Molecular targeted therapies in adrenal, pituitary and parathyroid malignancies

Anna Angelousi¹, Georgios K Dimitriadis², Georgios Zografos³, Svenja Nölting⁴, Gregory Kaltsas^{1,2,5} and Ashley Grossman⁵

¹Department of Pathophysiology, Sector of Endocrinology, National & Kapodistrian University of Athens, Athens, Greece

²Division of Translational and Experimental Medicine, University of Warwick Medical School, Clinical Sciences Research Laboratories, Coventry, UK

³Third Department of Surgery, Athens General Hospital “Georgios Gennimatas”, Athens, Greece

⁴Department of Internal Medicine II, Campus Grosshadern, University-Hospital, Ludwig-Maximilians-University of Munich, Munich, Germany

⁵Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford, Oxford, UK

Correspondence
should be addressed
to A Angelousi

Email
a.angelousi@gmail.com

Abstract

Tumourigenesis is a relatively common event in endocrine tissues. Currently, specific guidelines have been developed for common malignant endocrine tumours, which also incorporate advances in molecular targeted therapies (MTT), as in thyroid cancer and in gastrointestinal neuroendocrine malignancies. However, there is little information regarding the role and efficacy of MTT in the relatively rare malignant endocrine tumours mainly involving the adrenal medulla, adrenal cortex, pituitary, and parathyroid glands. Due to the rarity of these tumours and the lack of prospective studies, current guidelines are mostly based on retrospective data derived from surgical, locoregional and ablative therapies, and studies with systemic chemotherapy. In addition, in many of these malignancies the prognosis remains poor with individual patients responding differently to currently available treatments, necessitating the development of new personalised therapeutic strategies. Recently, major advances in the molecular understanding of endocrine tumours based on genomic, epigenomic, and transcriptome analysis have emerged, resulting in new insights into their pathogenesis and molecular pathology. This in turn has led to the use of novel MTTs in increasing numbers of patients. In this review, we aim to present currently existing and evolving data using MTT in the treatment of adrenal, pituitary and malignant parathyroid tumours, and explore the current utility and effectiveness of such therapies and their future evolution.

Key Words

- ▶ adrenocortical cancer
- ▶ pheochromocytoma
- ▶ paraganglioma
- ▶ pituitary carcinoma
- ▶ parathyroid carcinoma
- ▶ tyrosine kinase inhibitor
- ▶ molecular genetics

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Introduction

There are numerous specific guidelines developed for the relatively common malignant endocrine tumours such as thyroid cancer and gastrointestinal neuroendocrine tumours (NETs) (Haugen *et al.* 2016, Pavel *et al.* 2016),

but there is a paucity for other less common endocrine carcinomas involving the parathyroids, adrenals, and the pituitary gland. Parathyroid tumours have an incidence of 80 and 36 per 100,000 population in women and

men aged 50–59 years, respectively (Yeh *et al.* 2013), and occasionally can be multiple. Similarly, pituitary and adrenocortical tumours have a prevalence of 16.7% (range 14.4–22.5) and 4% (range 1.0–8.7), respectively, the latter increasing with age (Ezzat *et al.* 2004, Zeiger *et al.* 2009, Fassnacht *et al.* 2016). Tumours derived from the adrenal medulla occur less commonly with a prevalence of 1/2500–6500, (Kantorovich *et al.* 2015), although autopsy series have revealed a prevalence of 0.05–0.1% (McNeil *et al.* 2000, Lenders *et al.* 2014). Adrenocortical carcinomas (ACCs) account for up to 11% (range 1.2–12%) of adrenocortical tumours, whereas up to 25% of pheochromocytomas (PCs) may become malignant (Ayala-Ramirez *et al.* 2011, Fassnacht *et al.* 2016). Approximately, 0.2% of pituitary tumours can develop cranial and extra-cranial metastases (Kaltsas *et al.* 2005a, Heaney *et al.* 2011), whereas the incidence of parathyroid carcinomas is estimated at less than 1% in patients with primary hyperparathyroidism, although studies from Japan have reported a higher incidence of 5% (Hamill *et al.* 2002, Givi & Shah 2010, Mohebbati *et al.* 2012).

Currently, the optimal management of malignant tumours originating from the pituitary, parathyroid, and adrenal glands is not well defined. The standard treatments for these tumours include surgery, locoregional and ablative therapies, administration of somatostatin analogues (SSAs), radionuclides and systemic chemotherapy, albeit with limited efficacy, necessitating the development of more effective treatments.

Recent advances in our understanding of the genetic pathways implicated in the pathogenesis of these tumours are expected to lead to a more personalised approach directed at the specific molecular aberrations. The most common pathways involved in endocrine tumour pathogenesis are the phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and the RAS-mitogen-activated protein kinase (MAPK) cascades, both downstream of growth factor receptors such as the insulin-like growth factor-1 receptor (IGF1-R) (Nölting & Grossman 2012, Ribeiro *et al.* 2012, Favier *et al.* 2015) (Fig. 1A and B). Angiogenesis stimulation also seems to play a major role in tumorigenesis, with vascular epithelial growth factor receptors (VEGF-Rs), platelet-derived growth factor receptor (PDGF-Rs), endothelial growth factor receptors (EGF-Rs), and tyrosine kinase inhibitors (TKIs) being the most studied targeted pathways in preclinical and clinical studies (Hay & Sonenberg 2004, O'Reilly *et al.* 2006, De Martino *et al.* 2014).

In this review, we aim to present available novel and evolving *in vitro* and *in vivo* data on molecular pathways involved in the malignant transformation of adrenal malignancies, pituitary and parathyroid carcinomas, as well as evidence from current clinical applications of molecular targeted treatment (MTT).

Pheochromocytomas and paragangliomas

Introduction

Pheochromocytomas (PCs) arise from the adrenal chromaffin cells, whereas paragangliomas (PGLs) are derived from the extra-adrenal sympathetic chromaffin (sympathetic PGLs) and/or parasympathetic tissue (non-chromaffin PGLs) of the head and neck (HNPGs) (Lenders *et al.* 2005). In 2004, the WHO defined malignant PCs/PGLs in the presence of metastatic disease without considering locally recurrent or invasive tumours (Ayala-Ramirez *et al.* 2011). Based on this classification, PCs exhibit a 15–20% 10-year probability of recurrence with a 20% malignancy rate (Ayala-Ramirez *et al.* 2011). Overall, metastatic PCs/PGLs are rare with an incidence of less than 1/1,000,000 population per year, with sympathetic PGLs being more common than PCs (60% vs 25%, respectively). However, no current treatment for malignant PCs/PGLs has been shown to be particularly effective (Lenders *et al.* 2014). Better understanding of the molecular pathways for the PCs/PGLs pathogenesis has led to the development of potential new therapeutic agents. Data from clinical trials using MTT are summarised in Table 1.

