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Capecitabine (Xeloda®) and Temozolomide (Temodar®) as a Potential Therapy for Pituitary Tumors

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Abstract

We reviewed various cases and clinical studies of aggressive pituitary adenomas utilizing Capecitabine (Xeloda®) and temozolomide (Temodar®), hereon referred to as CAPTEM, as their last line of therapy after exhausting all other treatment options. The efficacy, safety, and pharmacological rationale of CAPTEM were evaluated along with the considerations and circumstances leading to its utilization. We discuss further potential applications of the CAPTEM regimen to cell-lines of similar nature to the ones that yielded clinical benefit beyond the standard of care. We suggest the performance of phase II and III clinical studies to elucidate the long-term survival and response rates in a larger-scale to define the efficacy of CAPTEM for the discussed tumor types. The preliminary reports we reviewed provide us with a positive outlook and reason to apply CAPTEM to tumor types of similar nature.

Keywords: *Capecitabine; Temozolomide; Pituitary; Adenoma; Adenocarcinoma; Adrenocorticotrophic; Neuroendocrine; Tumors*

Abbreviations

CAPTEM: Capecitabine and Temozolomide; CAP: Capecitabine, Aka Xeloda; TMZ: Temozolomide, Aka Temodar; NET: Neuroendocrine Tumors; 5-FU: 5-Fluorouracil from Capecitabine; MGMT: Methyl-Guanine-Methyl-Transferase; PRL: Prolactin; FSH: Follicle Stimulating Hormone; ACTH: Adrenocorticotropic Hormone; GH: Growth Hormone; PA: Pituitary Adenoma; MMR: Mismatch Repair; PARP: Poly ADP Ribose Polymerase; TSH: Thyroid Stimulating Hormone; TS: Thymidylate Synthase; PNETs: Pancreatic Neuroendocrine Tumors; PD: Progressive Disease; PFS: Progression Free Survival; RR: Response Rates; OS: Overall Survival; CR: Complete Response; SD: Stable Disease, ≤ 20% Increase or Decrease in Biperpendicular Dimensions; TUNEL: Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling; XRT: Radiotherapy; MRI: Magnetic Resonance Imaging; UFC: Urinary Free Cortisol

Introduction

The pituitary gland is an endocrine gland responsible for assisting in the hormonal control of various processes including, but not limited to, growth, blood pressure, thyroid function, and several elements of metabolism. Also referred to as the hypophysis, the pituitary gland is a pea-sized protrusion inferior to the hypothalamus. Resting upon the hypophysial fossa of the sphenoid bone, it is surrounded by a small bone cavity known as the *sella turcica.* In humans, the pituitary gland is composed of two parts: anterior and posterior. Both portions of the pituitary gland play key hormonal roles in the body. The anterior pituitary secretes PRL (prolactin), ACTH (adrenocorticotrophic hormone), TSH (thyroid-stimulating hormone), FSH (follicle- stimulating hormone), LH (luteinizing hormone), and GH (growth hormone), while the posterior pituitary secretes vasopressin and oxytocin [1]. The vast majority of pituitary tumors are pituitary adenomas (PAs), a diverse and typically benign group of tumors with an overall annual incidence of roughly 50 per 100,000 [3]. The most

common type of PA is prolactin secreting, followed by, with decreasing incidence: GH, ACTH, and TSH secreting adenomas also known as acromegaly, Cushing's disease, and thyrotropinoma, respectively [2]. PAs exhibit both physical and hormonal symptoms. Physically, PAs may lead to compression of surrounding organs, most notably the pituitary gland itself and the optic chiasm and its pathways. This can lead to symptoms such as hypopituitarism, headaches, and visual disturbance [3,4]. Hormonally, PAs may lead to hypersecretion of associated hormones intrinsic to the location of the adenoma, from which life-limiting symptoms may arise. Hypersecretion of GH causes acromegaly and results with elevated insulin-like growth factor 1 (IGF-1) circulation, as well as enlargement of various organs. Hypersecretion of ACTH leads to Cushing's disease associated with chronic hypercortisolism, resulting in fatty deposits around face and upper back, as well as centripetal weight gain around the abdomen. Excess prolactin production can lead to gonadal dysfunction and infertility as the result of sharp decline in oestrogen and testosterone in women and men, respectively. Further, hypersecretion of TSH due to thyrotroph adenomas can result with hyperthyroidism [3-7].

In rare cases, PAs may develop into invasive and aggressive tumors [8]. Most often when this occurs, it is in the context of Nelson's syndrome, defined as clinically significant enlargement of a corticotroph adenoma post bilateral adrenalectomy, with growth typically occurring over a period of months to years [9,10]. First-line treatment involves surgical resection of the tumor. Radiation therapy is often used as a third-line treatment if surgical and/or medical measures are insufficient [11]. In recent years, temozolomide (TMZ) has been used more frequently as the last-line of treatment for aggressive pituitary tumors resistant to the abovementioned treatment options [11-19].

