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Targeted Therapy for Advanced Thymic Tumors

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Abstract

The use of targeted therapies for the treatment of thymic malignancies is documented in the literature. However only a few drugs have undergone evaluation in phase II trials. Most of the evidence of the benefit of biologic therapies for thymic malignancies is in the form of case reports and small case series. No major activity has been observed with any agent so far, likely to the lack of selection of patients for targeted therapies and the small numbers studied. A better understanding of the biology of these tumors will be essential in furthering the field.

Keywords

Thymoma; Thymic Carcinoma; Targeted therapy; Gefitinib; Imatinib; Belinostat; Sorafenib; Cixutumumab; Octreotide

Introduction

Complete surgical resection is vital for the successful management of thymic malignancies. However thymomas can recur in 10% to 30% cases after an R0 resection. Chemotherapy and radiation therapy play an important role in the management of recurrent disease. The search for biologic agents in thymoma and thymic carcinoma has yielded disappointing results so far.¹⁻⁴ Although overexpression of the epidermal growth factor receptor (EGFR) and c-KIT can be demonstrated by immunohistochemistry, the paucity of drug-sensitizing mutations in these genes explains the lack of efficacy of targeted therapies in patients with thymic malignancies. In this chapter we present data from case reports and clinical trials that have explored the role of biologic therapy in thymoma and thymic carcinoma.

EGFR Inhibitors

Kurup et al reported results of a phase II study of gefitinib in advanced thymic malignancies.⁵ 26 patients with previously treated thymic malignancies were enrolled (19 thymomas, 7 thymic carcinomas) and treated with gefitinib at a dose of 250 mg orally once daily. Each treatment cycle was defined as 28 days and patients were treated to a maximum of 8 cycles. Mutational analysis for EGFR and KRAS mutations was performed in 5 cases. Only 1 partial response (PR) was noted among 26 patients. There was no complete response (CR). Fourteen patients had stable disease (SD), including 6 patients with SD lasting for >4 months. Grade 3/4 adverse events included dyspnea (12%), fatigue (4%), anemia/thrombocytopenia (4%), and myocardial infarction (4%). The median time to progression (TTP) was 4 months (1-17+ months). None of 5 samples evaluated by DNA sequencing showed evidence of EGFR or KRAS mutations.

There have been isolated case reports of response of advanced thymoma to erlotinib therapy.⁶ A phase II trial was conducted to evaluate the combination of erlotinib and bevacizumab in patients with recurrent thymoma and thymic carcinoma. Eighteen previously treated patients with advanced thymic malignancies were treated with erlotinib 150 mg orally once daily and bevacizumab 15 mg/kg i.v. on day 1 of a three week cycle.⁷ Responders or patients with SD after 2 cycles continued to receive treatment until progression or development of unacceptable toxicity. No responses were seen with this regimen although 11 patients (60%) achieved SD. There were no grade 4 toxicities.

Grade 3 toxicities included acneform rash (11%), dyspnea (11%), fatigue (6%), pericardial tamponade (6%), and aortic insufficiency (6%). Median survival time had not been reached at the time that the results were reported.

No prospective studies evaluating the role of cetuximab in thymic malignancies have been reported to date. However there have been a handful of case reports that have documented responses of advanced thymoma to cetuximab. Palmieri et al reported partial responses in two patients with previously treated thymoma. The tumors showed EGFR protein expression detected by immunohistochemistry.⁸ Farina et al described one patient with a previously treated B2 thymoma who achieved a partial response after 6 weeks of treatment with cetuximab. Although the tumor demonstrated overexpression of EGFR by immunohistochemistry, no EGFR amplification or mutation was detected in this tumor.⁹ Currently there is an ongoing phase II study evaluating the combination of cetuximab with chemotherapy (cisplatin, doxorubicin, and cyclophosphamide) in patients with stage III-IVA thymoma prior to surgical resection (ClinicalTrials.gov Identifier: NCT01025089).

