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Capecitabine and celecoxib as a promising therapy for thymic neoplasms

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Abstract

Objectives—For patients with unresectable or metastatic thymic epithelial neoplasms, few therapy options are available and outcomes are poor. This case series demonstrates that the combination of capecitabine and celecoxib may be a promising therapeutic option for these patients.

Methods—The current report describes the outcomes of 5 patients with thymic neoplasms treated on a drug-drug interaction study of capecitabine and celecoxib in patients with advanced solid malignancies (NCT01705106) conducted at the University of Chicago, plus a sixth patient treated with the same regimen outside of the protocol.

Results—Six patients with thymic neoplasms were treated with capecitabine 1000mg/m2 twice daily and celecoxib 200mg twice daily, d1–14 on a 21 day cycle. This included 3 patients with thymic carcinoma, 1 with thymic neuroendocrine tumor, and two with thymomas. Objective response rates were noted in 3/6 patients. Two of the 3 thymic carcinoma patients had complete responses, and the third had a partial response. Best response for the other patients included stable disease for both thymoma patients and progressive disease for the thymic neuroendocrine patient. Other than grade 3 palmar-plantar erythrodysesthesia, which developed in 4/6 patients and required dose reductions, the regimen was well tolerated.

Conclusions—This case series suggests that capecitabine plus celecoxib may be an effective and well-tolerated treatment option for patients with thymic carcinoma. Further studies should be carried out to establish the efficacy of capecitabine plus celecoxib in thymic carcinoma, and to determine whether monotherapy with capecitabine would be similarly effective.

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Keywords

thymic carcinoma; thymoma; celecoxib; capecitabine

Introduction

Thymic neoplasms, including thymic carcinomas and thymomas, are a heterogeneous group of cancers with a broad spectrum of clinical presentation and behavior. Thymomas are rare, with an annual incidence of 1.5 cases per million[1]. Despite this, they remain the most common primary anterior mediastinal mass. Thymic carcinomas are even more rare, with an annual incidence of 1.3 cases per million. Thymic carcinomas tend to have a more aggressive course and are more likely to be invasive. The five-year survival rate for all stage thymomas is 79%, compared to only 40% for thymic carcinomas[2,3,4].

In the unresectable and metastatic settings, chemotherapy with or without radiation therapy (RT) is the standard of care, but patients characteristically respond poorly and outcomes are poor[5]. Five-year survival rates decrease from 100% and 81%, for stage I and II disease, respectively, to 17% with stage IVb disease[6]. Patients with thymic neoplasms are in need of more effective treatment options.

5-Fluorouracil, and its oral equivalent capecitabine, are second-line therapies for thymic epithelial neoplasms. Celecoxib, an oral selective inhibitor of the cyclooxygenase-2 (COX-2) enzyme that catalyzes the conversion of arachidonate to prostaglandin H2, plays a critical role in carcinogenesis, angiogenesis, and chemoresistance[7,8,9]. While limited data exist regarding the combination of these two agents in treating thymic epithelial neoplasms, there are data in animal models of pancreatic tissue that capecitabine and celecoxib have synergistic effects[10]. Modest clinic benefit has also been noted with the combination in advanced pancreaticobiliary cancers[11]. The current report describes the outcomes of 6 patients with recurrent thymic neoplasms treated with the combination of capecitabine plus celecoxib.

Materials and Methods

In this study, 5 of the 6 patients were treated on a drug-drug interaction study of capecitabine and celecoxib in patients with advanced solid tumors (NCT01705106) conducted at the University of Chicago Comprehensive Cancer Center (one patient was treated off protocol due to patient convenience). Patients were treated with celecoxib 200mg by mouth twice daily. After one week, capecitabine was added at a dose of 1,000 mg/m2 (rounded to the nearest 500 mg) by mouth twice daily on days 1–14 every 21 days. If a dose reduction was required due to toxicity, therapy was held for one week and then the capecitabine dose was reduced to 750 mg/m2 by mouth twice daily (rounded to the nearest 500 mg). Patients began enrolling on study in December 2012, with last therapy administered in April 2016.

