

Thymic Malignancies in the Targeted Therapies Era

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Abstract

Objective: In the last years, significant efforts have been made in order to improve the knowledge of molecular biology of thymic malignancies. The purpose of this manuscript is to review the recent advances in the treatment of refractory, recurrent thymomas and thymic carcinomas, focusing on molecular targeted therapy and on the previous or actually ongoing clinical trials and genomic analysis.

Methods: Available literature on the topic of thymic malignancies was extensively reviewed, using the MEDLINE, CancerLit and ClinicalTrial.gov databases. We searched for targeted therapies studies between restricting our search to English-language publications, including the following search terms: “targeted therapy, octreotide, molecular alterations and pathways” in association with thymoma, thymic carcinoma and thymic neoplasms/malignancies.

Results: Recent thymic malignancies’ molecular characterization includes identification of several aberrant pathways such as epidermal growth factor receptor signalling, angiogenesis inhibition, c-KIT signalling, m-TOR inhibition, IGF-1 receptor signalling, all involved in the carcinogenesis, growth and different behaviours of thymic tumor. They also represents potentially targetable molecular bio-markers, although to date there are no clinical randomized prospective trials evaluating treatment efficacy available and the use of these new biological drugs is currently not recommended in the routine clinical practice. Despite the rarity of these neoplasms and lack of established cell lines and animal models, recently selected genes have been analyzed in small cohorts of patients, aimed to better understand the biology and the genetic and epigenetic aberrations drivers in thymic malignancies.

Conclusion: Novel strategies are needed, especially for refractory, recurrent thymic tumors after first-line chemotherapy failure. The investigation of molecular profiling and the analyses of genetic aberrations in thymic tumors could also allow determining potentially druggable new targets. Further clinical research directions and regional and international collaborative initiatives may be warranted to progress both in the understanding of biology and to define the most effective treatment.

Keywords: Thymoma; Thymic carcinoma; Somatostatin; Octreotide; Targeted therapy; Immunotherapy; Molecular alterations

Introduction

Thymic epithelial tumours are rare malignancies of the anterior superior mediastinum with an overall annual incidence of 0.15 per 100.000 inhabitants and they typically occur in people over 40. They represent a wide range of histological and molecular malignant entities that may have indolent or aggressive behaviours, especially with tendency of local invasiveness.

Emerging data further indicate that thymoma and thymic carcinomas (TC) are distinct entities, in terms of clinical and biological behaviours, emerging gene expression and sequencing data, due to the fact that there is probably considerable heterogeneity even among tumors presenting the same histotype [1-4].

The optimal management of thymic tumors consists in the multimodal approach among different types of physicians, like surgeons, pathologists, oncologists and radiotherapists since diagnosis [5].

To date surgery remains the only curative treatment, as well as complete resection represents the most significant prognostic factor, with regards to disease-free and overall survival [6].

However, thymomas can recur in 10 to 30% cases after R0 resection. Postoperative radiotherapy seems to lead to a decrease in recurrence rate from 60 to 80% in stage II completely resected thymomas and from 21 to 45% in more advanced stages, although its use is still highly debated and the global trend is moving towards a less frequent utilization of it [7-11].

Furthermore, postoperative is systematically recommended in case of incomplete resection (R1 or R2). Patients with surgically unresectable, metastatic or recurrent tumors are candidates to systemic chemotherapy. Cisplatin-based chemotherapy represents the most effective option, although there are several situations in which it could be contraindicated [12-13].

To date, worldwide investigators are focused on translational studies on cellular pathways which play a critical role in thymic neoplasm pathogenesis, in order to identify the biology and the genetic and epigenetic aberrations drivers in thymic malignancies. Moreover,

integrating genomic analyses represents a new way for the identification of innovative targets. Recent molecular characterization integrated with genomic analyses of thymoma and TC has allowed the identification of potentially “druggable” targets and the development of alternative therapeutic molecular drugs. Several Phase I-II Clinical Trials are currently ongoing to evaluate the safety and the efficacy of different Tyrosine Kinase inhibitors, mTOR inhibitors, Angiogenesis inhibitors, Histone deacetylase inhibitors, DNA Methyltransferase inhibitors, Cyclin-dependent Kinases/Thropomyosin receptor kinase A Inhibitors that have shown some activities in the pre-clinical setting. Moreover, a small sub-group of tumors expresses the Somatostatin (SS) and SS receptors (SSR), which are involved in cancerogenic processes and targetable by Octreotide.