Transcriptomic studies have identified two main activated molecular pathways leading to the development of these tumours: the hypoxic (cluster-1 genes), mainly involving the succinate dehydrogenase (*SDHx*) and the Von Hippel-Lindau (*VHL*) genes, and the mTOR (cluster-2 genes) pathways, mainly involving rearranged during transfection (*RET*) and neurofibromin 1 (*NF1*) genes (Dahia *et al.* 2005, 2014, Favier *et al.* 2015). DNA-methylation profiling studies have uncovered a hyper-methylator phenotype in the *SDHx* gene-related tumours (comprising *SDHA/B/C/D* and *SDHAF2* genes) and showed that succinate acts as an onco-metabolite, inhibiting 2-oxoglutarate-dependent dioxygenases. 'Omics' data have also identified new therapeutic targets (Favier *et al.* 2015).

Current treatment based on clinical trials

Current guidelines suggest that the optimal initial treatment for metastatic PCs/PGLs should be surgical,

Figure 1

(A) PI3K/Akt/mTOR pathway: The IGF1R activates tyrosine kinase receptor through the lipid kinase PI3K/Akt pathway. PI3K activation phosphorylates and activates Akt that inhibits TSC1/TSC2 suppressor complex, which in turn activates mTORC1. PTEN is a major negative regulator of A activation. Akt-mediated phosphorylation of TSC1-TSC2 leads to the activation of the Rheb-a GTPase- that activates the mTORC1. The mTOR signalling pathway serves as the central regulator of cell metabolism and proliferation. mLST8 is a common subunit of both mTORC1 and mTORC2, and is necessary for activation of the mTOR kinase. PRAS40 is another component and substrate of mTORC1 whose phosphorylation by mTORC1 results in its dissociation from mTORC1 inhibiting mTORC1 activity. Growth-factor-stimulated PI3K signalling also activates mTORC2, which regulates actin cytoskeletal organisation, ion transport and growth. mTORC2 consists of the mTOR catalytic subunit and at least five accessory proteins. Rictor, mSin1, and Protor are unique subunits of mTORC2. Everolimus is known to inhibit mTORC1, but increase Akt signalling. (B) MAPK pathway: Signalling via the RAS-RAF-MEK-ERK cascade leads to phosphorylation of many substrates that can have multiple cellular effects. RAS-GTP activates RAF that activates the mitogen-activated protein kinase kinase 1/2 (MEK1/2). MEK1 and MEK2 then phosphorylate ERK1 and ERK2. ERK also feeds back to negatively regulate the pathway. ERK kinase can phosphorylate transcription factors that control the cell cycle including TSC1/2 mediated by the p90RSK which in turn activates mTORC1. Akt, protein kinase B; eIF-4E, elongation initiation factor 4E; 4E-BP1, eukaryotic initiation factor 4E-binding protein 1; ERK/MAPK, extracellular-signal-regulated kinase/mitogen activated protein kinase; GSK3, glycogen synthase kinase 3; IGF1R, insulin-like growth factor 1 receptor; IKK, I κ B kinase; MAPK, Mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mLST8, mammalian lethal with SEC13 protein 8; MNK, mitogen protein kinase; mTORC, mammalian target of rapamycin complex; PI3K/AKT, phosphatidylinositol 3-kinase-AKT; PDK, 3-phosphoinositide-dependent protein kinase; PTEN, phosphatase and tensin homologue; PRAS40, raparoline-rich Akt substrate of 40kDa; Rheb, Ras homologue enriched in brain; P70 S6, Ribosomal protein S6 kinase beta-1; TSC1/2, tuberous sclerosis complex; HIF-1 α , hypoxia-induced factor 1 α ; VEGF, vascular growth factor.

including total resection of the tumour, locoregional lymph nodes and distant metastases (Zografos *et al.* 2009, Lenders *et al.* 2014). For unresectable disease, combination chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD) has been associated with short-term symptomatic and tumour responses of 33–65% (Averbuch *et al.* 1988, Ayala-Ramirez *et al.* 2012b). A recent meta-analysis showed that CVD achieved a 37% tumoural and a 40% hormonal response, but only 4% of patients obtained complete remission (Niemeijer *et al.* 2014).

Molecular targeted treatment for PCs/PGLs

mTOR inhibitors PCs/PGLs exhibit a significant overexpression of key mTOR complex (mTORC) signalling mediators (Nölting & Grossman 2012, Zhang *et al.* 2015) (Fig. 1A and B). Everolimus, a compound inhibiting mTOR and thus the PI3K/Akt/mTOR pathway, has been shown *in vitro* to inhibit the proliferation of human neuroblastoma cells, which are closely related to

PCs/PGLs cluster-2-related tumours (Kiessling *et al.* 2016). Everolimus has previously been evaluated in malignant PCs but only in small series (Semenza 2007, Druce *et al.* 2009, Nölting *et al.* 2012). In another study, all patients treated with everolimus experienced disease progression (Druce *et al.* 2009). This was attributed to the selective inhibition of HIF-1 without any effect on HIF2, or to the compensatory activation of the RAS/RAF/ERK pathway (Semenza 2007, Druce *et al.* 2009, Nölting *et al.* 2012). In a subsequent phase II study using everolimus as monotherapy, five of seven patients with metastatic PCs/PGLs achieved stable disease but with a progression-free survival (PFS) of only 3.8 months (95% CI: 0.5–7.0); four patients demonstrated tumour shrinkage (Oh *et al.* 2012). However, recent experimental studies with AZD8055, an ATP-competitive dual mTORC1/2 inhibitor, in metastatic mouse PC cell lines and in human primary cell models of patients with PCs/PGLs, showed a significant decrease in tumour load with a 50% reduction in the number of malignant cells (Giubellino *et al.* 2013a). A recent *in vivo* study in mice xenografts confirmed these

Table 1 Molecular-targeted agents used in different protocols of clinical trials completed or ongoing in patients with pheochromocytomas (PCs) and paragangliomas (PGLs).