Here, we propose the usage of temozolomide in concert with capecitabine (CAPTEM) for the treatment of aggressive pituitary carcinomas that fail the therapies mentioned above [10]. This regimen, developed by Fine., *et al*. relies on the synergistic effects of capecitabine (CAP) and temozolomide (TEM), which have been shown to potentiate each other when administered in a particular sequence. For the first part of the cycle, the patient is administered Xeloda (Capecitabine), an inactive oral pro-drug form of 5-Fluorouracil (5-FU; pyrimidine analog, antimetabolite family), for 9 days in a BID fashion. Xeloda suppresses the promoter region of the methylguanine-methyltransfase (MGMT) gene, thereby suppressing its production [20]. This is desirable, as MGMT is utilized in cells to repair damage done by alkylating agents such as temozolomide, and is thus a primary driver of resistance to alkylating agents. In addition the 9 days of capecitabine lowers the levels of thymidine via inhibition of DHFR. The decrease in thymidine and the inhibition of MGMT, inhibit DNA repair from the 5-FU and the starting of Temozolomide. Temodar is administered starting day 9-14 causing depletion of MGMT levels in the cell via Xeloda, which subsequently results in higher levels of apoptosis as the alkylation is less susceptible to repair (Figure 1) [20,21]. In neuroendocrine tumors, 97% of patients that had disease progression after receiving high dose Octreotide have achieved either shrinkage or stable disease with the use of CAPTEM [22]. The success of CAPTEM in neuroendocrine tumors, coupled with the relative success of temozolomide in treating pituitary adenomas [11-19] has led to discussion regarding the usage of CAPTEM for treatment of pituitary tumors.

General Mechanism of Action

The elegance of CAPTEM lies in its simple synergistic mechanism. The therapeutic regimen was originally tested on well-differentiated neuroendocrine tumors, as the vast majority of them (> 95%) contain wild-type p53 [23,24]. Thus, Fine., *et al*. proposed that the drug resistance mechanisms of well-differentiated NETs are not a function of mutant p53, but instead, the low Ki-67, and therefore slow growth rates of NET's, that may lead to cell cycle phase-specific chemotherapy resistance, also known as cytokinetic drug resistance [20,25]. With the above logic in consideration, Fine., *et al*. postulated that chemotherapy agents cytotoxic to slow-growing cells with a prolonged G_0 phase cell cycle would induce more cell damage and thus be more useful.

Lipophilic alkylators are one of the main chemotherapy classes that cause apoptosis in passive G_0 cells, leading Fine., *et al*. to utilize Temozolomide (TMZ), a lipophilic methylator. As opposed to previous regimens where TMZ alone is utilized, CAPTEM uses TMZ alongside continuous exposure to an antimetabolite, specifically Capecitabine (5-FU), due to its history of clinical efficacy records in this disease. Capecitabine diminishes thymidine pools utilizing 5-FdUMP-mediated inhibition of thymidylate synthase (TS), reducing dTMP synthesis from its precursor dUMP. This depletion of dTMPs is crucial prior to exposure to TMZ [20].

O^6-MGMT is a repair enzyme for methylated DNA, specifically in the mismatch repair (MMR) pathway. O^6-MGMT is relatively more resistant to TMZ compared to other repair enzymes in its family, and likewise, higher sensitivity to TMZ is observed in cell lines that are scarce in O^6-MGMT [26,27]. When the cells are deficient in O^6-MGMT, the O^6-methylguanines methylated by TMZ will not be removed. This results in the triggering of MMR. Combined with the lack of thymidine pools from the TS inhibition by capecitabine, there is a synergistic and more significant reduction in thymidines, thus leading to a break in the DNA [28,29]. These DNA breaks induce cell arrest/apoptosis as they initiate dramatic PARP ribosylation, given that the break is not repaired [30]. This combination of capecitabine and temozolomide allows for both the depletion of O^6-MGMT levels and interference with the cell's MMR system to achieve apoptosis more efficiently than observed when the agents are used individually [20].

Administration Protocol

As discussed above, to achieve the highest efficacy out of CAPTEM, careful timing in administration is important. The cycle consists of 28 days. Capecitabine is administered from days 1 - 14. TMZ is administered from days 10 - 14, following sensitization to TMZ by CAP via antimetabolite cytoactivity. TMZ is administered in BID dosing as opposed to daily dosing as it results in a reduction of the symptomatic nausea associated with once daily TMZ administration. In addition, BID dosing increases TMZs efficiency as the first dose results with binding and therefore reduction of O^6-MGMT levels, while the second dose methylates guanines more efficiently due to decreased prevalence of O^6-MGMT, and thus, a reduction in repair [31].

Fine., *et al.* in their phase II study of CAPTEM used a lower dosing of TMZ than is standard. In one CAPTEM cycle (one month period) the regimen delivers 150 - 200 mg/m^2/day throughout the cycle's last 5 days (10 - 14). Other regimens such as used by Kulke., *et al*. and Chen., *et al*. utilize 2.1 - 2.8 fold more TMZ, as they deliver 14 days of TMZ (at 150 mg/m^2/day for 7 days every other week). Kulke., *et al.* utilized TMZ and thalidomide in a phase II study, with the higher TMZ doses leading to severe toxicities. 69% of the patients developed grade 3 and 4 lymphopenia, as well as 10% of the patients presenting with severe opportunistic infections. In addition, TMZ is toxic to bone marrow, which can lead to CD34+ stem cell depletion. Lastly, aside from less toxicities, lower TMZ doses led to higher success with NET and PNET response rates of 61% and 70% respectively as compared to 45% in TMZ/thalidomide and 33% in TMZ/bevacizumab used for PNETs. The synergy with 5-FU and Temozolomide is not thought to exist between TMZ/Bevacizumab or TMZ/Thalidomide [20,32,33].