c-KIT inhibitors

A case of metastatic poorly differentiated epidermoid carcinoma of the thymus responding to imatinib at a dose of 400 mg orally daily has been described in the literature.¹⁰ This patient harbored an activating mutation in exon 11 of the KIT gene (V566del). However prospective studies evaluating imatinib for treatment of thymic malignancies have yielded disappointing results. Salter et al reported results of a pilot study of imatinib in patients with previously treated thymic carcinoma that stained positive for either c-KIT or PDGFR by immunohistochemistry.¹¹ Eleven patients were enrolled and treated with imatinib at a dose of 600 mg orally daily on a 21-day cycle. No objective responses were seen. However 3 patients (27%) achieved SD as their best response with a median duration of SD of 6 weeks. No grade 4 toxicities were noted in this study. Grade 3 toxicities related to treatment included dyspnea (n=1) and hyponatremia (n=1).

A phase II study of imatinib at a dose of 600 mg orally daily was conducted in 7 patients with thymic malignancies, including 2 B3 thymomas and 5 thymic carcinomas.¹² The dosage was increased to 800 mg daily if there was evidence of disease progression. Three patients had received no prior chemotherapy. No objective responses were seen with imatinib monotherapy. 2 patients (29%) achieved disease stabilization and 5 patients had progressive disease. The median time to progression was 2 months and median survival was 4 months. Grade 3/4 toxicities included emesis (n=1) and depression (n=1). Three tumor samples were analyzed for mutations in the c-KIT or PDGFRA genes and no mutations were detected.

Histone Deacetylase (HDAC) Inhibition

Histone deacetylases are enzymes that are involved in the post-translational modification of histones and thereby exert an influence on DNA packaging and chromatin remodeling. HDAC inhibition can alter gene expression and induce apoptosis. In a phase I study of the

HDAC inhibitor belinostat, a patient with heavily pretreated metastatic thymoma had disease stabilization that lasted for 17 months.¹³ A patient with previously treated thymic carcinoma on another phase I study of the HDAC inhibitor MGCD0103 experienced disease stability for 18 weeks.¹⁴ Based on this data a phase II study of belinostat was conducted in patients with thymoma or thymic carcinoma who had recurrent or refractory disease after receiving at least one platinum-containing chemotherapy regimen.¹⁵ 22 patients had been enrolled as of December 2008 (14 thymomas and 8 thymic carcinomas). Belinostat was administered at a dose of 1000 mg/m²/day i.v. for 5 days every 3 weeks (beyond 12 cycles of therapy: every 4 weeks). Of 21 patients evaluable for response there were 2 PRs (both thymomas), 13 SD and 6 PD. Treatment was well tolerated. The most common adverse event was nausea and it was well controlled with prophylactic antiemetics.

Since belinostat showed some activity in patients with thymoma, an ongoing phase 1/2 study is evaluating it in combination with cytotoxic chemotherapy (cisplatin, doxorubicin and cyclophosphamide) in chemotherapy-naïve patients with advanced or recurrent thymic malignancies (ClinicalTrials.gov Identifier: NCT01100944). Treatment consists of belinostat administered as a continuous intravenous (i.v.) infusion over 48 hours on days 1 and 2, with cisplatin given on day 2, doxorubicin administered on days 2 and 3, and cyclophosphamide given i.v. on day 3 of a 21-day cycle. Doses per cycle at dose level 1 are 1000 mg/m², 50 mg/m², 50 mg/m², and 500 mg/m² respectively. 2 patients have been enrolled on study so far. Treatment has been fairly well tolerated. The most common adverse event has been nausea that has been no worse than that associated with chemotherapy alone.

