Clinical Case Report

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Chemotherapy in patient with colon cancer after renal transplantation

A case report with literature review

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Abstract

Rationale: Experience of pharmacotherapy in posttransplantation colorectal cancer (CRC) patients is inadequate.

Patient concerns: A Chinese man had right renal transplantation and began immunosuppressive treatment at the age of 31 in 2009. He was diagnosed with colon cancer and underwent anterior resection in 2014. He was diagnosed with metastatic colon carcinoma by abdomen computed tomography (CT) and positron emission tomography-computed tomography in April 2017.

Diagnosis: Metastatic colon carcinoma in posttransplantation patient.

Interventions: Three cycles of FLOFOX (5- fluorouracil and leucovorin and oxaliplatin) chemotherapy were given since April 2017.

Outcomes: Plasma concentrations of immunosuppressant and kidney function were within normal during the chemotherapy. Abdomen CT revealed the progress of colon cancer at the end of the third course of chemotherapy.

Lessons: A few cases about monochemotherapy of posttransplantation CRC have been reported, whereas experience of doublet chemotherapy was currently unavailable. We shared the experience of FOLFOX in a patient with posttransplantation colon cancer. Neither of incompatibility with immunosuppressant nor serious adverse drug reaction was observed. It provides evidence for the pharmacotherapy of posttransplantation CRC.

Abbreviations: CRC = colorectal cancer, CT = computed tomography, PET-CT = positron emission tomography-computed tomography.

Keywords: chemotherapy, colon cancer, immunosuppressor, oxaliplatin, renal transplantation

1. Introduction

Renal transplantation, commonly performed for end-stage renal disease (ESRD), is an alternative to dialysis.[1] The long-term follow-up after renal transplantation has been reported increased risk of malignancy.[2] The increased incidence of malignancy may be related to impaired immune surveillance, direct neoplastic action of immunosuppressive agents, oncogenic viruses such as Epstein–Bar virus or cytomegalovirus, and chronic antigenic stimulation, uremia, or genetic predisposition.[3] These risks vary in different tumors. It has reported that the risk of colorectal cancer (CRC) is approximately 2 to 3 times higher in renal transplant recipients than in general population.[3] The mean onset time of CRC is 10.4 years after transplantation.[4] There is evidence that transplant patients develop CRC at a younger age and exhibit worse 5-year survival rates than the general population.[3,5]

Pharmacotherapy is especially important for the treatment of CRC. The median overall survival (OS) is approximately 6 months in untreated metastatic CRC (mCRC). OS has been extended up to 12 to 20 months by treatment with combined chemotherapy such as FOLFOX, 5-FU, leucovorin and irinotecan (FOLFIRI) and capecitabine and oxaliplatin (XELOX). OS was further improved to 24 to 41 months after adding target agents.[5] However, experience of pharmacotherapy in posttransplantation CRC patients is inadequate. Only a few cases have been reported. In this case, experience of using FLOFOX chemotherapy, not currently available data in the literature, on a patient with CRC, and under immunosuppressive treatment because of renal transplantation has been presented.

2. Case report

A Chinese man had right renal transplantation for ESRD at the age of 31 in 2009. He had been under immunosuppressive treatment including ciclosporin A (0.5 g bid) and sirolimus (1 mg qod) since then. He was diagnosed with colon cancer at the age of 36 in April 2014. He underwent anterior resection in May 2014. Pathological examination revealed a 5.0×5.0 cm moderately differentiated adenocarcinoma with invasion of the adjacent pericolic fatty tissues. Nineteen lymph nodes were found with no malignant lymph node involved (pT3N0M0, stage αA). The patient did not receive adjuvant chemotherapy. In April 2017, the patient underwent abdomen computed tomography (CT) for elevated alpha fetal protein (13.82 ng/mL), which revealed a

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Table 1

The level of blood immunosuppressant, kidney function, and BP during the treatment.

