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Case Report
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Advanced Adrenocortical Carcinoma Managed with Gemcitabine Plus Capecitabine as Second-Line Chemotherapy: A Case Report

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Abstract

Background: Patients with advanced Adrenocortical Carcinoma (ACC) have a poor prognosis. A Randomized-Control Trial (RCT) showed the efficacy and safety of mitotane plus a combination of Etoposide, Doxorubicin, and Cisplatin (EDP-M) for first-line therapy in patients with advanced ACC. However, second-line therapy has not been determined yet. Here, we report advanced ACC that was treated successfully with a combination of Gemcitabine, Capecitabine and Mitotane (Gem/Cape-M) as second-line therapy following EDP-M therapy.

Case Report: A 44-year-old woman who presented headache, palpitations, night sweats, acne, beard, menopause, edema, moon face, stretch marks on the abdomen and hypertension was diagnosed with ACC, stage T3N0M0, and underwent right adrenalectomy. Her high level of serum Dehydroepiandrosterone Sulfate (DHEA-S) of 757 μg/dL immediately decreased to 4 μg/dL after surgery. However, she developed lung and liver metastases and local recurrence with an increase of the serum DHEA-S level to 349 μg/dL 6 months after surgery. She received EDP-M as first-line chemotherapy, but the sites of metastases appeared to progress after 3 cycles. As second-line chemotherapy, Gem/Cape-M was chosen. She showed a Partial Response (PR) after 3 cycles of the treatment. Sixteen cycles of the treatment were delivered in 13 months and a partial response was maintained with a decrease of the DHEA-S level to 9 μg/dL. Grade 4 neutropenia and grade 3 thrombocytopenia were observed.

Conclusion: We reported a long-lasting durable response to Gem/Cape-M following failed EDP-M for advanced ACC. It is suggested that Gem/Cape-M can be an option as second-line therapy for advanced ACC after EDP-M.

Keywords: Adrenocortical carcinoma; Capecitabine; Gemcitabine; Second-line

Abbreviations

ACC: Adrenocortical Carcinoma; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EDP-M: Etoposide, Doxorubicin, Cisplatin, and Mitotane therapy; Gem/Cape-M: Gemcitabine, Capecitabine and Mitotane therapy; DHEA-S: Dehydroepiandrosterone Sulfate; ACTH: Adrenocorticotropic Hormone; IVC: Inferior Vena Cava; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ENSAT: European Network for the Study of Adrenal Tumors; RCT: Randomized-Control Trial; NGS: Next-Generation Sequencing; TP: Thymidine Phosphatase; 5-FU: 5-Fluorouracil

Introduction

Adrenocortical Carcinoma (ACC) is a rare malignant tumor, with an incidence rate ranging from 0.7 to 2 cases per 1 million population annually. Complete surgical resection is the only definitive treatment. Patients with advanced ACC have a poor prognosis with survival of less than 1 year [1]. A Randomized-Control Trial (RCT) showed the efficacy and safety of mitotane plus a combination of Etoposide, Doxorubicin and Cisplatin (EDP-M) for first-line therapy in patients with advanced ACC [2]. However, second-line therapy has not been determined yet. In this case, we report advanced ACC which was treated successfully with a combination of Gemcitabine, Capecitabine and Mitotane (Gem/Cape-M) as second-line therapy following EDP-M therapy.

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This case provides valuable insight into the evolving landscape of treatment options for advanced ACC.

