Systemic Therapeutic Options in Thymic Malignancies: A Glimmer of Hope

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Abstract: Progress in the systemic therapy of thymic malignancies has been hampered in the past by the rarity of this disease entity and the lack of a global collaborative effort in conducting phase II studies. Cisplatin-based therapy has been considered the standard of care, though data typically has been derived from a retrospective case-series approach. However, the arrival of novel cytotoxic agents and molecularly targeted agents into the clinic has helped provide the impetus for improved methodology in thymic malignancy research with an emphasis on more prospective phase II studies. This review discusses the results of traditional cytotoxic agents, novel cytotoxic agents, biologic therapy and the initial evaluation of molecularly targeted therapeutics, such as epidermal growth factor receptor inhibitors, for the treatment of thymic malignancies. In addition, potential novel targets such as VEGF, Bcl-2 and c-KIT are assessed.

Key Words: Thymoma, thymic carcinoma, targeted therapy, chemotherapy.

INTRODUCTION

Thymic malignancies are a heterogeneous group of rare neoplasms with an incidence of approximately 0.2-1.5% [1]. Despite divergent histologies [2-5], potential etiologies [6-12], genetic changes [13-16], biologic behaviour [17-22], and prognoses [23,24,25], these malignancies are typically evaluated together in clinical trials in efforts to meet accrual goals in a timely manner (Table **1**). Thymic neoplasms of epithelial origin include thymomas and thymic carcinomas. The World Health Organization (WHO) classification system is based on the cytological features of the thymic epithelial cells and the proportion of lymphocytes [2]. Thymic tumors are defined as medullary (Type A), cortical (Type B1, B2, B3), and mixed (Type AB). Thymic carcinoma used to be designated as a Type C thymoma but as of the WHO 2004 classification update it is now an entity of its own [26]. Thymic carcinomas are subdivided into low-grade and high-grade categories. Low grade thymic carcinomas have a relatively favorable course, a low incidence of local recurrence and distant metastases. High-grade thymic carcinomas are characterized by an aggressive clinical course and a high incidence of local recurrence and distant metastases [27]. The neuroendocrine tumor of the thymus, commonly referred to as thymic carcinoid, is postulated to arise from endodermal cell precursors [28]. Recently, in an effort to standardize terminology, thymic carcinoids have been reclassified into "neuroendocrine carcinoma" subgroups (Table **1**) [29,30]. The WHO classification 2004 update formally placed thymic carcinoids under the thymic carcinoma group, however, for the purposes of this review evaluating systemic treatment in thymic malignancies, thymic carcinoid will be considered separately [26]. The majority of carcinoid tumors (72%) are of intermediate-grade, similar to atypical carcinoid tumor of the lung. High-grade carcinomas are similar to small cell lung cancer and low-grade carcinoids are similar to typical carcinoids [31,32].

Classic thymomas have been described as cytologically "bland" tumors, however, "bland" should not be confused with benign as recurrences and metastases after resection have been reported for stage I thymomas and each histologic subtype of thymoma [33,34,35,36]. Thus, in contrast to other tumors, thymomas are defined not by histology but by their invasive characteristics including degree of encapsulation and invasion into adjacent organs at surgery (Table **2**) [37,38]. However, histologic classification of thymoma may predict recurrence; in one report, recurrences were not observed amongst medullary and mixed-type tumors despite the invasiveness of 30% of these samples [39]. Masaoka stage I and II tumors usually correlate with Type A, AB and B1 tumors while stage III and IV correlate with Types B2, B3 and thymic carcinoma [40]. Thymomas are typically indolent, locally invasive and may disseminate to the pleura. Thymic carcinoma and thymic carcinoid metastasize by hematogenous and lymphatic routes. The thymic carcinoids present with an aggressive biological behaviour in contrast to that of the typically benign carcinoids arising outside of the thymus. Mediastinal lymph node metastases have been noted in approximately 50% of patients with thymic carcinoid [22,41].

The most important prognostic factors in a retrospective analysis of 65 thymoma patients were stage and completeness of surgical resection, while the WHO classification category was not statistically significant [42]. Univariate and multivariate analyses performed by Ogawa *et al*. in patients with thymic carcinoma indicate that a Karnofsky performance status $\geq$ 70% and low-grade histology were favorable prognostic factors for overall survival. In this series, the median survival time in low-grade and high-grade thymic carcinoma was 29 and 11 months, respectively [27]. The prognostic significance of the paraneoplastic syndromes has also been assessed. Initially, myasthenia gravis was believed to be a negative prognostic factor [43], however, the majority of studies now show either a trend [44,45] or significantly improved survival in patients with thymoma associated with myasthenia gravis [46,47]. In contrast to this, Cushing's syndrome was found to have no impact on survival in patients with thymic carcinoid [32].

Genetic changes in thymoma correlate with WHO histologic classification and Masaoka stage of disease. Chromosomal alterations accumulate as there is progression from Type A to Type B3 thymoma, and, as expected, thymic carcinomas have a much higher incidence of genetic changes than thymomas [48]. Mutations of the chromosomal region 6q25 can be found in all thymoma samples and thymic squamous cell carcinomas. Losses of the APC gene at chromosome 5q21-22 occur principally in B2 and B3 thymomas and in a few AB thymomas. Type B2 and B3 thymomas also have deletion of chromosome 13q (retinoblastoma locus) and 17p (p53 locus) suggesting a progression from B2 to B3 thymoma. A third oncogenic pathway may be through the development of microsatellite instability as observed in Type AB and B2 thymoma [14]. Recently, a carcinoma with the t(15;19) translocation which generates a 6.4-kb BRD-4-NUT fusion oncogene has been described [15,16]. Limited investigation into the molecular aspects of thymic carcinoid have been performed to date.

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Table 1. Characteristics of Thymic Neoplasms

Characteristic	Thymoma (THY)	Thymic Carcinoma (TC)	Thymic Carcinoid (Neuroendocrine Carcinoma; NEC)
Cell of Origin	**Medullary Epithelial Cell**	**Medullary Epithelial Cell**	**Endodermal Cell Precursor**
Histopathologic subtypes	Type A: medullary THY Type AB: mixed THY Type B1: predominantly cortical THY Type B2: cortical THY Type B3: well differentiated TC [2]	Low-grade: Squamous cell (TSCC) Mucoepidermoid papillary Basaloid High-grade: Lymphoepithelial-like (LEL) Sarcomatoid Clear cell Adenocarcinoma Undifferentiated [2]	Well-differentiated: Grade 1 NEC, typical carcinoid Grade 2 NEC, atypical carcinoid Poorly-differentiated: Grade 3 NEC, large-cell NEC, small-cell carcinoma Variant: Carcinoid with prominent mucinous stroma [3]
Etiology or association	Largely unknown Familial [6,7] Thymic irradiation in childhood [8]	Epstein-Barr virus associated with LEL subtype [9,10,11,12]	Unknown
Genetic changes	6q25 mutation [13] LOH 5q21-22(APC) ± 16q22.1(CDH1) [14]	t(15;19)(q13;p13.1) translocation (BDR4-NUT fusion oncogene) [15,16] 6q25 mutation in TSCC only	Limited evaluation to date
Associated parathymic syndromes	Myasthenia gravis 30% PRC aplasia 5-10% Hypogammaglobulinemia 3-6%	Rare: Cushings MEN I and II SIADH	Frequent: Cushings MEN I & II (up to 30%) [2,18]
Biologic behaviour	Typically indolent Tend to recur locally 30-40% invasive [19]	Invasive Metastasize	Aggressive LN involvement common 30-76.9% metastasize
Response to chemotherapy	Sensitive	Typically resistant	Sparse data
Increased risk for second malignancies	Yes [20,21]	No	No
Prognosis	Masaoka 5-year survival rate by stage: I: 83-100% II: 86-98% III: 68-89% IV: 50-71% [1,9,23,30]	5 year survival 30-50% [24]	5-year survival rate 0-31% [25]