Protocol IDs in ClinicalTrials.gov/Reference	Tested drug in the Tested drug in the trial arm	Patients	Type	Status	Phase	Number of patients	Results
Kulke et al. 2006	Thalidomide (VEGF-R, bFGF inhibitor) and Temozolomide (Alkylating chemotherapy)	Metastatic PCs/PGLs	Treatment	Completed	II	3	1 had PR
NCT00466856, USA, 2007	Yttrium (Y) 90 octreotide acetate	Metastatic NETs including PCs/PGLs	Treatment	Completed	II	ND	ND
NCT00655655, USA, 2008	Everolimus (mTORC1 inhibitor) and vatalanib (EGFR-1 inhibitor)	Metastatic and recurrent PCs	Treatment	Active	I	Not yet completed	Not yet completed
Gonias et al. 2009	131I-MIBG	Metastatic PCs/PGLs	Treatment	Completed		50	22% had CR 35% had PR (35% developed PD within 1 year)
NCT00874614, USA, 2009	131I-MIBG	Relapsed malignant PCs/PGLs	Treatment	Active	II	Not yet completed	Not yet completed
NCT 00843037, Canada, 2009	Sunitinib (VEGF-R, PDGF-R inhibitor)	Recurrent PCs/PGLs	Treatment	Active	II	Not yet completed	Not yet completed
NCT01155258, USA, 2010	Temsirolimus (mTORC1 inhibitor) + vinorelbine ditartrate (anti-mitotic chemotherapy)	Recurrent or malignant PCs/PGLs	Treatment	Completed	I	ND	ND
NCT01163383, USA, 2010	131I-MIBG	Refractory/Relapsed PCs/PGLs in children	Treatment	Active	Expanded access	Not yet completed	Not yet completed
NCT01371201, France, 2011 (FIRST-MAPP)	Sunitinib (VEGF-R, PDGF-R inhibitor)	Progressive malignant PCs/PGLs	Treatment	Active	II	Not yet completed	Not yet completed
NCT01396408, Canada, 2011	Sunitinib (VEGF-R, PDGF-R inhibitor) vs Temsirolimus (mTORC1 inhibitor)	Unresected, advanced or metastatic rare tumours including PCs/PGLs	Treatment	Active	II	Not yet completed	Not yet completed
NCT 01340794, USA, 2011	Pazopanib hydrochloride (multi-TKI)	Advanced or progressive malignant PCs /PGLs	Treatment	Completed	II	7	ND
NCT0137753, USA, 2011	131I-MIBG	Malignant PCs/PGLs	Treatment	Active	Expanded Access	Not yet completed	Not yet completed
Oh et al. 2012	Everolimus (mTORC1 inhibitor)	Progressive PCs/PGLs	Treatment	Completed	II	7	5 had SD had PD, PFS=3.8 months
NCT01635907, USA, 2012	Dovitinib (FGF-R inhibitor)	Advanced PCs /PGLs	Treatment	Active	II	Not yet completed	Not yet completed
Park et al. 2013	Fostamatinib Disodium (TKI)	Advanced PCs	Treatment	Completed	II	2	1 had SD for >12 months
NCT01967576, USA, 2013	Axitinib (VEGF-R inhibitor)	Recurrent or primary unresectable PCs/ PGLs	Treatment	Active	II	Not yet completed	Not yet completed
NCT0183818, USA, 2013	131I-MIBG	Refractory PCs/PGLs in children	Treatment	Active	Expanded access	Not yet completed	Not yet completed
NCT 02302833, USA, 2014	Cabozantinib (TKI, c-MET, VEGF-R)	Advanced or metastatic PCs/PGLs	Treatment	Active	Pilot	Not yet completed	Not yet completed

VEGF-R, vascular endothelial growth factor-receptor; bFGF, b fibroblast growth factor; NET, neuroendocrine tumours; PC, pheochromocytomas; PGLs, paragangliomas; ND, no data; mTOR, mammalian target of rapamycin; EGFR-1, endothelial growth factor receptor-1; MIBG, meta-iodobenzylguanidine; PR, partial response; CR, complete response; PD, progression disease; PDGF-R, platelet derived growth factor; TKI, tyrosine kinase; SD, stable disease; PFS, progression-free survival.

results, showing strong anti-tumour activity of the dual mTORC1/mTORC2 inhibitor PP242 (Zhang *et al.* 2015). This was due to the dual effect on both complexes TORC1/TORC2 inhibiting the compensatory stimulation of the RAS/RAF/ERK pathway which is observed when a single mTORC1 inhibitor such as everolimus is used.

Anti-angiogenic molecules PCs are highly vascular, and aberrant angiogenesis has been associated with a malignant phenotype, especially in patients carrying *SDHB* gene mutations (Takekoshi *et al.* 2004). PC tumours express higher levels of VEGF and its receptors (VEGF-R), suggesting they may play an important role in their pathogenesis (Takekoshi *et al.* 2004). Interestingly, using antibodies against VEGF it was possible to reduce angiogenesis and tumour proliferation in a xenograft mouse model of PCs (Zielke *et al.* 2002). These findings have led to the evaluation of several angiogenesis inhibitors as therapeutic agents in malignant PGs/PGLs.

Thalidomide is an anti-angiogenic agent specifically targeting VEGF and the basic fibroblast growth factor (FGF) receptors. Only one phase II trial has been conducted, but due to the limited number of patients studied ($n=3$) it is impossible to draw definite conclusions regarding the efficacy of thalidomide in PC patients (Kulke *et al.* 2006).

Sunitinib, a potent oral multi-TK inhibitor with anti-angiogenic and anti-tumour activity, has demonstrated potential benefit in metastatic SDH- or VHL-mutated PCs (Jimenez *et al.* 2009, Saito *et al.* 2012). In cell lines, sunitinib decreased cell proliferation *in vitro* by targeting cell cycle, DNA metabolism and cell organisation genes (Cassol *et al.* 2014). In 17 patients with progressive metastatic PCs/PGLs, sunitinib was associated with a significant reduction in tumour size, a 30% decrease in ^{18}F fluoro-deoxyglucose (FDG)-PET/CT uptake, and a median overall survival of 26.7 months with a PFS of 4.1 months (95% CI: 1.4–11.0) (Ayala-Ramirez *et al.* 2012a). Most patients who experienced a clinical benefit were carriers of the *SDHB* mutation (Hahn *et al.* 2009, Ayala-Ramirez *et al.* 2012a). In VHL patients with metastatic PCs/PGLs, treatment with sunitinib for 6 months was associated with normalisation of patients' performance status and blood pressure, significant tumour shrinkage and reduction of plasma noradrenaline and chromogranin A levels (Jimenez *et al.* 2009). An ongoing phase II study (FIRST-MAPP) aims to determine the efficacy of sunitinib on PFS at 12 months in progressive malignant PCs/PGLs.

Vandetanib, which inhibits VEGF-R2, VEGF-R3 and VEGF-R1 and, at higher concentrations, EGF-R,

has demonstrated promising results in both *in vitro* and *in vivo* studies (Brave *et al.* 2011); it is known to be active in medullary thyroid carcinomas harbouring RET mutations (Vitagliano *et al.* 2011). The coexistence of medullary thyroid carcinoma and PCs in MEN2 syndromes suggests that vandetanib could also be a good candidate drug in PCs/PGLs.

Hypoxic-inducible factor inhibitors Although no data have been reported in human malignant PCs with these agents, hypoxic-inducible factor (HIF) inhibitors have shown marked anti-tumour activity in various human tumour xenografts in mice (Semenza 2007). Under normoxic conditions, site-specific hydroxylation of HIF-1 α allows recognition by the VHL protein resulting in proteasomal degradation. Under hypoxic conditions, hydroxylation of the HIF-1 α subunit is suppressed, leading to increased levels of HIF that regulate the expression of many target genes. (Jochmanová *et al.* 2013, Yang *et al.* 2015).

Recently, the selective HIF-2 antagonist, PT2399, has been shown to induce tumour regression in mouse models of VHL-defective clear cell renal carcinoma characterised by inactivation of the *VHL* gene and subsequent activation of HIF-2 (Cho *et al.* 2016). PT2399 had greater activity than sunitinib, was active in sunitinib-progressing tumours, and was better tolerated (Chen *et al.* 2016). These data suggest that this drug may be useful in PCs/PGLs associated with HIF-2a mutations.

