Effect of Maintenance Chemotherapy with Gemcitabine and Paclitaxel on Recurrent Squamous Cell Carcinoma of the Bladder: A Case Report

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Abstract. *Squamous cell carcinoma (SCC) of the bladder is a relatively rare malignancy and the standard treatment is surgical resection. Prognosis of unresectable and recurrent SCC of the bladder is poor because no effective treatment is available at present. Here, we describe the response of one patient with this cancer to combination chemotherapy of gemcitabine and paclitaxel. A 47-year-old man with recurrent bladder SCC underwent radical cystectomy, but initially refused any adjuvant therapy. The pathological diagnosis was pT3. The patient was treated with three cycles of methotrexate, vinblastin, epirubicin, and cisplatin but with no response (no decrease in tumor volume). Subsequently, he received the combination chemotherapy of gemcitabine (GEM, 700 mg/m^2 on days 1 and 8) and paclitaxel (PTX, 700 mg/m^2 on days 1 and 8) per each 28-day cycle. After five cycles, the tumor volume had decreased from 562 to 101 cm^3 (18.0%). The combination therapy was reduced to GEM monotherapy, but the tumor volume increased to 573 cm^3. GEM+PTX administration was re-instituted; however, the patient died 21 months after recurrence. The combination GEM+PTX chemotherapy was applied at the outpatient treatment and caused no severe side-effects. Although the maintenance chemotherapy of GEM+PTX did not induce complete remission, it improved quality of life and had no serious side-effects, making it a promising combination chemotherapy for recurrent SCC of the bladder. Although further studies are necessary to determine its therapeutic efficacy, we suggest that this combined therapy is a useful option in the treatment of this disease including recurrent cases.*

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Key Words: Squamous cell carcinoma, bladder cancer, recurrence, gemcitabine, paclitaxel.

Bladder cancer is the ninth most common cancer worldwide (1). More than 90% of all cases are urothelial cancer (UC) while approximately 5% are squamous cell carcinoma (SCC). Significant differences in the pathological features and the malignant potential have been reported between UC and SCC. The majority of bladder SCCs are diagnosed at an advanced stage with muscle invasion (2, 3). Radical cystectomy is reported to be the best available treatment option with respect to metastasis and overall survival rates (2). Other treatment options include neoadjuvant and adjuvant radiotherapy (4, 5), while no standard regimen of chemotherapy and no cases of down-staging have been reported in patients with unresectable disease (2). Although various chemotherapeutic regimens and molecular-targeting therapies have been tried for bladder SCCs (6), their anticancer effects are limited and, currently, no effective chemotherapeutic regimen is available. Based on these facts, the prognosis of patients with unresectable recurrent SCC is extremely poor because of the malignant aggressiveness and lack of standard chemotherapeutic regimen.

We report the case of a patient with recurrent SCC of the bladder who was treated with combination chemotherapy of gemcitabine (GEM) and paclitaxel (PTX). The treatment was provided at the Outpatient Department. Although it did not induce complete remission, it reduced the tumor mass volume, improved quality of life, allowed relatively long survival (21 months) after recurrence and was free of any side effects.

Case Report

A 47-year-old Japanese man presented with gross hematuria. He had no remarkable past medical history, such as catheterization, or urinary tract calculi. The initial laboratory results showed no remarkable abnormalities. Cystoscopy showed a walnut-sized mass on the posterior bladder wall. Computed tomography (CT) identified extravesical invasion of the tumor. One part of the mass was resected by transurethral

resection (TUR) and was histopathologically defined as SCC with UC and adenocarcinoma. No involvement of the lymph nodes or distant organs was noted, as confirmed by various imaging tests. Radical cystectomy was later performed without neoadjuvant therapy. The resected specimen exhibited SCC (Figure 1) with extravesical invasion (pT3). However, careful examination of all specimen showed no UC or adenocarcinoma. We recommended adjuvant therapy; however, the patient refused for personal and financial reasons.