Lastly, expression signature seems to correlate with metastasis-free survival for thymomas and TC. These results need to be validated in separate cohorts, while prospective studies are required to understand the clinical significance of these results. A new alternative strategy that is currently investigated is immunotherapy, which aims at increasing cytotoxic drugs efficacy. Because of the lack of data, the enrollment of patients with advanced thymic disease into available clinical trials has to be encouraged [7].

Recently, the International Thymic Malignancy Interest Group (ITMIG) is focusing its efforts in creating a registry of patients and tumors to better characterize the molecular alterations in thoracic malignancies and develop markers of early detection [14].

The aim of this literature review is to focus on the molecular targeted therapies and on the related Clinical Trials, although the use of these new biological drugs is not recommended at present in the routine clinical practice in patients with thymic malignancies.

Methods

Available literature on the topic of thymic malignancies was extensively reviewed. In particular we reviewed the published peer-reviewed journals using the MEDLINE, CancerLit and ClinicalTrial.gov databases. We searched for targeted therapies studies between 1982 and 2014 restricting our search to English-language

publications. We included the following search terms: “targeted therapy, octreotide, molecular alterations and pathways” in association with thymoma, TC and thymic neoplasms/malignancies.

Full publications were reviewed, and references were checked for additional appropriate references.

Somatostatin analogues

In human epithelial thymic cells SS and SSR are normally expressed, moreover expression of these bio-markers also characterizes a subgroup of malignant thymic cells [15].

Octreotide is an octapeptide SS analogue that can be used to select patients with a positive uptake on somatostatin receptor scintigraphy with ¹¹¹InDTPA-D-Phe1 (octreotide scan)[16] and it could be taken into account as alternative treatment in case of recurrent disease in this specific subgroup of thymomas. Lastoria et al. showed in a cohort of 18 patients with thymic masses who underwent octreotide-scintigraphy, an increased up-take in those with thymoma compared with patients affected by thymic hyperplasia or other benign disorders [17] (Table 1). In a Phase II trial 16 patients affected by thymic tumors were treated with subcutaneous octreotide (1.5 mg daily) in combination with prednisone, and the overall response rate (ORR) was 37% and the median survival time was 15 months [18]. The Eastern Cooperative Oncology Group (ECOG) enrolled 38 patients to receive Octreotide (1.5 mg/daily) alone or in combination with prednisone. The ORR were 10.5% and 30%, respectively [19].

Nevertheless, the real anti-tumor activity of octreotide against thymic neoplasms is still unclear. SS has antiproliferative activity probably through the blockage or inhibition of the insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF) and neo-angiogenesis and the activation of immunity[20].

Based on the lack of systematic studies with the commercially available long-acting SSA already used in high-dose treatments, a phase 2 trial with high doses Somatostatin analogue (30 mg subcutaneous/daily) in a long acting formulation in different settings of mediastinal neoplasms is currently ongoing.

Agent	Mechanism	ClinicalTrials.gov Identifier	Principal Investigator	N° of Patients	Dose
GEFITINIB	TKI EGFR	Phase 2	Loehrer PJ,MD	26 (7TC)	250 mg daily
ERLOTINIB	TKI EGFR	NCT00369889 (plus Bevacizumab) (Phase 2)	Loehrer PJ,MD	18 (7TC)	150 mg p.o.
		NCT01306045 (Pilot Study) (Phase 2)	Gula U,MD	Recruiting	150 mg p.o.
CETUXIMAB	EGFR antibody	NCT01025089 (plus chemotherapy CAP) (Phase 2) ONGOING	James Huang, MD	Recruiting	250 mg/m ² weekly
IMATINIB	TKI KIT, Bcr-Abl, and PDGFR	Phase 2	Giaccone G, MD	7 (5 TC)	600 mg p.o. daily
		Phase 1	Salter JT, MD	11 TC	600 mg p.o. daily
		Phase 2	Palmieri G, MD	15 (3 TC)	400 mg p.o. daily
		NCT00314873(Phase1)	Loehrer PJ, MD	11 TC	600 mg qd q 21