Results

The baseline characteristics, response to therapy, and reason for discontinuation for the thymic neoplasm patients are shown in Table 1. Median PFS for the entire cohort was 14.6 months. Five of the six patients remain alive at a median follow up of 33.5 months. The most significant responses were seen in the thymic carcinoma patients, with two patients achieving a complete response and the third achieving a partial response. The clinical course of these three thymic carcinoma patients is depicted in Figure 1. The radiographic response of patient #1 is shown in Figure 2.

The most common adverse event noted was palmar-plantar erthryodysethesia (PPE). Four of six patients developed grade 3 PPE that required dose reduction of capecitabine therapy. Otherwise, no Grade 3 or 4 adverse events were reported among these patients.

Molecular analysis was performed on tumor tissue from patients 1, 3 and 4 by gene sequencing with the Foundation One assay (Foundation Medicine, Cambridge, MA). The genomic alterations identified are documented in Table 2. Patient 4 did have an *MEN1* mutation identified. He had no personal or family history of pancreatic endocrine tumors, pituitary adenomas, or parathyroid adenomas. Germline testing for *MEN1* mutations was not performed on this patient. All three patients had loss or inactivating mutations of cyclin-dependent Kinase inhibitor 2A (CDKN2A).

Discussion

Of the 6 patients described, an objective response was noted in 3 of 6 patients. The responses were most notable in the thymic carcinoma patients. Two of the thymic carcinoma patients had complete responses. The third had a partial response with an 80% reduction in target lesions by RECIST version 1.1. Best response for the other patients included stable disease for both thymoma patients and progressive disease for the thymic neuroendocrine patient. Other than grade 3 PPE, which developed in 4/6 patients and required a dose reduction, the regimen was well tolerated.

Of the three patients with genomic profiling, loss or inactivating mutations in CDKN2A were noted in all of them. To our knowledge, there is no available data suggesting CDKNA-mutated tumors may be more prone to respond to either capecitabine or celecoxib therapy. This appears to be a common mutation in thymic neoplasms, with studies demonstrating loss of expression in 18.2% – 38% of of cases and correlating with higher recurrence rates and shorter overall survival[12,13]. Currently no targeted agents exist for these mutations, though a phase I clinical trial is currently evaluating a pan-Aurora kinase inhibitor in patients with CDKN2A-deficient tumors (NCT02540876), with accrual still ongoing[14].

Limitations of this study include the small sample size and also the lack of comparison to capecitabine monotherapy. Without this comparison, the exact impact of celecoxib cannot be confirmed, as limited data already exist suggesting that capecitabine and 5-Fluoruracil can be effective in the treatment of thymic neoplasms. These data include a phase II study of 30 patients treated with capecitabine in combination with gemcitabine that demonstrated responses in 12 patients[15]. Case reports have also demonstrated efficacy of 5-

fluorouracil[16,17], and a small case series demonstrated efficacy of second-line S1, an oral fluoropyrimidine agent, in thymic carcinoma[18].

Despite this, the durable responses and number of complete responses in the thymic carcinoma patients in this case series is notable and appears to improve on existing data. For instance, none of the thymic carcinoma patients in the capecitabine + gemcitabine phase II trial had a CR and 63% of patients had disease progression within 2 months of the last dose of systemic therapy. And while clinical data are lacking, pre-clinical data demonstrating the anti-apoptotic effect of celecoxib[19] and the previously mentioned synergistic effect of celecoxib with capecitabine[17] support the possibility of this combination improving outcomes compared to capecitabine monotherapy.

This case series reinforces the role of capecitabine in management of thymic epithelial neoplasms and suggests that capecitabine plus celecoxib may be an effective and well-tolerated treatment option for patients with advanced thymic malignancies, especially thymic carcinoma. Larger studies should be carried out to establish the efficacy of capecitabine plus celecoxib in thymic carcinoma, and to clarify whether monotherapy with capecitabine would be similarly effective.