Table 2. Modified Masaoka Staging of Thymic Epithelial Malignancies [33]

Stage	Diagnostic Criteria
I	Complete macroscopic and microscopic encapsulation
IIa	Microscopic transcapsular invasion
IIb	Macroscopic invasion into surrounding fatty tissue or grossly adherent but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ: a. without invasion of the great vessels b. with invasion of the great vessels
IVa	Pleural or pericardial dissemination
IVb	Lymphogenous or hematogenous metastasis

Thymoma

Chemotherapy

Thymoma chemotherapeutic trials are typically small; despite this, a number of studies have reported reasonable results with various systemic agents, either alone or in combination. Cisplatin, doxorubicin, and cyclophosphamide have demonstrated activity in thymoma. Platinum-based therapy has been used in the locally advanced or metastatic disease settings over the past decade with response rates ranging from 24% to 100% [49,50,51]. When combination chemotherapy is administered response rates improve to >50% [52,53]. Unfortunately, randomized trials comparing single-agent versus combination therapy in this disease setting have not been performed. In addition, compared to other malignancies, the number of phase II studies conducted in patients with advanced or metastatic thymoma with single-agent therapy [54,55], combination chemotherapy [52,56,57] and biologic therapy [58,59,60] are indeed sparse (Table **3**).

Two single-agent phase II studies have been reported in thymic malignancies. Cisplatin, 50 mg/m^2 intravenously (IV) every 3 weeks, and ifosfamide, 1.5 g/m^2 IV on days 1 to 5, with mesna as a uroprotector, every 3 weeks, have been evaluated as single-agents with response rates of 10% and 46%, respectively [54,55]. Single-agent cisplatin induced severe nausea and vomiting, however, life-threatening and lethal toxicities were not observed. In addition to severe nausea and vomiting, 3% of patients experienced grade 3 and 4 leucopenia with ifosfamide. The discrepant response rates in these two studies may be attributed to a number of issues. Cisplatin is typically dosed at 75 mg/m^2 and thus may have been underdosed in this single-agent study [54]. In addition, the cisplatin study enrolled a more heavily-pretreated population; $\geq$ 71% of these patients had previously received radiation therapy and 3 had received prior chemotherapy. In contrast, the ifosfamide study accrued only 3 patients who had previously received chemotherapy or radiation [54,55]. Indeed, the true improvement in response rate solely attributable to ifosfamide may be difficult to gauge as 59% of these patients subsequently received chemotherapy or radiation. Interestingly, patients who were $\leq$ 49 years of age on the ifosfamide study tended to have a longer survival rate (5 year survival 78% versus 22%, log-rank test x^2=2.286; p=.1306) [55].

Phase II studies in thymoma have been performed with three cisplatin-based multiple agent regimens in a non-randomized fashion. The overall response rates ranged from 32% to 56% and variant survival endpoints were reported. The phase II Intergroup study and the European Organization for Research and Treatment of Cancer (EORTC) trials evaluated PAC (cisplatin, adriamycin, cyclophosphamide) and CE (cisplatin and etoposide), respectively. These two regimens may be preferable as front-line therapy compared to the phase II Intergroup VIP (etoposide, ifosfamide and cisplatin) regimen [52,56,57]. The response rate with VIP was lower (32%) despite a higher dose of cisplatin (80 mg/m^2 total) in the VIP regimen compared to PAC and CE (50 and 60 mg/m^2, respectively). In addition, complete responses were not observed with VIP, while the two non-ifosfamide based regimens combined reported 8 complete responses. One explanation for the lower response rate may be the modest decrease in the total dose of etoposide compared to the EORTC trial (from 360 to 300 mg/m^2). However, Loehrer *et al.* speculate that this may be attributed to overlapping confidence intervals of the patient population and sample sizes in these trials [56]. The VIP study also treated more thymic carcinoma patients, which are comparatively more chemoresistant, than the other studies (8 compared to 0 and 1 for CE and PAC, respectively) [52,56,57]. The response rate also tended to decrease in the PAC study with worsening performance status (7 patients with KPS 60-70%), although the sample size is too small to make definitive conclusions regarding these relationships. There were no obvious differences in response rate noted for gender, age, performance status, or weight loss in the VIP study, although patients without prior surgery had a slightly higher response rate (50% versus 25%) compared to those who had undergone prior surgery. The toxicity profile for VIP was more severe. Notably, 47% of patients experienced grade 4 thrombocytopenia with VIP [56] while no severe thrombocytopenic events occurred in the CE study [57]. In the PAC study only 4 patients had grade 4 toxicity [52]. These studies demonstrate that durable responses are possible with combination chemotherapy. However, it is currently unknown whether combination therapy represents a true advantage over single-agent therapy as randomized comparisons have not been performed. Regarding the phase II studies performed to date, the VIP results were interpreted as being inferior to the other two cisplatin-base combinations and should not be considered as standard of care in previously untreated patients with thymic neoplasms [56].

Although not evaluated in a prospective phase II study an alternate combination has been widely used and cited. Notable activity with an every three week ADOC combination (adriamycin 40 mg/m^2 day 1, cisplatin 50 mg/m^2 day 1, vincristine 0.6 mg/m^2 on day 2, cyclophosphamide 700 mg/m^2 on day 4) have been reported by Fornasiero *et al.* The overall response rate in 37 patients with advanced stage III/IV thymoma was 91.8%; remarkably, 16 complete and 18 partial responses were noted. The median duration of response and the median survival were 12 months and 15 months, respectively [51].

The long-term outcomes after systemic therapy in locally advanced or metastatic thymic malignancies have not been extensively evaluated. Loehrer *et al.* recently conducted a review of 123 patients (thymoma n=111, thymic carcinoma n=12) treated in 5 prospective phase II ECOG studies in which cisplatin was administered as a single agent or as part of a combination regimen (PAC, VIP, PC). The objective (overall CR + PR) response and stable disease rates were 39% and 39%, respectively. A higher objective response rate (p<0.0001) and improved overall survival rate (p=0.035) were associated with combination regimens [*Loehrer PJ, Wang W, Aisner S, et al. Long-term follow-up of patients with locally advanced or metastatic thymic malignancies: the Eastern Cooperative Oncology Group (ECOG) experience. Proc Am Soc Clin Oncol 2004; 23: (Abstr 7050)*]. However, despite these high response rates and some durable remissions, the majority of patients with unresectable disease subsequently progressed.

Recently, investigators have sought to improve responses and survival to chemotherapy. These efforts have focused on dose intensive chemotherapy, high-dose chemotherapy with peripheral blood stem cell transplant (PBSCT) and methods to predict treatment response or resistance. Dose intensive chemotherapy with the CODE regimen (cisplatin 25/mg/m^2 days 1 weeks 1-9, vincristine 1 mg/m^2 day 1 weeks 1, 2, 4, 6, 8, doxorubicin 40 mg/m^2 day 1, and etoposide 80 mg/m^2 day 1, 2, 3 on weeks 1, 3, 5, 7, 9) was administered weekly for 9 weeks with GCSF support in 53 patients with unresectable stage III or IV thymoma. Thoracotomy was performed in 13 stage III patients. Successful surgical resection was accomplished in 11 patients, of which 9 were complete (39%). Three pathologic complete responses were achieved. The overall response rates and median PFS for the CODE regimen in stage IV and III thymomas were 59% and 62% and 9.5 months and 4.5 years, respectively [*Kunitoh H, Tamura T, Fukuda H, et al. Dose intensive chemotherapy (Cx) in advanced thymoma: Initial report of Japan Clinical Oncology Group trials (JCOG 9605 and 9606). Proc Am Soc Clin Oncol 2006; 24: (Abstr 7080)]*.