Case Presentation

A 44-year-old woman presented with headache, palpitations, night sweats, acne, beard, menopause, edema, moon face, stretch marks on the abdomen and hypertension in July 2019. She had no prior medical history nor any relevant family history of any illness or medical condition. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) demonstrated a 90 mm-sized tumor in the right adrenal gland with hemorrhagic components that invaded into the Inferior Vena Cava (IVC) (Figure 1a, 1b). She had high levels of serum steroid hormones, including an Adrenocorticotropic Hormone (ACTH) -independent cortisol level of 26.1 μg/dL without circadian rhythm of cortisol secretion, a testosterone level of 1.43 ng/mL, Dehydroepiandrosterone Sulfate (DHEA-S) level of 757 μg/dL and estradiol level of 14.7 pg/mL. She was diagnosed with stage III ACC (T3N0M0) in the European Network for the Study of Adrenal Tumors (ENSAT) classification [3] and underwent right adrenalectomy in September 2019. Pathological findings that met 8 of 9 of the Weiss criteria confirmed the diagnosis of ACC [4] (Figure 1c). The tumor was exposed at the edges of the IVC, although the IVC wall was removed together with the tumor, it was diagnosed as having a positive surgical margin.

Although serum DHEA-S immediately decreased to 4 μg/dL after surgery, CT findings at 6 months revealed multiple lung metastases, solitary liver metastasis and local recurrence with an increase of the DHEA-S level from 4 μg/dL to 349 μg/dL (Figure 1d-1f). Because the massive recurrence was deemed unresectable, she received EDP-M therapy (etoposide: 100 mg/m^2 on day 5 to 7, doxorubicin: 20 mg/m^2 on day 1 and 8, cisplatin: 40 mg/m^2 on day 2 and 9, and mitotane: 4 g/day) every 4 weeks. However, all sites of metastases had enlarged after 3 cycles, indicating progressive disease (Figure 2a-2c).

On deep Next-Generation Sequencing (NGS) using FoundationOne® CDx, neither microsatellite instability nor actionable genetic alteration was identified in her tumor tissue. As second-line therapy, Gem/Cape-M (gemcitabine: 800 mg/m^2 on day 1 and 8, and capecitabine: 1.5 g/day) every 3 weeks was started concomitant with mitotane 4 g/day in May 2020. She exhibited a Partial Response (PR) after 3 cycles of the treatment (Figure 2d-2f). Sixteen cycles of the treatment were delivered in 13 months and the partial response was maintained with a decrease of the DHEA-S level to 9 μg/dL. The reduction rates of the metastatic sites were 95% in the lung, 26% in the liver, and 53% for local recurrence, respectively. Grade 4 neutropenia and grade 3 thrombocytopenia were observed.

Discussion and Conclusion

In this report, we present noteworthy findings regarding a sustained response to Gem/Cape treatment subsequent to the ineffectiveness of EDP-M therapy for advanced Adrenocortical Carcinoma (ACC).

EDP-M was determined to be the only treatment option that prolonged Progression-Free Survival (PFS) for advanced ACC in an RCT [2].

In the study, 304 patients with advanced ACC were randomized into two groups for first-line therapy: An EDP-M group and a Streptozocin (1 g on days 1 to 5 in cycle 1; 2 g on day 1 in subsequent cycles, every 3 weeks)-Mitotane (S-M) group. Although there was no significant difference in overall survival (14.8 months *vs.* 12.0 months; the Hazard Ratio [HR], 0.79; 95% Confidence Interval [CI], 0.61-1.02; p=0.07), rates of response and PFS were significantly better with EDP-M than with S-M (23.2% *vs.* 9.2%; p<0.001, 5.0 months *vs.* 2.1 months; HR, 0.55; 95% CI, 0.43-0.69; p<0.001, respectively), with similar rates of toxic events. Nevertheless, it is important to note that there is currently no established second-line therapy following EDP-M.