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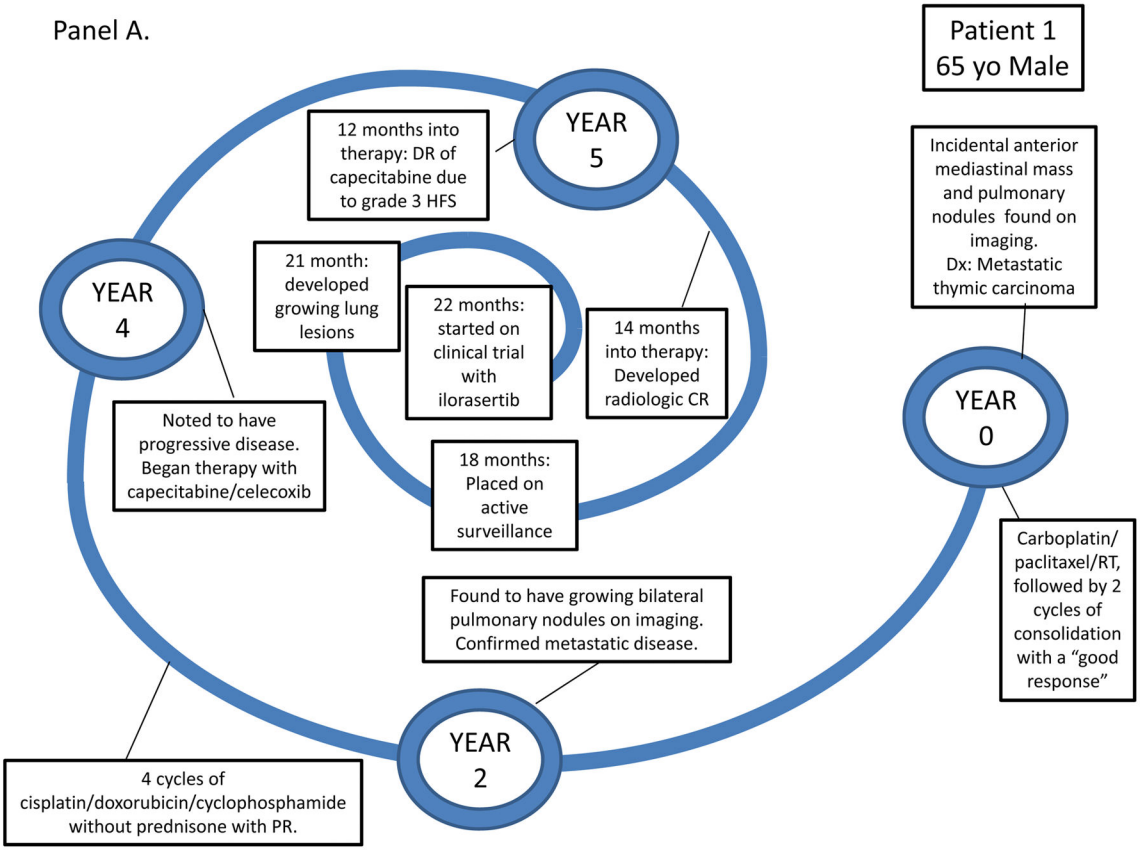