SUNITINIB	TKI VEGFR1-3, FMS-like TK3, c-KIT, PDGFR, FLT-3, RET-receptor and CSF1	NCT01621568 Phase 2 ONGOING	Ragan A,MD	Ragan A,MD	50 mg daily
SU14813	TKI VEGFR2, PDGFR, c-KIT, FLT-3	NCT00982267 (Phase 1)	Pfizer	4	Escalating doses from 50 to 250 mg daily
MOTESANIB (AM 706)	TKIKIT,VEGFR -1, -2, -3 and PDGFR	NCT00093873 (Phase 1)	Amgen	1	Escalating doses from 50 to 175 mg daily
SARACATINIB (AZD0530)	Src non-receptor tyrosine kinase inhibitor	NCT00718809 (Phase 2)	P.Loehner,MD	21 (7TC)	175 mg daily
EVEROLIMUS	mTOR inhibitor	NCT01563354 (Phase 2)	Novartis	Recruiting	10 mg p.o. daily
CIXUTUMUMAB (IMC-A12)	IGF-1R antibody	NCT00965250 (Phase 2)	Giaccone G,MD	49 (12TC)	20 mg/kg iv q21
FIGITUMUMAB (CP-751.871)		Phase 2	Haluska P, MD	1	dose escalation from 3 to 20 mg/kg iv q21
BEVACIZUMAB	VEGFR antibody	NCT00369889 (Plus Erlotinib) (Phase 2)	P. J Loehrer, MD	18 (7TC)	15 mg/kg iv q21
AFLIBERCEPT (AVE0005)	TKI VEGFR-A, VEGFR-B and PIGF	NCT00545246 with docetaxel (Phase 1)	Sanofi	1	dose escalation 2, 4, 6, 7, 9 mg/kg iv
BELINOSTAT (PDX101)	Pan-HDAC inhibitor	NCT00589290(Phase 2)	Giaccone G,MD	41 (16 TC)	1000mg/m2 1-5 days q21
FR901228 (DP) and FLA	HDAC inhibitor and CDK inhibitor	NCT01100944 in combination with PAC (Phase 1/2) ONGOING	Rajan A ,MD	26	four dose levels and dose escalations
DECITABINE	DNMT inhibitor	(Phase 1)	Stewart DJ	4	dose escalation 2,5-10 mg/m2 and 8,12,15,20 mg/m2
MILCICLIB MALEATE (PHA-848125AC)	CDK2, CDK1, CDK4 and TRKA Inhibitor	NCT01011439(Phase 2) ONGOING	Weiss G, Besse B, Mazieres J, Novello S, Rajan A, Garassino MC, MD	Recruiting TC	150 mg/daily
		NCT01301391(Phase 2) ONGOING	Rajan A and Garassino,MD	Recruiting Thymomas	150 mg daily 1-7
Octreotide-LAR		NCT00990535(HIDONET) (Phase 2) ONGOING	Colao A,MD		30 mg sc/daily
Octreotide +/- prednisone		NCT00003283 (Phase 2)	Loehrer PJ, MD	38 (5 TC)	1.5 mg/daily subcut
Octreotide-LAR NCT00332969(Phase 2) ONGOING		NCT00332969(Phase 2) ONGOING	Novartis	25	30 mg sc/daily

Table 1: Phase 1 and phase 2 trials with new targeted therapies in thymic malignancies.

Targeted therapy

To date, the deeper knowledge of several genetic abnormalities and molecular pathways involved in potentially “druggable” thymic malignancies carcinogenesis has encouraged the use of biological therapies. Given the currently available targeted agents outside of a clinical trial, the signalling pathways that are at present considered the most relevant in clinical care, are EGFR, IGF Receptor (IGF-1R) and c-KIT signalling pathways (Table 1).

Furthermore, tumor suppressor genes (TP53, p16INK4A), chromosomal aberrations (LOH 3p, 6p, 6q, 7p, 8p), angiogenic factors (vascular endothelial growth factor [VEGF]), and tumor invasion factors (matrix metallo-proteinases and tissue inhibitors of metallo-proteinase) that are involved in tumor growth and proliferation are also considered as promising molecular targets. Several phase I-II clinical trials aim to evaluate the safety and the efficacy of different tyrosine kinase inhibitors, mTOR inhibitors, angiogenesis inhibitors, Histone deacetylase inhibitors, DNA methyltransferase inhibitors, cyclin-dependent kinases/thrombospondin receptor kinase A Inhibitors, which have shown some activity in thymomas and in TC [21].

EGFR and Her2/Neu Inhibitors

EGFR is a transmembrane glycoprotein with intrinsic tyrosine-kinase activity. The ligand-binding with the receptor induces the homodimerization or heterodimerization that activates the intracellular signal transduction cascades, including Ras, PI3k, and Akt, the Stat pathways and MAP kinases. The activation of these pathways results in a variety of cellular responses including cell proliferation and differentiation [22]. EGFR is over-expressed in approximately 70% of thymomas and 50% of TC. High percentage of staining is associated with advanced stages and capsule invasion [23-25].

