Case Report

Amrubicin is effective against small cell carcinoma of the prostate as a second-line chemotherapeutic agent: A case report

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Abbreviations & Acronyms
AC = adenocarcinoma
ADT = androgen deprivation therapy
ALP = alkaline phosphatase
AMR = amrubicin
CAB = combined androgen blockade
CE = carboplatin and etoposide
CI = carboplatin and irinotecan
CMR = complete metabolic response
CT = computed tomography
FDG = fluorodeoxyglucose
GS = Gleason score
OS = overall survival
PE = cisplatin and etoposide
PET = positron emission tomography
PI = cisplatin and irinotecan
ProGRP = pro-gastrin-releasing peptide
PSA = prostate-specific antigen
RP = radical prostatectomy
RT = radiation therapy
SCC = small cell carcinoma
SCCP = small cell carcinoma of the prostate
SCLC = small cell lung cancer

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Introduction: Small cell carcinoma of the prostate has a poor prognosis. Furthermore, treatments for small cell carcinoma of the prostate have not been established. We report a case where amrubicin was effective for second-line chemotherapy.

Case presentation: A 50-year-old man complaining of painful micturition was referred to our hospital. Due to high prostate-specific antigen level (16.57 ng/mL) and abnormal magnetic resonance imaging findings (cT2c), prostate biopsy was performed; mixed adenocarcinoma and small cell carcinoma of the prostate were observed. Radical prostatectomy was performed following a cT2cN0M0 diagnosis. One month after prostatectomy, fluorodeoxyglucose positron emission tomography/computed tomography showed metastatic lesions in the bone; the patient received androgen deprivation therapy and two cycles of cisplatin plus irinotecan. Due to new metastatic lesions and sustained abnormal pro-gastrin-releasing peptide levels, amrubicin was administered for second-line chemotherapy. Pro-gastrin-releasing peptide was normalized and positron emission tomography/computed tomography showed a complete metabolic response after 15 cycles of amrubicin.

Conclusion: Amrubicin could serve as a second-line chemotherapeutic agent against small cell carcinoma of the prostate.

Key words: small cell carcinoma of the prostate, amrubicin, FDG-PET.

Keynote message

SCCP, a tumor seen in 0.5–2% of prostatic primary tumors, is rarely detected and has a poor prognosis. Our findings suggest that AMR, a synthetic anthracycline derivative made in Japan, could serve as a second-line chemotherapeutic agent against SCCP. Moreover, PET/CT should be considered to estimate the response of chemotherapy against SCCP.

Introduction

SCCP is a rare tumor seen in 0.5–2% of prostatic primary tumors.[1,2] Localized SCCP is rarely detected in patients at the time of diagnosis; 92–96% of cases have locally advanced SCCP or metastasis, and micrometastasis often exists even when metastasis is not diagnosed.[1] Most patients with SCCP have poor prognosis (mean survival time: 17.7 months (without metastasis) and 12.5 months (with metastasis)).[3] Standard treatment for SCCP has not been established. The National Comprehensive Cancer Network guidelines 2016 (version 3) suggest that SCCP treatment can be performed according to that for SCLC;[4] therefore, SCCP patients receive treatment with cisplatin and irinotecan (PI) or etoposide (PE). However, these therapies have limited efficacy against SCCP.[5,6] Some recent reports[7–10] have shown that second-line chemotherapy with AMR is effective against SCCP. Herein, we report a case where AMR was effective against SCCP as a second-line chemotherapeutic agent.

Case presentation

A 50-year-old man consulted a local doctor complaining of painful micturition. His PSA level was 16.57 ng/mL and findings in contrast-enhanced magnetic resonance imaging of the prostate were suggestive of prostate cancer (cT2cN0) (Fig. 1a–d).

The patient was referred to our hospital 1 month after the first doctor's visit. His PSA level was 22.1 ng/mL and prostate volume was 34.8 mL without abnormal findings on digital rectal examination. Pathological findings of transrectal ultrasound-guided prostate needle biopsy showed lesions of AC diagnosed as GS 5 + 5, and SCC positive for synaptophysin, chromogranin A, and CD56 (Fig. 1e). CT of the whole body and bone scintigraphy showed no metastasis. Preoperative PSA, ProGRP, and neuron-specific enolase levels were 19.5, 98.7, and 14.5 ng/mL, respectively.

