Complete response to FOLFOX4 therapy in a patient with advanced urothelial cancer: a case report

Yu Ri Seo\(^1\), Se Hyung Kim\(^1\), Hyun Jung Kim\(^1\), Chan Kyu Kim\(^1\), Seong Kyu Park\(^1\), Eun Suk Koh\(^2\), Dae Sik Hong\(^1\)*

**Abstract**

No standard has been established for salvage therapy in gemcitabine refractory advanced urothelial cancer. We report the complete response to FOLFOX4 therapy of a metastatic urothelial cancer patient, for whom adjuvant gemcitabine plus cisplatin combination chemotherapy had failed. A 54-year-old male patient with urothelial cancer (transitional cell carcinoma) in the right kidney underwent three rounds of adjuvant gemcitabine-cisplatin chemotherapy after extensive radical nephrectomy. However, he had new liver, lung metastases and synchronous two separate primary colon cancer. The lung metastasis lesion was confirmed as a metastatic urothelial cancer via percutaneous transthoracic needle biopsy (PTNB). Liver and lung metastasis lesions disappeared after the 4th cycle of FOLFOX4 chemotherapy. In addition, colon cancer also disappeared after the 8th cycle of FOLFOX4 chemotherapy. The patient was still showing a complete response after 4 months. Clinical trials using the FOLFOX regimen as salvage therapy for gemcitabine-refractory advanced urothelial cancer are warranted.

**Background**

Most urothelial cancer develops from the urinary bladder, while urothelial cancer of the upper urinary tract is uncommon, accounting for only 5 to 10% of all renal tumours\(^1\). The standard therapy for urothelial cancer is surgical resection, although cisplatin-based combination chemotherapy increases the survival in metastatic advanced urothelial cancer\(^2-4\). Nevertheless, a complete response is very rare, and most patients die within 2 years of diagnosis\(^5\). At present, the standard therapy is gemcitabine-cisplatin combination therapy because M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin), which was previously the standard therapy, has a mortality due to toxicity exceeding 3% \(^5-7\). No standard has been established for salvage therapy in gemcitabine-refractory advanced urothelial cancer, and many ongoing clinical trials are examining new agents.

**Case presentation**

A 54-year-old male with urothelial cancer (transitional cell carcinoma) was transferred to the hemato-oncology department after the discovery of lung metastases. Three months previously, he had undergone a radical nephrectomy and hilar lymphadenectomy for a left kidney mass, which was identified as invasive papillary urothelial carcinoma, extending to the renal parenchyma. The resection margin was free from carcinoma, although there was metastatic carcinoma in one out of two lymph nodes (pT3N3 M0) (Figure 1A). No metastatic lesion was found on chest computed tomography (CT) or on abdomen CT before surgery. Postoperatively, he underwent three rounds of adjuvant chemotherapy with gemcitabine (1000 mg/m\(^2\) D1, 8, 15) and cisplatin (75 mg/m\(^2\) D1).

While performing a colonoscopy to investigate hema-tochezia, a second primary cancer, an adenocarcinoma of the colon, was discovered in the transverse (anal verge 50 cm) and sigmoid (anal verge 20 cm) colon. The level of carcinoembryonic antigen (CEA) was normal, and abdominal CT showed 1.7-cm wall thickening in the sigmoid colon, but no measurable changes in the transverse colon. Moreover, multiple lung metastases were seen on chest CT (Figure 2A, 2C). A lung
metastasis was confirmed to be urothelial cancer after a percutaneous transthoracic needle biopsy (Figure 1B) performed on a left lower lobe posterior segment metastatic lesion. The patient underwent FOLFOX-4 (oxaliplatin 85 mg/m² IV over 2 hours D1; leucovorin 200 mg/m² over 2 hrs, D1, 2; 5-fluorouracil (5-FU) 400 mg/m² IV bolus, and 5-FU 600 mg/m² IV over 22 hrs as a continuous infusion repeated every 2 weeks) for colon cancer and metastatic urothelial cancer, because he refused surgery for the colon cancer. After four rounds of chemotherapy, the lung metastases all disappeared, except one fibrotic cavitory lung lesion (Figure 2B, 2D). There was no hematologic or non-hematologic toxicity other than mild grade 1 nausea, and no delayed treatment schedule. Abdominal and chest CT performed after eight rounds of chemotherapy still showed no metastatic lesions, and positron emission tomography-computed tomography (PET-CT) showed no metastatic lesion (Figure 3A), with no ¹⁸F-fluoro-2-deoxyglucose (FDG) uptake in the fibrotic cavitory lesion in the lung (Figure 3B). In addition, CR of the colon cancer seen in the transverse and descending colon was also confirmed by colonoscopy and PET-CT after eight rounds of chemotherapy. Nevertheless, regional radiotherapy and rescue chemotherapy are being considered because of enlargement of a left para-aortic lymph node seen on abdominal and chest CT after the twelve rounds of FOLFOX chemotherapy. Therefore complete response was maintained for four months, from after four rounds (11/2008) until twelve rounds (3/2009) of FOLFOX chemotherapy.