A high-dose carboplatin approach with etoposide (700 mg/m^2 and 750 mg/m^2, respectively, IV day -5, -4, -3) and tandem transplants with G-CSF mobilized peripheral blood stem cells was evaluated in 5 patients with non-cisplatin refractory disease [61]. Progression-free survival ranged from 3.5-16.5 months. A durable complete response of 12.8 months was noted in one patient. At 2

Table 3. Phase II Systemic Studies Conducted in Thymic Neoplasms

Author/ Ref.	Agent or Regimen	N	Histology	Dose, route	Frequency	Measurable Response Parameters						Other Response Parameter	Grade 3-4 Toxicity
						SD	PR	CR	PD	NA	Overall RR (PR +CR)		
Bonomi *et al.* [54]	cisplatin	24	THY	50mg/m^2 IV	Q 3 wks	8	2	0	10	4	10%	Median survival 76 wks 2-yr survival 39%	Nausea Emesis
Highley *et al.* [55]	ifosfamide	15	TH n=13 TC n=2	1.5 g/m^2 IV d 1-5 with mesna	Q 3 wks	6	1 THY =1	5 THY =5	3	2	46%	Median duration CR 66+ mos Est. 5 yr survival 57%	2% cycles N/V 3% cycles leucopenia
Loehrer *et al.* [52]	PAC	31	THY n=30 TC n=1	P 50mg/m^2 A 50 mg/m^2 C 50 mg/m^2	Q 3 wks	10	12 THY =12	3 THY =3	5	1	50%	Median survival 37.7 mos 5-yr survival 32%	3 G 3 N/V 1 G3 mucositis 1 G3 paresthesias
Loehrer *et al.* [56]	VIP	34	THY=20 TC n=8	V 75mg/m^2 d1-4 I 1.2mg/m^2 d1-4 P 20mg/m^2 d1-4	Q 3 wks	4	9 THY =7 TC=2	0	15	6	32%	1 & 2=yr survival rates: 89% & 70%	47% pts G4 heme tox 3 pts G 3-4 V
Giaccone *et al.* [57]	CE	16	THY	C 60 mg/m^2 d1 E 120mg/m^2 d 1-3	Q 3 wks	6	4	5	0	1	56%	Median response duration 3.4 yrs Median survival 4.3 yrs	81% N/V 51% leucopenia 69% alopecia 6% diarrhea 6% mucositis 6% infection
Hanna *et al.* [61]	HDC + E	5	THY n=4 TC n=1	HDC 700mg/m^2 E 750 mg/m^2	Tandem transplant 4 wks apart	0	4	1 THY =1	0	0	100%	PFS 3.5-16.5 months	5 G 4 neutropenia 5 G4 thrombocytopenia 4 G3 anemia 4 G3 nausea 2 G3 emesis 2 G3 mucositis
Loehrer *et al.* [58]	C1, C2 octreotide	38	THY n=32 TC n=5 TD n=1	O 0.5 mg sq tid P 0.6 mg/kg	Daily to 1 yr		4 THY =4			4	31.6%	1- & 2-yr survival 86.6% & 75.7%, overall survival pending	1febrile neutr death 3 G3 diarrhea 3 G3 decr plts 2 G3-4 decr ANC 3 G3-4 anemia 1 G4 dyspnea
	C3+ octreotide + prednisone	21				14	6 THY =6	2 THY =2	12				
Palmiere *et al.* [59]	Octreotide n=9 or Lanreotide n=8 + prednisone	16	THY	O 1.5 mg sq L 30mg IM P 0.6 mg/kg IM x 3 mos, then 0.2 mg/kg	O daily L q 14 d P daily	6	5	1	4	4	37%	Med survival 25 mos Med TTP 14 mos	None

(Table 3). contd….

Author/ Ref.	Agent or Regimen	N	Histology	Dose, Route	Frequency	Measurable Response Parameters						Other Response Parameter	Grade 3-4 Toxicity
						SD	PR	CR	PD	NA	Overall RR (PR +CR)		
Gordon *et al.* [60]	IL-2	14	THY	$12x10^6$IU/m^2sq qdx5dx4wks	Q 6 wks	1 MR	0	0	-	0	0%	Not specified	1 G3 anorexia 1 G3 N 1 G3 incr tot bili 1 G3 incr SGPT 1 G3 desquamation
Loehrer *et al.* [Footnote 1]	pemetrexed	27	THY n=16 TC n=11	500 mg/m^2 IV	Q 3 wks	18#	2	2	5	4*	17%*	Med TTP 45 wks	G3 tox: dyspnea, infection, fatigue, decr ANC, abnl chemistries
Kurup *et al.* [Footnote 2]	gefitinib	26	THY n=19 TC n=7	250 mg po qd	Q 28 days	14	1	1	10	0	3.8%	Median TTP 4 mos (1-17+)	3 G3-4 dyspnea 1 G4 fatigue 1 G4 anemia/decr plts 1 myocardial infarction

Abbreviations: CR: complete response; HDC+E: high-dose carboplatin plus etoposide; MR: minor response; PAC: cisplatin, adriamycin, cyclophosphamide; PD: progressive disease; PFS: progression free survival; PR: partial response; THY: thymoma; TC: thymic carcinoma; TD: thymic carcinoid; TTF: time to treatment failure; VIP: etoposide, ifosfamide, cisplatin

#2 patient off-study due to intolerance, 1 patient off-study due to progressive Morvan's syndrome.

*At time of data reporting 4 patients still on pemetrexed and radiologic assessment pending.

Footnotes:

1. [(*Loehrer PJ, Yiannoutsos CT, Dropcho S, et al. A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma. Proc Am Soc Clin Oncol 2006; 24: (Abstr 7079)*].

2. [*Kurup A, Burns M, Dropcho S, Pao W, Loehrer PJ. Phase II study of gefitinib treatment in advanced thymic malignancies. Proc Am Soc Clin Oncol 2005; 23: (Abstr 7068*)].

years three of five patients had been alive for 26+, 36+, and 49+ months. This approach while feasible and tolerable, does not appear to be superior to standard–dose salvage therapy. Preliminary data with an alternate approach of high-dose ifosfamide, carboplatin and etoposide (ICE) followed by PBSCT in combination with an ADOC regimen, surgery and radiotherapy was performed in two patients [62]. A complete response was observed in one patient that was ongoing at 5 years. A second patient had a partial response that was ongoing at 2 years.

The ability to predict which patients will respond to a given treatment will avoid toxicity and loss of time and opportunity in finding "the successful treatment". While this is the goal of "molecularly targeted therapy", it is also an area of investigation with approved cytotoxic drugs. In thymic malignancies, investigations are focusing on the ability to predict which tumors will respond to anthracycline containing regimens. Gains in chromosome 17q occur in one third of thymic carcninomas and are thought to be linked to amplification of the enzyme topoisomerase 2α (topo-2α), the enzyme targeted by adriamycin. Liu *et al.* conducted a prospective study of PAC (cisplatin 50 mg/m^2, adriamycin 50 mg/m^2, cyclophosphamide 500 mg/m^2) followed by radiation with infusional 5-FU in patients with stage IV thymoma and thymic carcinoma with a retrospective evaluation of tumor topo-2α levels [63]. The overall response rate in 28 patients treated with PAC was 71.4% (3 CR and 17 PR). Overexpression of topo-2α, which was observed in all responders, was a significant predictor of response to PAC (p=0.001). Due to the survival advantage in those patients with co-amplification of topo-2α and Her-2 in the breast cancer CALGB 8541 study, the authors suggest that a higher dose of adriamycin (60 mg/m^2) should be considered in thymic malignancies with this co-amplification pattern [64]. Further evaluation is needed to confirm the role of topo-2α in predicting response and resistance to anthracycline therapy.

