Activity and safety of temozolomide in advanced adrenocortical carcinoma patients

Activity and safety of temozolomide in advanced adrenocortical carcinoma patients with disease progression to standard chemotherapy plus mitotane

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Abstract

Background: Temozolomide has shown a significant anti-proliferative activity on adrenocortical cancer (ACC) cells *in vitro*. On the basis of these results the drug was prescribed as second/third line in advanced metastatic ACC patients in some referral centers in Italy.

Methods: We retrospectively collected anagraphic, clinical and pathological data of advanced ACC patients with disease progression to standard chemotherapy plus mitotane who were treated with temozolomide at the dose of 200 mg/m2 die (g: 1 -> 5 q28) in 4 italian Institutions. The primary end-point was the clinical benefit, defined as objective response or disease stabilization after 3 months. Secondary endpoints were overall survival (OS), progression free survival (PFS) and drug safety.

Results: Twenty-eight patients have been included in the study. Ten patients (35.8%, 95% CI 17.8-53.8) obtained a clinical benefit from temozolomide treatment. In particular, 1 patient had a complete response, 5 patients a partial response and 4 patients stable disease. Median PFS was 3.5 months and median OS 7.2 months. Disease response was more frequently observed in patients with metilation of O6-methylguanine-DNA methyltransferase (MGMT) gene. Temozolomide therapy was well tolerated and most toxicities were limited to grade G1-2 according to WHO criteria.

Conclusion: Temozolomide appeared to be active in the management of advanced ACC patients. The clinical benefit obtained, however, was short lived and the prognosis of treated patients was poor.

Keywords

adrenocortical tumor, treatment, temozolomide, MGMT

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive tumor with an incidence of 0.5-2 new cases per million population per year (1). Surgery is the mainstay of therapy but a significant proportion of patients are not operable at diagnosis, and most patients radically resected are destined to relapse within the first 2 years (1). This is the reason why adjuvant mitotane therapy is recommended by recent guidelines (2,3), despite the low evidence of efficacy (1-6).

The standard systemic treatment for advanced/metastatic ACC patients, not eligible to surgery, is mitotane. This drug is administered either alone (1), or in combination with Etoposide, Doxorubicin and Cisplatin (EDP-M regimen) (7). The efficacy of the EDP-M regimen, however, is limited as shown by the results of a randomized clinical trial reporting a disease response in about 25% of treated patients with a median survival of 14 months (8). No effective therapies are available for patients with disease progression after EDP-M (9). The combination of gemcitabine and capecitabine, which is recommended by currently available guidelines (2,3), is poorly efficacious (10,11). Other treatment strategies, including modern molecular target therapies and immunotherapy (12,13,14), failed to demonstrate significant activity. New therapeutic options are therefore urgently needed.

Temozolomide is an alkylating drug initially used in the treatment of brain tumors (15). The drug has been demonstrated to be efficacious also in the management of neuroendocrine tumors (16) and malignant pheochromocytoma/paraganglioma (17). Creemers and colleagues recently published a pre-clinical study exploring the activity of temozolomide in ACC cells *in vitro*. Their data showed that the drug has cytotoxic and cytostatic effects through a strong inhibition of cell growth, apoptosis and cell cycle arrest (18). Moreover, a slight relationship was found between the *in vitro* cytotoxicity of temozolomide and the epigenetic silencing of the MGMT (O6-methylguanine-DNA methyltransferase) DNA-repair (MGMT) gene, which is associated with temozolomide efficacy in patients with glioblastoma (19-21) and advanced neuroendocrine tumors (16).

Given these results and the limited therapeutic strategies available in the management of advanced ACC, some reference centers for this rare disease in Italy used temozolomide in ACC patients with disease progression to standard therapies. In this study, we did a retrospective assessment of temozolamide activity and toxicity in this peculiar clinical setting.

