Two cases of recurrent small-cell carcinoma of the uterine cervix treated with amrubicin as salvage chemotherapy

N. Kosaka, K. Hasegawa, K. Kiuchi, S. Ochiai, E. Motegi, I. Fukasawa
Department of Obstetrics and Gynecology, Dokkyo Medical University, Mibu, Tochigi (Japan)

Summary
Small-cell carcinoma of the cervix (SCCC) is a rare and aggressive tumor; however, no definitive treatment guidelines for SCCC exist. A review of case series revealed that the most frequently used first-line chemotherapy regimen is combination etoposide and cisplatin, which is also used for small-cell lung cancer (SCLC). For recurrent SCLC, the utility of amrubicin (AMR) has recently been reported. However, optimal second-line chemotherapy for recurrent SCCC has remained unclear. Herein the authors report their experience using AMR as salvage chemotherapy for two patients with recurrent SCCC. AMR resulted in disease stabilization in both patients, with relatively long progression-free survival (PFS) of five and 14 months for platinum-refractory and -sensitive disease, respectively. No severe (grade >3) hematological or non-hematological toxicities were observed. In conclusion, AMR may be as effective and safe for recurrent SCCC as it is for recurrent SCLC. To further evaluate the efficacy and safety of AMR for recurrent SCCC, it is necessary to collect additional case studies or conduct a phase II trial.

Key words: Small cell carcinomas; Uterine cervix; Amrubicin; Recurrence.

Introduction
Small-cell carcinoma of the cervix (SCCC) is a rare and aggressive tumor with a propensity for rapid recurrence and a high mortality rate. The reported incidence is approximately 1-6% of all cervical malignancies [1-4]. Even patients with early-stage SCCC who undergo radical surgery tend to have a high rate of recurrence, due to significant vessel invasion and a high rate of lymph node involvement (40-86%) [1-4]. However, previous studies have primarily consisted of case reports or case series, because of the low incidence of this disease; thus, it has been difficult to establish the optimal treatment strategy for SCCC. Based on a review article of these case series, the EP (etoposide and cisplatin) regimen, which is also used in the treatment of small-cell lung cancer (SCLC), is the most frequently used first-line chemotherapy regimen for SCCC [5]. In contrast, the optimal second-line chemotherapy regimen for recurrent SCCC has remained unclear. For patients with relapsed SCLC, the utility of amrubicin (AMR) in both platinum-sensitive and -refractory relapsed disease has been recently reported [6-9]. However, the clinical efficacy of AMR for recurrent SCCC has not been evaluated, and to the best of the present authors’ knowledge, no reports of AMR for recurrent SCCC exist in the English literature. Herein they report their experience using AMR as salvage chemotherapy for two patients with recurrent SCCC.

Case Report
Case 1 was a 33-year-old gravida 3, para 2 Japanese female who was diagnosed with International Federation of Gynaecology and Obstetrics (FIGO) Stage Ib1 invasive cervical adenocarcinoma, and underwent radical hysterectomy. The tumor pathologically consisted of round to oval, polygonal, and spindle-shaped cells with finely dispersed hyperchromatic nuclei, indistinct nucleoli, and scanty cytoplasm. The tumor showed trabecular nesting and a sheet-like or alveolar pattern interspersed with thin fibrovascular septa. Nuclear molding and high mitotic activity were present throughout the tumor. The tumor was finally diagnosed as a small-cell carcinoma of the uterine cervix with significant lymph and blood vessels invasion and pelvic lymph node metastases (pT1b1N1M0), and demonstrated positive immunohistochemical staining for CD56, synaptophysin, and chromogranin A. After surgery, the patient received adjuvant chemotherapy consisting of five cycles of the cyclophosphamide, doxorubicin, and vincristine alternating with etoposide and cisplatin (CAV-EP) regimen. Twenty-seven months after initial surgery, lung metastases were observed, and the patient received two cycles of CAV-EP and six cycles of TC (paclitaxel and carboplatin) as this was deemed a platinum-sensitive relapse. However, the tumors did not respond to these regimens and instead were classified as progressive disease (PD) by Response Evaluation Criteria in Solid Tumors (RECIST). The patient received ten cycles of PI (cisplatin and irinotecan), after which the lung metastases stabilized (stable disease [SD] by RECIST) for five months; however, PD was observed based on the appearance of a new lesion on the left labia majora. The serum level of the tumor marker neuron-specific enolase (NSE) was elevated to 30 ng/mL (normal, < 12.0 ng/mL). After resection of the painful mass in the left labia majora, the patient received AMR (40 mg/m² for three consecutive
days, every 21 days), as treatment for a platinum-refractory relapse, after informed consent was obtained and approval of the present institutional review board. The patient received five cycles of AMR; a slight reduction in the size of the lung metastases was observed at the beginning of treatment, and the tumors were stabilized for five months by CT scan (Figures 1a, b). The NSE level ranged from 21 to 26 ng/mL during treatment. However, the lung metastases were finally judged as PD after 5 cycles of AMR. After that, the patient received 3 cycles of EP; however, none of the tumors responded, and new lesions appeared in the brain accompanied by an elevated NSE level of 63 ng/mL. The patient was treated with palliative whole-brain irradiation (30 Gy) for multiple brain metastases; however, the lung metastases became progressively worse and the patient died of disease 68 months after initial surgery.

