Metronomic chemotherapy may be active in heavily pre-treated patients with metastatic adreno-cortical carcinoma

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ABSTRACT. Objective: The potential benefit of further chemotherapy approaches in patients with adrenocortical carcinoma (ACC) showing progressive disease after 2 chemotherapy lines is actually unknown. This study provides explorative information on the activity of metronomic chemotherapy in heavily pre-treated ACC patients. Design and methods: We tested the activity of cytotoxic treatments administered on a metronomic schedule in metastatic ACC patients showing disease progression after treatment with gemcitabine and capecitabine scheme. Results: Eight patients out of 28 consecutively enrolled in that trial were treated with several metronomic cytotoxic regimens. Six of them showed disease progression, but 2 patients obtained a clear benefit. The first patient was treated with oral etoposide (50 mg daily) as the 6th-line therapy and obtained a partial response lasting 24 months, while the second patient obtained a partial response lasting 10 months with metronomic oral cyclophosphamide (50 mg daily) as the 5th chemotherapy line. Both patients had sex hormone secreting tumors and were bearing a rather indolent ACC. Conclusions: The administration of several chemotherapy lines in advanced ACC patients cannot be routinely recommended outside prospective clinical trials. Few patients with indolent tumors, however, may benefit from this approach. According to our experience, oral cyclophosphamide and oral etoposide may be used in this setting.


INTRODUCTION

Adrenocortical carcinoma (ACC) is a highly malignant disease whose treatment remains challenging. The mainstay of treatment for ACC patients is surgery (1), but most radically resected patients are destined to progress, frequently within the first 2 yr following operation (2, 3). The standard treatment for advanced patients not amenable to surgery is the polychemotherapy with etoposide, doxorubicin, and cisplatin in combination with oral mitotane (EDP-M). The efficacy of the EDP-M regimen, however, is modest and most patients progress after treatment; therefore, new treatment strategies are urgently needed (4).

Metronomic chemotherapy is the administration of antineoplastic drugs at low doses, on a frequent or continuous schedule, with no extended interruptions (5). Metronomic chemotherapy protocols are characterized by the absence of a dose-escalation up to the maximal tolerated dose (MTD), no need for hematopoietic growth factor support, possibility of oral administration in an outpatient regimen, and low incidence of treatment related side effects. Interestingly, metronomic chemotherapy has the potential for delayed resistance to treatment.

We have recently published the results of a Multicenter Italian Trial, aimed to test the activity of gemcitabine associated with fluoropyrimidines such as 5-fluorouracil and capecitabine given on a metronomic schedule in patients with adrenocortical carcinoma (6). This regimen led to a disease response or stabilization lasting 4 months in 46% of the 28 patients consecutively enrolled. In case of disease progression, if the performance status was good and the patients were able to tolerate further treatment, additional chemotherapy regimens with a metronomic schedule were given. In this paper, we report on the outcome of these patients, focusing particularly on the case history of 2 patients who showed a durable partial response after several chemotherapeutic lines.

PATIENTS AND METHODS

As outlined in Figure 1, 8 of the 28 patients enrolled in the “gemcitabine plus capecitabine” trial, were addressed to further chemotherapy lines. We detail below the case history of two patients obtaining a clear benefit from oral metronomic chemotherapy with etoposide or cyclophosphamide. Both drugs were administered at a dose of 50 mg daily without interruption until progression or unacceptable toxicities. Concomitant mitotane was maintained during chemotherapy treatment and plasma levels of mitotane were regularly monitored (every 2-3 months).

A computed tomography (CT) scan was repeated every 3 months. The evaluation of disease response was performed by “Response Evaluation Criteria In Solid Tumors (RECIST) criteria” (7), toxicity was assessed by means of the “National Cancer Institute (NCI) criteria”.

Key-words: Adreno-cortical carcinoma, cyclophosphamide, etoposide, mitotane, metronomic chemotherapy.

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RESULTS

The outcome of the 2 patients is summarized in Table 1 (8).