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Patients and methods

Study design and patient characteristics

This is a multicentric, retrospective study. Twenty-eight consecutive ACC patients treated with temozolomide from January 2016 to January 2018 at four Italian Institutions were included. All patients met the following eligibility criteria: age ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; life expectancy of at least 3 months; pathological diagnosis of ACC; locally advanced or metastatic disease not suitable for surgery; at least one unidimensional (RECIST criteria) measurable lesion; adequate bone marrow reserve (neutrophils ≥1500/mm3 and platelets ≥100 000/mm3, hemoglobin ≥9.0 g/dl); total bilirubin ≤1.5 times the upper limit of normal; serum creatinine ≤1.5 the upper limit of normal; effective contraception in premenopausal female and male patients; written informed consent. Exclusion criteria were history of prior malignancy, except for cured non melanoma skin cancer, cured in situ cervical carcinoma, or other treated malignancies with no evidence of disease for at least 3 years; active clinically serious infections (greater than grade 2 National Cancer Institute - Common Toxicity Criteria (NCI-CTC) version 3.0); symptomatic metastatic brain or meningeal tumors; seizure disorder requiring medication (i.e. steroids or antiepileptics); decompensated heart failure (ejection fraction ≥45%); myocardial infarction or revascularization procedure during the last 6 months; unstable angina pectoris; uncontrolled cardiac arrhythmia; hypertension not controlled by medications; pregnant or breast-feeding patients; treatment with temozolomide; other anticancer chemotherapy or immunotherapy during the study or within 4 weeks of study entry; radiotherapy during study or within 3 weeks of study start (palliative radiotherapy was allowed); major surgery within 4 weeks of study start; concomitant treatment with another investigational drug. The off label use of temozolomide was authorized by the hospitals of each participating institutions. The retospective study was approved by the Ethical Review Board of ASST-Spedali Civili in Brescia (n.).

Treatment consisted in temozolomide at the planned dosage of 200 mg/m2 die (g: 1 -> 5 q28). Maintenance of previous mitotane treatment was allowed but not mandatory and blood drug levels monitored. Disease re-staging by CT scan and/or MRI was performed every 3 cycles. The following demographic, clinical and pathological data were collected: sex, age, medical history, physical examination, performance status, routine laboratory tests, endocrine work-up, chest and abdominal CT scan, other imaging data (i.e. brain CT, magnetic resonance imaging, bone scan) performed at baseline and during temozolomide treatment.

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The study primary endpoint was the clinical benefit of the therapy, defined as disease response or stabilization at CT scan after 3 months, using RECIST criteria version 1.1. Secondary endpoints were the evaluation of progression-free survival (PFS), overall survival (OS) and treatment toxicity. PFS was defined as the time elapsing from the beginning of the treatment until disease progression or death whatever event occurred first. Non-progressing patients still alive were consored at the last follow-up examination. Overall survival was defined as the time interval between the date of treatment start and the date of death from any cause or the last known alive date. The mENSAT classification and GRAS parameters (22), as defined by grade (Weiss score <6 or >6 or Ki67 <20% or >20%), resection status of the primary, age younger than or older than 50 years, and absence or presence of tumor related or hormone-related symptoms at diagnosis, were used to assess prognosis. The CTCAE v4.03 score was used to assess toxicity.

Assessment of MGMT promoter methylation in tumor samples

As ancillary study, we evaluated the predictive role of MGMT (O^6-methylguanine–DNA methyltransferase) promoter methylation in a patient subset included in this study for which tumor samples were available. MGMT promoter methylation status was performed by means of pyrosequencing technique. Ten methylated CpG sites were analyzed, located in the promoter region (NG_052673.1-chr10:131,265,507-131,265,556) of MGMT gene exon 1 and involved in the regulation of gene expression. Genomic DNA (gDNA) was automated obtained from FFPE tissues after manual microdissection, for neoplastic cell enrichment (at least 50% of tumor cells), using the Maxwell® RSC instrument and tissue DNA Kit (Promega s.r.l, Milan, Italy). A total of 500ng of gDNA was modified by bisulfite conversion using a commercial available and certified CE-IVD kit (MGMT plus, Diatech pharmacogenetics, Ancona, Italy) following manufacturer's instructions. Sequencing analysis was performed on PyroMark Q96MA apparatus (Biotage, Uppsala, Sweden) with PCR and sequencing primers supplied in the MGMT plus kit according to the manufacturer's instructions.

Analysis of methylation (corretto? Data analisi è nel capitol seguente) was performed using the PyroMarkCpG software (Biotage), obtaining a mean pencentage of the ten CpG methylated islands for each case. A cut-off of 5% (mean of the CpG islands) of methylation was used to define "methylated" (>5%) and "unmethylated" (< or =5%) samples. Methylated and un-Methylated controls were properly used to take control of all workflow.