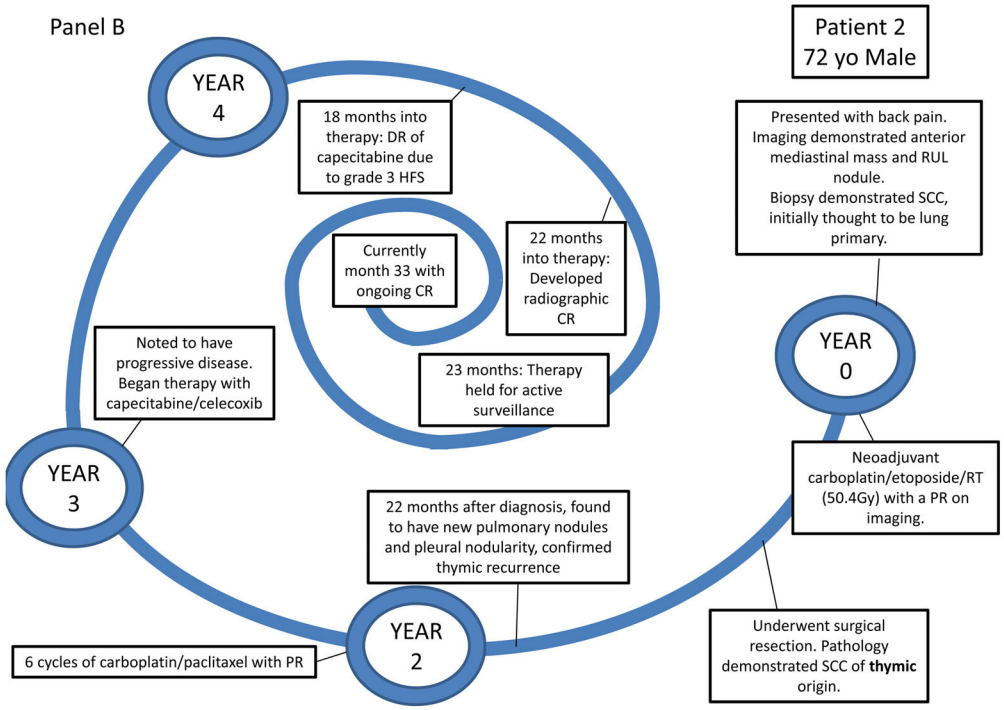

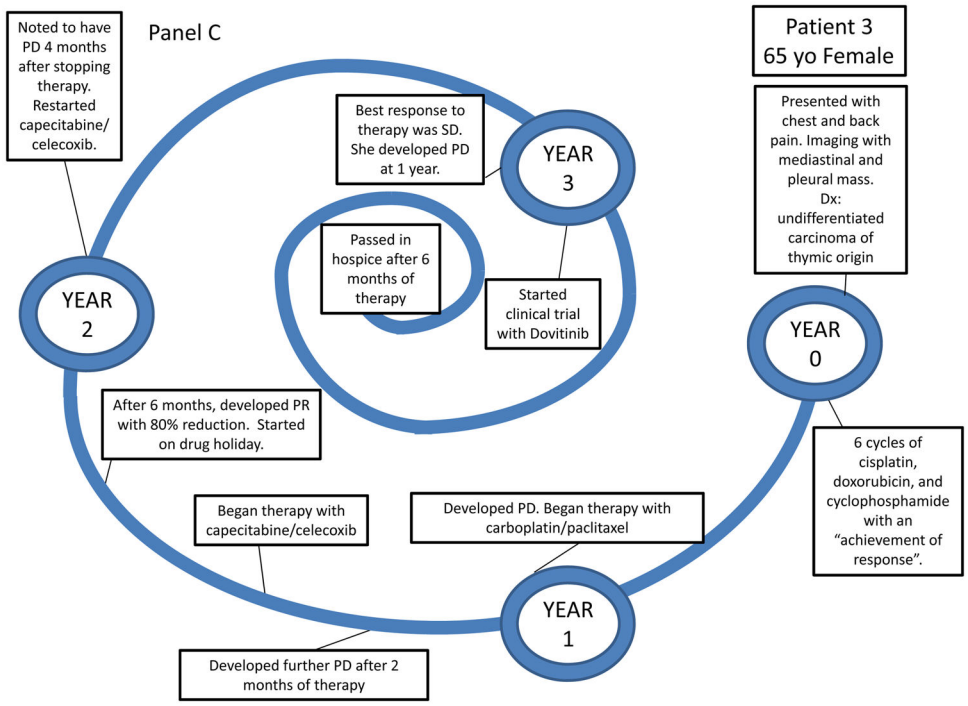

Figure 1.

Clinical presentation and course of the three thymic carcinoma patients. Patients 1 and 2, in Panels A and B, respectively, both had a CR. Patient #1 had a CR after 14 months and was placed on active surveillance after 18 months of therapy. He remained in CR until month 23, when he developed growing lung lesions with pathology confirming recurrence. He was started on a clinical trial with the drug ilorasertib for CDKN2A deficient tumors. Patient 2 had a CR after 22 months of therapy and was placed on active surveillance after 23 months; he remains in a CR at 33 months. Patient 3, in Panel C, developed a PR as best response (80% reduction in tumor size by RECIST criteria). Patient 3 was placed on a drug holiday after 6 months of therapy. She progressed 4 months later and was restarted on therapy, with best response SD. She developed progression of disease after another 12 months of therapy.