Numerous cytotoxic agents have been approved in the last 10-15 years for various solid tumors, however, the only one to complete evaluation in a phase II setting in thymic malignancies is pemetrexed. Pemetrexed has broad-spectrum antitumor activity and has been approved for the treatment of two other thoracic malignancies, non-small cell lung cancer and mesothelioma. A mixed population of both thymoma and thymic carcinoma were eligible for this study. Promising activity was seen in this heavily-pretreated population (median number of prior therapies = 2; range 1-6) with 4 responders (2 CR and 2 PR) in patients with stage IV disease for an overall response rate of 17%. The median overall survival had not been reported yet as only 3 patient deaths had occurred [*Loehrer PJ, Yiannoutsos CT, Dropcho S, et al. A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma. Proc Am Soc Clin Oncol 2006; 24: (Abstr 7079)*]. In addition to this pemetrexed study, a cytotoxic combination not previously tested in thymic malignancies is currently being evaluated in the phase II setting. Patients with thymoma and thymic carcinoma are eligible for treatment with the combination of carboplatin and paclitaxel in a study being conducted by ECOG (ClinicalTrials.gov).

Biologic Therapy

The combination of octreotide and prednisone is the most promising biologic therapy for thymoma evaluated to date. Octreotide targets the somatostatin receptor on malignant cells while prednisone promotes apoptosis, primarily amongst the lymphocytic component [65,66]. The mechanism by which octreotide exerts its cytotoxic effect is unclear. Possibilities include direct or indirect effects on insulin-like growth factor-1, angiogenesis or other mechanisms [67,68,69]. Case reports have documented responses with octreotide and prednisone. Palmieri *et al.* reported a complete remission in a patient with thymoma and pure red-cell aplasia after 15 months of octreotide and prednisone [70]. This patient had previously only achieved a partial response with chemotherapy and anemia had remained uncontrolled despite corticosteroids. The relative contribution of octreotide and prednisone to this CR is unclear due to the fact that they were administered concomitantly. In addition, Tiseo *et al.* noted a complete response in a patient who had been progressing through octreotide therapy and had prednisone added [71]. The authors propose this may have been due to a synergistic interaction between the two agents or simply due to the corticosteroid as single-agent steroid use resulted in a response in 14 (77%) of 18 patients in one series [72].

The activity of octreotide in thymoma has been assessed in two phase II studies (Table **3**). The study conducted by Loehrer *et al.* required a positive pretreatment octreotide scan and was designed to evaluate the role of octreotide alone as prednisone was not added to octreotide until course 3 [58]. The overall response rate was 31.6% with 2 CRs and 10 PRs; 4 of these PRs occurred with single-agent octreotide. The objective response rate for octreotide alone was modest at 10.5% in this heavily-pretreated population (18 patients with $\geq$2 prior therapies). However, a few patients with only minor responses at the end of course 2 did not immediately receive prednisone but continued on single-agent octreotide and subsequently converted to objective responses. The authors concluded that adding prednisone to octreotide at tumor progression would have more clearly defined this agent's role. In addition, patients with an ECOG performance status of 0 lived significantly longer than those with a performance status of 1 (p=.031). Currently, it is unknown whether the short-acting and long-acting octreotide formulations have equivalent activity. Interestingly, in this study, one patient with stable disease after one year of the short-acting formulation changed to the long-acting formulation for convenience issues. Subsequent progressive disease prompted a change back to the short-acting octreotide formulation which again led to disease stabilization. A similar response rate of 37% (1 complete response and 5 partial responses) was observed in 16 patients treated with either octreotide or its long-acting analogue lanreotide in combination with prednisone [59]. In this study, the use of the long-acting analog improved patient compliance. The combination of octreotide and prednisone is an attractive treatment option compared to cytotoxic chemotherapy due to durable antitumor activity and a milder toxicity profile [58].

The only other alternate biologic therapy evaluated in thymoma is interleukin-2. Initially, administration of interleukin-2 was noted to result in a durable complete remission in a heavily-pretreated patient. However, in the phase II setting administration of interleukin-2 in 14 patients led to a negative trial with no partial or complete responders [60].

Thymic Carcinoma

The aggressive nature of thymic carcinoma, with locally invasive and metastatic disease found in 70% and 30% of cases, respectively, at diagnosis argues for the prudence of systemic therapeutic strategies in this malignancy [27,73]. However, due to the rarity of thymic carcinoma a formal systematic evaluation of chemotherapy has not been performed. Thymic cancer patients are typically included in thymoma Phase II studies, and thus only data on small numbers of patients are available. In fact in the phase II studies published to date for cytotoxic and biologic therapy and molecularly targeted agents that included thymic carcinoma, only 19.9% (35/176) of the treated patients had thymic carcinoma (Table **3**). The fact that only 2 objective responses were observed in these 35 patients is even more sobering. Indeed, the relative treatment resistant qualities of thymic carcinomas are illustrated in a recent long-term follow-up of patients with locally advanced or metastatic thymic malignancies which showed that patients with thymic carcinoma (n=12) had a poorer response rate (p=0.047) and PFS (p=0.014) and a trend towards worse overall survival (p=0.064) than patients with thymoma (n=111) treated with cisplatin-based regimens in the first-line setting [*Loehrer PJ, Wang W, Aisner S, et al. Long-term follow-up of patients with locally advanced or metastatic thymic malignancies: the Eastern Cooperative Oncology Group (ECOG) experience. Proc Am Soc Clin Oncol 2004; 23: (Abstr 7050)*].

Thus, when trying to assess the value of chemotherapy in thymic carcinoma, data must be extrapolated from case reports or retrospective reviews performed at single-institutions. Retrospective reviews that include at least 7 or more patients are depicted in Table **4** [74-79]. Yoh *et al.* reported results of 12 patients with unresectable advanced disease treated with the weekly CODE regimen. A partial response was obtained in 5 patients for an overall response rate of 42%. The median progression-free and overall survivals were 5.6 and 46 months, respectively [74]. Kitami *et al.* analyzed seven patients treated with modified ADOC (nedaplatin 50 mg/m^2 day 1, doxorubicin 40 mg/m^2 day 1, vincristine 0.6 mg/m^2 day 3, cyclophosphamide 700 mg/m^2 day 4), PVB (cisplatin 100 mg/m^2 day 1, vinblastine 0.15 mg/kg days 1 and 2, bleomycin 15 IU/m^2 days 2, 8, 15 and 21) and CHOP-E [75]. Both PVB and CHOP-E were ineffective. However, all 4 patients (anaplastic carcinoma n=2; moderately differentiated squamous cell carcinoma n=2; stage III n=1; stage IVb n=3) treated with modified ADOC experienced partial responses after 1 to 3 courses with response ranging from 7 to 15 months (one unreported). The authors conclude that an anthracycline is necessary in the regimen for thymic carcinoma whether or not a platinum drug is included. This conclusion is also supported by two successful partial responses in thymic squamous cell carcinoma treated with VAC (cyclophosphamide, adriamycin, vincristine) [80].

Another series was reported by Koizumi *et al.* with 8 patients (including 2 patients with small cell carcinoma) treated with ADOC at 3- to 4-week intervals. Six partial responses that were observed were deemed clinically relevant due to response duration (7, 7, 8, 10, 12, and 15 months). The histologic type of the patient with the longest survival was squamous cell. The authors conclude that the ADOC regimen appears to be an attractive option for the treatment of thymic carcinoma, with a median survival time in this study of 19 months [76]. Additional partial responses and 1 complete response were obtained using the PACE regimen with G-CSF support [77] and an epirubicin-based regimen in the neoadjuvant setting [78].