Discussion

For the last 15 years, M-VAC chemotherapy was used to treat metastatic or advanced urothelial cancer, and gave a tumor response of 50~70% with increased survival in 15~20% of patients[2,8,9]. However, the reported mortality related to therapy exceeded 3%, and 25% of the patients developed neutropenic sepsis, so its use was limited to young patients or those with good general performance[10]. Gemcitabine was reported to give a good response in urothelial cancer and has low toxicity [7]. Finally, a phase III study of gemcitabine-cisplatin
(G-C) showed a similar response rate and survival compared with M-VAC, but lower toxicity and better safety. Consequently, G-C is now used widely to treat urothelial cancer[5]. Unfortunately, the tumor recurs in most patients within one year[9,10], necessitating secondary therapy after the failure of standard therapy. Although many ongoing clinical trials are examining this, no treatment has been established as secondary therapy after failure of G-C or M-VAC chemotherapy.

Oxaliplatin is more potent than cisplatin in vitro and has shown efficacy in preclinical studies against many tumor cell lines[11,12]. It has also proved efficacious in several phase II trials and is considered less nephrotoxic than cisplatin and causes less bone marrow suppression than carboplatin[10,13,14]. However, the activity of an oxaliplatin single regimen for urothelial cell cancer was minimal in phase II studies by Moore et al.[13] and Winquist et al. [14]. Therefore, we suggest that our case of TCC showed a complete response due to synergistic effects of FOLFOX-4, rather than to those of oxaliplatin as a single drug. The efficacy of 5-FU and leucovorin combination therapy for colorectal cancer is widely known[15,16]. The efficacy of 5-FU in advanced urothelial cancer is unclear, but a review of published studies in 1987 described response rates of about 15% using unmodulated single agent 5-FU[17]. In combination with alpha interferon, a partial response rate of 30% was obtained[18]. Recently, a phase II trial of continuous 5-FU infusion showed a median progression-free survival of 1.9 months and a median overall survival of 6.5 months[19].

The FOLFOX regimen, which is a combination of 5-FU, leucovorin, and oxaliplatin, can involve various doses and schedules. It shows low toxicity and good efficacy for colon cancer and stomach cancer, so it is used widely at present. The addition of new agents such as bevacizumab is expected to increase the complete response and survival rates for patients with metastatic colorectal cancer [20,21]. There are few reports of FOLFOX therapy for urothelial cancer, only a phase II trial by Lorenzo et al., published in 2004. They used FOLFOX-4 in 18 patients who had previously been treated for urothelial cancer, and reported only low-grade toxicity and a 19% overall response rate, all partial responses[22].

Our patient was given FOLFOX therapy because the urothelial cancer failed to respond to G-C combination therapy, as metastases were discovered and there was an accompanying second primary colon cancer. He showed a complete response in both the metastatic urothelial cancer and colon cancer. In addition to the ongoing clinical studies of gallium nitrate, ifosfamide, pemetrexed, vinflunine, and molecular targeting agents, a clinical trial of FOLFOX-4 therapy for urothelial cancer seems to be warranted[23].

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author details
1Division of Hematology Oncology, Department of Internal Medicine
Seonchunhyang University College of Medicine, Bucheon, Korea.
2Department of Pathology, Soonchunhyang University College of Medicine, Bucheon, Korea.

Authors’ contributions
SFY was responsible of the acquisition of data, drafting the manuscripts; KHU was responsible of the clinical management of the patient, scientific revision, discussion and editing of the manuscript; KSH, KCK, PSK were involved in clinical management of the patient and interpretation of data; KES was responsible of the interpretation of pathology; HDS was supervisor of clinical management of the patient and interpretation of data.

Competing interests
The authors declare that they have no competing interests.