Six months later, the patient was re-admitted because of lower abdominal pain, and detection of recurrence with lymph node metastasis in the pelvic cavity. Further examination showed the tumor mass had invaded the large intestine. Accordingly, a colostomy was performed and a biopsy was taken from the tumor simultaneously. Histopathological examination of the biopsy sample showed SCC. The patient received therapy consisting of three cycles of cisplatin (CDDP) (70 mg/m^2), vinblastine (3 mg/m^2), methotrexate (30 mg/m^2), and epirubicin (30 mg/m^2) (MVAC). However, the treatment failed to reduce the tumor size as demonstrated on CT examination. Based on these results, the patient requested outpatient-based treatment and provided informed consent for a new chemotherapeutic regimen that had been already approved by the Human Ethics Review Committee of Nagasaki University Hospital. We commenced the combination therapy of GEM (700 mg/m^2) on days 1 and 8 and PTX (700 mg/m^2) on days 1 and 8 of each 28-day cycle. The pelvic mass volume decreased significantly after 5 cycles of GEM+PTX. Although no side-effects were noted, such as leukopenia, interstitial pneumonia, or liver dysfunction, during the therapy, it was necessary to change the combination therapy to GEM monotherapy in order to reduce the costs of treatment. However, CT taken five months later showed re-growth of the pelvic mass. Accordingly, we started the GEM+PTX combination chemotherapy again using the above schedule. Three months later, the patient was re-admitted because of one-month bleeding from the pelvic mass. Radiotherapy was applied at that stage. While radiotherapy resulted in increased tumor size, it also resulted in necrosis of the tumor. Finally, the patient was admitted with septic shock associated with infection of the necrotic tumor and died later, 21 months after the recurrence. GEM+PTX combination chemotherapy had continued until five weeks before death (total of 11 cycles), after which the patient wished to stay at home. Figure 2 summarizes the course of treatment and changes in tumor volume.

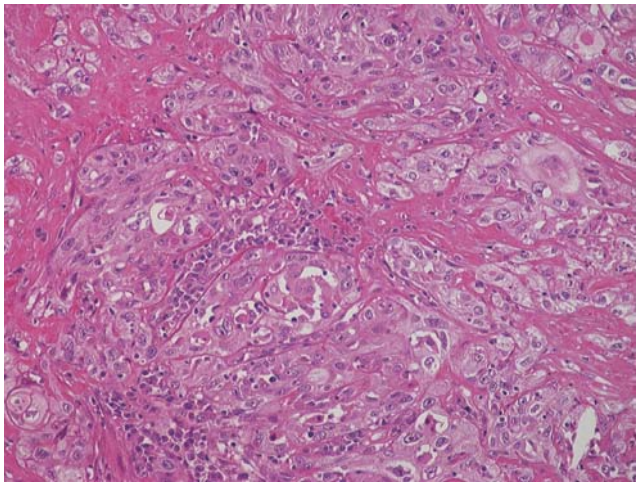

Figure 1. *Microphotograph of the resected specimen showing squamous cell carcinoma. Magnification, ×200.*

Discussion

Bladder SCCs tend to exhibit aggressive invasive tendency. On the reported patient, the locally recurrent tumor had invaded the rectum when first detected. The prognosis of patients with bladder SCC varies widely according to clinicopathological features, treatment strategy, and method of diagnosis (3, 7-10). However, in patients with recurrent and unresectable SCC, survival and outcome are extremely poor due to the lack of effective treatment, with one study indicating that the median survival time after recurrence in patients who underwent cystectomy was only 7 months (3).

However, another report described complete pathological remission in a patient treated with intra-arterial nedaplatin and pirarubicin plus intravenous methotrexate and vincristine (11). However, the histopathological diagnosis on that patient was based on examination of a specimen obtained by cold-cup biopsy. Previous data indicate that the diagnosis of SCC based on biopsy or TUR material may not reflect the overall morphology of the larger underlying tumor (3). In fact, for our patient, the pathological diagnosis based on examination of a specimen obtained through TUR differed from that of tissues obtained by radical cystectomy.

Another report indicated the effectiveness of long-term low-dose infusion of GEM and CDDP (overall response rate of 59.4%) for advanced bladder SCC (12). However, the patients of that study were confirmed to have bladder cancer associated with bilharzial cystitis (i.e. schistosomal bladder cancer). In this regard, previous studies demonstrated significant differences in biological, pathological, and genetic characteristics of schistosomal and non-schistosomal bladder cancer (13, 14). On this regard, the incidence, epidemiology, and natural history of the two types of bladder cancer are different (15). Thus, to our knowledge, there is no effective and reliable therapy for bladder SCC, especially in patients with recurrent SCC. Although MVAC therapy was used as the first-line treatment for the recurrent tumor, it was ineffective on this patient. Subsequent therapies including radiotherapy