Open RP and lymph node dissection were performed 3 months after the first doctor's visit. Pathological findings of the prostate showed AC of GS 5 + 5 and SCC, and invasion of SCC to the bladder neck, while the lymph nodes showed mixed AC and SCC (pT4N1). After surgery, both PSA and ProGRP levels decreased to 0.053 and 62.7 ng/mL, respectively.

FDG-PET/CT 1 month after RP showed abnormal uptake in multiple bones (Fig. 2a). Furthermore, his ALP level was increased. PI (cisplatin; 60 mg/m^2, day 1, monthly and irinotecan; 60 mg/m^2, days 1, 8, and 15, monthly) and ADT was prescribed 2 months after RP. However, new osteolytic changes at the second lumbar vertebrae were revealed with CT (Fig. 2b), both ProGRP and ALP levels were elevated to 80.5 and 562 ng/mL, respectively, and he complained of back pain, while his PSA level decreased to <0.003 ng/mL. AMR (40 mg/m^2, days 1, 2, and 3, every 3 weeks) was prescribed as a second-line chemotherapeutic agent along with palliative radiotherapy for the lesions (irradiation dose, 37.5 Gy/15 sessions).

After two cycles of AMR and radiotherapy, CT showed no changes to the bone lesions and no new lesions, and both the ProGRP and ALP levels were normal. Another 13 cycles of AMR were administered, and the CT showed no changes, while the ALP and ProGRP values remained normal. G1 constipation, G1 anorexia, G2 peripheral neuropathy, and G3 leukopenia (National Cancer Institute common toxicity criteria, version 2) occurred during AMR therapy and were controlled with the administration of granulocyte colony-stimulating factor.

Following AMR therapy, no abnormal uptake by lesions was observed with FDG-PET/CT, and the patient was diagnosed as showing CMR (PERCIST version 1.0) (Fig. 2d). Because FDG-PET/CT showed no metastasis, and the patient wished to stop AMR chemotherapy due to social factors, AMR chemotherapy was stopped and only ADT was continued. Thereafter, the ProGRP and ALP levels were normal, and PSA was undetectable. The patient is still alive at 28 months since the diagnosis of SCCP, without relapse or metastasis.

Discussion

SCCP is often found with AC as a primary cancer (only SCC, 36%; with AC, 64%).[3] However, there are no significant differences in OS between patients with only SCCP, and SCCP and AC.[11] Therefore, treatment for AC may not contribute to the improvement of the prognosis of SCCP and AC patients. Intermittent ADT can be considered for this patient; we offered the patient intermittent ADT for AC when AMR was stopped. However, the patient wished to continue ADT.

There is no established treatment for SCCP without metastasis.[3,11] Reports indicate the feasibility of surgical resection combined with systemic therapy,[3,5] neoadjuvant therapy,[3] and RT and chemotherapy[4,12,13] for SCCP. In our patient, chemotherapy had been planned after prostatectomy.

