
8. Stay in the intensive care unit

Supplementary Table 4: Risk factors for drug-resistant bacterial infection in patients with febrile neutropenia.

Treatment course of antibacterial drugs

After receiving the empirical antimicrobial therapy, the subsequent adjustment of antimicrobial therapy should be determined based on the comprehensive judgment of risk stratification, confirmed pathogenic bacteria and patients' response to the initial treatment. The duration of antibacterial drug treatment depends on the type of pathogen and the site of infection. Use of antibacterial drugs should be continued for the entire duration of neutropenia until $ANC > 0.5 \times 10^9$. Fever of the patient disappeared on D13, and his condition improved within 48h. Now, his neutrophil count is $0.579 \times 10^9/L$, indicating that the antibiotic treatment is effective and the antibiotics could be stopped. Then imipenem and cilastatin sodium is continue to use to anti-infection for another 2 days so as to prevent the disease rebound. In a word, the treatment course is reasonable.

Conclusion

In this case, the patient suffered from rectal cancer with postoperative metastases in lung and bone. He was hospitalized for acute spinal cord injury due to tumor compression. According to the patient's condition, general state and wish, as well as the clinical guidelines, clinical pharmacists and doctors designed individualized treatment programs for the patient. It consisted of a series of symptomatic, causative and supportive treatment, e.g. analgesic, anti-inflammatory, stomach-protecting, antiemetic, parenteral nutrition, hypoglycemic, anti-tumor, anti-infection, anti-anemia, leukocyte elevation, and immunity enhancement. In the meanwhile, clinical pharmacist treated morphine intoxication, FN and other ADRs. In the course of treatment, clinical pharmacist used their professional advantage to provide pharmaceutical care such as the initial treatment with large dose of methylprednisolone to alleviate the symptoms of oppression, control of cancer pain, selection, dosage, course, adjustment of antibiotics, and so on. Besides, the clinical pharmacist suggested the patient participated in clinical trials and tried their best to improve the quality of life of the patient, and strengthen medication therapy management and patient care, put forward suggestions on rational drug use, provided medication education and guidance. The doctor adopted the clinical pharmacist's suggestion which improved the safety, effectiveness and compliance of the patient's medication. The treatment of the patient achieved satisfactory outcomes.

Author's Contributions

- Participate in case analysis: Guo Ma and Ye Liu.
- Participate in the literature retrieval: Ye Liu, Yuping Liu, Xiaoyu Qiu, Qing Yang and Xuan Huang.
- Wrote or contribute to writing the manuscript: Ye Liu and Guo Ma.

Acknowledgements

This work was supported by grants from the National Natural Science Funds of China (81873078, 81374051), the Science and Research Program of Shanghai Municipal Health Commission (201740094), the Science and Research Program of Traditional Chinese Medicine of Shanghai Municipal Health Commission (2018YP001) and MHHFU-SPFU Joint Research Fund (RO-MY201707) to Guo Ma. 2018 Medical Education Research Project of Chinese Society of Medical Education & Medical Education Committee of Chinese Association of Higher Education (2018A-N19014); 2019 Shanghai Education Science Research Project of Shanghai Education Committee (C19077), 2019 Fudan University Undergraduate Teaching Research and Reform Practice Projects (2019B020).

Disclosure of Conflicts of Interest

The authors declare no conflicts of interest.

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Volume 7 Issue 6 June 2019

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