CASE REPORT

Long-term disease free survival in a patient with metastatic adreno-cortical carcinoma after complete pathological response to chemotherapy plus mitotane

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ABSTRACT. Adreno-cortical carcinoma (ACC) is a rare cancer with poor prognosis. Complete surgical resection of the primary tumor and, when feasible, of the local and distant metastases offers the best prospects for long-term survival; conversely, the role of systemic therapy in patients developing unresectable metastatic disease is unclear. We describe the case of a young female patient (36 yr) who presented with an androgen-releasing metastatic ACC. Treatment consisted of five courses of chemotherapy with etoposide, doxorubicin and cisplatin (EDP scheme) plus oral mitotane, which caused the complete disappearance of distant metastases and reduction of the primary tumor, as documented by serial computed tomography (CT) scans of the chest and the abdomen. Moreover, during treatment, clinical and biochemical resolution of the hypersecretory status occurred. The left adrenal gland was then removed and histopathological examination showed extensive tumor necrosis and the absence of viable cancer cells. The patient is currently alive without evidence of recurrence 3 yr after surgery. This report shows that chemotherapy plus mitotane could result in complete pathological remission, which may be a surrogate for long-term progression-free survival in metastatic ACC patients. (J. Endocrinol. Invest. 29: 560-562, 2006) ©2006, Editrice Kurtis

INTRODUCTION

Adreno-cortical carcinoma (ACC) is a very rare disease with an annual incidence ranging from 0.5 to 2 cases per million population (1, 2). Complete surgical resection is the treatment of choice, but it remains a crucial problem that many patients present with locally advanced or metastatic disease, and about 20 to 30% of those radically resected at diagnosis will relapse (1, 3). The prognosis of patients with non operable or metastatic disease is dismal, with an estimated 5-yr survival rate close to 0% (1, 2).

The role of systemic therapy in advanced adreno-cortical carcinoma remains controversial. The adrenolytic drug mitotane [1,1 dichloro-2 (o-chlorophenyl)-2-(p-chloro-phenyl) etane] is historically the first agent used in the treatment of advanced ACC, particularly when the tumor produces high levels of hormones. In retrospective studies, mitotane has been associated with partial response rates ranging from 19 to 34% (4). Cisplatin is the cytotoxic agent most frequently used in this disease. Studies combining cisplatin with other cytotoxic agents such as etoposide, doxorubicin, and 5-fluorouracil did not suggest superior activity, compared to its use as a single agent (5-8). The combination of mitotane with cisplatin has determined a response rate of about 30% (9). The observation that mitotane could reverse in vitro the activity of the p-glycoprotein (the product of the multidrug resistance 1 gene-MDR-1), which is highly expressed in ACC cells (10, 11), provided the rationale for combining cisplatin and mitotane with other cytotoxic drugs whose activity is neutralised by this enzyme (12, 13).

Key-words: Advanced adreno-cortical carcinoma, mitotane, chemotherapy.
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Accepted December 20, 2005.

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We describe a case of long-term disease free survival in a patient with metastatic adreno-cortical carcinoma after complete pathological response to chemotherapy plus mitotane.

CASE REPORT
A 36 yr-old woman was referred to our Internal Medicine Department in September 2001 because of a 1-yr history of menstrual disorders. Her family history and prior medical history were unremarkable. Physical examination showed a mild hirsutism. Blood tests were normal. Endocrine assessment revealed increased serum levels of cortisol, dehydroepiandrosterone sulfate, testosterone, 11-deoxycortisol, 17-hydroxyprogesterone, androstenedione and free cortisol in urine. Ultrasonography of the abdomen revealed a mass located in the left adrenal gland. A computed tomography (CT) of the chest and abdomen confirmed the presence of a solid heterogeneous left adrenal mass, 15x15 cm in size with thrombosis of the renal vein (Fig. 1) and multiple lung metastases. Bone scan showed no abnormalities. A biopsy of the mass was performed and histopathology revealed a diagnosis of ACC. Due to the extension of the adrenal mass and the pulmonary involvement, surgery was excluded and six cycles of systemic chemotherapy were planned, according to our experience (EDP scheme: etoposide 100 mg/m² on days 5, 6, 7, doxorubicin 20 mg/m² on days 1 and 8, cisplatin 40 mg/m² on days 2 and 9, every four weeks). Oral mitotane was given concomitantly with chemotherapy and between cycles, at the starting dose of 1 g/day, with further dose escalation of 0.5 g/day up to the maximum tolerated dose. Because of gastrointestinal toxicity, the maximum dose administered was 3 g/day. Blood levels of mitotane were determined at baseline, after three cycles of chemotherapy, and upon the completion of the program. To prevent adrenal insufficiency, hydrocortisone at a daily dose of 37.5 mg was given. Chemotherapy was well tolerated, with World Health organization (WHO) grade 2 nausea/vomiting, leucopenia and anemia being the only side effects reported by the patient. A CT scan of the chest and abdomen, performed after three courses of chemotherapy, showed a reduction in the size of the adrenal mass (5x5 cm) and in the number and size of lung metastases. At the same time, serum and urine concentration of adreno-cortical hormones was found to be returned in the normal range. The patient received two of the three additional planned cycles of chemotherapy, refusing to undergo the sixth cycle. A CT scan of the chest and the abdomen, performed in April 2002 after the last chemotherapy administration, showed persistence of the adrenal mass with no change in size (Fig. 2), and complete regression of the pulmonary metastases. In May 2002, the patient underwent a complete surgical resection of the left adrenal gland with removal of the thrombus located in left renal vein. Histopathological examination showed extensive tumor necrosis and the absence of viable cancer cells. Maintenance therapy with oral mitotane at dose of 1.5 g/day was then started. The patient was followed-up regularly with CT scan of the chest and abdomen, assessments of blood levels of mitotane and serum and urine concentration of adreno-cortical hormones at 4 to 6 month-intervals. At the last visit, on 15 July 2005, she was still alive and without evidence of disease.

DISCUSSION
ACC is a rare and heterogeneous disease characterized by poor prognosis; for this reason, therapeutic guidelines for this disease are not well defined (1). Surgery of the primary tumor and, when feasible, of the local and distant metastases is the mainstay of the ACC management (1, 3). Conversely, the role of systemic therapy in patients developing unresectable metastatic disease is unclear (3). In fact, based on phase II studies reporting response rates ranging from 10 to 36 % with mitotane (4) or with conventional chemotherapy (5-8), it is commonly believed that systemic treatment has a palliative role.

At the time of diagnosis our patient was considered not eligible for surgery, and we decide to treat her.

Fig. 1 - Computed tomography (CT) scan at diagnosis: the image shows a 15x15 cm heterogeneous left adrenal mass, with thrombosis of the renal vein.