Literature data report sporadic cases of TCs carrying G719A in exon 18 and L858R in exon 21 mutations that showed some responses to gefitinib [24]. However, Kurup et al. performed a phase II clinical trial with 26 patients with thymic tumors (19 thymomas and 7 thymic carcinoma) treated with gefitinib 250 mg per day. As a result, only 1 PR and 14 SD were observed and time to progression (TTP) was 4 months in 6 patients. Five samples were evaluated by DNA sequencing and no EGFR-activating or KRAS mutations were found, neither in the patient with PR [26]. The rarity of activating mutations involving EGFR gene in thymic malignancies maybe could be justify the low rate of ORR with EGFR-tyrosine kinase inhibitors [24,27]

Another EGFR tyrosine kinase inhibitor, erlotinib (150 mg daily), has also been tested in a phase II trial with 18 patients with pre-treated thymomas and TC, in association with the VEGF inhibitor bevacizumab (15 mg/kg q21), hypothesizing a synergistic effect on this tumor. Sixty percent (60%) obtained SD, without any PR [28]. Another phase II trial is currently ongoing, aimed to evaluate the effectiveness of pre-treatment genetic analysis in determining targeted therapy for individuals with advanced non-small cell lung cancer, small cell lung cancer, and thymic cancer.

To date, there is no evidence for EGFR evaluation in patients with metastatic or recurrent TC in routine clinical practice and for the use of EGFR inhibitors outside of a clinical trial.

Furthermore, Her2/Neu is over-expressed on the cell membrane in 33-50% cases of TC [29,30], although it is rare in thymomas [31]. Several observations of pretreated recurrent thymoma exhibiting PR to the EGFR-antibody, represents the basis of an ongoing Phase II

Clinical trial, which was designed to investigate the feasibility of delivering cetuximab in combination with CAP in unresectable locally advanced thymoma. Several observations of pre-treated recurrent thymoma exhibiting PR to the EGFR-antibody [32,33], has led to a phase II Clinical trial in order to analyse cetuximab activity in combination with CAP regimen in thymoma with clinical Masaoka II-IVA also in the neoadjuvant setting.

K-Ras

K-RAS proto-oncogene encodes the p21 protein and plays a central role in the EGFR pathway [34]. The p21 expression in thymomas is higher than in TC and has demonstrated a prognostic role in a small setting of patients [35]. Previously, investigators have assessed the status of RAS gene finding KRAS (G12V – G12A) and HRAS (G13V) mutations [26,34,36]. Although the rarity of RAS mutations, further investigations and randomized studies are required with the aim to assess the potential role of EGFR inhibitors in thymic malignancies.

c-KIT Inhibitors

KIT (CD117) is a transmembrane growth factor with tyrosine kinase activity and represents the product of the proto-oncogene c-KIT. CD117 is expressed in approximately 80% of TC, whereas thymomas usually do not express CD117 or very rarely (approximately from 0 to 5%) [37-39]. Then Henley et al found KIT overexpressed in EGFR negative thymic tissue, as if EGFR and KIT were alternative patterns of staining in the setting they analysed. For this reason, KIT expression was put forward as specific diagnostic biomarker for carcinoma with thymic origin versus other mediastinal malignancies [40]. Despite the high frequency of KIT expression, KIT mutant TC represent a small molecular subset such as 9% (13 out of 128 collectively analyzed) [38,41]. The genes involved most in activating mutations are the exons 9, 11, 14 and 17 and not all KIT mutations in these types of tumors will respond to KIT inhibitors. V560 deletion (typical of GISTs tumors), Y553N substitution, W557R and V559A in the exon 11, are sensitive to imatinib. The D820Y substitution is related with resistance to imatinib [5,42]. Although L576P substitution is imatinib and sunitinib – responsiveness, H697Y substitution in exon 14 is associated with in vitro higher sensitivity to sunitinib only. Lastly, D820E substitution in exon 17 and P577-579 deletion in exon 11 lead to sorafenib-sensitivity [5,43,44]. Although the encouraging previous evidences of imatinib activity in a TC squamous cell G3 [45], subsequent clinical trials were disappointing. Two previous small prospective trials have failed in treating with imatinib patients not selected in TETIMAX trial [46] or selected according to histologic type (WHO B3 thymomas or thymic carcinoma) [47] or KIT staining by IHC, not with KIT genotyping [48]. A Phase I Clinical trial has been recently completed with the aim to evaluate the activity of imatinib against TC in patients selected for c-KIT or PDGF expression.