	Ciclosporin A (ng/mL)	Sirolimus (ng/mL)	Cr (μmol/L)	BUN (mmol/L)	BP (mm Hg)
April 4, 2017	80.17	3.12	75.5	5.87	120/75
April 14, 2017	80.70	2.43	78.5	3.65	125/85
May 7, 2017	–	–	76.0	4.44	111/75
May 10, 2017	62.95	1.98	79.0	5.37	120/70
June 1, 2017	–	–	83.3	5.84	125/70
June 5, 2017	93.06	2.15	80.8	5.73	101/62
June 28, 2017	–	2.28	73.0	5.01	134/87

BP = blood pressure; BUN = blood urea nitrogen; Cr = creatinine.

4.8×3.8 cm mass at the front of the horizontal part of duodenum. Positron emission tomography-computed tomography showed high uptake of fluorodeoxyglucose at colonic anastomosis. He was diagnosed with metastatic colon carcinoma. The patient had a history of "hypertension" for 9 years and took orally nifedipine and metoprolol. His blood pressure (BP) was controlled in the range of 130 to 140/75 to 85 mm Hg.

Eastern Cooperative Oncology Group performance status of this patient was 1. Her body mass index was 19.10 kg/m^2, body surface area was 1.53 m^2. Routine laboratory tests, including blood counts, liver function, renal function, blood sugar, lipid profile, and blood electrolytes were within normal limits. The patient was given FOLFOX regimen on April 11, 2017. FOLFOX regimen included oxaliplatin 80 mg/m^2 intravenous injection (IV), day 1, levoleucovorin 200 mg/m^2 IV, day 1, 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus on day 1, then 2400 mg/m^2/day $\times$ 2 days. The patient tolerated well, and the second and third cycle of FOLFOX regimen was given, too. On June 30, 2017, abdomen CT revealed a 5.8×5.1 cm mass at the front of the horizontal part of duodenum, which meant the progress of colon cancer. The patient was recommended to test RAS gene and take the FOLFIRI regimen. Unfortunately, he refused further chemotherapy and discharged from the hospital.

During the treatment, the plasma concentration of ciclosporin A and sirolimus was not affected by chemotherapy (Table 1). Blood urea nitrogen and creatinine was always within normal, BP had no obvious fluctuation (Table 1). No serious adverse drug reaction (ADR) was observed.

3. Discussion

Clinical researches have revealed that the incidence of post-transplantation CRC is higher than the standard incidence. These patients have a worse 5-year survival rate than the general population (overall, 44% vs 62%, $P < .001$; Dukes A and B, 74% vs 90%, $P < .001$; Dukes C, 20% vs 66%, $P < .001$; and Dukes D, 0% vs 9%, $P = .08$).[1] The decreased survival was not only because of immunosuppressive drugs, but also ineffective treatment of CRC.[5] In the study of Kim et al,[2] 42.8% (3/7) of III-IV patients in the transplant group received adjuvant chemotherapy compared with 83.5% of control patients who received chemotherapy.

Some advanced stage patients in the transplant group did not receive adequate chemotherapy because of the concern of incompatibility with immunosuppressant. The metabolism and excretion pathways of immunosuppressant and anticancer drug were showed in Table 2. Capecitabine, irinotecan, and mycophenolic acid are all catalyzed by carboxylesterases (CES) 1 and CES2. CES is abundant in the liver, no competition for CES between drugs have been reported. So it seems impossible for capecitabine or irinotecan to compete for CES with mycophenolic acid. UDP-glucuronosyltransferase1A catalyzes the metabolism of irinotecan and mycophenolic acid. We consider that the combination of irinotecan and mycophenolic acid should be avoided, though no drug–drug interaction has been reported. 5-FU, oxaliplatin, bevacizumab, and cetuximab have no pharmacokinetical interaction with immunosuppressant.