Heat shock protein-90 (HSP90) This multi-chaperone ATP-dependent complex is responsible for protein folding and plays an important role in the stability and function of a number of oncoproteins and telomerase (Banerji 2009). Overexpression of HSP90 has been observed in malignant PCs, and it has been identified as a promising therapeutic target (Banerji 2009). In a xenograft mouse model, the use of two different HSP90 inhibitors, benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin (17-AAG), and the second-generation ganetespib, demonstrated significant inhibition of proliferation and migration in PC cell lines and induced degradation of HSP90. In these metastatic models of PCs, both inhibitors achieved reduction of tumour burden and reduced cell survival (Giubellino *et al.* 2013b). HSP90 may thus represent a potential therapeutic target for metastatic PCs/PGLs, although the relatively non-specific mode of action may limit its use.

HER2/neu inhibitors HER2 is a tyrosine kinase receptor involved in the cell growth and differentiation and it leads to the synthesis of HIF when activated. HER2 is overexpressed in malignant PCs and is associated with tumour metastases and resistance to treatment; however, no trials have been conducted to date using HER2/neu inhibitors (Tavangar et al. 2010, Mohammed et al. 2014).

Other agents Carboxypeptidase E (CPE) is a prehormone-processing enzyme expressed in different types of cancer including NETs, mainly of the lung and pituitary (Murthy et al. 2010). Extremely high CPE mRNA copy numbers of the N-terminal splice isoform variant were found in various human metastatic tumour cell lines, including metastatic PCs. Interestingly, this high copy number in tumours was shown to predict tumour recurrence and/or metastatic disease, suggesting that CPE could be a potential therapeutic target in metastatic PCs.

NVP-AEW451 acts as IGF-1 receptor antagonist that significantly reduced mouse PC cell proliferation and tumour cell viability, albeit at relatively high doses. However, at suboptimal doses this agent led to a compensatory upregulation of ERK and mTORC1 signals whereas PI3K/AKT inhibition remained stable (Nölting et al. 2012). More recently, LB1, a small molecule inhibitor of serine/threonine protein phosphatase 2A, inhibited mouse PC cells *in vitro* and *in vivo* in a mouse model of metastatic PCs, either alone or in combination with temozolomide (Martiniova et al. 2011).

Temozolomide, an oral derivative of dacarbazine, was studied as monotherapy in 15 patients with metastatic PCs/PGLs. There were five partial responses (33%), seven (47%) patients experienced stable and three (20%) developed progressive disease after a median follow-up of 35 months. Partial responses were observed only in patients with SDHB mutations. The silencing of O(6)-methylguanine-DNA methyltransferase (MGMT) expression as a consequence of MGMT promoter hypermethylation in SDHB-mutated tumours may explain this finding (Hadoux et al. 2014).

Another promising therapeutic agent could be the use of lipophilic statins (simvastatin and fluvastatin) either alone (Fliedner et al. 2014) or in association with 13-cis-retinoic acid (Nölting et al. 2014). Statins can induce apoptosis of PC cells through inhibition of MAPK-1 and -3 phosphorylation in aggressive mouse PC cells *in vitro* (Fliedner et al. 2014, Nölting et al. 2014).

In vitro studies in tissues as well as in cell cultures have revealed the expression of somatostatin receptors

(SSTRs) (particularly subtype 2A and 3) in PCs/PGLs and have suggested that by targeting SSTRs it might be able to control tumour growth and secretion (Ziegler et al. 2009, Elston et al. 2015). However, these results have not been widely confirmed, as only some case series have shown symptom and tumour control in a subset of patients (van Hulsteijn et al. 2013, Elshafie et al. 2014). More promising results with radioisotopes bound to synthetic somatostatin analogues (SSAs) in patients with high tumoural uptake have been published, especially significant in the light of the impressive results of peptide receptor radiotherapy (PRRT) reported in the NETTER-1 study in patients with midgut neuroendocrine tumours (Strosberg et al. 2017). To date, PRRT using ⁹⁰Yttrium or ¹⁷⁷Lutetium-labelled SSAs has been evaluated in only a limited number of PCs/PGLs. In a total of 25 patients from three different clinical trials including patients with progressive or metastatic PCs/PGLs, four patients showed a partial response and 14 had stable disease, suggesting that PRRTs could be an effective therapeutic option for these tumours (van Essen et al. 2006, Zovato et al. 2012, Puranik et al. 2015). Larger studies including hereditary and non-hereditary PCs/PGLs are needed to identify which PCs/PGLs can be best treated using this therapy, and whether PRRT should be used alone or with other treatment modalities.

Radionuclide therapy with ¹³¹I-metaiodobenzylguanidine (MIBG) has also been used either as a single or sequential cumulative doses administered in patients with significant tumour burden and adequate ¹²³I-MIBG uptake on diagnostic imaging (Mukherjee et al. 2001, Kaltsas et al. 2005b). A recent meta-analysis of the efficacy of ¹³¹I-MIBG-therapy in malignant PCs/PGLs showed that disease control and partial hormonal responses were obtained in 50 and 40% of patients, respectively (van Hulsteijn et al. 2014). In a multicentre registry, partial response or stability of the disease according to the RECIST criteria was achieved in 85% of patients, with minor side effects in approximately 90% of patients (Yoshinaga et al. 2014). However, there may also be long-term sequelae such as myelodysplastic disorders and haematological malignancies (Sze et al. 2013). Nevertheless, the prognosis for malignant PCs/PGLs still remains relatively poor, highlighting the need for the development of new personalised therapeutic strategies.

In summary, for metastatic PCs/PGLs that do not respond or cannot be treated with the current established therapies, radionuclide therapy with a labelled SSTR-active analogue or ¹³¹I-MIBG should be considered, depending on the diagnostic uptake. At present, it is not possible to differentiate between these two possible therapies. MTT

with a TKI such as sunitinib is another option. However, MTT using monotherapy seems to show limited clinical meaningful benefit, and it is suggested that in the longer term combination MTT with a TKI, an mTOR inhibitor plus possibly other agents (statins, retinoic acid, HSP inhibitors, etc), may be most effective. It is also likely that molecular analysis of individual tumours may guide treatment in the future.

Adrenocortical carcinoma

Introduction

Adrenocortical carcinoma (ACC) is a rare tumour with an estimated incidence of 0.7 new cases/1,000,000 per year (Assie et al. 2014). The genomic landscape of ACCs has revealed that it is a biologically and genetically heterogeneous malignancy with transcriptome clusters associated with distinct drugable clinical behaviour (Assie et al. 2014). Various molecular agents used in recent years in clinical trials as well as *in vitro* studies for treating patients with ACC have been already well-described in a recent review (Creemers et al. 2016). Therefore, here we summarise most of these data as well the newer studies published since this review in Tables 2 and 3.

Current treatment based on clinical trials

Currently 'R0', complete surgical resection, is the gold standard treatment for non-metastatic ACC or following local recurrence (Berruti et al. 2012b). Mitotane is the only FDA-approved drug for locally advanced inoperable and metastatic disease displaying single-agent activity of 10–30% tumour response rates based on its adrenolytic action, albeit with a high toxicity profile (Veytsman et al. 2009). The only prospective phase III randomised clinical trial, FIRM-ACT, showed that in advanced ACCs mitotane combined with etoposide, doxorubicin and cisplatin (EDPM) provided some additional clinical benefit compared to mitotane plus streptozocin alone, but was associated with more serious adverse events (Fassnacht et al. 2012). A further prospective study evaluating mitotane vs. placebo in high-risk for recurrence patients, ADIUVO, is currently under way (Terzolo et al. 2007) (<https://www.epiclin.it/adiuvo>).

