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Do thymic malignancies respond to target therapies?

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Abstract

A best evidence topic in cardiothoracic surgery was written according to a structured protocol. The question addressed was 'Do thymic malignancies respond to target therapies?' Altogether, 347 papers were found using the reported search, of which, in our opinion, 16 papers represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers were tabulated. We did not find any randomized controlled trials on target therapies for the thymic malignancies, due to the very small incidence of this tumour, and it seems unlikely that there will be any such trials in the foreseeable future. Three studies on target therapies showed that several cases of thymic malignancies were reported to have partial response (PR) to epidermal growth factor receptor tyrosine kinase inhibitors such as cetuximab and erlotinib, whereas, one study on erlotinib and another on gefitinib showed no activity. Proto-oncogene c-KIT (KIT) mutant thymic carcinomas were noted to benefit from target therapies, implying that systematic sequencing of KIT in thymic carcinoma tumours may be warranted for optimal patient selection. A study that investigated the efficacy of cixutumumab, a fully human IgG1 monoclonal antibody that binds to insulin-like growth factor 1 receptor, indicated that relapsed thymomas tended to respond, whereas thymic carcinoma did not. The antiangiogenesis agent belinostat had modest antitumour activity in heavily pretreated thymoma, but no response to thymic carcinoma was found. Several cases with metastatic thymic carcinoma showed that multitargeted kinase inhibitors, such as sunitinib and sorafenib, were effective. We concluded that, as the side-effects of the agents were tolerable in almost all reported cases, target therapies can be an option for patients with heavily pretreated thymoma.

Keywords: Targeted therapies • Thymic malignancies

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [patients with thymoma] does treatment with [targeted therapies] result in [increased survival]?

CLINICAL SCENARIO

During a national thoracic oncology meeting, a case of heavily pretreated thymoma patient is presented. The patient is considered unable to tolerate additional surgery or chemotherapy. One of the oncologists advises that the patient should be commenced on target therapies to improve survival. You resolve to check the literature yourself.

SEARCH STRATEGY

We searched Medline from 1950 to March 2014 using the pubmed interface with the search terms [thymoma OR thymic malignancy OR thymic tumour OR thymic carcinoma] AND [sunitinib OR belinostat OR motesanib OR dasatinib OR sorafenib OR imatinib OR cetuximab OR erlotinib OR gefitinib OR target therapy OR targeted therapy].

SEARCH OUTCOME

A total of 347 papers were found using the reported search. Among them, 16 papers were identified that provided the best evidence to answer the question and these papers are presented in Table 1.

RESULTS

Target molecular therapy is a new paradigm in the treatment of thymus tumours. Several major signalling pathways with potential targets that have been identified as playing important roles in thymus tumours include the epidermal growth factor receptor (EGFR) inhibitors, cetuximab and erlotinib, the KIT/mast/stem-cell growth factor receptor inhibitors, imatinib and sorafenib, the insulin-like growth factor 1 receptor (IGF-1R) cixutumumab, mammalian target of rapamycin (mTOR) inhibitor, antiangiogenesis pathway inhibitor belinostat and multitargeted kinase inhibitors such as sunitinib, sorafenib and dasatinib.

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Palmieri *et al.* (2007), Front Biosci, Italy [2] Case report (level V)	Two patients with metastatic and chemorefractory thymoma received cetuximab	Response and [18F] FDG uptake	Both patients achieved PR and reduced [18F] FDG uptake in metastases at 3 months	This report showed the metabolic tumour response to cetuximab (EGFR -TKI), though there was no apparent reduction in tumour size
Farina *et al.* (2007), Lancet Oncol, Italy [3] Case report (level V)	A recurrent patient with metastatic heavily pretreated B2 lymphocytic thymoma received cetuximab	Response	A PR with recession in tumour mass and metastases was detected after 6 weeks, and the treatment continued for SD after 12 months	This report showed the reduction in tumour size of thymoma in response to cetuximab
Christodoulou *et al.* (2008), Ann Oncol, Greece [4] Case report (level V)	A recurrent patient with mixed epithelial cells, lymphocytes stage IV thymoma and severe myasthenia gravis, received erlotinib	Response Survival Myasthenic symptom control	The patient had an excellent response and gained a 12-month survival, and myasthenic symptom	Tumour-controlled, myasthenic symptom improved and a better survival gained on the treatment with erlotinib
Pedersini *et al.* (2008), Tumori, Italy [5] Case report (level V)	A patient with heavily pretreated type B3 and stage IVb TC received erlotinib	Response	No response was detected after 4 months	Erlotinib showed no activity in the case of TC
Nakagiri *et al.* (2014), Ann Thorac Cardiovasc Surg, Japan [6] Case report (level V)	A patient heavily pretreated for a thymoma received gefitinib	Response Survival	The 3-month therapy led to no reduction of the tumour size and no improvement in survival	Gefitinib showed no activity in the case of thymoma
Giaccone *et al.* (2009), J Thorac Oncol, Netherlands [7] Report of results (level IV)	Seven patients with unresectable B3 (2 patients) thymomas and TC (5 patients) received imatinib	Survival	All 5 patients with TC had rapid PD and died; the 2 patients with B3 thymomas had SD and more than 38-month survival	Imatinib had no activity in TC, but improved survival in cases of thymoma
Ströbel *et al.* (2004), N Engl J Med, Germany [8] Case report (level V)	A c-KIT mutation (c-KIT exon 11 V560del) patient with hepatic metastatic TC received imatinib	Survival Clinical performance TTP	The patient died 20 months after the treatment. The therapy improved clinical performance for 4 months. The tumour progressed after 6 months	Patients with KIT mutation TCs can benefit from imatinib
Buti *et al.* (2011), J Clin Oncol, Italy [9] Case report (level V)	A c-KIT mutation (c-KIT exon 11 Y553N missense mutation) patient with heavily multiple bilateral pulmonary, hepatic and sternal metastatic TC received imatinib	Response Symptom and performance status	The treatment improved clinical performance after 1 week, and radiographic responses lasted for 9 months with liver function negative	Treatment with imatinib achieves a partial response with improvement in symptoms and performance status in patients with c-KIT mutation TCs
Bisagni *et al.* (2009), J Thorac Oncol, Italy [10] Case report (level V)	A patient with heavily pretreated metastatic TC with c-KIT mutation (c-KIT exon 17 missense mutation D820E) received sorafenib	Response	The clinical response was confirmed after 8-week treatment. After 15 months, it was still in PR	Patients with a hitherto unreported c-KIT missense mutation TC can benefit from imatinib