Case 1

A 39-yr-old man underwent radical (R0) surgical resection of an estrogen-secreting ACC (15 × 9 × 10 cm at CT scan). Pathologic examination revealed the subsequent characteristics: spleen infiltration; Ki-67 positivity in 22% of neoplastic cells, Weiss score 4, and a mitotic count of 5 × 50 HPF. One month later, bilateral lung metastases become evident, and chemotherapy with EDP-M was introduced. At disease progression, there was no evidence of hormonal hypersecretion and circulating adrenal cortical hormones (estrogen, testosterone, androstenedione, DHEAS, 17O-H-progesterone) were not elevated. A stable disease was documented after 3 cycles, but after 6 cycles disease progression was observed. From September 2003 to April 2004, the patient received a second-line chemotherapy with weekly paclitaxel (60 mg/m²) with a partial response. In May 2004, the patient underwent surgical removal of lung lesions and became disease free. In July 2006, a CT scan revealed disease progression in the lung, therefore he was treated with a 3rd-line treatment with streptozotocin plus mitotane, but the regimen was not active and a disease progression was observed after 4 cycles of therapy. The patient was then enrolled in the previously mentioned Multicenter Clinical Italian Trial of metronomic oral capecitabine and gemcitabine plus mitotane. A stable disease was obtained that lasted 6 months. On May 2007, radiological examination proved an increase in size and number of the pulmonary lesions. The clinical general conditions of patients were good, so a 5th-line treatment with metronomic oral cyclophosphamide (50 mg/daily) was prescribed. The disease remained stable till February 2008, when a further progression was detected. The patient discontinued any systemic treatment and the disease remained stable till December 2008, when further progression of lung metastases was observed at the CT scan. The patient started a 6th-line therapy with oral metronomic etoposide (50 mg daily) associated with oral mitotane. A CT scan, performed after 3 months, showed a partial disease response (Fig. 2). The disease response further improved in the subsequent CT scans till December 2010. Treatment was continued till January 2011, when disease progression was observed. Mitotane serum levels during etoposide treatment ranged between 6 and 9 mg/l. Oral etoposide treatment was rather well tolerated and was only temporarily interrupted due to asthenia lasting for 15 days.

Case 2

A 59-yr-old woman presented in December 2007 with a metastatic ACC involving liver, lymph nodes, and lung (bilateral metastases). The disease was androgen secreting, causing severe testosterone excess (6 ng/ml; normal values in women: 0.11-0.78 ng/ml) and androstenedione excess (>10 ng/ml; normal values: 0.30-3.30 ng/ml). ACTH and serum cortisol were normal. A fine needle aspiration of the adrenal mass was performed and the histology revealed a malignant tumor with Ki-67 positivity in 20% of cancer cells and presence of atypical mitoses (Weiss score was not calculated). She was in good clinical conditions, her performance status was 1 according to the Eastern Cooperative Oncology Group (ECOG) scale, the physical examination showed a clear hirsutism on face and chest. On the basis of the histology and the disease stage, the patient started a first-line chemotherapy regimen with EDP-M. From January 2008 to March 2008, she received 3 cycles with evidence of pulmonary and hepatic disease progression according to RECIST criteria (7) on image restaging. Mitotane serum levels achieved after 3 months of treatment...
Table 1 - Disease characteristics and outcome of the two patients treated with oral metronomic chemotherapy.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Stage at diagnosis</th>
<th>Ki-67</th>
<th>Hormone secretion</th>
<th>1st line CT</th>
<th>Best R</th>
<th>Best R to GMC-C</th>
<th>1st line therapy before GMC-C</th>
<th>Best R</th>
<th>Best R after GMC-C</th>
<th>Best R</th>
<th>2nd line therapy after GMC-C</th>
<th>Best R</th>
<th>3rd line therapy after GMC-C</th>
<th>Best R</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG</td>
<td>Locally advanced</td>
<td>22%</td>
<td>estrogen</td>
<td>EDP+M</td>
<td>SD</td>
<td>Weekly PXT Strepto + M PR lasting 7 months</td>
<td>SD lasting 6 months</td>
<td>CTX</td>
<td>SD lasting 8 months</td>
<td>VP-16</td>
<td>PR lasting 24 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CP</td>
<td>Metastatic</td>
<td>20%</td>
<td>androgens</td>
<td>EDP+M</td>
<td>PD</td>
<td>none</td>
<td>-</td>
<td>MR lasting 10 months</td>
<td>Weekly PXT+ sorafenib (PAXO trial)</td>
<td>PD</td>
<td>VP-16</td>
<td>PD</td>
<td>CTX</td>
<td>PR lasting 10 months</td>
</tr>
</tbody>
</table>

Pt: patient; CT: chemotherapy; EDP: etoposide, doxorubicin, cisplatin; M: mitotane; R: response; SD: stable disease; PD: progression disease; GMC: gemcitabine; C: capecitabine; PXT: paclitaxel; Strepto: streptozotocine; PR: partial response; MR: minimal response; CTX: cyclophosphamide on metronomic schedule; VP-16: etoposide on metronomic schedule; PAXO trial: weekly paclitaxel + sorafenib (8).