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Statistical analysis

Descriptive statistics were used to analyze the patient clinical characteristics. Differences between categorical variables were assessed by a chi-square or the Fisher test when indicated. The PFS and OS curves were calculated with the Kaplan–Meier method and compared with the log-rank test. The primary end point of the study was to estimate the activity of the therapy in terms of proportion of patients attaining a clinical benefit. With 28 patients recruited, this study has a potency of 80% to refuse a clinical benefit rate of 15% (p0) and to assess the activity of the therapy as a clinical benefit rate of 40%; given an alpha error of 0.05. Statistical significance was set at $p < 0.05$. SPSS v17.0 software was used for the statistical analyses (SPSS Inc., Chicago, IL).

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Results

Patient characteristics

The characteristics of the 28 enrolled patients are summarized in **Table 1**. Median age at baseline was 54 years (range 31-72). Thirteen patients (46.4%) had a hormone-secreting tumor at diagnosis and 10 of them (35.7%) had Cushing syndrome. Twenty-six patients (92.8%) underwent primary surgery as the first treatment and 20 of them (71.4%) obtained a complete resection (R0). Median disease free survival of surgical treated patients was 19.9 months (range 5-49). Twelve patients (42.9%) received post-operative adjuvant mitotane.

Cisplatin alone or the EDP combination regimen, both administered in association with mitotane were the first line cytotoxic therapies adopted after the diagnosis of metastatic disease. At baseline conditions, before starting temozolomide, the majority of patients (71.4%) had a performance status ≤1. According to mENSAT classification, 16 patients (57.1%) had a stage IV-A disease, 9 (32.2%) stage IV-B, 3 (10.7%) stage IV-C. GRAS parameters were favorable in 6 (21.4%), unfavorable in 9 (32.2%) and pejorative in 13 (46.4%) patients.

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Treatment administered and activity

Temozolomide was administered as second line in 9 patients (32.2%), third line therapy in 16 patients (57.1%) and fourth line approach in 3 (10.7%). All patients maintained previous mitotane therapy and the drug levels were within the therapeutic range in 10 (35.7%) of them.

The median number of temozolomide cycles was 4 (range 2-16). One patient (3.6%) obtained complete clinical response evaluated by RECIST 1.1 criteria, while partial response was observed in

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5 patients (17.9%), and 4 patients (14.3%) obtained disease stabilization. However, 18 patients (64.2%) had disease progression. The overall response rate was 21.5% (95% CI 6.5-27.5) and a clinical benefit was obtained in 10 patients (35.8%) (95% CI 17.8-53.8) **(Table 2).**

At disease progression, further chemotherapy was administered in 6 patients; in particular, 4 patients received gemcitabine and capecitabine whereas 2 patients received cisplatin as single agent.

Patient outcome

Median PFS was 3.5 months (range 1.2-24.2) (**Figure 1a**) and OS was 7.2 months (range 2-24.2) (**Figure 1b**). No significant difference in PFS was seen stratifying patients on the basis of whether they received temozolomide as second or further line of treatment (p=0.26). In addition, the attainment of a clinical benefit did not have any positive impact on OS: median 8.1 (range ..-..) in patients attaining a clinical benefit vs 7.1 months (range ..-..) in those who did not (p=0.77). Additional analyses were done to explore the potential prognostic significance of several patient and tumor characteristics. The patients with ECOG PS 0 had longer PFS and OS than those with PS 1 or 2 (p 0.008 and p 0.003 respectively) (data not shown). Favourable GRAS score was associated with a longer PFS (median 8.4 months) and OS (median 12.2 months) than unfavorable/pejorative GRAS (PFS: 4.2 months and OS: 6.9 months), although these differences were not statistically significant (p=0,16 and p=0.17, respectively)(Figure 2a, Figure 2b). PFS and OS curves were similar in patients with unfavorable and pejorative GRAS score (Figure 2). However, mENSAT and the combination of mENSAT with GRAS failed to be associated with either PFS (p=0.33 and 0.39, respectively) or OS (p=0.97, 0.83 respectively). Stratifying patients according to circulating mitotane levels, PFS and OS were 6.6 months and 12.6 months, respectively in patients in which blood mitotane was within the therapeutic range (14-20 mcg/L) while they were 3.5 and 6.8 months respectively in those in which the drug was below 14 mcg/L (p= 0.45 for PFS, p= 0.36 for OS) (Figure 3).