Other targeted therapies

Sorafenib

Sorafenib is a multikinase inhibitor that inhibits RAF, VEGFR, PDGFR, c-KIT and p38. There are a handful of case reports describing responses to sorafenib in patients with previously treated metastatic thymic carcinoma. In one case a patient was found to have a missense mutation in exon 17 (D820E) of the c-KIT gene that was detected by direct sequencing. He achieved a PR 8 weeks after initiation of sorafenib therapy at a dose of 200 mg orally twice daily.¹⁶ At the time of reporting the patient continued to demonstrate a partial response after 15 months of therapy. An identical mutation has been identified in patients with gastrointestinal stromal tumor (GIST) that is unresponsive to treatment with imatinib mesylate. A second case of sorafenib-responsive thymic carcinoma was reported by Li et al.¹⁷ In this case the patient had disease progression despite receiving three prior regimens of cytotoxic chemotherapy. He was then treated with sorafenib at a dose of 400 mg orally twice daily and achieved disease stabilization which had lasted for more than 9 months at the time of reporting of results. Although no mutational analysis was performed in this case, the tumor did show strong immunohistochemical expression of KIT, p53 and vascular endothelial growth factor (VEGF).

IMC-A12 (Cixutumumab)

Zucali et al conducted a retrospective analysis of a surgical series of 132 patients with thymic epithelial tumors to determine the extent of insulin-like growth factor-1 receptor (IGF-1R) expression by immunohistochemistry (IHC).¹⁸ Among 111 samples that were evaluable for IGF-1R IHC staining, 22 cases (20%) were found to be positive. IGF-1R expression was significantly less common among WHO type A, AB and B1 thymomas as compared to B1/B2, B2, B2/B3, B3 and C subtypes (3.4% vs. 37.2%, $p < 0.0001$).

In a phase I dose escalation study of the anti-IGF-1R monoclonal antibody, CP-751,871, a patient with metastatic thymoma demonstrated a 10% reduction in tumor size with disease stabilization lasting for more than 1 year.¹⁹

Based on this data a phase II study was designed to evaluate cixutumumab, a monoclonal antibody directed against IGF-1R, in patients with unresectable thymoma or thymic carcinoma who have progressed after receiving at least one platinum-containing chemotherapy regimen.²⁰ Cixutumumab is administered at a dose of 20 mg/kg on day 1 of a 21-day cycle until disease progression or development of intolerable adverse effects. As of December 2009, 13 patients had enrolled at the National Cancer Institute including 5 patients with thymoma and 8 patients with thymic carcinoma. A median of 3 cycles of treatment had been administered (range, 1-7). The best response was SD in 8 patients (4 thymoma, and 4 thymic carcinoma); 5 patients experienced disease progression. Treatment has been well tolerated. Frequent adverse events include asymptomatic hyperglycemia, and pain at the site of metastatic disease that is responsive to non-steroidal anti-inflammatory drugs (NSAIDs).

Octreotide

The Eastern Cooperative Oncology Group conducted a phase II trial of octreotide alone or with prednisone in patients advanced, unresectable, octreotide scan-positive thymoma and thymic carcinoma.²¹ There were 38 assessable patients (32 thymoma, 5 thymic carcinoma, 1 thymic carcinoid) treated with octreotide at a dose of 0.5 mg subcutaneously three times a day for a maximum of 1 year. An assessment for response was made at 2 months. Those patients who were responding continued with octreotide therapy and patients with progressive disease were taken off treatment. For patients with stable disease prednisone therapy was started at a dose of 0.6 mg/kg/day along with octreotide for a maximum of 1 year. Two patients had stage III disease, 34 patients had stage IV disease, and staging was incomplete for 2 patients. Responses included 2 CRs (5%) and 10 PRs (26%) for an overall response rate of 32% (95% CI, 17.5% to 48.7%). Fourteen patients (37%) had SD and 12 patients (32%) had PD. All 38 patients were initially treated with octreotide alone and 4 PRs (11%) were seen. Prednisone was added to octreotide for 21 patients and 2 CRs and 6 PRs were seen with the combination. Toxicities included 1 grade 5 and 7 grade 4 adverse events. One patient treated with the combination had a grade 5 infection not associated with neutropenia. Three patients treated with octreotide alone and 4 patients treated with the combination had grade 4 metabolic abnormalities and dyspnea. Grade 4 hematological abnormalities included anemia and leucopenia. Overall the combination of octreotide and prednisone exhibited modest activity and could be considered for the treatment of recurrent disease in selected patients.