Little data exists regarding the treatment of thymic carcinoma with cytotoxic agents approved in the last decade or as a second-line regimen. Maruyama *et al.* recently reported results with the combination of carboplatin and paclitaxel and cisplatin (CT) and gemcitabine and vinorelbine (CGV). Treatment with TC and CGV led to 6 (5 partial responses as first-line therapy and 1 partial response as second-line therapy) and 2 responses (1 partial response each in the first-line and second-line settings), respectively. All of these occurred in patients with non-keratinizing squamous cell carcinoma of the thymus [79]. Another case report details the use of docetaxel. Oguri *et al.* reported a partial response after three courses of single-agent docetaxel at 60 mg/m^2 every 4 weeks [81]. This patient had previously had a short-lived partial response of 2 months after a nedaplatin, etoposide and ifosfamide regimen. The

Table 4. Retrospective Reports of Systemic Treatment of Thymic Carcinoma with Sample Size ≥ 7

Regimen	Stage	N	Overall Response Rate				Grade 3-4 Toxicity (# of Patients)	Author & Ref.
			PR	CR	SD	PD		
CODE	Unresectable advanced disease	12	5	0	6	1	Neutropenia 11/12 Anemia 9/12 Decr platelets 4/12 Febrile neutropenia 4/12 Nausea 1/12	Yoh [74]
Mod-ADOC	Stage III-IV	4	4	0	0	0	None	Kitami [75]
CHOP-E		1	0	0	1	0		
PVB		2	0	0	1	0		
PACE + G-CSF	Advanced TC	7	3	0		4	Neutropenia 13/14[#] Anemia 8/14[#] Thrombocytopenia 6/14[#]	Oshita [77]
PE + epirubicin	Masaoka Stage III, neoadjuvant	7	6	1	0	0		Lucchi [78]
ADOC	Advanced TC [*]	8	6 [*] (75%)	0	2	0	Neutropenia 4/8 (G3) N/V 2/8 (G3)	Koizumi [76]
Carboplatin + paclitaxel	Not specified	6	6	0	0	0	Not specified	Maruyama [79]
Cisplatin + gemcitabine + vinorelbine		4	2	0	1	1		
PE		4	2	0	2	0		
CPA/ADR based		4	1	0	2	1		

Abbreviations: ADOC: cisplatin, doxorubicin, vincristine and cyclophosphamide; CODE: cisplatin, vincristine, doxorubicin, etoposide; CPA/ADR: cyclophosphamide/adriamycin; PACE: cisplatin, doxorubicin, etoposide, cyclophosphamide; PE: cisplatin, etoposide; TC: thymic carcinoma.
#this reference includes 7 patients with thymoma, while response data is broken down by histology, toxicity data is not, thus, toxicity data includes 7 patients with thymoma treated with this regimen
*includes 2 patients with small cell neuroendocrine tumors

literature is beginning to show that more recently approved cytotoxic agents are being incorporated into regimens for thymic carcinoma and that therapy in the second-line setting is active in some patients.

Irinotecan has also been used in the neoadjuvant setting. Neoadjuvant irinotecan was administered to a 72-year-old male with thymic basaloid carcinoma concomitantly with radiotherapy (40 Gy). Irinotecan and radiotherapy were then given adjuvantly after successful surgical resection. This patient died 6 months after surgical resection due to a non-tumour related event [82]. Investigation into establishing an effective regimen of neoadjuvant chemotherapy is currently lacking and is an area of need due to the aggressive nature of thymic carcinoma [83].

Less data is available in thymic carcinoma detailing transplant approaches. A multimodal approach including autologous stem cell transplantation was reported by Geffen *et al.* [84]. A patient with metastatic thymic carcinoma to the pleura, pericardium, retroperitoneum and neck nodes was treated neoadjuvantly with etoposide, ifosfamide and cisplatin followed by surgical resection, high-dose chemotherapy with stem cell support and finally radiation therapy. This patient remained in complete remission after 4 years at the time of data reporting.

Thymic Carcinoid

The development of standard systemic treatment of thymic carcinoid is hampered by the rarity of this tumor as only 150-200 cases have been reported worldwide [32]. Numerous agents such as 5-fluorouracil, streptozotocin, etoposide and cisplatin as single-agents and in combination have been assessed in the thymic carcinoid setting, however, these agents do not appear to impact survival or recurrence rates [22,85]. Spaggiari *et al.* reported one neoadjuvant failure in which 3 courses of ifosfamide and cisplatin were administered prior to surgical resection [86]. A more intricate multimodality approach was reported by Filosso *et al.* [87]. A patient experienced a moderate reduction in tumor with 4 courses of neoadjuvant cisplatin (100 mg/m^2 day 1) and etoposide (100 mg/m^2 days 1-3 and 5) and octreotide followed by irradiation of 45 Gy and subsequent surgical resection with continuation of adjuvant octreotide. This patient was reported to be disease free at 18 months. Adjuvant therapy with octreotide has been proposed after neoadjuvant chemoradiotherapy due to the expression of sst2 receptors on thymic tumors, the aggressive nature of thymic carcinoids and the limited experience in treatment of this entity [87].

Recently, Pan *et al.* used comparative genomic hybridization to detect genomic instability in sporadic thymic carcinoid. Chromosomal imbalances were found in 9 cases and included gain of chromosomal material in regions X, 8, 18, and 20 and losses on 3, 6, 9q, 13 q and 11q. Unexpectedly, there was no deletion of 11q13 which is the location of the MEN1 gene [88]. This indicates that distinct cytogenetic mechanisms lead to the development of thymic carcinoids and foregut carcinoids. The therapeutic relevance of these findings remains to be determined. In fact, differential response to

systemic therapy by carcinoid organ of origin has not been evaluated clinically, however, interesting clinical results were just published with the alkylating agent temozolomide.

Ekebald *et al.* performed a retrospective review of single-agent temozolomide for the treatment of advanced malignant neuroendocrine tumors [89]. A total of 36 patients (bronchial carcinoid n=13; pancreatic endocrine tumor n=12; thymic carcinoid n=7; and other carcinoids n=4) were treated with temozolomide 200 mg/m^2 for 5 days every 4 weeks. The radiologic response rate was 14% and consisted of 4 partial bronchial carcinoid responses and 1 partial pancreatic endocrine response. Complete responses were not observed in any category and radiographic responses were not observed in the thymic carcinoid category. The thymic carcinoid stable disease rate was 71% (n=5). Comparison of time to tumor progression amongst the bronchial carcinoid, thymic carcinoid and pancreatic endocrine tumor categories revealed no statistically significant difference in this parameter. Immunohistochemistry of O^6-methylguanine DNA methyltransferase (MGMT), the DNA repair enzyme that induces tumor resistance to O^6-alkylating agents, was performed in 23 tumor samples. Low expression of MGMT was found in 10 tumors. The best response in this cohort of 10 patients was: partial response n=4; stable disease n=5; and progressive disease n=1. However, no significant difference in response rate was found for low-, medium- and high-MGMT expressing tumors. The MGMT grading of the 7 patients with thymic carcinoid was not reported. Clearly, temozolomide appears to be a promising agent for the treatment of carcinoids as a group. Further prospective evaluation of temozolomide in the thymic carcinoid subgroup, ideally with MGMT correlation given the correlation of low MGMT expression with response to temozolomide treatment in low-grade oligodendroglioma [90], is warranted.