Molecular profile

The main signalling pathways involved in ACC tumourigenesis include the PI3K/Akt/mTOR cascade and

the RAS-MAPK pathway, both activated by the IGF-1R when occupied by IGF2 (Pollak 2008). IGF2 mRNA and protein are overexpressed in more than 90% of ACCs (Ribeiro et al. 2012). Genetic studies have identified alterations in the FGF-R cascade (Laurell et al. 2009), and overexpression of VEGF-R, PDGF-R, EGF-R, and the FGF-R signalling pathways (Xu et al. 2011, Wang et al. 2012). Preclinical studies support the idea that mTOR inhibitors can upregulate Akt phosphorylation in ACCs (Liu et al. 2009, De Martino et al. 2014).

Other key molecular events contributing to the formation of ACC are tumour protein 53 (TP53) inactivating mutations (Libè et al. 2007) and constitutive activation of the Wnt/ β -catenin signalling pathway via activation of the β -catenin gene (*CTTNB1*) (Tissier et al. 2005). The increased occurrence of adrenocortical tumours in Li-Fraumeni and Beckwith-Wiedemann syndromes, as well as in the Carney complex, has highlighted the roles of susceptibility genes: *TP53*, *IGF2*, and protein kinase cAMP-dependent type I regulatory subunit alpha (*PRKARIA*) (de Joussineau et al. 2012), respectively.

Alterations in the nuclear transcription steroidogenic factor 1 (SF-1) are also involved (Val et al. 2003, Duregon et al. 2013). SF-1 induces proliferation of ACC cell lines and tumour growth *in vivo* (Doghman et al. 2009) and its increased expression has been associated with a worse prognosis (Sbiera et al. 2010). SF-1 inhibitors in ACC cell lines inhibited cell proliferation associated with SF-1 overexpression along with steroid hormone oversecretion and CYP21 and CYP17 mRNA expression (Doghman et al. 2010).

Interferon- β (INF- β) may exert an inhibitory effect *in vitro* on ACC cell lines and primary cultures of human ACC (van Koetsveld et al. 2013), and increases sensitivity of ACC cells to mitotane (van Koetsveld et al. 2013).

Topoisomerase- α 2 (*TOP2A*), a gene consistently overexpressed in ACC, is involved in cellular invasion as it regulates anchorage-independent growth and invasion. Several *TOP2A* inhibitors have been screened for their anti-proliferative activity in ACC cells (Jain et al. 2013).

Molecular therapy

Different drugs targeting the molecular pathways described above have been tried in clinical trials phase I–III (Table 2) or *in vivo* and *in vitro* studies (Table 3).

IGF-1R inhibitors including mTOR inhibitors and monoclonal anti-IGF-1R antibodies, as well as anti-angiogenic agents, have been used as monotherapy in

Table 2 Molecular-targeted agents used in clinical trials completed or ongoing in patients with adrenocortical carcinoma.

Molecular-targeted treatments	Molecular pathway	Design of the study	N (patients)	Response	Toxicities	References
<i>IGF-1 blocker</i> Linsitinib (OSI-906)	Inhibitor IGF-1R and insulin receptor	I	9	2 had PR and 7 had SD	Grade 1 (nausea, vomiting, fatigue, diarrhoea, hyperglycaemia)	Jones et al. 2015
Linsitinib (OSI-906)	Inhibitor IGF-1R and insulin receptor	III	139	Stopped prematurely due to failure to improve PFS or OS	Grade 1 (fatigue, nausea, hyperglycaemia)	Fassnacht et al. 2015
Everolimus	mTOR inhibitor	Case series	4 (2/4 of them were also on mitotane)	All patients had PD	Well tolerated	Fraenkel et al. 2013
<i>Immunotherapy</i> Figitumumab	Monoclonal Ab targeting IGF-1R	I	14	8 (57%) had SD	Grade 1 (hyperglycaemia, nausea, fatigue, anorexia)	Haluska et al. 2010
Nivolumab	Monoclonal Ab PD-1	II	ND	Recruiting	Recruiting	NCT02720484, USA, 2016
Pembrolizumab	Monoclonal Ab IgG4	II	ND	Recruiting	Recruiting	NCT02673333, USA, 2016
Cixutumumab	Monoclonal Ab targeting IGF-1R	II	ND	Recruiting	Recruiting	NCT01514526
<i>Angiogenetic factors</i> Axitinib (AG-013736)	Inhibitor of VEGF-R (TKIs)	II	13	Median PFS=5.48 months, median OS=13.7 months,	Most Grade 1,2	O'Sullivan et al. 2014
Sunitinib	Multiple TKIs	II	35	5 had SD, median PFS=2.8 months	Grade 1,2 (fatigue, hand-foot reactions, rash, mucositis)	Kroiss et al. 2012
Imatinib	Inhibitor of PDGFR	II	4	0/4 (No response to any patients)	Grade 1 (nauseas, diarrhoeas, fatigue) 1 patient had grade 4 (psychiatric adverse events)	Gross et al. 2006
Dovitinib	Inhibitor of FGF-R	II	17	1 had PR, 13 had PD, median PFS=1.8 months no improvement in OS	Grade 1 (rash, asthenia, diarrhoea, nausea, hypertriglyceridaemia, hypertension, hyperkalaemia)	Jesús García-Donas et al. 2014
Gefitinib	Inhibitor of EGF-R	II	ND	ND	ND	NCT00215202, USA, 2005
Suramin (Polysulphonated naphthylurea)	Inhibitor of EGF, PDGF, TGF-beta	II	ND	ND	ND	NCT00002921, USA, 2009
Sorafenib + paclitaxel	Inhibitor of VEGF-R2, VEGF-R3, PDGF-R, RAF-1 + chemotherapy	II	25	Stopped prematurely due to failure to improve PFS or OS	Grade 2,3 (fatigue, hypophosphatemia)	Berruti et al. 2012a
Erlotinib + gemcitabine	Inhibitor of EGF-R inhibitor + nucleoside analogue (chemotherapy)	Case series	10	1 had PR, median PFS=8 months	Grade 1 (rash, fatigue)	Quinkler et al. 2008
Bevacizumab + capecitabine	Anti-VEGF Ab + 5-FU analogue (chemotherapy)	I	10	All patients had PD	Grade 1 (hand-foot syndrome)	Wortmann et al. 2010