Therefore, a selection of TC on the strength presence/absence of c-KIT mutations is mandatory, as routinely in GIST, because the potential benefit of target therapy with different RTK inhibitors in TC. Schirosi et al. [49] analysed 48 patients with TC, more than half showed c-KIT mutation but only six cases harbouring activating mutations. They proposed a therapeutic algorithm based on Immunostaining for CD117 and, when over-expressed, expanding molecular test to exons 9, 11, 13, 14 and 17.

KIT signalling represents a key pathway in thymic cancer development, therefore the implementation of KIT genotyping both within the clinical practice and within clinical trials are warranted.

Multitargeted Kinase Inhibitors

Sorafenib and Sunitinib are oral Multikinase Inhibitors (mTKI) with also antiangiogenic potential targeting VEGFR-1, -2 and -3. The VEGFR pathway plays a key role in neovascularization and so in tumor development and progression. Ströbel in 2004 reported a PR in three patients and SD in another one with metastatic TC, obtaining an OS ranging from 4 to 40 months with sunitinib in 4 metastatic TCs [50]. A Phase II Clinical Trial with Sunitinib 50 mg in patients with relapsed or refractory thymoma or TC after first-line chemotherapy failure is actually ongoing.

An other Phase II Clinical Trial is enrolling patients with thymic tumors pre-treated with chemotherapy based on molecular analysis screening, aimed at treating, in the arm with Sunitinib, patients patients with KIT mutation, PDGFR-A mutation or PDGFR-A gene amplification by FISH (gene to chromosome ration > 2) in the arm with Sunitinib.

In non-clinical studies SU14813, an oral inhibitor of VEGFR2, PDGFR, Kit, and Fms-related tyrosine kinase 3 (Flt-3), demonstrated an antitumor activity equivalent to sunitinib and in a phase I trial obtained PRs in 2 patients, between the four refractory thymomas enrolled [51,52]. On the other hand, no Clinical Trials have been performed with Sorafenib in thymic tumor setting. To date, there are three clinical case in literature reporting the activity of sorafenib in heavily pre-treated, chemotherapy-resistant metastatic patients [53-55]. Furthermore, P577-D579 deletion in exon 11 and D820E78 in exon 17 were identified as the mutations most sensitive to sorafenib [44,53]. Recently, a phase I study investigated Motesanib, an oral VEGFR-1, -2, -3, KIT, and PDGFR inhibitor, and showed clinical activity in one patient with advanced heavily pre-treated thymoma [56].

Dasatinib, an oral multitargeted kinase inhibitor of Bcr-Abl, KIT, PDGFR, and Src family kinases, ephrin receptor kinases, platelet-derived growth factor receptor [57] was used in a patient with Masaoka stage I, B2-type thymoma expressing EGFR (KIT negative), obtaining a PR that allowed a radical resection [58]. Authors speculated that the response was mediated by Arg tyrosine kinase, often overexpressed in thymomas [59] and targeted by Dasatinib.

Furthermore, despite thymic tumors frequently appear as large masses involving or infiltrating mediastinal vascular structures, no hemorrhagic adverse events have been reported in patients treated with these drugs [5].

mTOR Inhibitors

The mTOR pathway plays a critical role in neoplastic growth and it is also implicated in regulation of actin cytoskeleton, angiogenesis and cellular response to hypoxia and energy depletion.

The mTOR complex is involved in signaling downstreaming of many soluble factors, including such as the EGF and the IGF-1 which show a role in TETs biology [60,61]. This knowledge suggests that mTOR pathway may probably have a role in thymoma biology also, although there are no in vitro data, thus providing the biological rationale to support the use of everolimus in TETs. Palmieri G reported two cases of patients with thymoma pre-treated with several

line, whom underwent treatment with Everolimus at last and experienced a PFS longer than one year and a considerable improvement of clinical conditions and quality of life; one of those showed remission of myasthenia gravis, may be due to the immunosuppressant properties of everolimus [61].

Furthermore, a Phase I trial with the mTOR inhibitor ridaforolimus showed a prolonged disease stabilization (>16 wk) in a patient with TC [62]. Another Phase I trial was conducted at the MD Anderson Cancer Center and randomizing 10 patients with thymic tumors in a mTOR arm obtained SD or PR in all and TTF of 11,6 months vs 2,3 months with last conventional regimens [63]. A phase II Clinical Trial with Everolimus or Pasireotide LAR alone or in combination in adult patients with advanced (unresectable or metastatic) neuroendocrine carcinoma (typical and atypical) of the lung and thymus, is ongoing.