Molecularly Targeted Therapy of Thymic Neoplasms

Targeted therapy offers the hope of further progress in the treatment of thymic neoplasms. Molecularly targeted agents have been approved in a number of malignancies including epidermal growth factor receptor inhibitors (EGFRIs) in non-small cell lung cancer and colon cancer, c-KIT inhibitors in gastrointestinal stromal tumors and hematologic malignancies, VEGF inhibitors in lung cancer and multitargeted kinase inhibitors in renal cell carcinoma. However, the data evaluating these novel molecular targets and the drugs designed to modulate them is still scarce in the thymic neoplasm literature compared to data available for other malignancies. One obstacle to *in vitro* and xenograft testing of targeted therapy is the lack of cell lines from epithelial thymic neoplasms. To date three case reports and one phase II study with these agents have appeared in the literature. Table **5** depicts possible molecular targets supported by available data in thymic neoplasms. The majority of work performed to date has focused on c-KIT, EGFR and p53. Variances in expression by IHC may be attributed to small sample size, sensitivity of antibodies used, and different detection methods and differences in interpretation [91].

C-KIT

c-KIT (CD117) is overexpressed in 73-86% of thymic carcinomas evaluated by IHC and reverse transcriptase-polymerase chain reaction, however, except for one exception c-KIT mutations have not been observed [92,93]. Thus, the underlying mechanism for KIT overexpression in thymic carcinoma is unclear. C-KIT overexpression is not a prominent feature of thymoma and at this time its status is unknown in thymic carcinoid. Three case reports with the multitargeted kinase inhibitors dasatinib and imatinib have been reported in thymic malignancies. Chuah *et al.* report a recent response to dasatinib in a patient with both CML and thymoma that was unresectable due to thrombocytopenia [94]. This patient experienced not only a complete hematologic and cytogenetic remission of CML but also a 41% decrease in thymoma burden, the residual of which was subsequently resected. The thymoma cells stained negative for c-KIT and EGFR was amplified, consistent with previously reported results [92,93,95]. The authors speculate that the mechanism of response to dasatinib includes not only inhibition of Src and EGFR, but also of Arg tyrosine kinase which is overexpressed in thymomas [96] and a known target of dasatinib at nanomolar concentrations [94]. A similar clinically significant symptomatic and radiographic response to another c-KIT inhibitor, imatinib, that lasted 6 months, has been reported in a patient with thymic carcinoma metastatic to the liver. Biopsy of the liver metastasis allowed detection of the V560del in exon 11 mutation which is commonly found in GIST that respond to imatinib [97,98]. Unfortunately, imatinib did not elicit a response in a patient with thymic carcinoid after a 5-month course of treatment despite CD117 positivity [99]. However, this patient had brain metastases which worsened after 3 months of imatinib. Lack of response in the brain reflects the lack of penetration of imatinib into the CNS and recommendations in other malignancies include continuing imatinib for treatment of disease outside of the CNS, if controlled, while initiating appropriate treatment for metastatic disease to the brain [100]. Imatinib (300mg/d) was also administered to a 10 year-old male with HIV who had EBV-negative and CD117-negative staining thymic carcinoma with unknown mutation status. This patient failed therapy after 4 months of treatment [101]. Currently, the suggestion has been made that thymic neoplasms be screened for c-KIT mutations prior to use of anti-KIT treatment due to their rare mutational status as the efficacy of imatinib in GIST without mutations is low [97].

HER-1/HER-2

Receptors in the HER family that have been evaluated in thymic malignancies are HER-1 and HER-2. In contrast to c-KIT, HER-1 (the epidermal growth factor receptor/EGFR) is strongly overexpressed in thymomas, especially the WHO B2 and B3 subtypes, but not in thymic carcinomas [102,103]. However, some researchers have found strong expression of EGFR in A, AB and B1 subtypes [104]. In a more recent series conducted by Ionescu *et al.* that specifically investigated EGFR gene amplification, there was a striking discrepancy between EGFR protein expression and EGFR whole gene amplification with only 7 of 23 (30%) specimens with EGFR overexpression actually exhibiting gene amplification. In this series, thymomas associated with myasthenia gravis more frequently were hyperdiploid versus sporadic tumors but there was no difference in EGFR gene amplification [95]. In addition, EGFR gene amplification was associated with invasive and advanced stage disease (B3 and C or thymic carcinoma). Hayashi *et al.* noted that all 4 patients testing positive for EGFR by IHC had thymic squamous cell carcinoma [102]. Mutational status of the EGFR tyrosine kinase is important as it predicts sensitivity to inhibitors of this receptor [105]. Mutation in the EGFR gene has been observed in a 29-year old Japanese non-smoking female with thymic squamous cell carcinoma. This patient had previously received 4 cytotoxic chemotherapy regimens when deletion of exon 19 and three point mutations (G719A in exon 18, T790M in exon 20 and L858R in exon 21) were determined. This patient was treated with 250 mg of gefitinib and although only minimal objective response was detected, improvements in performance status, anemia and albumin were noted [106]. Another study that evaluated EGFR mutations found them lacking in both thymoma and thymic carcinoma [107]. Similar to c-KIT, the HER-1 status of thymic carcinoid is unexplored.

A second member of the HER family, HER-2, was overexpressed (>2+) by IHC in 50% of thymic carcinomas compared to only 6% of 63 thymoma samples, however, there was no evidence of gene amplification [108]. Suzuki *et al.* specifically tested for HER-2 mutations and found these lacking in both thymoma and thymic carcinoma samples [107]. The preliminary low level of HER-2 neu expression in thymic malignancies does not portend well for the use of trastuzumab in this setting.

Table 5. Evaluation of Molecular Targets in Thymic Neoplasms

Molecular Target, Author, Reference	Thymoma (THY)				Thymic Carcinoma (TC)				Thymic Carcinoid			
	N	IHC^ [#(%): Grading Intensity]	A	M	N	IHC^ [#(%): Grading Intensity]	A	M	N	IHC [#(%): Grading Intensity]	A	M
EGFR												
Ionescu [95]	28	22 (THY + TYC)* (79%)	6 # (21%)	NA	4	*	1# (25%)	NA				
Rieker [104]	30	29 (97%): + - +++ (predominantly ++ - +++)			4	2 (50%): + - +++						
Suzuki [107]	13			0	11			0				
Kurup [Footnote 1]	No mutations in 5 patients: not specified if THY or TC											
Henley [103]	31	26 (82%): + - +++			6	2 (33%): ++ - +++						
Yamaguchi [106]					1			1				
Hayashi [102]					6	4 (67%): all 4 SQCC						
Chuah [94]	1	1 (100%): + - ++										
P53												
Hirabayashi [113]	36	9 (25%)		0	3	0		0				
Hiroshima [112]	36	2 (5%)			10	6 (60%)						
Hino [116]	17	1 (6%)			19	14 (74%)		2/18 point mutations				
Tomita [117]	38	5.6% (1/18) NIT 60% (12/20) IT										
Pan [108]	63	18 (28%): + - ++ (14% low +)			17	17 (100%): ++-+++						
Gal [111]									21	8 (38%): ++ - +++ (1 specimen 1+)		
De Montpreville [115]									14	4 (29%): + - +++		
Tiffet [114]									12	12 (100%)		
Fukiwake [110]	20	6 (30%)			4	3 (75%)						
c-KIT												
Henley [93]	20	1 (5%)			15	11 (73%)						
Strobel [97]					1	+		+				
Pan [92]	110	0			22	19 (86%): ++ - +++		0				

(Table 5). contd.…

Molecular Target, Author, Reference	Thymoma (THY)				Thymic Carcinoma (TC)				Thymic Carcinoid			
	N	IHC^ [#(%): Grading Intensity]	A	M	N	IHC^ [#(%): Grading Intensity]	A	M	N	IHC [#(%): Grading Intensity]	A	M
Chuah [94]	1	0										
McDonald [101]					1	1 (100%)						
Talton [99]									1	1 (100%)		
HER-2												
Suzuki [107]	13			0	11			0				
Pan 03 [108]	63	4 (6%): + - +++			17	9 (53%): + - +++	0	0				
K-RAS												
Suzuki [107]	13			0	11			0				
Kurup [Footnote 1]	No mutations in 5 patients: not specified if THY or TC											
B-CL2												
Hiroshima [112]	36	12 (33%)			10	9 (90%)						
Pan [108]	63	9 (14%): + - +++			17	17 (100%): all +++						
Gal [111]									21	15 (71%): predominantly ++ - +++		
COX-2												
Rieker [104]	30	30 (100%): + - +++			4	4 (100%): + - +++						
Cyclin D1												
Hirabayashi [113]	36	6 (17%): all +++		0	3	3 (100%): +						
Survivin												
Hiroshima [112]	36	27 (75%)			10	10 (100%)						
RB												
Hirabayashi [113]	36	28 (78%)			3	2 (67%)						
Gli1												
Tasaki [122]	Gli1 + vs normal thymus (P<0.0001)											
CD-70												
Hishima [119]	18	1 (5%)			8	7 (88%)			1	0		

Abbreviations: A: amplification of target; IHC: immunohistochemistry; IT: invasive thymoma; M: mutation of target; NIT: non-invasive thymoma; SQCC: squamous cell carcinoma histology.