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Imatinib + dacarbazine + capecitabine	Inhibitor of PDGF-R + imidazole carboxamide + 5-FU analogue (chemotherapy)	I	7	1 had PR (1 had minor response)	Grade 1 (oedema and fatigue)	Halperin et al. 2014				
Cixutumumab + temsirolimus	Monoclonal Ab IGF-1R + mTOR inhibitor	I	10	4 had SD, median PFS=8 months, 42% of the 26 patients had SD for 6 months	Grade 1,2 (mucositis, thrombocytopenia, hypercholesterolaemia, hyperglycaemia)	Naing et al. 2011, 2013				
Cixutumumab (IMC-A12) + mitotane	Monoclonal Ab IGF-1R + adrenolytic chemotherapy	II	20	1 had PR, 7 had SD, median PFS=6 weeks	Hyponatremia, Grade 4 in 2 patients Grade 5 in 1 patient (multiorgan failure) in 1 patient	Lerario et al. 2014				
Inhibitors of steroidogenesis ATR-101	Inhibitor of Acyl-CoA acyltransferase 1	I	ND	Recruiting	Recruiting	NCT01898715				
Others IL-13-pseudomonas exotoxin	Anti-IL-13 receptor $\alpha 2$	I	5	1 had SD	Grade 1,2 (thrombocytopenia and renal insufficiency)	Liu-Chittenden et al. 2015				

IGF-1R, insulin-like growth factor 1 receptor; PR, partial response; SD, stable disease; PFS, progression free survival; OS, overall survival; mTOR, mammalian target of rapamycin; ND, no data; Ab, antibody; VEGF-R, vascular endothelial growth factor receptor TKI, tyrosine kinase inhibitor; EGF-R, epidermal growth factor; receptor; FGF-R, fibroblast growth factor receptor; PDGF-R, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitors; TGF-beta, transforming growth factor; FU, fluorouracil.

patients with advanced progressive ACCs, albeit without promising results. The most probable explanation for this finding is that the inhibition of IGF-R1 leads to the compensatory activation of the MEK/ERK pathway leading to sustained activation of mTOR (Xu et al. 2016). FGF-R4 overexpression and amplification (identified in 13% of paediatric and 30% of adult ACCs) was associated with a worse outcome, supporting the potential role of selective FGF-R inhibitors in ACC treatment (West et al. 2007, Brito et al. 2012).

Treatments combining different molecular targeting agents or a molecular targeting agent with classical chemotherapy have been also studied. Preclinical data suggest increased efficacy of sunitinib when combined with an ERK pathway inhibitor (Lin et al. 2012). However, the plasma levels of sunitinib might be reduced by mitotane-induced CYP3A4 activity, thereby attenuating its anti-tumour activity when used in combination (Kroiss et al. 2012). Co-inhibition of IGF-R1 and EGFR has also shown promising results in ACC cell lines.

Based on the premise that many ACCs require substantial intracellular cholesterol as a substrate for steroidogenesis, drugs disrupting cholesterol uptake might have therapeutic potential. A selective inhibitor of acetyl-CoA acetyl-transferase 1 (ACAT1), which catalyses cholesterol ester formation from cholesterol and long-chain fatty acyl-CoA, has been investigated in phase II study of patients with advanced ACC (Aun Naing et al. 2015).

Other molecules including inhibitors of polo-like kinase (PLK-1), such as BI-236 (Bussey et al. 2016), inhibitors of TOP2A such as aclarubicin (Jain et al. 2013) and IL-13-pseudomonas exotoxin (Liu-Chittenden et al. 2015), are attractive strategies in ACC. Three other compounds that have been investigated in preclinical ACC models are thiazolidinediones (TZDs), HSP90 inhibitors and decitabine, a DNA methyl-transferase inhibitor, with all showing inhibition of ACC cell proliferation (Suh et al. 2010, Huang et al. 2014).

In clinical practice, the gold standard treatment for metastatic ACC is cytoreductive surgery along with mitotane in combination with chemotherapy (EDF) according to the FIRM-ACT study. For progressive disease despite these treatments their outlook remains still grim with little assistance as yet from monotherapy with MTTs. The combination of imatinib with dacarbazine and capecitabine, or cixutumumab and temsirolimus has shown encouraging clinical responses, albeit with considerable adverse events. As yet, MTTs have had little impact on the therapy of this sinister disease.

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IGF-1R, insulin-like growth factor 1 receptor; PR, partial response; SD, stable disease; PFS, progression free survival; OS, overall survival; mTOR, mammalian target of rapamycin; ND, no data; Ab, antibody; VEGF-R, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; EGF-R, epidermal growth factor receptor; FGF-R, fibroblast growth factor receptor; PDGF-R, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitors; TGF-beta, transforming growth factor; FU, fluorouracil.

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Table 3 Molecular-targeted agents used in *in vitro/in vivo* studies of adrenocortical carcinoma.

Molecular-targeted treatments	Molecular pathway	<i>In vitro/in vivo</i>	Response	References
<i>IGF-1 blocker</i> Everolimus	mTOR inhibitor	<i>In vitro</i> ACC cell lines in childhood	Inhibition of cell proliferation and reduced tumour cell growth	Doghman et al. 2010
<i>Angiogenetic factors</i> Sunitinib	Multiple TKIs	<i>In vitro</i> (H295R and SW13 ACC cells lines)	Reduce cell proliferation by 20%	Lin et al. 2012
Erlotinib	Anti-EGF-R	<i>In vitro</i> (H295 and SW13 cells lines)	Reduction of cell viability in ACC lines	Gagliano et al. 2015
<i>Combinations</i> Sorafenib+everolimus	VEGF-R2, VEGF-R3, PDGF-R and RAF-1 + mTOR inhibitors	<i>In vitro</i> (SW13 cells lines)	Significant apoptosis	Berruti et al. 2012b
Sorafenib+everolimus	VEGF-R2, VEGF-R3, PDGF-R and RAF-1 + mTOR inhibitors	<i>In vitro</i> (SW13 and H295R cells lines)	Inhibition of cell viability in SW13 cells	Mariniello et al. 2012
		<i>In vivo</i> SW13 xenografts mice	Increased apoptosis	
Sirolimus+mitotane	mTORC1/C2 and adrenolytic treatment	<i>In vitro</i> (H295 and SW13 cells lines)	Synergistic growth inhibition of SW13 xenografts mice Mitotane significantly inhibited cell proliferation. Sirolimus showed statistically significant additive effects	De Martino et al. 2016
Sunitinib+PD98059	TKIs+ERC inhibitor (Raf/MEK inhibitor)	<i>In vitro</i> (H295R and SW13 cells lines)	Decrease proliferation by 68% and 64% in H295R and in SW13 cells	Lin et al. 2012
Erlotinib+NVP-AEW541	EGF-R inhibitor+IGF-1R inhibitor	<i>In vitro</i> (H295R and SW13 cells lines)	Inhibition of cell viability and increase apoptosis.	Xu et al. 2016
		<i>In vivo</i> (ACC mice xenografts)	Antitumor activity <i>in vivo</i>	
IFN- β +mitotane	Interferon- β +adrenolytic chemotherapy	<i>In vitro</i> (2 ACC cells lines)	Inhibitory effect on cell number and cortisol secretion.	Van Koetsveld et al. 2013
<i>Inhibitors of steroidogenesis</i> High-density lipoprotein (HDL) nanoparticles	SR-BI inhibitors	<i>In vitro</i> (H295R and SW13 cells lines)	Enhanced the apoptosis induced by etoposide, cisplatin or mitotane	Subramanian et al. 2016
<i>Others</i> Alkyloxyphenol and isoquinolinone	SF-1 inhibitors	<i>In vitro</i> (H295R and SW13 cells lines)	Inhibitory effect on both SF-1-positive and -negative cells	Doghman et al. 2010
Bi-2536	Inhibitors of PLK-1	<i>In vitro</i> (H295R and SW13 cells lines)	70% loss of viability	Bussey et al. 2016
Aclarubicin	TOP 2A inhibitors	<i>In vitro</i> (H295R and SW13 cells lines)	Decrease of the proliferation and tumour spheroid size ($P < 0.05$).	Jain et al. 2013