Modified chemotherapy, such as single agent therapy, were attempted to improve the survival and compliance of post-transplantation CRC patients. In the study of Kim et al.,[2] 5 posttransplantation CRC patients were treated with oral 5-FU or 5-FU-leucovorin regimen. A few cases about single agent therapy of posttransplantation CRC are noted in the literature (Table 3). In the study of Liu HY et al.,[1] 3 advanced rectal cancer patients after renal transplantation were treated with capecitabine adjuvant chemotherapy after surgery. Gu et al[6] reported a case

Table 2

The metabolism and excretion pathways of immunosuppressant and anticancer drugs.

Drug	Metabolism	Excretion	Renal toxicity
Ciclosporin	CYP3A4, 3A5;	Bile (main)	Very low
Tacrolimus	CYP3A4, 3A5;	Bile (main)	Very low
Sirolimus	CYP3A4, 3A5,2C8;	Bile (main)	Very low
Mycophenolic acid	CYP3A4, 3A5; CES1,CES2; UGT1A7, 1A8, 1A9, 1A10, 2B7;	Urine (main)	Very low
5-FU	DPYP, DPYS, UPB1;	Bile (~80%) Urine (~20%)	Low
Capecitabine	CES1,CES2; DPYP, DPYS, UPB1;	Urine (main)	Low
Oxaliplatin	Nonenzymatic conversion	Urine (main)	rare
Irinotecan	CES1, CES2; BCHE, UGT1A1, 1A3, 1A4, 1A6, 1A8, 1A9, 1A10,	Bile and urine	rare
Bevacizumab	No-CYP conversion	—	Proteinuria, Arterial Thromboembolic Events
Cetuximab	No-CYP conversion	—	hypomagnesemia, hypocalcemia, hypokalemia

5-FU = 5- fluorouracil, BCHE = butyrylcholinesterase, CES = carboxylesterases, CYP = cytochrome P450, DPYP = dihydropyrimidine dehydrogenase, DPYS = dihydropyrimidinase, UGT = UDP-glucuronosyltransferase, UPB1 = beta-ureidopropionase.

Table 3

Parameters of patients with CRC after renal transplantation.

	Age (y)	Sex	Location	Immunosuppressant	Chemotherapy	Cycles	ADR	Outcome
Liu et al 2011[1]	68	Male	Rectum	—	Capecitabine	3	Not reported	Died after 31 mo
Liu et al 2011[1]	44	Male	Rectum	—	Capecitabine	1	Not reported	Alive after 21 mo
Liu et al 2011[1]	54	Male	Rectum	—	Capecitabine	1	Not reported	Alive after 8 mo
Gu et al 2017[6]	57	Female	Rectum	FK506 and MMF and Pred	Oxaliplatin	—	Not reported	Died after 10 mo
Trivedi et al 1999[7]	44	Female	Colon	Pred and Aza and CsA	continuous 5-FU infusion	—	Not reported	Died after 7 mo
Musri et al 2015[8]	64	Male	Colorectum	Eve and FK506	FOLFIRI and bevacizumab	5	proteinuria per 4 g/d, GFR 24 mL/min	—

5-FU = 5- fluorouracil, ADR = adverse drug reaction, Aza = azathioprine, CRC = colorectal cancer; CsA = cyclosporin A, Eve = everolimus, GFR = glomerular filtration rate, MMF = mycophenolate mofetil, Pred = prednisone, FK506 = Tacrolimus.

of 57-year old woman with advanced rectal cancer after renal transplantation, which was received 3 cycle of oxaliplatin chemotherapy. Trivedi et al[7] also reported the application of continuous 5-FU infusion in a post-transplantion colon cancer. These patients all tolerated well during the chemotherapy.

The application of combination therapy for posttransplantion CRC has been explored. The question of whether CRC patients should receive combination therapy or fluoropyrimidine monotherapy has been addressed in 2 randomized trials (FOCUS and CAIRO), neither of them showed that survival was adversely impacted by single agent therapy.[9–11] For patients who are able to tolerate it, National Comprehensive Cancer Network and European Society of Medical Oncology guidelines suggest combination chemotherapy with a doublet (FOLFOX, XELOX or FOLFIRI) rather than single agent therapy for the treatment of CRC. In our case, an advanced colon cancer patient after renal transplantation was treated with 3 cycles of FLOFOX chemotherapy. Plasma concentration of ciclosporin A and sirolimus and renal function were not affected by chemotherapy (Table 1). No serious ADR was observed.