CAPTEM in slow-growing NET BON cells

The significant increase in cytotoxicity when CAPTEM is administered in a time- and sequence-dependent fashion is shown below (Figure 1). Fine., *et al.* utilized a slow-growing NET carcinoid cell-line (BON) in in vitro rat studies, and have showed higher apoptotic rates in the cells exposed to 5-FU 5-7 days prior to TMZ as opposed to simultaneous exposure, as shown using terminal deoxynucleotidyl dUTP nick end labeling (TUNEL) analysis [20]. In their phase II study, the patient population used in the study consisted of a median age of 54 (range 33-70) including nine women. All patients continued having progressive disease (PD) documented in MRI and CT scans while treated with 60 mg/month of Sandostatin LAR™. Ten patients presented with elevated tumor markers (Chromogranin A, serotonin, urinary 5-HIAA, gastrin, insulin, proinsulin, and/or glucagon), and these patients reduced their dosing to 30 mg/month as to allow for some degree of hormonal control. Those who did not present with hormonal excess had completely stopped any Sandostatin LAR™ administration when utilizing CAPTEM, until PD occurred [20].

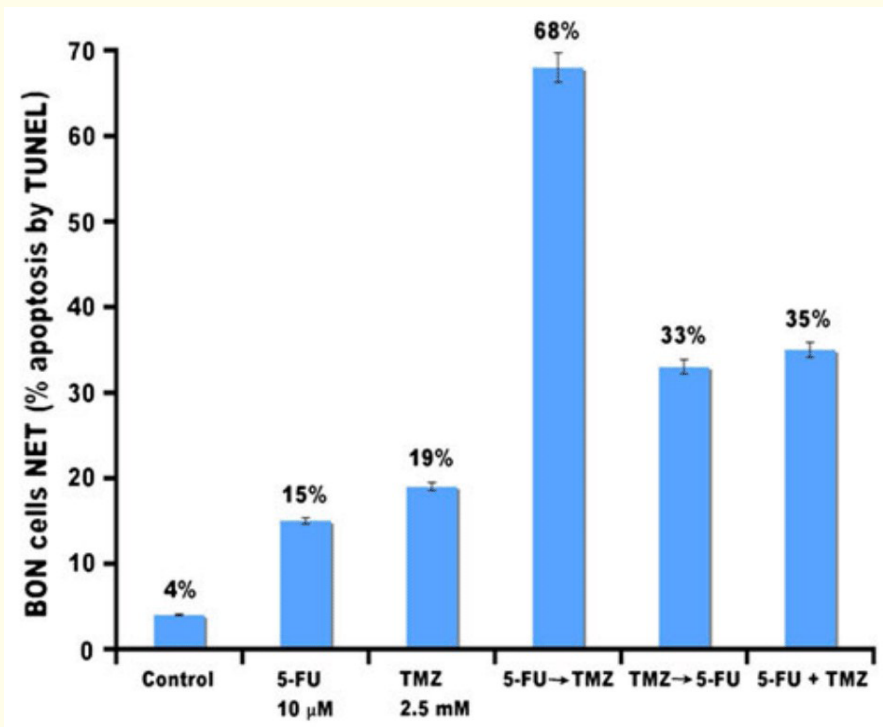

Figure 1: *Synergistic cytotoxicity of the CAPTEM regimen is time and sequence dependent. BON cell line exposure and cell apoptosis by terminal deoxynucleotidyl dUTP nick end-labeling (TUNEL) analysis. 5-FU 5- fluorouracil, TMZ temozolomide, 5-FU + TMZ pre-exposure to 5-FU for 7 days prior to TMZ for 48h, 5-FU + TMZ both agents given concurrently for 9 days, TMZ → 5-FU pre-exposure to TMZ for 7days prior to 5-FU for 48h. Maximal synergy shown at 9 days [20].*

CAPTEM in aggressive coritcotroph pituitary tumors

Fine., *et al*. have conducted an additional case study using CAPTEM, this time with a patient containing an aggressive corticotroph pituitary tumor. It is rare that corticotroph pituitary tumors become aggressive and invasive, and few treatment options are offered. The case is of a 50-year old male who appeared with headaches and sudden diplopia as a result of cranial nerve (CN) VI palsy. It was soon revealed that he had a pituitary mass. Initially, he underwent gross total transphenoidal resection of the tumor, resolving the above symptoms. While pathology revealed the tumor to be a 1.5cm adenoma, two months later his CN VI palsy reappeared, and pituitary magnetic resonance imaging (MRI) revealed a recurrence of a 2.8 cm tumor in the left cavernous sinus encapsulating the left internal carotid artery. Following an 80% partial resection due to the recurrent tumor's location, despite symptomatic improvement the diplopia returned after a few short weeks. After an additional MRI appeared unchanged, the patient underwent gamma knife radio-surgery that led to no clinical or radiographic changes [10].