VEGFR/VEGF Inhibitors

VEGFR/VEGF pathway plays a key role in thymic tumors carcinogenesis VEGF-A, VEGFR-1 and VEGFR-2 receptors are overexpressed in thymoma and TC compared to controls [64]. The upregulation of this pathway is associated with the advanced clinical stages, predominantly in TC [65].

In a phase II trial in 18 patients with refractory thymoma and TC Bevacizumab in combination with erlotinib showed disappointing results [28]. A phase I trial exploring escalating doses of Afibercept associated with docetaxel lead to PR in one patient with thymoma [66].

Although currently there are limited data, antiangiogenic agents might be a promising treatment for patients with invasive thymic epithelial tumors and further evaluations and clinical trial should be performed.

IGF-1R Inhibitors

IGFs family, such as IGF-1, IGF-2, the IGF-1R and the IGF-binding proteins (IGFBPs), are involved in cancerogenesis and tumor progression [67,68]. IGF-1R activation is implicated in the resistance to anticancer therapies, including cytotoxic chemotherapy, biological therapies, hormonal agents, and radiation [69,70]. Recent retrospective analysis conducted in a total of 195 thymic tumors, demonstrated that higher IGF-1R expression was associate with more aggressive histological subtypes, advanced stages and recurrent disease. Although IGF-1R did not show any prognostic value, it may be considered a predictive marker of response to IGF-1R inhibitors [71,72]. Recently two monoclonal antibodies and small molecule kinase inhibitors have been developed against IGF-1R. In phase I trials Figitumumab (CP-751,871) induces IGF-1R down-regulation, antagonizing the IGF-1 binding to IGF-1R and obtained a 10% reduction in tumor size and SD for over 1 year in 2 patients with refractory thymomas. Furthermore, CP-751,871 exhibited different activities that consist in down-regulating of IGF-1R in vitro and in vivo and in inhibiting IGF-1-mediated and IGF-2-mediated phosphorylation of IGF-1R and Akt [73]. So, it could antagonize both activating ligands, at the same time.

Encouraging results have been obtained with Cixutumumab (IMC-A12), an IGF-1R antibody [74], in patients with advanced platinum-refractory thymic neoplasm in a Phase II Clinical trial [75].

Furthermore, heat-shock protein 90 chaperone inhibitors whom contribute to the stability and activity of IGF-1R, CDK4, and EGFR,

were shown to target IGF-1R over-expressed by a neoplastic thymoma cell in vitro studies. Molecular chaperone Hsp90 could represent a potential therapeutic strategy in thymic neoplasm and further investigations and clinical trials are required [76].

Histone Deacetylase Inhibitors

Histone deacetylases (HDAC) enzymes catalyze the removal of an acetyl group in nucleosomes, which mediates changes in chromatin conformation, leading to regulation of gene expression with tumour suppressor and oncogene role [77]. In a phase I study of Belinostat, one patient with thymoma had a minor response that lasted for 17 months [78]. In another Phase I trial the HDAC inhibitor MGCD0103 provided SD for 18 weeks in one patient with TC [79]. Based on these data a phase II study was performed with 41 patients with thymomas

and TC which underwent Belinostat, after received at least one platinum-containing chemotherapy regimen. Two patients only achieved PR and 25 had SD; no responses among patients with TC were observed. Median TTP and survival were 5.8 and 19.1 months (longer in thymoma than TC), respectively [80] (Figure 1).

A phase I/II study of belinostat in first line in combination with cisplatin, doxorubicin and cyclophosphamide in chemotherapy-naïve advanced or recurrent thymic malignancies is actually ongoing.

Furthermore, a Phase I trial with Depsipeptide FR901228 (DP), another HDAC inhibitor, in combination with the CDK inhibitor Flavopiridol (FLA) is ongoing. In pre-clinical studies these drugs have shown a synergic activity that consists in mediating apoptosis in cultured cancer cells of the mediastinum.