Targeted therapy played an important role in CRC therapy. In a pooled analysis of trials comparing chemotherapy with and without bevacizumab in the first-line setting, the addition of bevacizumab was associated with a significant 19% reduction in the risk of death (hazard ratio for death 0.81, 95% confidence interval 0.70–0.93), and this translated into a median OS advantage of 2 months (19.8 vs 17.6 months).[12] Müsri et al,[8] reported a case of posttransplantation mCRC treated with bevacizumab and FLOFIRI. The dose of bevacizumab was 5 mg/kg/d for 14 days. Proteinuria was 2.5 g/d at the start of the treatment, and increased to 4 g/d at the end of the fifth course. Proteinuria appears to be an effect common to all agents targeted at the vascular endothelial growth factor (VEGF) pathway.[13] The United States prescribing information recommends intermittent monitoring for the development of proteinuria during the anti-VEGF therapy. It is recommended to temporary withholding of the drug if protein excretion if >2 g/24 h, and permanent discontinuation for the nephrotic syndrome.

Hypertension is other common ADR of anti-VEGF therapy.[12] The incidence of hypertension ranged from 2.7% to 32% for patients with cancer receiving a low dose of bevacizumab (3, 5, or 7.5 mg/kg per dose), from 17.6% to 35.9% for patients receiving a high dose (10 or 15 mg/kg per dose).[13,14] A previous history of hypertension is one of the additional factors that impact the development and/or grade of hypertension while using anti-VEGF therapy.[13,14] The accurate determination of the rates of significant hypertension for anti-VEGF agents has been confounded by several issues. In general, most clinical trials will formally exclude patients with poorly controlled hypertension. In this case, the patient had a history of 'hypertension,' and took nifedipine and metoprolol treatment for 9 years. BP was controlled in the range of 130 to 140/75 to 85 mm Hg. For fear of severe hypertension, which can affect kidney function, the patients were not treated with bevacizumab.

Cetuximab is useful in combination with irinotecan for patients with wild type RAS CRCs who are refractory to irinotecan and as a single agent for those who are intolerant of irinotecan-based chemotherapy. The nephrotoxic effect of cetuximab showed as hypomagnesemia,[14] hypocalcemia, and hypokalemia.[15] The frequency of this complication with cetuximab was illustrated in a meta-analysis of 19 clinical reports totaling 3081 patients assigned to cetuximab-based treatment.[15] Thirty-seven percent of patients developed hypomagnesemia of any grade during therapy; the incidence of grade 3 or 4 hypomagnesemia (<0.9 mg/dL) was 5.6%.[15–17] Hypomagnesemia may lead to secondary hypocalcemia. Cetuximab also causes hypokalemia in approximately 8% of patients.[18] Thus, periodic monitoring of serummagnesium, calcium, and potassium is warranted during therapy with cetuximab and for 8 weeks after treatment discontinuation. The experience of cetuximab has not been reported in patients with mCRC after renal transplantation.

Graft rejection, is another concern for the chemotherapy of transcription patients, though the relation with chemotherapy is uncertain. In Kim et al,[2] of 5 patients who received adjuvant chemotherapy in advanced malignancy, 2 patients rejected the graft within 1 year. However, it could not be certain whether the graft failure was related to adjuvant chemotherapy. Periodic monitoring of plasma concentration of immunosuppressant should be warranted during therapy.

4. Conclusion

Effective treatment is the important management strategy for improving the survival time and quality of life of posttransplantation CRC patients. Only limited information for chemotherapy options in transplant recipients is currently available. We shared the experience of FOLFOX in a patient with posttransplantation colon cancer. Further research and reports will be necessary for the increase of experience.

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