IGF-1R, insulin-like growth factor 1 receptor; mTOR, mammalian target of rapamycin; ACC, adrenocortical cancer; TKI, tyrosine kinase inhibitor; VEGF-R, vascular endothelial growth factor receptor; EGF-R, epidermal growth factor; receptor; FGF-R, fibroblast growth factor receptor; PDGF-R, platelet-derived growth factor receptor; ERK, extracellular signal-regulated kinases (MAP kinases), SR-BI, scavenger receptor class B type I; SF-1, steroidogenic factor 1; PLK1, Polo-like kinase 1; TOP2A, topoisomerase (DNA) II Alpha.

Pituitary tumours

Introduction

Pituitary tumours are for the most part benign monoclonal adenomas presenting with excessive hormone secretion and/or tumour mass effects, albeit a small minority may become frankly malignant (Melmed *et al.* 2003). Although surgical resection remains the mainstay of therapy for macroadenomas causing compression of neurovascular structures, pharmacotherapy can play a crucial role in their treatment. Recent advances in the genetic and molecular analysis of pituitary tumours have provided new insights into the growth patterns and secretory function of these tumours, and have allowed for a more precise characterisation of individual lesions.

Molecular profile

The PI3K/Akt and MAPKs pathways are the two major signalling pathways responsible for regulating cell growth and proliferation, which are activated by growth factor receptors (McCubrey *et al.* 2007). The PI3K/Akt/mTOR pathway is also upregulated in pituitary tumours (Muşat *et al.* 2005, 2010, Cakir *et al.* 2009). Notch-3 and Jagged-1 have been implicated in the pathogenesis of human non-functioning pituitary adenomas, thereby providing a potential therapeutic target for the medical treatment of these tumours. Several elements of the Notch pathways have also been identified in the transcriptome of prolactinomas and multi-hormonal pituitary adenomas (Jiang *et al.* 2012). Hedgehog (Hh) signalling exerts differential effects on pituitary cell growth (with stimulatory effects on progenitor cells and inhibitory effects in differentiated cells), and is able to modulate hormone secretion and proliferation in pituitary tumours. Moreover, exogenous treatment with Hh proteins in cell cultures has been shown to increase hormone secretion from pituitary tumour cells, reflecting their role as hypophysiotropic factors that regulate pituitary hormone release in normal and tumoural tissue cells (Yavropoulou *et al.* 2015). More specific targeting treatment depends on the type of pituitary adenoma.

Approximately, 30–45% of pituitary tumours invade the cavernous or sphenoid sinus (Zada *et al.* 2011), and a significant number are considered as aggressive based on their resistance to conventional treatment or recurrence during the follow-up (Raverot *et al.* 2012) (Fig. 2). Some rare aggressive tumours that develop metastases are considered as carcinomas (Heaney *et al.* 2011, Batisse *et al.* 2013, Chatzellis *et al.* 2015) and cannot be controlled

by any available treatment (McCormack *et al.* 2009, Heaney *et al.* 2011, Jouanneau *et al.* 2012, Raverot *et al.* 2012). Pituitary carcinomas are rare (0.2%), defined by the presence of systemic or cerebrospinal metastases (Kaltsas *et al.* 2005a, Heaney *et al.* 2011). The 2004 WHO classification considered all benign tumours as either typical adenomas or atypical adenomas tumours showing 'borderline or uncertain behaviour' (Keblad *et al.* 2007). The latter tumours exhibited invasive growth, high mitotic index, an elevated mitotic index, a Ki-67 labelling index (LI) >3% as well as extensive nuclear staining for p53 (Del Basso De Caro *et al.* 2016, Kim *et al.* 2016). In recent studies, pituitary tumour recurrence could be predicted by using mitoses, invasion, Ki-67 labelling index (>3%), or extensive p53 immunoreactivity (≥20%) (Del Basso De Caro *et al.* 2016, Kim *et al.* 2016). However, it should be noted that the revised WHO classification, due for publication in 2017, has rejected the 'typical/atypical' classification, and instead emphasises staining with Ki-67, and the degree of invasiveness as revealed by surgical and radiological findings; p53 staining should be reserved for special cases, whereas electron microscopy is rarely of value.

Current treatments for aggressive tumours

Because of the rarity of these tumours, data from randomised controlled studies comparing the efficacy and safety of

Figure 2

Post-contrast T1-sequence MRI showing an aggressive pituitary macroadenoma recurring after initial surgery.

the various therapeutic modalities are lacking. Patients with incompletely resected aggressive tumours may require further surgery and additional medical treatment with SSAs and/or cabergoline. Recently, dopamine agonist therapy in non-functioning pituitary adenomas with post-surgical remnants showed stabilisation or shrinkage of the tumour (Greenman et al. 2016). Conventional or targeted radiotherapy is worthy of consideration, whereas conventional systemic chemotherapy has been shown to have an unpredictable and generally minor response (Kaltsas et al. 2005b, Raverot et al. 2012).

Somatostatin receptor expression is found within normal pituitary cells including corticotrophs and lactotrophs, and binding of somatostatin to its receptor triggers a G-protein-mediated signal cascade that inhibits secretory function in these cells. The two long-acting SSAs in use today are octreotide and lanreotide. More recently, the somatostatin analogue pasireotide, showing increased binding affinity for SSTR-1, 3 and 5, was compared to octreotide and lanreotide, and has apparently shown superior efficacy in the biochemical control of patients with acromegaly (Colao et al. 2014). Pegvisomant, a pegylated analogue of human GH, is currently the only GH-receptor antagonist approved by the FDA available for the treatment of acromegaly. It directly competes for receptor binding with plasma GH resulting in decreased IGF-1 production (van der Lely et al. 2012).

Recent clinical trials have demonstrated the successful application of temozolomide in pituitary carcinomas and aggressive pituitary tumours, and this agent has shown to be efficient in controlling tumour progression and metastasis in approximately 50% of cases (McCormack et al. 2009, McCormack et al. 2011, Raverot et al. 2012). Despite these encouraging results with temozolomide showing long-term control in 40% of patients (Bush et al. 2010, Losa et al. 2010, Raverot et al. 2010), some tumours develop secondary resistance during the follow-up (McCormack et al. 2009, Raverot et al. 2010). The development of new therapeutic options is particularly necessary for pituitary carcinomas resistant to temozolomide (Jouanneau et al. 2012). Some case reports suggest the need to combine temozolomide with other chemotherapeutic agents such as capecitabine (Thearle et al. 2011) or with the new SSA pasireotide (Bode et al. 2010).