Both gemcitabine and capecitabine are synthetic pyrimidine nucleoside prodrug nucleoside analogs that interfere or compete with nucleoside triphosphates in the synthesis of DNA or RNA or both [5]. In addition, capecitabine is converted to 5-Fluorouracil (5-FU) through Thymidine Phosphatase (TP), which has been shown to be present at high levels in the tumor cells of ACC [6]. This indicates that capecitabine has anti-tumor effects on ACC. Gemcitabine and

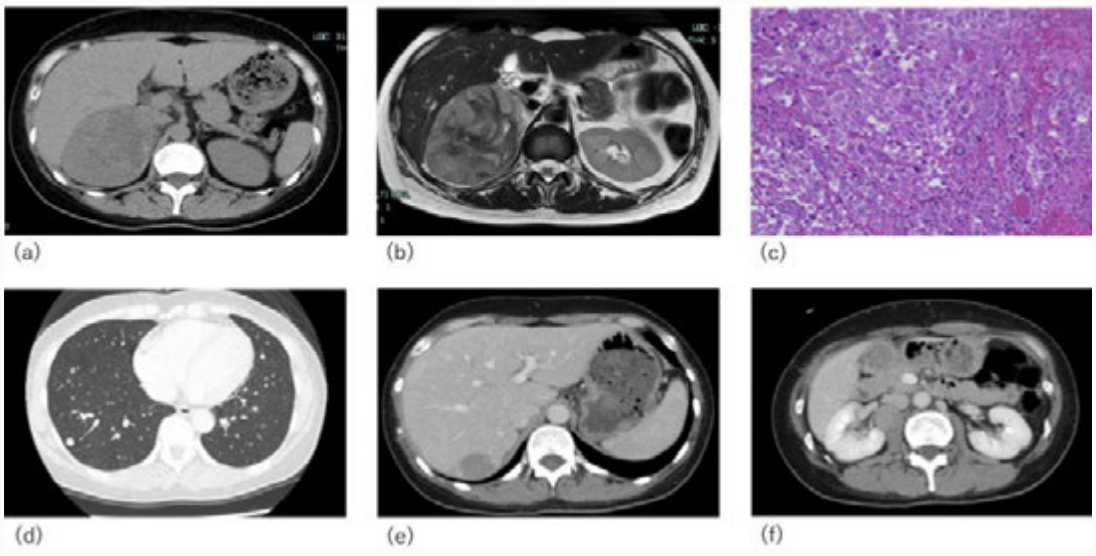

Figure 1: (a) a 90 mm-sized tumor in the right adrenal gland on Computed Tomography (CT), (b) tumor with hemorrhagic component and the Inferior Vena Cava (IVC) invasion on Magnetic Resonance Imaging (MRI), (c) histopathology showed that the tumor met 8 of the 9 Weiss criteria (x400 magnification), (d-f) CT 6 months after surgery. (d) 9 mm lung metastasis, (e) 31 mm liver metastasis, (f) 29 mm local recurrence.