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Rajan *et al.* (2014), Lancet Oncol, USA [11] Cohort and time series (level III)	49 patients (37 with thymomas and 12 with TC) who had chemorefractory and progressive disease received cixutumumab	Response TTP Survival	14% thymoma patients achieved PR. The median TTP was 9.9 months and median survival was 27.5 months. None of 12 TC patients had PR	Thymomas can respond to cixutumumab, whereas TC does not
Wheler *et al.* (2013), Oncotarget, USA [12] Cohort and time series (level III)	11 patients with advanced/ metastatic thymoma or TC treated with conventional regimen and 10 patients treated with mTOR inhibitor combination regimen	TTF	For patients treated on mTOR inhibitor regimens, median TTF was 11.6 months versus 2.3 months on last conventional regimen prior to referral	The mTOR inhibitor combination regimen prolonged TTF in patients with advanced/metastatic thymoma or TC
Giaccone *et al.* (2011), J Clin Oncol, USA [13] Report of results (level IV)	41 patients had previous systemic regimens, of which 25 had thymoma, and 16 had TC received belinostat	TTP Survival Response	Median TTP and survival were 5.8 and 19.1 months, respectively. Two patients achieved PR, 25 had SD. All the 13 patients with TC had PD	Belinostat has modest activity in these heavily pretreated thymic malignancies
Azad *et al.* (2009), Acta Oncol, Australia [14] Case report (level V)	A patient with heavily pretreated thymoma received motesanib diphosphate (AMG 706)	Response	A modest increase in tumour measurements that reached a maximum after 11 cycles, and after 17 cycles there had been a 28% decrease	This case illustrated that the benefit of motesanib diphosphate can be delayed
Ströbel *et al.* (2010), Br J Cancer, Germany [15] Report of results (level IV)	Four patients with metastatic refractory TCs received sunitinib	Survival Response	The overall survival ranges from 4 to 40+ months. A PR (lasting 2 to 18+ months) in 3 patients and SD with excellent metabolic response in 18F-FDG-PET in another one was observed	Sunitinib can be effective in patients with metastatic refractory TCs
Chuah *et al.* (2006), J Clin Oncol, Germany [16] Case report (level V)	A patient with pretreated chronic myeloid leukaemia, developed lymphoid blast crisis and a B2 thymoma received dasatinib	Response	CT showed a PR in the size of the mediastinal mass (from 69.3 to 40.6 cm^3)	Dasatinib may potentially benefit thymoma patients
Neuhaus and Luyken, (2012), Targ Oncol, Germany [17] Case report (level V)	A heavily pretreated patient with CD117(c-KIT)-negative TC with widespread metastases received sorafenib	Response Survival	A 50% reduction of tumour size was documented after 3 months, and this effect lasted for 15 months	Sorafenib led to tumour-control and prolonged survival in patients with CD117-negative TC

FDG: fluorodeoxyglucose; PR: partial response; TC: thymic carcinoma; TTF: time to treatment failure; TTP: time to progression; SD: stable disease; PD: progressive disease.

Palmieri *et al.* [2] evaluated the effect of cetuximab on two metastatic and chemorefractory thymomas. After 3 months of cetuximab treatment, these two patients achieved PR as the [18F] fluorodeoxyglucose uptake was significantly decreased at metastatic sites. Similarly, it has been reported in the study of Farina *et al.* [3], which showed that a recurrent patient with metastatic heavily pretreated World Health Organization (WHO) international histological classification of tumours of thymus B2 lymphocytic thymoma received cetuximab treatment and a PR was detected after 6 weeks of therapy. In addition, the patient was still treated with cetuximab for stable disease after 12 months.