The patient presented with Cushing's syndrome symptoms six months following his initial presentation. He was treated with 400 mg of oral Ketoconazole three times a day, which alleviated his symptoms for a six-month period, after which he had a complete left CN VI palsy, with tumor growth of 0.7 cm and the Ketoconazole ceased containing the symptoms. 2 months of standard conformal external beam radiotherapy (XRT) with 5040 cGY in 28 fractions were administered and led to an ACTH decrease (767 pg/ml to 375 pg/ml) yet his urinary free cortisol (UFC) and MRI remained unchanged [10].

After medical therapy failed to control the patients Cushing's disease symptoms, he underwent a bilateral adrenalectomy, two years after presentation. Despite presenting short term symptomatic improvement, two weeks after the operation he was readmitted after experiencing a near constant headache with more severe symptoms such as dysphagia and aspiration of liquids, lateral eye movement hardships, left jaw numbness and increased hoarseness. Physical examination revealed additional symptoms such as hyperpigmentation, anosmia, bitemporal hemianopsia, decreased lateral right eye movement, fixed medial left eye deviation with minimal pupil reactivity among other symptoms. It is noteworthy that ACTH levels increased 347% from preoperative levels to 2541 pg/ml. MRI showed additional growth into the sphenoid sinus, left cavernous sinus, and the posterior margin of the clivus and into the basion. The patient's severe dysphagia now required he be fed enterally, and the patient was deemed to not be a candidate for any other neurosurgical or radiation therapies [10].

Due to prior success with other neuroendocrine tumors, the patient underwent CAPTEM treatment. The patient tolerated the regimen well, not presenting with any grade 2,3 or 4 toxicities, myelotoxicity, hand-foot syndrome or diarrhea. Figure 2 shows MRIs at different times of the disease. After two cycles of CAPTEM the tumor decreased 75% in size, including residual in the cavernous sinus as well as the left sella. Hormonally the patient's ACTH has decreased to 309 pg/ml from 1874 pg/ml. The patient's dysphagia has decreased and he regained extraocular movements, showing substantial symptomatic improvement, also indicated by his performance status improving from three to one. Figure 3 shows monthly ACTH counts, used as a reputable tumor marker, showing a > 95% production decrease to 85 pg/ml. The patient resumed eating solid food, his headaches resolved, and hyperpigmentation decreased [10].

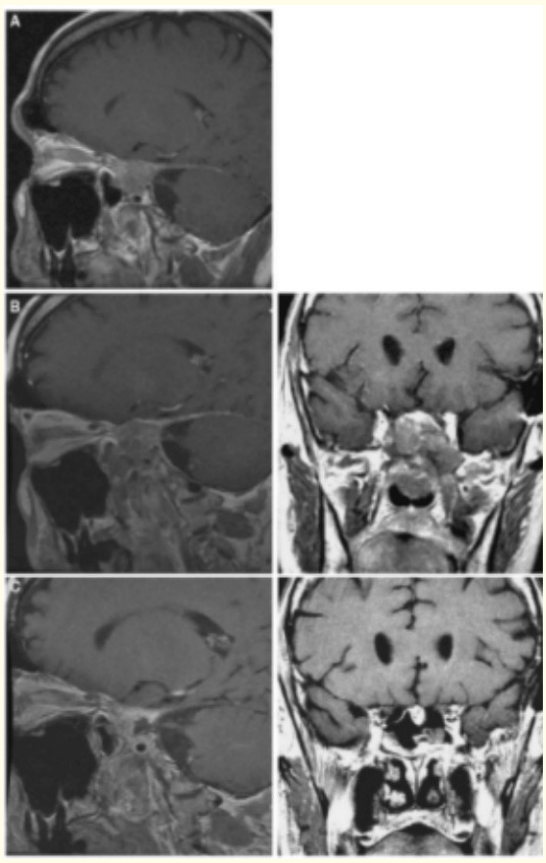

Figure 2: *Magnetic Resonance Imaging (MRI) demonstrating changes in the tumor over time. A: Sagittal view of tumor prior to adrenalectomy. B: Sagittal and coronal views of the tumor 2 weeks after adrenalectomy demonstrating aggressive growth of tumor anteriorly into the sinuses, inferiorly to invade multiple cranial nerves as well as anteriorly into the suprasellar region. C: Sagittal and coronal views of tumor after two cycles of the CAPTEM regimen with marked decrease in the size of the tumor [10].*