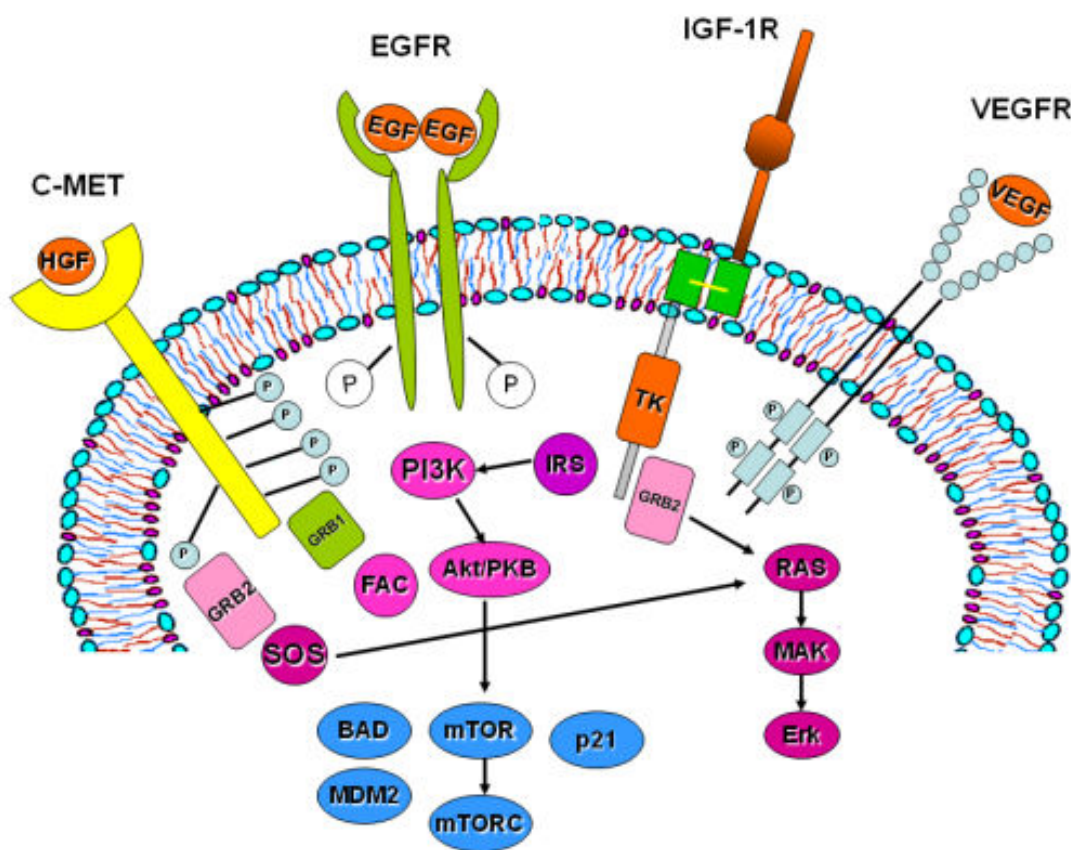


Figure 1: Main intracellular signaling pathway that may be activated in thymic malignancies.

SrcInhibitors

The proto-oncogene c-Src (Steroid receptor coactivator) belongs to Src family kinases, a series of enzymes involved in proliferation, cell growth, differentiation, cell shape, motility, migration, angiogenesis, and survival by facilitating the action of other signaling proteins [81].

A phase II study was performed with Saracatinib (AZD0530) in 21 patients with relapsed/refractory thymic malignancies. Treatment was well tolerated, but according to pre-specified criteria, the study was

terminated after no clinical activity has been seen in all thymoma enrolled. No further studies were being developed [82].

DNA Methyltransferase Inhibitors

DNA methylation represents an important which is linked with epigenetic modulating. In a Phase I trial of decitabine in 31 patients with refractory solid tumors, a DNMT inhibitor, one out of 4 patients with thymoma developed a PR [83]. Furthermore, decitabine was shown to reduce platinum-resistance mediated by the decrease of copper/platinum uptake transporter CTR1 and the increase of DNA

methylation [84] in platinum-resistant tumor cells and it could be used in combination with other cytotoxic agents. Given the potential role of DNMT inhibitors as resistance modulator, their further evaluation in terms of activity on thymic malignancies are required.

Cyclin-dependent Kinases/ThropomyosinReceptor Kinase A Inhibitors

Cyclin-dependent kinases(CDKs) play a role as “check point” of cell cycle in G1-S transition.

Thropomyosin receptor kinase family (TrkA, TrkB, TrkC and p75NTR) contribute to neuronal plasticity and neuronal survival and differentiation through several signal cascades. An altered expression of Trk is involved in carcinogenesis and metastasis [85].

Kelly et al. evaluated neurotrophin receptors expression in thymomas and in TC by IHC and all tumors included, except one TC, demonstrated cytoplasmic TrkA immunostaining, and no one's showed TrkB or TrkC immunoreactivity. The authors proposed immunostaining with neurotrophin receptors (Trk-A and p75NTR) for a definitive diagnosis of thymomas [86].