^Scoring system for IHC results: +: weak positive stain; ++: moderate positive stain; and +++: strong positive stain.

*Immunohistochemistry results given for 32 samples not broken down into number of thymomas and thymic carcinoma.

#Amplification defined as a ratio of EGFR signals to chromosome 7 centromere signals of $\geq$ 1.30.

Footnote:

1. [*Kurup A, Burns M, Dropcho S, Pao W, Loehrer PJ. Phase II study of gefitinib treatment in advanced thymic malignancies. Proc Am Soc Clin Oncol 2005; 23: (Abstr 7068)*].

Angiogenesis Pathway Targets

In an effort to evaluate the relationship between angiogenesis and thymic neoplasms, Sasaki *et al.* measured vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (BFGF) serum levels in patients with thymic neoplasms. Significantly elevated levels of both VEGF and BFGF ($p<0.05$ and $p<0.05$, respec-

tively) were found in thymic carcinoma serum samples but not in those of thymoma [109]. To date, there is one clinical report of an angiogenesis inhibitor effect in the literature in a thymic malignancy. The combination of thalidomide, an angiogenesis inhibitor, and interferon was administered to a patient with metastatic carcinoid. Four months of this combination therapy led to mediastinal disease control in this patient but there was a new asymptomatic brain metastasis. This patient received a total of 18 months of thalidomide therapy, due to lack of other therapeutic options, without disease stabilization in the brain [99]. A phase II study with sunitinib (an inhibitor of VEGFR, PDGFR and c-KIT) has also been performed in patients with unresectable neuroendocrine tumors. The preliminary partial response rate in islet cell carcinoma (n=52) and "carcinoid" (organ of origin not otherwise specified; n=39) was 13.5% (n=7) and 5.1% (n=2), respectively. The overall stable disease rate was 81% [*Kulke M, Lenz HJ, Meropol NJ, et al. A phase 2 study to evaluate the efficacy and safety of SU11248 in patients (pts) with unresectable neuroendocrine tumors (NETs). Proc Am Soc Clin Oncol 2005; 23: (Abstr 4008)*]. The clinical relevance of angiogenesis inhibitors is currently being investigated in a cutting edge phase II study, on par with research in other malignancies, evaluating the combination of bevacizumab, a VEGF inhibitor, and erlotinib, an EGFR inhibitor. Accrual to this study is open to all thymic neoplasms (ClinicalTrials.gov).

Apoptosis Pathway Targets

Other possible targets include the anti-apoptotics Bcl-2 [108,110-112], p53 [108,110,111,113-117], survivin [112, 118] and CD70 [119-121]. Elevated levels of p53 expression and a stronger immunopositive pattern of Bcl-2 were found in thymic carcinomas compared to thymomas indicating greater dysregulation of the apoptotic pathway in the former [108]. In addition, higher expression of p53 was observed in invasive thymoma (clinical stage II, III or IV) compared to non-invasive thymoma (clinical stage I) at 60% and 5.6%, respectively [117]. However, PCR analysis performed by Hirabayashi *et al.* revealed no p53 mutations in a series of 36 thymoma and 3 thymic carcinoma samples [113].

Survivin is a relatively novel target that has garnished interest due to inhibitors of this target that have entered early clinical trials and have already demonstrated activity. There is one report in the literature of diffuse survivin expression in the cytoplasm of cancer cells from a case of thymic carcinoma [112]. The survivin inhibitor YM155 was evaluated in a phase I study and was active in 5 patients: 3 patients with non-hodgkins lymphoma had partial responses (1 patient had a near CR, was transplanted and is now in remission 14+ months); 2 PSA responses in hormone refractory prostate cancer; and 1 minor response in non-small cell lung cancer. Major regressions in xenograft models predicted response in these 3 tumor types [*Mita AC, Antonia S, Lewis LD, et al. Final safety, pharmacokinetic and antitumor activity results of a phase I study of YM155, a novel survivin inhibitor, when administered by 168 hour continuous infusion. Eur J Cancer 2006; 4: (Abstr 29LB1)*]. These results suggest that further evaluation of survivin expression in thymic malignancies is warranted.

CD70 is a member of the tumor necrosis family that mediates B- and T-lymphocyte interactions. CD70 expression was evaluated in 27 thymic epithelial tumors and was expressed in 88% of thymic carcinomas and in one atypical thymoma, but not expressed in thymoma or one carcinoid sample. In this series, intensity of staining was not described, however, there was diffuse staining in 3 thymic carcinomas while in the others it was restricted to a moderate number of neoplastic cells [119]. Preclinical data with an engineered anti-CD70 antibody demonstrates the potential future viability of CD70 targeted therapy in thymic carcinoma [120].

Other Targets

A number of other targets that could be clinically relevant but that have been less extensively evaluated to date include K-RAS [107, *Kurup A, Burns M, Dropcho S, Pao W, Loehrer PJ. Phase II study of gefitinib treatment in advanced thymic malignancies. Proc Am Soc Clin Oncol 2005; 23: (Abstr 7068)*], COX-2 [104], cyclin D1 [113], RB [113], and the sonic hedgehog pathway target Gli1[122].

Finally, there is another potential target in a rare form of thymic carcinoma, that of carcinoma with t(15;19)(q13;p13.1) translocation, an entity that was only recognized approximately 15 years ago [15]. This translocation creates a 6.4-kb BRD4-NUT fusion oncogene which confers an aggressive and fatal outcome with survival quoted in weeks. This translocation results in aberrant expression of NUT (normally expressed only in the testis) precipitated by the ubiquitous promoter BRD4 [123, 124]. The precedent set by the successful treatment of CML with c-KIT inhibitors which modulate the BCR/ABL oncogene activity suggests that targeted treatment to modulate BRD4-NUT may be feasible.

Phase I/II Molecular Targeted Studies

Phase II evaluations of thymic malignancies have only been completed with one molecularly targeted agent. Kurup *et al.* report the results of a phase II study of gefitinib, an EGFR inhibitor, in patients with both thymoma and thymic carcinoma [*Kurup A, Burns M, Dropcho S, Pao W, Loehrer PJ. Phase II study of gefitinib treatment in advanced thymic malignancies. Proc Am Soc Clin Oncol 2005; 23: (Abstr 7068)*]. Only one partial response of short duration (5 months) was observed. Stable disease was observed in 14 patients, however, only 6 patients had disease that was stable for >4 months. The authors conclude that gefitinib in this heavily-pretreated population (median prior systemic therapies 2.5, range 0-6), had limited activity. In this gefitinib study, 5 patients, including the patient with the partial response, had DNA sequencing of tumor which showed no EGFR or KRAS mutations.