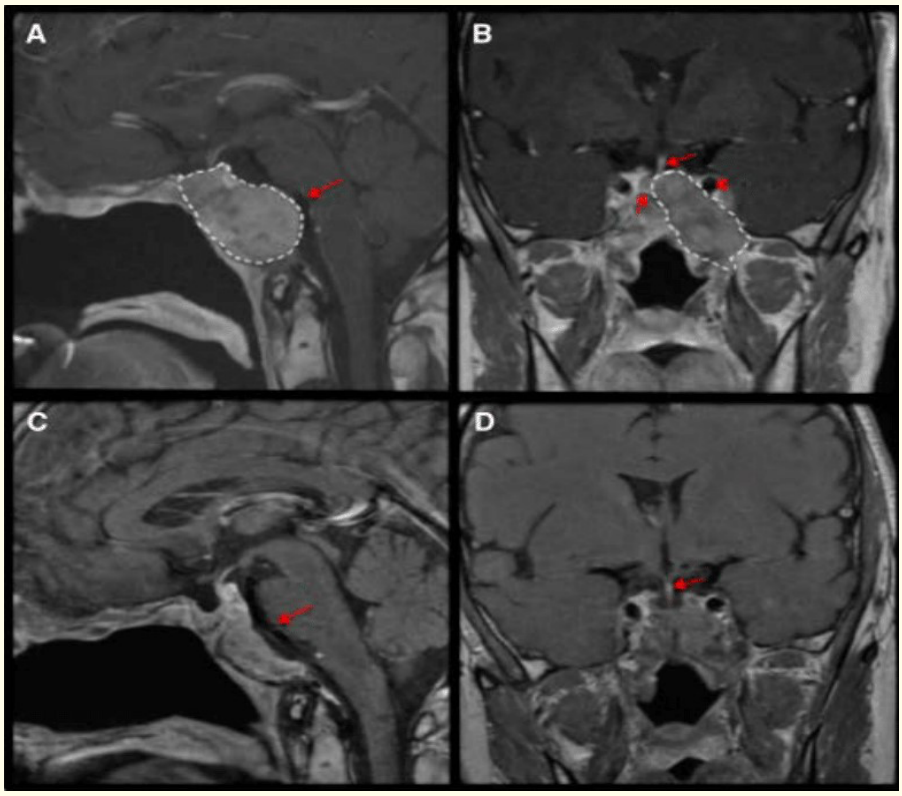

Figure 3: *Response images from patient 3. T1-weighted magnetic resonance imaging (MRI) of patient 3 before (A and B) and after (C and D) initiation of Capecitabine and Temozolomide (CAPTEM) therapy. A: pre-CAPTEM midline sagittal MRI through the sellar region demonstrating a large mass (white dashed outline) expanding and eroding the sella and clivus, resulting in pontine compression (red arrow). B: pre-CAPTEM coronal MRI through the pituitary gland and stalk (red arrows), which are displaced to the right. The lesion (white dashed outline) is again noted expanding and eroding the sella and abutting the left cavernous carotid artery (red arrowhead). C: post-CAPTEM midline sagittal MRI demonstrating resolution of the previously noted mass lesion and resolution of the previously noted pontine mass effect (red arrow). D: post-CAPTEM coronal MRI demonstrating resolution of the previously noted mass lesion with recovery of the midline position of the pituitary stalk (red arrow). In both C and D, the space where the previous tumor existed has been replaced by fat in the MRI. All tumor markers returned to normal.*

Nonetheless, 5 months after beginning CAPTEM treatment the patient returned to the hospital due to resumption of his CN dysfunctions, and although his ACTH levels at the time were 36 pg/ml, MRI evidence showed tumor re-growth to its prior dimensions, including further sinus extension. This led to the impression that CAPTEM resolved the well-differentiated neuroendocrine cortiocotroph tumor cells, yet a poorly differentiated small neuroendocrine cell population had escaped, leading to the tumor behaving as a small cell carcinoma [10].

Two years following the above case study, Zacharia., *et al*. have conducted four case studies published in a case series in 2013 [34]. The four patients had also been diagnosed with aggressive, adrenocorticotrophic hormone-producing pituitary tumors, and have exhausted the standard treatment options for the condition such as surgery, radiation, and hormonal therapies. This case series was the first reported prolonged response antitumor response to and complete radiographic remission utilizing CAPTEM in this patient population. The CAPTEM protocol is the same as described in the case above. The overall aggregate treatment outcomes were a 5.5 month progression-free survival (PFS), radiographic tumor regression of 75%, ACTH level reduction and symptomatic relief. The individual patient cases are presented below, with a detailed summary of the patient's baseline characteristics as well as subsequent treatments shown in table 1 [34].

	Patient 1	Patient 2	Patient 3	Patient 4
Age, Y	50	50 (64 when had recurrence with the CNV involvement)	46	44
Sex	M	M	F	M
Clinical Presentation	CN VI, VII deficits, Cushing syndrome	CN III, IV, V, VI deficits, Cushing syndrome	CN IX, XII deficits, Cushing syndrome, pons compression	CN V deficit, pons compression
Tumor subtype	ACTH secreting	ACTH secreting	ACTH secreting	Silent ACTH secreting
Pathology	ACTH (+) Ki-67 index, 31%	ACTH (+) Ki-67 index, < 5%	ACTH (+) Ki-67 index, 5% Recurrent tumor: ACTH (+); Ki-67 index, 15%-20%; p53 (+)	ACTH (+) Ki-67 index, < 5%
Diameter, cm	1.5	1.5	4.3	5.1
Prior treatment	2 Transspehenoidal surgical resection s External beam radiation Gamma knife radiosurgery Ketoconazole Metyrapone Octreotide Cabergoline Bilateral adrenalectomy	2 Transspehenoidal surgical resection s External beam radiation Gamma knife radiosurgery Cabergoline Bilateral adrenalectomy	2 Transspehenoidal surgical resections External beam radiation Pasireotide Ketoconazole Dexamethasone	2 Transspehenoidal surgical resections External beam radiation Sandostatin LAR Dexamethasone