Fig. 2 - Disease response at computed tomography scan after 3 months of metronomic chemotherapy with etoposide in case #1.
were 16.9 mg/l (therapeutic range: 14-20 mg/l). The patient was then treated with gemcitabine plus metronomic capecitabine. At the planned first restaging after 3 months, there was evidence of minimal response at CT scan (mild regression of pulmonary and mediastinal lymph nodes). This regimen was continued till a total of 8 cycles. At the end of the 8th cycle, in October 2008, the CT showed a further reduction in the size of pulmonary and lymphnodal metastases. On January 2009, a new disease progression both in liver and lung was detected. She was included in a prospective clinical trial (PAXO trial NCT 00786110) and treated with the association of weekly paclitaxel (60 mg/m²) and daily sorafenib (800 mg). Unfortunately, after two cycles, the CT scan documented a clear progressive liver disease. This experimental therapy was therefore discontinued, but the patient, whose conditions still remained good, asked for further treatment. A 4th-line treatment with etoposide administered with metronomic schedule at the dosage of 50 mg orally was given for three months, in association with oral mitotane. After 3 cycles (July 2009) a CT scan showed a disease progression both in lung and liver. Mitotane serum levels were 6.4 mg/l. A moderate dyspnea that hampered significantly her quality of life become apparent. Since the patient strongly requested a further treatment, metronomic chemotherapy with cyclophosphamide (50 mg once daily) was instituted. Mitotane therapy was not interrupted. Radiological examination performed after two months showed an objective response (regression of pulmonary and mediastinal lymph nodes, with no change of abdominal lesions): A complete remission of dyspnea was observed while the patient reported only a mild asthenia. Mitotane serum levels were 15.6 mg/l. The disease response lasted 10 months and afterwards a further progression become evident, leading to death on January 2011. The patient also obtained a transient reduction of hormone hypersecretion (testosterone serum levels dosed after 3 months of metronomic cyclophosphamide were 2.8 ng/ml; and androstenedione serum levels were 4.7 ng/ml) lasting 6 months.

DISCUSSION

It is held that ACC is poorly responsive to chemotherapy. The EDP-M regimen is considered one of the standard first-line therapies in the management of metastatic ACC (9) and the combination of gemcitabine and capecitabine (6) represents a second-line option, although the benefit is limited. There is sparse demonstration of efficacy of other cytotoxic drugs beyond these 2 chemotherapy lines (4). A number of patients, however, are still in good general condition despite ACC progression to systemic therapy and frequently ask for further treatment. The metronomic schedule, targeting the tumor microenvironment and not directly the tumor cells, has the potential for efficacy. In addition, the relatively low toxicity profile makes this approach feasible in such patients, in whom the tolerability to cytotoxic agents may be reduced because they have been often heavily pre-treated (10, 11).

Among the 28 patients enrolled in the gemcitabine + capecitabine study, eight were eligible for further thera-
pies, and 6 of them received cytotoxic drugs outside a clinical trial. A disease progression was observed in 6 of these patients; however, two patients obtained a substantial benefit. In the first patient, oral cyclophosphamide administered as the 5th-line led to a stable disease lasting 7 months, but more importantly, the 6th-line therapy with metronomic etoposide that was subsequently done led to partial response lasting 24 months. In the second patient, oral cyclophosphamide administered as the 5th-line therapy, led to a significant partial response of lung lesions, oral cyclophosphamide, administered as the 5th-line therapy, may be important for therapeutic efficacy. It should be noted that endothelial cells within tumor tissues can harbor cytogenetic and chromosomal abnormalities similar to those observed in cancer cells (12). Accordingly, it is unlikely that a single drug administered on a metronomic schedule may have a universal efficacy (13). The patients included in the present study received either metronomic cyclophosphamide or metronomic etoposide, but their tumors showed a different sensitivity to the drugs administered. These data suggest that some tumors may be sensitive to specific drugs, and tumors that acquire resistance to a given drug may retain sensitivity to a cross-resistant agent administered also on a metronomic schedule.

The role of maintaining mitotane in patients showing disease progression to previous mitotane-containing schemes is controversial. In our cases, mitotane treatment was maintained, but in the first patient serum mitotane levels were below the therapeutic range (14), making unlikely that mitotane contributed to tumor response.

In conclusion, this paper suggests that some patients with a clinical history of slow-progressing ACC could benefit from a metronomic approach. According to our preliminary results, oral cyclophosphamide and oral etoposide could be well suitable to be used in this setting due to the good tolerability and low costs of such drugs. These data therefore deserve confirmation.

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Declaration of interest
The authors declare that there is no conflict of interest that would prejudice their impartiality.

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Author contribution
Drafting of the manuscript: A. Ferrero, A. Bernuti, P. Sperone and M. Terzolo. Radiological revision: A.M. Priola performed the centralized revision of CT images.

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