Case 2 was a 64-year-old gravid 2, para 2 Japanese female who was diagnosed with FIGO Stage IVB invasive cervical adenocarcinoma, because of para-aortic lymph node metastases detected by positron emission tomography (PET)-CT. The patient received DP (docetaxel and cisplatin) chemotherapy for advanced cervical adenocarcinoma; however, after two cycles, the tumors were stabilized but had not responded to treatment. Therefore, the patient underwent concurrent chemoradiation consisting of external-beam radiotherapy up to 59.4 Gy uniformly to the whole pelvis and para-aortic lymph node lesions over six weeks with weekly intravenous cisplatin administration (40 mg/m²) for five cycles. A total of 33 fractions of 1.8 Gy per fraction were administered. Unfortunately, a residual tumor was histologically and radiologically detected in the cervix. Radical hysterectomy with para-aortic lymph node dissection was performed. The tumor was pathologically diagnosed as a small-cell carcinoma of the uterine cervix with degeneration and necrosis of tumors due to chemoradiation, with significant vessel permeation and pelvic and para-aortic lymph node metastases (pT1b1N1M1), and showing immunohistochemically positive staining for CD56, synaptophysin, and chromogranin A. After surgery, the patient received five cycles of adjuvant CAV-EP. However, at 37 months after initial surgery, the serum NSE level was elevated up to 17.5 ng/mL, and para-aortic lymph node metastasis, bilateral adrenal glands metastases, and retroperitoneal dissemination at the pelvis and in front of the left kidney were detected by PET-CT. The patient received AMR (AMR, 35 mg/m² for three consecutive days, every 21 days) for five months by CT scan. The NSE level was elevated up to 17.8 ng/mL, and para-aortic lymph node metastasis (after three cycles of AMR, SUV max 4.0), para-aortic lymph node metastasis (before treatment, SUV max 4.4), bilateral adrenal gland metastasis (before treatment, SUV max 6.6), and retroperitoneal dissemination at the pelvis and in front of the left kidney were detected by PET-CT. After three cycles of AMR, the metastatic tumors were classified as SD by RECIST, and FDG uptake and the size of some metastatic tumors, particularly para-aortic lymph node metastases as detected by PET-CT, were decreased. a) r-adrenal gland metastasis (before treatment, SUV max 4.4), b) r-adrenal gland metastasis (after three cycles of AMR, SUV max 4.0), c) para-aortic lymph node metastasis (before treatment, SUV max 6.6), d) para-aortic lymph node metastasis (after three cycles of AMR, SUV max 6.6). PET-CT: positron emission tomography-computed tomography, SD: stable disease, RECIST: Response Evaluation Criteria in Solid Tumors, FDG: fluorodeoxyglucose, SUV: standardized uptake value.

Discussion

Small-cell carcinomas of the cervix represent a unique entity, having unusual pathological findings, including immunohistochemical results and molecular patterns, among gynecologic malignancies [10, 11]. The prognosis is worse than that associated with other histologic types of cervical cancer [1-4]. Recurrence sites primarily include lymph nodes, lungs, liver, brain, and bone, as well as unexpected sites [1-4]. The recurrent disease is generally incurable, and overall survival after diagnosis of recurrence is unfortunately short, only 7-8 months [12]. Therefore, the role of chemotherapy is critical. No definitive treatment guidelines for SCCC have been developed; however, the management algorithm for neuroendocrine carcinoma of the cervix, including SCCC, was published by the Society of Gynecologic Oncologists.
logic Oncology (SGO) [13]. According to this management algorithm, for early-stage disease, radical hysterectomy is recommended as primary therapy or after neoadjuvant chemotherapy, followed by adjuvant chemotherapy with or without radiotherapy. In contrast, for advanced-stage disease, concurrent chemoradiotherapy or systemic chemotherapy is recommended [13]. Recently, Gudducci et al. also presented the therapeutic algorithm from the systematic review [14]. The contents of this algorithm is almost same with that published by SGO [13]. Moreover, Gudducci et al. indicated the first-line chemotherapy with EP regimen for SCCC in their algorithm [14].