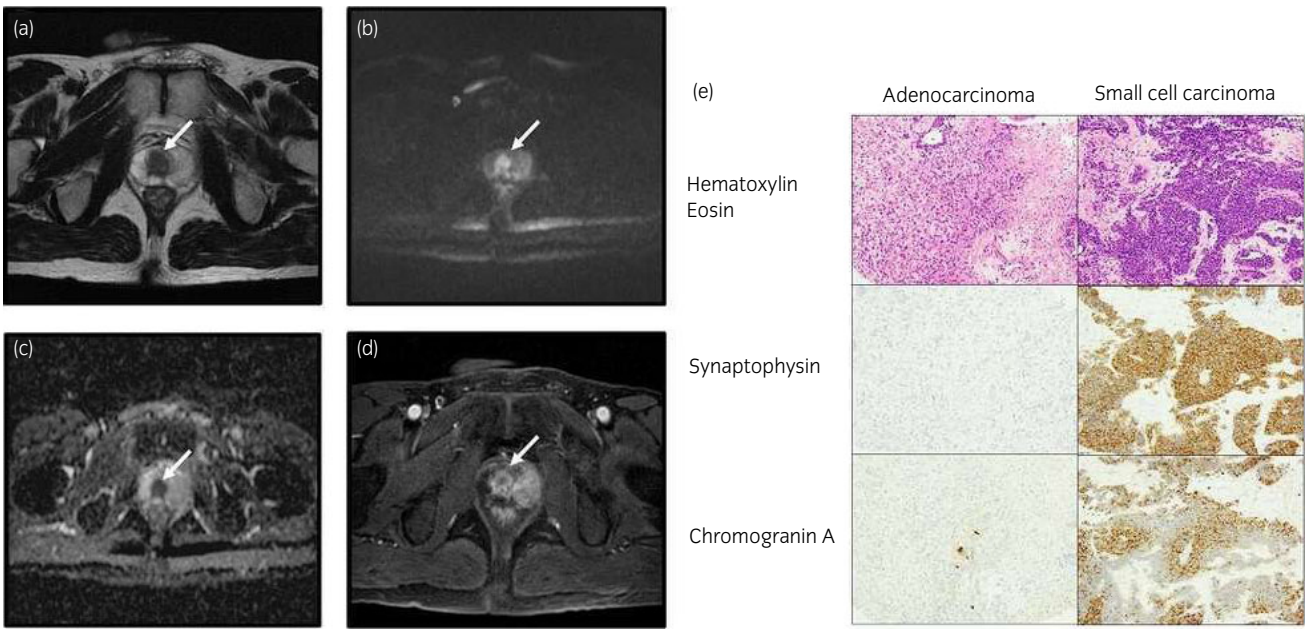

Fig. 1 Magnetic resonance imaging before the patient was referred to our hospital. T2-weighted (a) and diffusion-weighted (b) images, apparent diffusion coefficient map (c), and enhanced image (d). The white arrows show abnormal lesions. (e) Histopathological findings from transrectal prostatic needle biopsy. Hematoxylin and eosin staining, synaptophysin, and chromogranin A in AC and SCC have been shown.