Despite only one published molecularly targeted study in thymic malignancies, a review of thymic malignancy trials on ClinicalTrials.gov leaves room for optimism. Accrual to a phase I study with the agent imatinib for thymic advanced stage carcinoma in patients with c-KIT+ and /or PDGFR+ disease was recently completed after a study inception date of April 2006. The successful completion of a phase I trial with a molecularly targeted agent in thymic carcinoma is indeed a milestone. In fact, enrollment of thymic malignancy patients on phase I studies can provide useful information and benefit some patients (Table **6**) [*Faivre S, Pierga J-Y, Delbaldo C, et al. A phase I and pharmacokinetic (PK) trial of CYC202, a novel oral cyclin-dependent kinase (CDK) inhibitor in patients with advanced solid tumors: exploration of 3 administration schedules. Proc AACR-NCI-EORTC Molec Targets Cancer Ther 2003; (Abstr A154), Weitman SD, Smith S, Eder J, et al. Irofulven monotherapy: impressive phase I and II clinical antitumor activity in heavily-pretreated patients. Proc Am Soc Clin Oncol 2001; 20: (Abstr 2081), Hutson TE, Plavney D, Mekhail T, et al. A dose finding and pharmacokinetic study of the novel isoflavanoid phenoxodiol in patients with refractory malignancies. Proc Am Soc Clin Oncol 2003; 22: (Abstr 886), de Bono JS, Steele N, Vidal L, et al. Updated results of the first in man evaluation of the histone deacetylase (HDAC) inhibitor, PXD101 in cancer patients (Pts). Proc Molec Target Cancer Ther 2005; 220s (Abstr C88), Fiedler W, Giaccone G, Lasch P, et al. Phase I study of SU014813, a novel oral multi-targeted receptor tyrosine kinase (RTK) inhibitor. Proc Molec Target Cancer Ther 2005; 157s (Abstr B119), Yamamoto N, Andoh M, Kawahara M, Fukuoka M, Niitani H. Phase I study of TZT-1027, an inhibitor of tubulin polymerization given weekly x 3 as a 1-hour intravenous infusion in patients (pts) with solid tumors. Proc Am Soc Clin Oncol 2002: 21: (Abstr 420).* The recent approval of sorafenib for advanced and metastatic renal cell carci-

Table 6. Thymic Neoplasm Activity in Recent Phase I Studies

Investigational Agent/ Reference	Mechanism of Action	Dose Level	N	Prior Therapy	Pathology	Response	# of Courses or Duration of Treatment
CYC202 [Footnote 1]	CDK2/cyclin E complex inhibitor	Not specified	1	Not specified	Thymoma	Stable disease	$\geq$ 5 months
E7070 [125]	Chloroindoyl sulfonamide CDK inhibitor	800 or 1000 mg/m^2	1	Anthracycline, cisplatin, etoposide	Epithelial cancer of thymus with PD in 3 months previous to C1D1 E7070	Stable disease	6 months
Exatecan [126]	Topoisomerase I inhibitor	0.2 mg/m^2/d IV	1	Several combination regimens	Malignant thymoma	Minor response (36% decrease)	4
Exatecan [127]	Topoisomerase I inhibitor	0.15-0.23 mg/m^2/d CIV x 21 days	1	Various regimens without response	Malignant thymoma	Radiographic & symptomatic improvement allowing oxygen cessation	12
Irofulven [Footnote 2]	Induces DNA alkylation, MAPK activation, apoptosis	Qd x 5 days	1	Not specified	Thymoma	Minor response	1
Phenoxodiol [Footnote 3]	Isoflavanoid cell cycle inhibitor induces G1/M arrest	2.2 mg/kg/d IV x 7 days q 2 wks	2	Not specified	Thymic carcinoma	Stable disease	$\geq$ 12 cycles
PDX101 [Footnote 4]	HDAC inhibitor	Not specified	1	Not specified	Epithelial T-cell thymoma	Partial response (70% decrease)	> 1 year
SU014813 [Footnote 5]	Multi-targeted RTK inhibitor: VEGFR-1 & -2, PDGFR, KIT, FLT-3	Not specified	1	Not specified	Thymus malignancy	Partial response	Not specified
TZT-1027 [Footnote 6]	Inhibitor of tubulin polymerization	1.5 mg/m^2 q wk x 3	1	Not specified	Thymoma	Partial response	183 days

Abbreviations: CDK: cyclin dependent kinase; HDAC: histone deacetylase; NS: not-specified; PD: progressive disease; PR: partial response; RTK: receptor tyrosine kinase.
Footnotes:
1. [*Faivre S, Pierga J-Y, Delbaldo C, et al. A phase I and pharmacokinetic (PK) trial of CYC202, a novel oral cyclin-dependent kinase (CDK) inhibitor in patients with advanced solid tumors: exploration of 3 administration schedules. Proc AACR-NCI-EORTC Molec Targets Cancer Ther 2003; (Abstr A154)*].
2. [*Weitman SD, Smith S, Eder J, et al. Irofulven monotherapy: impressive phase I and II clinical antitumor activity in heavily-pretreated patients. Proc Am Soc Clin Oncol 2001; 20: (Abstr 2081)*].
3. [*Hutson TE, Plavney D, Mekhail T, et al. A dose finding and pharmacokinetic study of the novel isoflavanoid phenoxodiol in patients with refractory malignancies. Proc Am Soc Clin Oncol 2003; 22: (Abstr 886)*].
4. [*de Bono JS, Steele N, Vidal L, et al. Updated results of the first in man evaluation of the histone deacetylase (HDAC) inhibitor, PXD101 in cancer patients (Pts). Proc Molec Target Cancer Ther 2005; 220s (Abstr)*].
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noma is the fruition of an observation in a phase I study in which responses in this typically chemotherapy-resistant tumor were noted [128]. Similarly, approval of bortezomib in multiple myeloma was sparked by the observations of an astute investigator who noted subtle signs of response in a patient with multiple myeloma on one of the original phase I studies [129]. In addition, an ongoing phase II trial is evaluating the biologic agent octreotide in primary inoperable thymoma. Clearly, there are indications of progress with thymoma and thymic carcinoma however, little research to date has been geared towards thymic carcinoid.

Clinical trials in thymic malignancies optimally should be conducted globally and not just in the national multi-institutional setting in order to enroll sufficient patients in a timely manner. While the United States Food and Drug Administration (FDA) and the European Union (EU) have each taken steps to facilitate international collaboration this area remains fraught with hurdles. While recent efforts by the EU and FDA sought to simplify the regulatory burden, improve patient safety and speed approval of new therapies, a recent editorial lamented the fact that measures taken by the EU to increase the incentive to engage in international trials had the

opposite effect [130, 131]. Clearly a drop in international collaboration, increased outsourcing of trials and loss of diversity of new treatments would affect progress in thymic malignancies more so than in other more common tumor types. Another critical aspect of drug development in thymic malignancies is the issue of tumor banking and translational studies. The rarity of thymic malignancies makes it prudent to create a pool of shared resources from which researchers, clinicians and patients may all benefit. Clearly this will require resolution of bureaucratic issues as previously described.

CONCLUSION

In conclusion, progress in the systemic therapy of thymic malignancies has been achieved. In 1999, Thomas *et al.* stated that "the rarity of this tumor somewhat obscured the optimal treatment for this disease" [132] and the role of chemotherapy in this malignancy was debatable. Today, almost a decade later, despite the lack of phase III trials, the consensus is that cisplatin-based therapy is beneficial. In addition, phase II studies are not only being conducted in thymoma but also in thymic carcinoma, and not only with novel cytotoxic agents but also with novel molecularly targeted agents. Dedication to prospective translational multi-institutional trials, tumor banking and further elucidation into the molecular characteristics of thymic neoplasms portend an even brighter future with the possibility of more substantial progress being made in the next ten years than in the previous ten years.

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