EP is the most frequently used adjuvant chemotherapy regimen for advanced disease, as in the treatment of SCLC. The PI regimen has also been used for advanced or recurrent SCLC [15-19]. However, optimal first-line chemotherapy for patients with SCCC has not been established, because of the absence of randomized controlled trials for SCCC, which are difficult to conduct, as only a small number of patients are diagnosed with this disease. Furthermore, no effective regimens for recurrent SCCC have yet been established. A definitive regimen for sensitive or refractory relapsed patients with SCLC is also lacking; however, the results of several clinical trials of AMR [6, 7] and topotecan (TOP) [6, 20] have been reported. Sensitive relapse is defined as a relapse ≥ 90 days after the completion of first-line chemotherapy, while refractory relapse is defined as a relapse during first-line chemotherapy or a relapse within 90 days after completion of first-line chemotherapy. Jotte et al. conducted a randomized phase II trial that evaluated the efficacy and safety of single-agent AMR versus TOP as second-line treatment for patients with SCLC sensitive to first-line platinum-based chemotherapy [6]. These investigators reported that AMR resulted in a significantly higher response rate (RR) than TOP (44% vs. 15%; p = 0.021). Median progression-free survival (PFS), median overall survival (OS), and tolerability were similar between groups; however, a trend of more frequent grade 3 or worse neutropenia and thrombocytopenia was observed in the TOP group compared to the AMR group. These researchers concluded that AMR shows promising activity as second-line treatment in patients with SCLC sensitive to first-line platinum-based chemotherapy. For refractory relapsed patients with SCLC, effective chemotherapy has not yet been defined; however, AMR also appears to be promising in this setting [7-9].

In a single-arm confirmatory phase II study of AMR (40 mg/m^2 for three consecutive days, every 21 days) for patients with refractory relapsed SCLC (Japan Clinical Oncology Group Study: JCOG0901), the overall RR was 32.9%, and median PFS and OS were 3.5 months and 8.9 months, respectively. Thus, AMR monotherapy can be considered as an effective and safe treatment option for refractory SCLC [8]. In contrast, effective salvage chemotherapy regimens for both platinum-sensitive and -refractory relapsed SCCC are uncertain. Moreover, no reports about AMR for recurrent SCCC have been published. Herein the present authors report the efficacy of AMR as salvage chemotherapy in two patients with recurrent SCCC, one with a platinum-sensitive relapse and one with a platinum-refractory relapse. AMR did not yield any complete or partial responses; however, relatively long PFS (five and 14 months for the patients with platinum-refractory and -sensitive disease, respectively) was observed. No severe (grade 3 or higher) hematological or non-hematological toxicities were observed; thus, the feasibility and safety of this regimen was confirmed. In recurrent SCLC, AMR has been reported to yield an overall RR and median PFS in patients with sensitive and refractory relapse cases of 44.0% and 4.5 months, and 32.9% and 3.5 months, respectively [6-8]. In this study, PFS in two patients treated with AMR were comparable to those observed in clinical trials for recurrent SCLC (both sensitive and refractory relapse cases) [6-8]. In the present series, AMR was given based on the results of SCLC clinical trials: 40 mg/m^2 for three consecutive days, every 21 days. However, if patients experienced severe myelosuppression during previous chemotherapy, or underwent entire pelvic irradiation, the AMR dose was reduced to 35 mg/m^2. The AMR dose was therefore reduced to 35 mg/m^2 for Case 2, since she had undergone entire pelvic irradiation; only grade 2 neutropenia was observed.

The most common severe toxicity associated with AMR is myelosuppression; Grade 4 neutropenia and febrile neutropenia have been observed in 79% and 14% of SCLC patients who received AMR (40 mg/m^2 on days 1 through 3), respectively [7], and grade ≥ 3 non-hematologic toxicities were also more frequently observed in the AMR group compared to the TOP group [7]. In contrast, Jotte R et al. reported that the tolerability was similar between SCLC patients who received AMR vs. TOP, although grade 3 or worse neutropenia and thrombocytopenia occurred more frequently in the TOP group (78% and 61% vs. 61% and 39%, respectively) [6]. Thus, the toxicity grades associated with AMR somewhat differ between studies; however, most cases of toxicity were manageable.

Recently, the efficacy of the combination of topotecan, paclitaxel, and bevacizumab (TPB) was reported in patients with recurrent SCCC (n=13), showing 23% of complete response and 23% of partial response, and with 7.8 months of median PFS and 9.7 months of median OS [21]. The TPB regimen may become a promising therapeutic choice, however, the number of patients recruited in this study was relatively small, and the adverse events were not precisely mentioned. Therefore further evaluation of the efficacy and safety of TPB regimen for recurrent SCCC is needed.

In conclusion, the present results suggest that AMR may be effective and safe for recurrent SCCC. To further evaluate the efficacy and safety of AMR for recurrent SCCC, additional case studies or a phase II trial should be conducted if possible. The rarity of recurrent SCCC poses a
challenge to evaluating AMR. Case report series are currently the most viable option for characterizing recurrent SCCC and developing optimal treatment strategies.

References