A report by Christodoulou *et al.* [4] showed that a patient with a recurrence of malignant mixed stage IV thymoma responded to erlotinib with a confirmed PR for 12 months and with limited side-effects. However, Pedersini *et al.* [5] reported that erlotinib did not show any beneficial impact on a patient with heavily pretreated thymic carcinoma, and strong EGFR expression, after 4 months of treatment.

Nakagiri *et al.* [6] reported a 56-year old woman with heavily pretreated thymoma. After positive evidence of EGFR mutation was obtained, gefitinib was administrated for 3 months, but this led to no reduction in tumour size.

In a single institutional report of imatinib treatment by Giaccone *et al.* [7], 7 patients including unresectable WHO B3 thymomas (2 patients) and thymic carcinoma (5 patients) underwent imatinib treatment. Two patients had stable disease and 5 progressed. Median survival was 4 months and median time to progression (TTP) was 2 months.

Ströbel *et al.* [8] also showed that the liver metastases shrank within 4 months of imatinib treatment in a thymic carcinoma patient with KIT mutation and multiple liver metastases. A report by Buti *et al.* [9] found that a heavily pretreated patient with metastatic c-KIT mutated thymic carcinoma received imatinib treatment and improvement of clinical performance was documented with radiographic responses lasting for 9 months. In addition, an earlier report by Bisagni *et al.* [10] also reported a 15-month PR to sorafenib in a heavily pretreated patient with metastatic thymic carcinoma and with c-KIT missense mutation on exon 17 (D820E). This evidence suggests that screening for activating KIT mutations might identify KIT expressing carcinomas, which could benefit from target therapies.

Rajan *et al.* [11] investigated the efficacy of cixutumumab, a fully human IgG1 monoclonal antibody targeting IGF-1R in 49 patients with recurrent or refractory thymic epithelial tumours (37 with thymomas and 12 with thymic carcinomas) after failure of previous chemotherapy. With a median follow-up of 24 months, five of 37 (14%) thymoma patients achieved PR. The median TTP was 9.9 months and median survival was 27.5 months. However, none of 12 thymic carcinoma patients had a PR, and the median TTP and overall survival were 1.7 and 8.4 months, respectively. These reports indicate that thymomas can respond to this form of target therapy, whereas thymic carcinoma generally does not.

Evidence shown by Wheler *et al.* [12] found that, for thymoma patients (with advanced thymoma or metastatic thymic carcinoma) treated on mTOR inhibitor regimens, the time to treatment failure (TTF) was 11.6 vs 2.3 months on their last conventional regimen prior to referral.

There was also a phase II study of belinostat by Giaccone *et al.* [13] in 41 patients with recurrent or refractory advanced thymic epithelial tumours. Two patients achieved PR, 25 had stable disease and all 13 thymic carcinoma patients had progressive disease after belinostat treatment.

Azad *et al.* [14] investigated the effect of motesanib in a heavily pretreated thymoma patient. Although there was a modest increase in tumour measurements that reached a maximum after 11 cycles, it achieved a meaningful effect for over 12 months.

Ströbel *et al.* [15] also reported that four patients with metastatic thymic carcinoma refractory to conventional therapies were treated with sunitinib. A partial remission (lasting 2 to 18+ months) in 3 patients and a stable disease in another one were documented.

Chuah *et al.* [16] reported a patient with pretreated chronic myeloid leukaemia who developed lymphoid blast crisis and a B2 thymoma. After 2-month treatment with dasatinib, a clinical remission and tumour size reduction was obtained, and the mass was completely resected.

Thomas *et al.* [17] evaluated the effect of sorafenib in a heavily pretreated patient with widespread metastatic thymic carcinoma. After a few weeks, the general condition of the patient improved and a 50% reduction in tumour size was documented, which lasted 15 months.

CLINICAL BOTTOM LINE

The evidence we have presented shows that several cases of thymic malignancy responded to EGFR-TKIs such as cetuximab and erlotinib: these agents can be regarded as a worthwhile treatment option for heavily pretreated thymoma. Evidence also shows that screening for activating KIT mutations can identify KIT expressing carcinomas that may benefit from target therapies. In addition, treatments combined with an mTOR inhibitor have been shown to prolong the TTF in patients with thymic carcinoma. Antiangiogenesis agents, such as belinostat, had modest antitumour activity in heavily pretreated thymoma, but no response in thymic carcinoma. Multitargeted kinase inhibitors such as sunitinib and sorafenib seem to be a particularly good choice of second-line therapy for thymic carcinoma. Target therapies can be an option for patients with heavily pretreated thymoma, as the side-effects of the agents have been tolerable in almost all reported cases.

Conflict of interest: none declared.

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