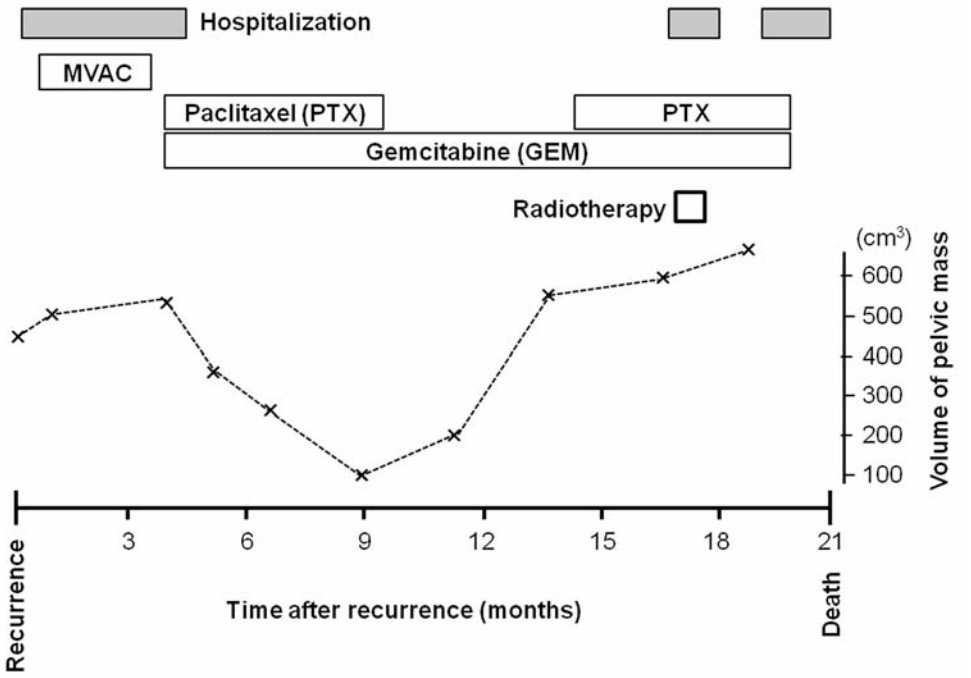

Figure 2. *Clinical course and changes in tumor size according to treatment. Tumor volume decreased from 562 to 101 cm^3 following treatment with gemcitabine and paclitaxel. However, it was increased to 573 cm^3 following the switch to gemcitabine monotherapy. Re-treatment with gemcitabine and paclitaxel failed to reduce the tumor volume, although it seemed to slow the tumor growth. Tumor volume was calculated by the equation: $4\pi/3$ abc, where a is tumor length, b tumor width and c tumor height, on computed tomographic images).*

were recommended, but they were discontinued based on patient request. Finally, a therapeutic regimen was selected for outpatient treatment, which also met the patient's needs. At first, the combination of GEM and CDDP was thought to be the most likely candidate. However, we choose GEM+PTX therapy because CDDP had been reported to be ineffective, while GEM and PTX were reported to be effective for SCC in other organs (16, 17). Two interesting phenomena relate to GEM+PTX therapy. Firstly, GEM monotherapy is considered to have antigrowth effect in SCC. Secondly, the beneficial effects of chemoradiotherapy, including GEM+PTX therapy, on SCC include marked tumor necrosis. Further studies are needed to determine whether these effects are induced by PTX monotherapy and/or combination of GEM and PTX. After the commencement of GEM+PTX therapy, the patient was re-admitted to the hospital for further treatment on two occasions. The first was for bleeding from the invasive mass of approximately one month's duration, while the second was for the worsening of the general condition of the patient (at two months). With the exception of this three-month period, the patient was an actively self-employed business owner in the last 14 months before the development of cancer. With regard to other therapies, the patient had never received adjunct therapy, such as injection of granulocyte colony-stimulating factor. Although the effect of discontinuation of GEM+PTX therapy on outcome needs to be examined thoroughly, we plan to use GEM+PTX combination chemotherapy in similar patients in the future.

In conclusion, we report the case of a patient with recurrent SCC of the bladder who responded to maintenance chemotherapy with GEM and PTX. Although chemotherapy with GEM and PTX did not induce complete remission, the combination is promising for treatment SCC of the bladder as it has anticancer activity, improves quality of life and is free of serious side-effects.

Conflict of Interest

All Authors declare no conflict of interest.

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Received September 9, 2011
Revised October 24, 2011
Accepted October 25, 2011