Table 1: *A detailed summary of baseline characteristics for all study patients, including sex, clinical presentation, tumor subtype and pathology, size of presenting lesion, and detailed list of subsequent treatments [34].*

Patient 1 is a male, 50-years old who presented with left CN VI compression culminating in acute diplopia (patient 1, Table 1). During the two years following diagnosis, the patient underwent 2 transsphenoidal surgical resection, maximal Gamma Knife radiosurgery, standard conformal external beam radiotherapy, adrenalectomy, and medical management treatments involving ketoconazole, octreotide, and cabergoline trials. Despite the many measures listed, the patient's tumor progressed. The tumor was pathologically shown to an aggressive adenoma/adenocarcinoma with a Ki-67 rate of 31% and ACTH positive cells. The patient showed further neurological deteriora-

tion, with the expanding tumor resulting with CN VI and VII along with dysphagia. His ACTH levels spiked to 2541 pg/ml (compared to the normal 20 - 90 pg/ml). At this time the patient had begun CAPTEM therapy. Following the first 2 cycles the patient's clinical benefits were drastic. He showed a 75% radiographic tumor burden decrease, 90% drop in ACTH levels, neurological deficits improvement and no grade 3 or 4 toxicities. After a 5.5 month PFS from CAPTEM the patient's neurological symptoms returned despite an ACTH level of 36 pg/ml. It appeared that CAPTEM treatment eradicated the well-differentiated corticotroph tumor cells, yet not addressing small-cell carcinomas with bone metastases [34].

Patient 2 is a previously healthy 50-year-old male presented with Cushing's disease symptoms (patient 2, Table 1). Pathology did not indicate tumor presence following a right hemi-hypophysectomy, yet the patient's Cushing's symptoms persisted including elevated cortisol levels. A later petrosal sinus sampling confirmed the elevated ACTH levels resulted from a pituitary source. The patient underwent a second transsphenoidal resection, confirming an ACTH-positive adenoma. He continued to produce excess cortisol, and presented dysfunction of the remaining anterior pituitary hormones. At this point the patient begun external beam radiation therapy coupled with hormone replacement that resulted in cortisol levels dropping and 8 years free of disease. Following the disease free period the patient presented with a recurrent tumor in the cavernous sinus with diplopia, right eye ptosis, and recurring Cushing symptoms. The patient's symptoms subsided following Gamma Knife radiosurgery, except his ptosis. Two years following Gamma Knife radiosurgery the patient's Cushing disease resurfaced with elevated ACTH and cortisol counts. Magnetic resonance imaging (MRI) showed a recurrent 1.2 cm lesion in the right cavernous sinus. Despite undergoing a bilateral adernalectomy, the lesion had progressed to 2.6 cm and his ACTH level was 8800 pg/ml a year after the procedure. Despite the patient's ACTH levels dropping to 2800 pg/ml as a result of cabergoline treatment, his tumor progressively grew, leading to the patient developing severe retro-orbital headaches along with CN V involvement. After an octreotide scan returned negative and the patient had no other treatment options he began CAPTEM therapy. Following completion of the first 2 cycles, retro-headaches and numbness were resolved, along with MRI showing stable disease along with tumor density reduction. Asides from ptosis, all CN deficits were resolved, ACTH level dropped from 2800 to 1817 pg/ml. Despite presenting with grade 2 neutropenia and diarrhea side effects due to CAPTEM, he did not require Neupogen administration. Due to grade 3 thrombocytopenia the interval between cycles was delayed, leading to CAPTEM administration at 2-month intervals as opposed to the standard 1- month intervals (2 weeks on CAPTEM followed by 6 weeks off). The patient had an ongoing PFS of > 4.5 years after completion of 30 CAPTEM cycles. The patient's ACTH levels varied between 3000 - 6000 pg/ml over the last two years of treatment, and serial MRI have shown stable disease subsequent to therapy initiation, along with clinical symptoms remaining stable throughout that time [34].