Treatment toxicity

Patients were evaluated after each cycle with both clinical examination and blood chemistry (complete blood count, liver and renal function). The observed temozolomide toxicities are summarized in **Table 3**. As expected, nausea and vomiting were the most frequent side effects, occurring in 35.8% and 25% of patients, respectively. These symptoms were classified as grade 3 in 14.3% and 10.7% of patients, respectively. Liver toxicity was observed in 25% of patients, being

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grade 3 in 7.2% of cases. Only 1 patient (3.6%) developed grade 3 neutropenia. The other observed toxicities were: renal impairment and thrombocytopenia, involving 25% and 21.4% of patients, respectively. A one-week delay in the start of a new cycle was needed in 12 patients due to toxicity, whereas no dose reduction was prescribed.

MGMT status and relevant correlation with drug activity

MGMT status was evaluated in 15 patients, eight of them showing MGMT promoter methylation. In the methylated MGMT group, 4 patients out of 8 (50.0%) obtained a disease response, in particular, 1 had a complete response and 3 had a partial response. Conversely, in the non-methylated MGMT group, only 1 patient out of 7 (14.3%) had a partial response, whereas 1 patient (14.3%) had a stable disease and the others had progressive disease (Table 4). No differences in PFS or OS were observed comparing patients with (median .. months [range .. - ..) or without (median .. months [range .. - ..) MGMT methylation (p 0.08, p 0.45 respectively).

Discussion

Alkylating agents have been shown some activity in ACC. Our group has observed a clinical benefit of the administration of oral cyclophosphamide on a metronomic schedule in 2 heavily pre-treated patients (24). Moreover, streptozotocyn (Sz) demonstrated a response rate of 35% in 40 advanced ACC assessed retrospectively in Sweden (23). On the basis of these results, the association Sz was considered as the best treatment to be tested against EDP in the FIRM-ACT trial (8). Since this combination appeared inferior to EDP, Sz is not generally used as first line approach. However, it is still recommended as a possible second line therapy by currently available guidelines (2,3).

Due to the demonstrated activity of alkylating agents in the management of ACC and the preclinical findings showing that temozolomide exerted a potent antitumor effect on ACC cells *in vitro* (..), 4 Italian reference centers obtained the authorization for the off label administration of the drug at dose of 200 mg/m2 die in ACC patients with disease progression after first line chemotherapy with cisplatin containing regimens plus mitotane. In this retrospective evaluation of these patients, temozolomide was as whole well tolerated and toxicities were manageable.

Indeed the drug showed an appreciable activity, since the diseases responses according to RECIST criteria observed in 20% of patients appears superior to the 4% response rate obtained by the association gemcitabine plus capecitabine, a recommended second line regimen in ACC (10, 11). The clinical benefit (clinical response and stable disease) of 35% obtained by temozolomide,

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however, was comparable to that reported by the association of gemcitabine and capecitabine (10, 11). However, the responses obtained in this study were short-lived and, more importantly, the disease response did not influence the patients survival, which was only of 7 months on average. This finding is in contrasts to what it is commonly observed in chemotherapy trials, in which disease response usually discriminates two patient populations with different prognosis (25).

In these pre-treated ACC patients, poor performance status was the strongest negative prognostic factor, whereas mENSAT stage failed to correlate with PFS and overall survival. Favorable GRAS score was associated with better outcome in terms of PFS and OS without attaining the statistical significance than either unfavorable and pejorative scores, which showed similar prognosis. The low number of patients enrolled conferred to our series a low potency to test these prognostic factors.

It was found in other malignancies that the therapeutic benefit of temozolomide depends on its ability to alkylate/methylate DNA. This methylation damages the DNA, thus triggering cell death by apoptosis. Primary resistance to temozolomide in glioblastoma and in neuroendocrine tumors is often directly related to high MGMT expression (16,19). So MGMT inactivation by metylation is a marker of temozolomide tumor cell sensitivity. In our series, we were able to assess MGMT expression in 15 cases. Despite the low numbers, the objective response rate was of 50% in methylated ACC vs 14% in non-methylated ACC, and this finding is consistent with the potential role of MGMT inactivation in favoring temozolomide cytotoxicity in ACC patients.

In conclusion, temozolomide, administered as second line approach in ACC, induced a significant tumor shrinkage in about one out of five patients. Despite this non-negligible activity, the drug failed to demonstrate to be efficacious, since the responses observed were short lived and did not influence patient survival. On the basis of these data, we believe that temozolomide should not be recommended as second line therapy in unselected ACC patients. However, temozolamide could be a potential option in patients with good PS bearing MGMT methylated ACC, and this may represent a first step toward a personalized medicine approach in advanced ACC.

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Acknowledgement

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