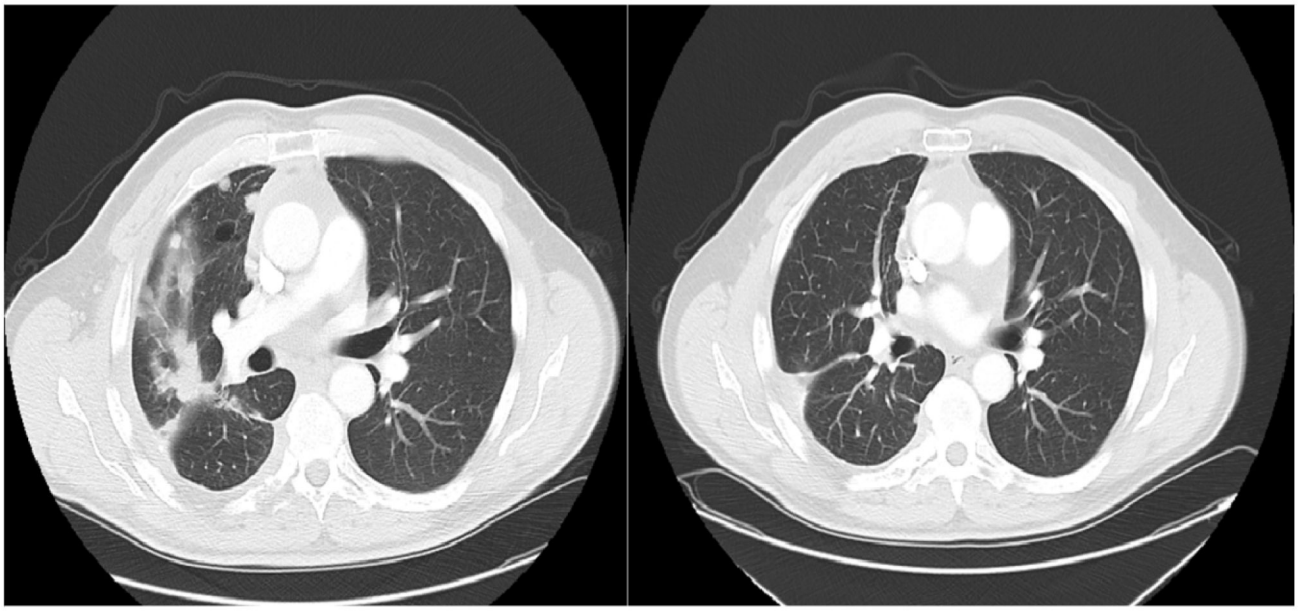

Figure 2.

Radiographic Response in patient #1. CT scan for patient #1 at baseline (left panel) and after 14 months of capecitabine/celecoxib (right panel). The patient had a complete response, with complete resolution of his pulmonary metastases.

Table 1

Patient Characteristics. Six patients and their responses to Capecitabine/Celecoxib.

Patient	Type	Age	Sex	# of Prior Therapies	# of Months of Capecitabine/ Celecoxib	Best Response	% Change in Tumor Size at Best Response	Reason for Discontinuation	PFS (months)	OS (months)
1	Thymic Carcinoma	65	Male	2	18	CR*	−100%	PD	21 (Patient was then started on clinical trial IRB 15-0083 with ilorasertib)	28 (ongoing)
2	Thymic Carcinoma	72	Male	2	23	CR	−100%	On surveillance	33 (ongoing)	33 (ongoing)
3	Thymic Carcinoma	65	Female	2	6	PR*	−80%	Drug Holiday	10 (Patient was then restarted on capecitabine/ celecoxib, with SD for 12 months)	28 (ongoing)
4	Thymic Neuroendocrine Tumor	53	Male	3	6	PD*	1.1%**	PD	1	34 (ongoing)
5	Thymoma	63	Male	3	8	SD*	0%	Drug Holiday	19 months (Patient was then restarted on capecitabine/ celecoxib, with PD after 3 months)	39 (ongoing)
6	Thymoma	52	Male	2	8	SD	0%	PD	8	39 (ongoing)

*PR = Partial response, CR = Complete Response, PD = Progressive Disease, SD = Stable Disease.

**Concern for vascular invasion of tumor led to cessation of therapy despite only 1.1% increase in tumor size.

Table 2

Genomic Profiles. Specific genomic alterations identified on molecular analysis.

Patient 1	**Patient 3**	**Patient 4**
Thymic Carcinoma	**Thymic Neuroendocrine**	**Thymic Carcinoma**
CDKN2A/B (loss)	*CDKN2A/B* (loss)	*CDKN2A* (R24P)
CHEK2 (T38fs*15)	*FGFR3* (Y373C)	*MEN1* (I85fs*33, loss)
CYLD (S344)	*MLL2* (L900fs*61)	
	SETD (Q2140)	