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References
1. Oosterlinck W, Salsano E, Meijden van der APM, Sylvester R, Böhle A, Rintala E, Lobel B. EAU Guidelines on Diagnosis and Treatment of Upper Urinary Tract Transitional Cell Carcinoma. European Urology 2004, 46:147-154.
2. Sternberg CN, Yagoda A, Scher HI. Methotrexate, vinblastine, doxorubicin, and cisplatin for Advanced Transitional Cell Carcinoma of the Urethrum. Efficacy and patterns of response and relapse. Cancer 1989, 64:2448-2458.
3. Harker WG, Freiha FS, Palmer JM, Scher HI,蜾iddott L, Harnigan JF, Orchetti KM, Torti FM. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. J Clin Oncol 1985, 3:1463-1470.
4. Roth BJ, Bajorin DF. Advanced bladder cancer: the need to identify new agents in the post-M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin), world J Urol 1995, 135:894-900.
5. Massé von der H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Kruth A, Lippert CM, Kerbrat P, Sanchez Rivara P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF. J Clin Oncol 2000, 18:3068-3077.
6. Lorusso V, Pollera CF, Antimi M, Luporini G, Gridelli C, Frassineti GL, Oliva C, Pacini M, De Lena M. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer 1998, 34:1208-1212.
7. Moore MJ, Tannock IF, Ernst DS, Hame S, Murray N. Genticabine: a promising new agent in the treatment of advanced urothelial cancer. J Clin Oncol 1997, 15:3441-3445.
8. Bajarin D, Dodd MP, Mazumdar M, Fazzari M, McCaffrey AJ, Scher IH, Herr H, Higgin G, Boyle GM. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999, 17:3173-3181.
9. Bellmunt J, Albanell J, Paz-Ares L, Climent MA, Gonza-zalez-Larriba JL, Carles J, de la Cruz JJ, Guillem V, Diaz-Rubio E, Cortes-Funes H, Baselga J. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase III trial with paclitaxel, cisplatin, and gemcitabine. Cancer 2005, 95:751-757.
10. Carles J, Esteban E, Climent M, Font A, Gonzalez-Larriba JL, Benocca A, Garcia-Ribas I, Marfa X, Fabregat X, Albanell J. Bellmunt J. Gemicinabine and oxaliplatin combination: a multicenter II phase II trial in unfit patients with locally advanced or metastatic urothelial cancer. Annals of Oncology 2007, 18:1359-1362.
11. Dunn TA, Schmolz HJ, Granvald V, Bokemeeyer Y, Casper J. Comparative cytotoxicity of oxaliplatin and cisplatin in non-senomimotous germ cell cancer cell lines. Invest New Drugs 1997, 15:109-114.
12. Rice O, Ortizuez W, Alvarez M, Parker R, Reed E, Paul K, Foyo T. Oxalipatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute’s Anticancer Drug Screen panel. Biochem Pharmacol 1996, 52:1655-1665.
13. Moore MJ, Winquist E, Vokes E, Hine H, Hoving K, Stadler WM. Phase II study of oxaliplatin in patients with inoperable, locally advanced or metastatic transitional cell carcinoma of the urethral tract (TCC) who have received prior chemotherapy. Proc Am Soc Clin Oncol 2003, 22:48-52.
14. Winquist E, Vokes E, Moore MJ, Schumm LP, Hoving K, Stadler WM. A Phase II study of oxaliplatin in urothelial cancer. Urologic Oncology: Seminars and Original Investigations 2005, 23:150-154.
15. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Fagguolo R, Focan C, Chollot P, Lory JF, Letouroune Y, Coudert B, Bertheaut-Crkirovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Levi F. Phase III multicenter randomized trial of oxaliplatin added to chemo-modulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000, 18:136-147.
16. Rothenberg ML, Oza AM, Bygelm RW, Berlin JD, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, Burger BG, Le Gall N, Haller DG. Superiority of oxaliplatin and S-FU/leucovorin over either therapy alone in patients with progressive colorectal cancer following irinotecan and S-FU/leucovorin: interim results of a phase III trial. J Clin Oncol 2003, 21:2059-2069.
17. Yagoda A. Chemotherapy of urothelial tract tumors. Cancer 1987, 60:574-585.
18. Logothetis CJ, Hossan E, Sell A, Deues FH, Amato RJ. Fluorouracil and recombinant human interferon alpha-2a in the treatment of metastatic chemotherapy-refractory urothelial tumors. J Natl Cancer Inst 1991, 83:285-288.
19. Highley MS, Griffiths GO, UCSINSKI BA, Huddaels JB, Barbers P, Parmary MW, Harper PG. A Phase II Trial of Continuous S-Fluorouracil in Recurrent or Metastatic Transitional Cell Carcinoma of the Urinary Tract. Clinical Oncology 2009, 21:394-400.
20. Javle M, Hsueh CT. Updates in Gastrointestinal Oncology - insights from the 2008 44th annual meeting of the American Society of Clinical Oncology. Journal of Hematology & Oncology 2009, 2:9.
21. Malavasi N, Ponti G, Deperrini R, Bertolini F, Zironi S, Luppi G, Conte PF. Complete pathological response in a patient with multiple liver metastases from colon cancer treated with Folfox-6 chemotherapy plus bevacizumab: a case report. Journal of Hematology & Oncology 2009, 2.
22. Lorenzo GA, Autorino R, Giordano A, Giuliano M, A'Nirmiento M, Bianco A, De Placido S. FOLFOX-4 in Pre-treated Patients with Advanced Transitional Cell Carcinoma of the Bladder. Jpn J Clin Oncol 2004, 34:747-750.
23. Peralo FEG, Muller SC. New agents for treatment of advanced transitional cell carcinoma. Annals of Oncology 2007, 18:835-843.