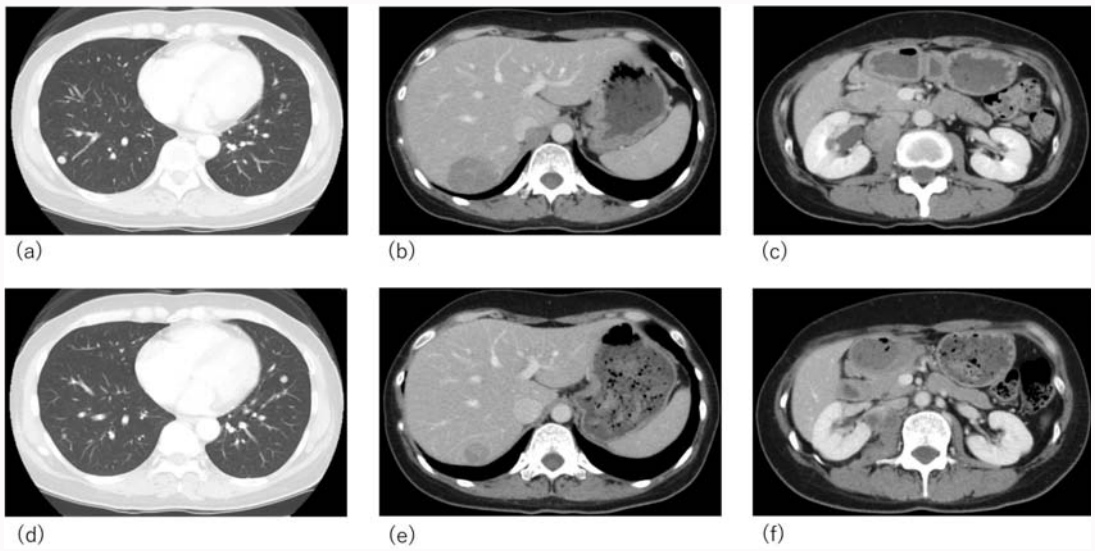

Figure 2: (a-f) CT findings after 3 cycles of EDP-M therapy. (a) the size of lung metastases increased by 10% and new lesions appeared, (b) the size of the liver metastasis increased by 49%, (c) the size of local recurrence increased by 44%. (d-f) CT findings after 3 cycles of Gem/Cape-M therapy. (d) the size of lung metastases decreased by 95%, (e) the size of liver metastasis decreased by 52%, (f) the size of local recurrence decreased by 53%.

fluoropyrimidines such as capecitabine and 5-FU have been found to have synergistic efficacy for pancreatic cancer [7]. A multicenter phase II study provided substantial evidence that the combination of gemcitabine with metronomic Fluoropyrimidines (5-FU or capecitabine) was well-tolerated and moderately effective, even in heavily pretreated ACC patients [8]. Of patients with advanced ACC progressing after mitotane plus one or two systemic chemotherapy lines, 22 received Gem/Cape and 6 a combination of gemcitabine (800 mg/m^2, on days 1 and 8) and 5-FU (200 mg/m^2, daily) every 3 weeks. Concomitant administration of mitotane was maintained in all cases (3 g/day). A Complete Response (CR) was observed in 3.5%, a PR in 3.5% and Stable Disease (SD) in 39.3%. The proportion of non-progressing patients after 4 months of treatment was 46.3%. Grade 3 or more toxicities consisted of leukopenia in 21.4%, thrombocytopenia in 3.5%, and mucositis in 3.5%. PFS and OS were 5.3 and 9.8 months, respectively. Henning et al. reported the efficacy of gemcitabine-based chemotherapy for 145 patients with advanced ACC [9]. Most of those (91.0%) received Gem/Cape as second-line or later therapy and 78.6% had administration of concomitant mitotane. No patient had CR, although 7 (4.9%) and 36 (25.0%) had PR and SD, with a median duration of 26.8 weeks (range, 4 to 94). A total of 30 (20.8%) experienced a clinical benefit from treatment of 4 months or more. In the present case, Gem/Cape-M following EDP-M maintained PR for a long period regardless of metastatic sites. This outcome without severe adverse events suggests that Gem/Cape-M could be useful as a second-line therapy.

Future research in the field should delve into the exploration and discovery of potential biomarkers capable of accurately predicting individual responses to specific therapeutic interventions. Approximately 30% to 50% of ACC cases are known to be hormonally active [10]. This is responsible for excess levels of multiple hormones produced by dedifferentiated and immature malignant cells, which indicates disorganized steroidogenesis. Suzuki et al. demonstrated that all basal levels of steroid precursors were significantly increased in cortisol-producing ACC compared to cortisol-producing adenomas, in particular, 17-hydroxypregnenolone, 11-deoxycorticosterone, androstenedione and DHEA-S showed high specificity with high accuracy [11]. In the present case, the patient had overt signs of Cushing's syndrome due to steroid hormone excess. Consequently, the levels of DHEA-S changed in parallel to clinical remission and progression during surgical removal, recurrence and chemotherapy. This underscores the potential necessity of screening multiple steroids for the early diagnosis and ongoing monitoring of ACC. In conclusion, we suggest that Gem/Cape-M could be an option as second-line therapy for managing advanced ACC following initial treatment with EDP-M.

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