Furthermore, they demonstrated that the pattern of expression of the neurotrophin TRKA and p75 can be correlated with the WHO histologic subtypes of thymic malignancies.

Inhibition of CDKs and TRKA may result in cell cycle arrest and apoptosis of tumor cells that express these kinases. A phase I trial with an oral CDK and TRKA inhibitor (PHA-848125AC) showed activity in two out of three thymic tumors at a dose of 150mg daily [87]. Based on these encouraging results, two phase II clinical trials with milciclib maleate are up to date ongoing in patients with thymic carcinoma (NCT01011439) and in patients with advanced thymomas (NCT01301391).

Immunotherapy

A pilot study is also ongoing aimed to test the allogenic tumor cell vaccine's activity against lung, esophageal cancers, thymic neoplasms, and malignant pleural mesotheliomas. In particular originates from specific antigens (protein molecules) expressed on tumor surfaces. The vaccine is associated with the use of the chemotherapy drug cyclophosphamide and the anti-inflammatory drug celecoxib.

Genomic Analysis and Molecular Alterations

Although the molecular biology of thymic malignancies is poorly known because of the rarity of the disease and the lack of preclinical models and of cell lines [88], cytogenetic studies have identified several chromosomal abnormalities and genetic alterations across the spectrum of thymic malignancies. A relatively large body of data exists from comparative genomic hybridization (CGH) and microsatellite/loss of heterozygosity studies [41,89].

LOH (Loss of Heterozygosity) is very difficult to study in thymoma for the presence of healthy lymphocytes mingles with epithelial tumor tissue. Two studies in particular tried to dissect LOH by microsatellite markers; Zhou et al. discovered loss of heterozygosity in the region 6q23.3-25.3. Thymomas commonly show the 6q23.3-25.3 deletion that occurs already in early stage disease and then in all advanced stages. The identification of a common genetic alteration on 6q25 across all histologic subtypes suggests the of a yet undefined common tumor suppressor gene (“gate keeper”) that may be absent in the more

aggressive phenotypes [50]. Further LOHs were detected in regions 3p22-24.2, 3p14.2 (FHIT gene locus), 5q21 (APC), 6p21, 6q21-22.1, 7p21-22, 8q11.21-23, 13q14 (RB), and 17p13.1 (p53) and they usually affect the aggressive subtypes B3 and B3. No LOH involving the APC, RB, and p53 gene loci or the 3p22-24.2 and 8q11.21-11.23 regions were detected in type A Thymomas. The APC LOH was exclusively associated with advanced stages (III or IV) of disease [90,91]. The frequency and number of genomic aberrations increases from type Athymoma to TC [41]. The oncosuppressor gene p53 is overexpressed both in invasive thymoma and in TC and it is considered a poor prognostic marker in TETs [92-95].

On the other hand, p53 mutations usually occur in TC, while they are very rare or absent in thymoma. Then, CDKN2A or p16INK4A loss of expression was detected in approximately in 50% of thymomas and in 70% of TCs, but no mutations was found. Further p16INK4 loss may alter CDK proteins involved in the control of cell cycle G1-S phase transition [96]. A recent analysis with CGH in TETs founded FOXC1, transcription factor, frequently included in regions of copy number loss and copy number gain. It may probably present tumor suppressor-like activity and its loss of expression could be associated with poorer time to progression in patients with TET [90-92,94,96,97]. A retrospective analysis of biological characteristics of thymoma and TC in a different series of all WHO-defined subtypes using high resolution microarray-comparative genomic hybridization (CGH) of patients is actually ongoing and investigates the genetic alterations in 138 tumor samples.

Conclusions

Novel strategies are needed, especially for refractory, recurrent thymic tumors and TC after first-line chemotherapy failure. Because of the rarity of these malignancies, clinical trials enrolment is difficult and has prevented from designed large randomized studies. Recently, several early phase clinical trials obtained both disappointed and promising results with biologic drugs and at present targeted therapy cannot be recommended for the routine management of patients with thymic malignancies. Furthermore, the investigation of molecular profiling and the analyses of genetic aberrations in thymic tumors could also allow determining potentially druggable new targets. Moreover, several trials based on pre-treatment molecular analyses are currently ongoing. Further clinical research directions and regional and international collaborative initiatives may be warranted to progress both in the understanding of biology and almost to define the most effective treatment,

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