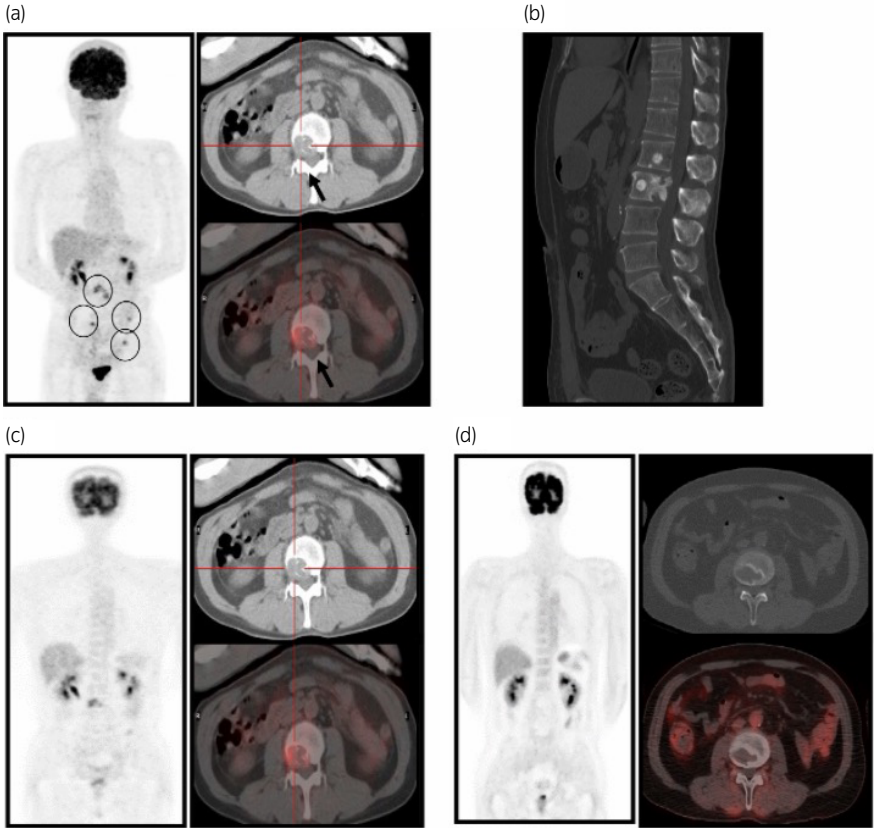

Fig. 2 (a) FDG-PET/CT 1 month after RP. The black circles show abnormal uptake. (b) CT after two cycles of PI. The white arrow shows new osteolytic changes. FDG-PET/CT (c) before treatment with two cycles of PI and (d) after treatment with 15 cycles of AMR.

Table 1 Cases with SCCP treated with AMR

			Findings at diagnosis			Clinical course			
No.	Author	Age	PSA (ng/mL)	ProGRP (pg/mL)	Staging (TNM)	Treatment	After diagnosis survival (months)	Best overall rating (RECIST, PERCIST)	Outcome
1	Kageyama 2006	65	3	82.9	cT4N1M1c	Surgery, CAB, PE, PI, AMR	16	Stable disease	Death
2	Kageyama 2006	73	18.4	16.6	cT4N1M1a	CAB, PE, AMR, RT	15	Progressive disease	Death
3	Katou 2008	23	1.38		cT4N1M1b	AMR, PE	5	Partial response	Death
4	Kikuchi 2012	58	92.65	190.1	cT3bN1M1c	CAB, PI, CI, AMR, RT	27	Progressive disease	Death
5	Asai 2014	76	26	46	cT3bN1M0	CAB, CI, docetaxel, AMR, RT	17	Partial response	Survival
6	Asai 2014	58	2.54	41	cT4N1M0	CI, AMR, RT	6	Stable disease	Survival
7	Hirai 2015	69	352	15500	cT3bN1M1b	CAB, CE, AMR, RT	39	Stable disease	Death
8	Case 2017	50	22.1	98.7	cT2cN0M0	Surgery, CAB, PI, AMR	28	CMR	Survival

Currently, there are only eight reported cases in Japan. All patients received various treatments and not just amrubicin.

However, pathological findings of RP showed pT4N1. As the pathological findings were very poor, we performed FDG-PET/CT for detecting new metastases. The feasibility of FDG-PET/CT for the staging and prediction of the prognosis of SCLC has been reported.[14,15] In our patient, surgical resection was followed by chemotherapy.

The use of AMR against advanced SCLC for second-line chemotherapy has been reported.[5] The Japanese guidelines for SCLC suggest that PI- or PE-unresponsive patients could be treated with AMR.[16] AMR is a synthetic anthracycline derivative made in Japan.[16] AMR does not show dose-dependent cardiotoxicity like other anthracycline derivatives.[17,18] The appropriate number of cycles of AMR for SCCP or even SCLC has not been established. Higashiguchi *et al.*[18] reported the safety and effects of long-term AMR chemotherapy on SCLC (median, 12 cycles; range, 8–20 cycles). In our patient, AMR treatment was stopped after 15 cycles. More cycles of AMR may be considered when SCCP progression appears based on reports demonstrating the feasibility of repeated AMR administration.[19] To date, eight patients with SCCP received second-line chemotherapy with AMR[7–10] (Table 1), and their mean survival time was longer (20.4 months) than that reported for conventional therapies. Tumor volume reduction of 74% has been achieved with AMR.[8] And for the

patient, AMR was covered by Japanese national health insurance. But, we needed to report the history of the patient and the necessity of administering AMR every month.

In our patient, metastatic lesions were observed using PERCIST, a response evaluation criterion for PET/CT.[14] Although this criterion has not been established for SCCP, its usefulness has been reported for SCLC.[14,15] CMR on PET/CT in SCLC patients indicated a better OS, and post-therapeutic standardized uptake values corrected for lean body mass were significantly associated with OS.[15] Therefore, PET/CT should be considered to estimate the response to chemotherapy against SCCP, especially when it is difficult to estimate the response by conventional examination methods.

Conflict of interest

The authors declare no conflict of interest.

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