Sunitinib and SU014813

Sunitinib is a multi-kinase inhibitor that targets VEGFR1-3, PDGFR, c-KIT, FLT3, colony stimulating factor-1 (CSF1) and the RET receptor. Strobel et al treated four patients with refractory thymic carcinoma with sunitinib at doses of 25 mg per day to 50 mg per day.²² In three cases tumor samples were available to perform molecular analyses which showed activation of multiple receptor tyrosine kinases including PDGFR- β and VEGF3. Three patients demonstrated a PR with sunitinib therapy lasting between 2 and 18+ months and the fourth patient had stable disease lasting 22 months. Overall survival with sunitinib therapy in this series of patients was 4 months to 40+ months.

SU014813 is an orally administered multi-kinase inhibitor that targets VEGFRs, PDGFRs, KIT and FLT-3.²³ A phase I study of SU014813 was conducted in patients with advanced solid tumors using two different dosing schedules (escalating doses administered for 4 weeks with a 1 week break in therapy or doses of 100 mg or 150 mg administered using a continuous dosing schedule). Seventy seven patients were enrolled with chemorefractory solid tumors including four patients with thymoma. Adverse events included fatigue (64%), diarrhea (61%), nausea (44%), anorexia (43%), and emesis (42%). The most common

hematological adverse event was thrombocytopenia(22%). Twelve patients had an objective response to treatment including 2 patients with thymoma with PRs that lasted 15.3 months and 9 months respectively. 24 patients had SD including 5 patients with disease stabilization lasting more than 12 months.

PHA-848125-AC

Decreased expression of cell cycle proteins such as p21 and p27 predicts for poor response to neoadjuvant chemotherapy in invasive thymoma.²⁴ p21 and p27 are natural inhibitors of cyclin-dependant kinases (CDKs). In addition the pattern of expression of the neurotrophin receptors TRKA and p75 can be correlated with the WHO subtype of thymic malignancies.²⁵ PHA-848125 is an orally administered potent inhibitor of the CDK2/Cyclin A complex and TRKA. In an ongoing phase I study two out of three patients with thymic malignancies (type B3 and C histologies) demonstrated a PR after 10 and 6 months of treatment respectively at a dose of 150 mg per day. Based on these results an ongoing multicenter phase II study is evaluating PHA-848125-AC in patients with thymic carcinoma (ClinicalTrials.gov Identifier: NCT01011439). The study drug is administered at a flat dose of 150 mg once daily for 7 consecutive days of a 2-week cycle. The primary endpoint is the PFS rate at 3 months.

Saracatinib

Wakelee et al reported results of a phase II study of the Src inhibitor Saracatinib (AZD0530) in previously treated patients with advanced thymic malignancies.²⁶ Saracatinib was administered orally at a dose of 175 mg once daily and treatment was repeated in 28-day cycles. 21 patients enrolled on the study including 14 patients with thymoma and 7 patients with thymic carcinoma. 19 patients were evaluable for response. The best response was SD in 8 patients; no objective responses were seen. Treatment was generally well tolerated. Grade 3/4 adverse effects included one case each of dyspnea, neutropenia, and anemia. According to pre-specified criteria, the study was terminated after no clinical activity was seen in the first 13 patients with thymoma who were enrolled on study.

Conclusions

So far targeted therapy has yielded modest results in the treatment of thymic malignancies in patients who have failed chemotherapy. Anecdotal reports of response to biologic agents have been associated with the presence of rare mutations in specific genes. At present targeted therapy cannot be recommended for the routine management of patients with thymoma and thymic carcinoma. As data becomes available from ongoing systematic analyses of genetic aberrations in thymic tumors it is possible that newer targets will be uncovered in the future which can be treated with biologic therapy.

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