Patient 3 is a 46-year-old previously healthy woman exhibiting Cushing symptoms (Patient 3, Table 1). Her MRI showed a mass infiltration to the tuberculum sella, clivus, and both sphenoid sinuses, leading her to undergo a transsphenoidal surgery, yet without complete resection due to a bony invasion. Pathology indicated an ACTH-positive adenoma with a Ki-67 rate of 5%. An MRI 3 months post-operation indicated tumor residuals in the clivus, occipital condyles, sphenoid and cavernous sinuses (bilaterally). After the patient refused the recommended radiotherapy she underwent treatment with a somatostatin analog, pasireotide. 4 weeks following somatostatin analog treatment initiation, the patient presented with tongue weakness and difficulty speaking. An MRI indicated a tumor invading the skull base with additional compression of bilateral CN IX and XII with compressed pons, leading to airway compression followed by intubation and tracheotomy. External beam radiotherapy was initiated and led to 50% tumor shrinkage, cortisol levels stabilization, and neurological symptom resolution. After 2.5 asymptomatic years she presented with Cushing including a growing sellar mass approaching the optic chiasm, and presented with 754 ug/24h cortisol count alongside 88pg/ml ACTH. To achieve decompression a second transsphenoidal resection was performed, and pathology indicated an aggressive atypical PA with a Ki-67 level of 15% - 20%, and evidence for p53 mutation in the tumor. The tumor was called malignant. Ketoconazole treatment failed to yield hormonal benefit with cortisol levels at 1028 ug/24h and an ACTH level of 85 pg/ml. The patient than exhibited progressive neurological decline, tongue weakness, and slurred speech due to tumor intrusion into the hypoglossal canal. After exhausting radiation and surgical therapy options, the patient resorted to CAPTEM. Following 3 cycles of CAPTEM MRI showed a 30% tumor reduction, ACTH level dropped from 68 to 15 pg/ml and cortisol level dropped to 1.3

ug/dL. After 5 cycles tumor size decreased 50% in size along with Cushing disease, CN deficits, and pons compression resolved. After 10 cycles, MRI showed a complete response of her tumor (Table 1 and Figure 3), along with ongoing hormonal improvement (ACTH at 2pg/ml and < 0.5 ug/dL cortisol level). In addition, the patient exhibited no grade 3 or 4 toxicities, asides from non-infectious lymphopenia following the 16th cycle. At the time of the case series publication, she remained a complete response patient with a PFS of 32 months, 22 of which were complete response under CAPTEM therapy [34].

Patient 4 was previously healthy until he presented with a large skull mass base mass in the sphenoid sinus (patient 4, Table 1). Following a transsphenoidal resection, his tumor was first diagnosed as an esthesioneuroblastoma. External beam radiation therapy yielded the patient 8 years free of disease, after which he developed a primary tumor encompassing the entire clivus, protruding the sphenoid bone. Biopsy of the recurrent mass revealed an ectopic ACTH-secreting PA, as opposed to the initially perceived esthesioneuroblastoma. With no signs of Cushing disease present and being neurologically intact, the tumor was characterized as a silent ACTH-secreting PA (Ki-67 < 5%). Throughout the next year the patient showed progressive facial pain, alongside CN V and pons compression yielding paresthesias. Since radiation or surgical therapies were not plausible due to the tumor location and his treatment history, the patient began treatment on Sandostatin LAR 30 mg/mo (shown to be octreotide positive) preceding CAPTEM. After presenting with grade 2 oral candidiasis and lymphopenia following the first cycle, both tied to concurrent dexamethasone use, and the facial pain and paresthesias. After 10 CAPTEM cycles, MRI showed 50% response, and after 16 cycles evidence indicated an 80% shrinkage. The patient had 7 months of stable disease utilizing Sandostatin LAR 30mg/mo and CAPTEM. After 23 cycles Sandostatin LAR was discontinued since it was perceived to inhibit tumor growth and potentially decreasing the effects of CAPTEM. At the 27th cycle, the patient showed complete response as indicated by an MRI scan and resolution of all neurological symptoms. At the time of the case series publication the patient had a PFS of > 70 months along with ongoing complete response, along with excellent quality of life, without toxicities higher than grade 2, able to work full-time [34].

Discussion

Capecitabine (Xeloda®) and Temozolomide (Temodar®) used in the synergistic fashion discussed above present an efficient therapy regimen for certain tumor types that traditionally utilize it as alternative therapy. Initially, CAPTEM was tested in patients with NETs that metastasized to the liver, and have shown radiographically progressive disease. The patients in the study were heavily treated; 61% had progression following either multi-agent or single agent chemotherapy, 50% showed progression after hepatic chemoembolization(s), and 100% had failed Sandostatin LAR™ (60 mg/month) [20]. In studies conducted prior, the OS from time of diagnosis of liver metastases until the death of the patient was shown to be 40 months [35], 70 months [36], and 76 months in patients that went through aggressive surgical extirpation [37]. The median OS for all patients in the CAPTEM treatment group was 83 months. In addition, the CR rate was 5.5%; PR rate, 55.5%; with an SD rate of 22.2%. Their clinical benefit totaled 83.2%, along with a median PFS of 14 months [20]. From a toxicity standpoint, the regimen was shown to be very well-tolerated, with grade 1/2 neutropenia and lymphopenia shown in 44% and 50% of the patients, respectively, alongside grade 3 thrombocytopenia in 11% of the patients, yet no grade 3 lymphopenias or neutropenia as well as no grade 4 toxicities. These toxicities can be compared to a TMZ/thalidomide regimen that yielded 69% grade 3/4 lymphopenias, 10% with opportunistic infections, and some cases of thalidomide intolerance leading to treatment cessation [32].

These results indicate that CAPTEM has the potential to prolong survival in patients with metastatic liver NETs that failed Sandostatin LAR™ (60 mg/month), chemotherapy, and chemoembolization, in a well-tolerated fashion. When extrapolating the possible pharmacological rationale for CAPTEM's success, along with relative success of Temozolomide treatment in pituitary adenomas, a discussion to apply CAPTEM in pituitary adenomas arose.

Thearle., *et al*. at Columbia utilized CAPTEM in treating a patient with a highly atypical and aggressive corticotroph pituitary tumor. Despite maximal radiotherapy treatment, the patient's tumor grew swiftly only a short two weeks following an adrenalectomy, alongside a 346% rise in ACTH levels [10]. This presentation is indicative of life-threatening unprecedented growth after an adrenalectomy, evident of the unusually aggressive nature of his tumor. Considering the patient's severe cranial neuropathies and exhaustion of all conventional

treatments alongside failure of alternative treatments such as rosiglitazone, CAPTEM treatment was initiated, making this the first reported case of CAPTEM use for a pituitary tumor. The CAPTEM therapy led to a dramatic decrease in the patient's tumor volume (~75%) alongside a reduction in ACTH from 1874 to 309 pg/ml. The patient had tumor re-growth, despite of continuous decrease in ACTH levels. This finding was postulated by Thearle., *et al*. to be as a result of the less differentiated cells in the tumor acting as a small cell carcinoma and continuing to grow, alongside the relatively differentiated neuroendocrine corticotroph tumor cells continuing to respond to the CAPTEM. This hypothesis is supported by the patient's response to etoposide and cisplatin (40%), a regimen known to be highly efficacious in small cell carcinoma treatment. Even though radiotherapy therapy that the patient underwent prior to CAPTEM administration does not allow us to be certain CAPTEM was the sole agent for tumor shrinkage, radiotherapy is not associated with sharp tumor shrinkage as shown in this patient, supporting the effect of CAPTEM. Thus, while past literature presents durable responses to temozolomide, this case reports a dramatic short-term response (5 months) to CAPTEM with subsequent tumor progression likely due to selection of poorly differentiated, small neoplastic cells [10].

Lastly, Zacharia., *et al*. at Columbia applied CAPTEM in a case series of patients with aggressive corticotroph pituitary tumors and refractory Cushing Disease. The four patients in the study have exhausted all other possible therapeutic options, yet showed encouraging results with CAPTEM. Two of the 4 patients have demonstrated complete responses, 1 patient maintained stable disease for > 4.5 years, and the last patient failed CAPTEM after a PFS of 5.5 months and initial response of 75% tumor reduction. It is noteworthy to mention that considering the patients have exhausted all other treatment options, without CAPTEM therapy their disease would have likely progressed.

In patient 1, despite CAPTEM's ability to eradicate ACTH-producing cells, poorly differentiated neuroendocrine cells that behaved as small cell carcinomas metastasized to his bones as he was diagnosed with AIDS. Asides from maintaining stable disease for > 4.5 years, patient 2 showed significant improve in quality of life in aspects such as crippling neurological impairments, enabling to re-pursue his normal daily living. Patients 3 and 4 showed complete response according to radiological measurements, and resolution of all neurologic deficit symptoms, all whilst maintaining PFS of 32 and 45 months, respectively. Thus, these are the first 2 reported cases of a temozolomide-based regimen leading to complete response in ACTH-producing pituitary tumors, following progression after multiple surgeries, maximal radiation, and hormonal therapies [34]. The slow growth kinetics of these tumors is extrapolated to explain the responses. Patient 3 had a Ki-67 of 15% and responded within 10 months of CAPTEM treatment, while patient 4 showed an 80% shrinkage following 16 cycles of CAPTEM, and following 7 cycles with cessation of Sandostatin LAR the patient showed complete response. From a toxicity standpoint, CAPTEM was tolerated relatively well, as grade 1/2 neutropenia and thrombocytopenia were the primary observed side effects. The only grade 3 toxicity was thrombocytopenia and was observed in 1 patient. 2 of the 4 patients exhibited grade 2/3 lymphopenia, yet none of the patients showed grade 4 toxicities. Asides from a treatment delay in patient 2 due to thrombocytopenia, no treatment delay or cessation were needed as a result of intolerable side effects or any other treatment delaying circumstances [34].

Conclusion

We have reviewed various studies utilizing the CAPTEM regimen as alternative therapy for aggressive tumors, both NETs and PAs, in patients that have exhausted all other therapy options. CAPTEM has shown in those tumor types significant clinical benefits combined with low toxicities. This series of cases provides us with a potential option for rare and aggressive cases that have shown inevitable progression prior to CAPTEM treatment. Clinical studies to elucidate the long-term survival and response rates are needed in a larger-scale to define the efficacy of CAPTEM for these tumor types, yet these preliminary reports provide us with a positive outlook and reason to apply CAPTEM to tumor types of similar nature in which the pharmacological rationale of CAPTEM my apply and the standard of care provides a poor prognosis.

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