Molecular targeted treatment

A number of preclinical and clinical studies have suggested that new MTT may also be useful in controlling pituitary tumour growth. The anti-proliferative effect of an mTOR

inhibitor on different pituitary cell lines or primary cultures has been demonstrated *in vitro* (Cerovac et al. 2010). *In vitro* data have also shown an effect of everolimus on cell viability in cell cultures from non-functioning pituitary adenomas (Zatelli et al. 2010). Furthermore, a mutation of the mTOR pathway, STK11, was found in a woman with an adrenocorticotrophic-secreting pituitary carcinoma refractory to surgical resection, radiation, and chemotherapy with capecitabine and temozolomide. After the combination of radiation and everolimus, significant clinical improvement and radiological stability was obtained, although the patient died of metastatic disease (Vlotides et al. 2008).

There is also some evidence supporting the role of the EGF-R pathway in pituitary proliferation (Vlotides et al. 2008, Cooper et al. 2011), and the potential use of TKIs (Fukuoka et al. 2011) for targeted therapy in pituitary tumours. Anecdotal cases have shown control of tumour growth by the administration of bevacizumab, an anti-VEGF agent, in a single patient (Ortiz et al. 2012), and in another case 26-month disease control was observed (Ortiz et al. 2012). The previously highlighted importance of EGF and its receptor EGF-R has also prompted research concerning the use of TKIs, especially the EGFR inhibitor gefitinib, as a targeted medical therapy for ACTH-adenomas, demonstrating promising *in vitro* results (Fukuoka et al. 2011).

Recently, an exhaustive exome-wide screening has led to the identification of somatic mutations in the ubiquitin-specific protease 8 (USP8) in ACTH-producing adenomas (Reincke et al. 2015). This gene codes for a protein with deubiquitinase (DUB) activity that inhibits the lysosomal degradation of EGF-R (Mizuno et al. 2005). Mutated USP8 leads to higher DUB activity than the wild type, therefore increasing EGF-R stability and enhancing EGF-R-induced pro-opiomelanocortin (POMC) transcription and ACTH secretion. The absence of USP8 mutations in other types of pituitary tumours, including silent ACTH-producing adenomas, suggests that these alterations are specific traits of secretory corticotroph adenomas causing Cushing's disease (Reincke et al. 2015). The high prevalence of mutations in USP8 in patients with Cushing's disease, but not in any other pituitary adenomas, provides a plausible explanation for the dependence of corticotrophinomas on EGF-R signalling and suggests that the mutational status of USP8 can be used to stratify the patients for targeted therapies against EGFR (Fukuoka et al. 2011, Ma et al. 2015). *In vitro* studies showed that targeting EGF-R to mouse corticotroph cell nuclei resulted in higher POMC expression and ACTH

secretion, both of which were inhibited by gefitinib (Fukuoka *et al.* 2011).

The cyclin-dependent kinase (CDK) inhibitor p16 is downregulated in pituitary tumours, probably by methylation of its promoter, leading to a loss of suppression of CDK4 and CDK6 and progression through the checkpoint inhibition into the cell-cycle S phase (Farrell & Clayton 2003). Recently, CDK4/6 antagonists have entered into clinical practice, with palbociclib showing potential in the treatment of breast cancer, causing either cellular quiescence or senescence (Finn *et al.* 2016). It will be of interest to see whether such treatment will be of value in the therapy of aggressive pituitary adenomas or carcinomas. However, it should be noted that corticotroph tumours are more dependent on alterations in p27, cyclin E and CDK2; therefore, these tumours may be less likely to respond (Dworakowska & Grossman 2012).

Although PRRT directed against SSTR2 and SSTR5 subtypes using either ⁹⁰Yttrium and most recently ¹⁷⁷Lutetium could be used for aggressive or recurrent pituitary tumours expressing SSTRs, this modality has not been significantly used in pituitary carcinomas. There are only few case reports in the literature demonstrating the use of PRRT in atypical or aggressive pituitary adenomas or carcinomas. ¹⁷⁷Lutetium DOTATOC improved local complications for more than 8 years after ineffective surgery and gamma-knife therapy in a patient with a non-functioning pituitary macroadenoma (Komor *et al.* 2014). In another case, a patient with an aggressive, giant GH-secreting tumour refractory to all treatments developed a partial biochemical remission and reduction in tumour mass using ⁹⁰Y-DOTATATE (Waligórska-Stachura *et al.* 2016). In a further case series including one patient with a pituitary carcinoma and two with atypical adenomas, results were inconsistent as stable disease was achieved in the sole patient with the more slowly progressive tumour (Maclean *et al.* 2014). Furthermore, a patient with a giant prolactinoma, refractory to medical treatment, showed substantial tumour shrinkage after four cycles of ¹¹¹Indium-DTPA-octreotide (Baldari *et al.* 2012), but this radiobiological therapy is far from ideal.

Overall, for malignant pituitary tumours there is limited evidence for the role of MTT, although TKIs such as gefitinib and mTOR inhibitors such as everolimus have demonstrated promising results *in vitro* and *in vivo* in animals. However, as these tumours exhibit SSTRs, treatment with PRRT appears an attractive option, probably best in the context of a therapeutic trial. Nevertheless, in desperate situations there may be a place for attempted therapy with either gefitinib or

everolimus. The potential role of chemosensitisation with temozolomide to enhance the therapeutic response could also be explored in the future.

Parathyroid carcinoma

Introduction

Most cases of primary hyperparathyroidism are sporadic, but may occur as a part of hyperparathyroidism-jaw tumour syndrome (HJTS), or multiple endocrine neoplasia type-1 or 2A syndromes (McClenaghan *et al.* 2015). Histologically, primary hyperparathyroidism is caused by a single adenoma in 80–85% of cases, by hyperplasia or multiple adenomas in 15–20% of cases, and by a carcinoma in 0.5–5% of cases (Givi & Shah 2010, Mohebbati *et al.* 2012) (Fig. 3). Differentiation of parathyroid carcinoma from parathyroid adenoma, especially atypical adenoma, can be very difficult in some cases (Mohebbati *et al.* 2012).

Molecular profile

Gene expression profiling of parathyroid adenomas and carcinomas may provide an explanation for the formation of parathyroid carcinomas and aid in the differential diagnosis of these lesions (Arvai *et al.* 2012).

To date, mutations of one hyperparathyroidism gene (*HRPT2*, also known as *CDC73*) has been established as the underlying genetic mechanism in parathyroid

Figure 3

An axial MRI post-contrast T1 sequence demonstrating a parietal lobe metastasis from a parathyroid carcinoma.

carcinoma tumourigenesis (Carpén et al. 2002). Inactivating *HRPT2* mutations are frequently revealed in germ line cells of these patients, and are associated with a syndromic form of the disease known as the HJTS (Juhlin et al. 2006).

Parafibromin, the protein product of *HRPT2*, has also been linked to the Wntless type (Wnt) pathway through its nuclear association with β -catenin (Mosimann et al. 2006). In the absence of Wnt signalling, β -catenin is phosphorylated and subsequently degraded by a protein complex consisting of axin, adenomatous polyposis coli (APC) and glycogen synthase kinase 3- β (GSK3- β) (Van Noort et al. 2002), which have been associated with parathyroid carcinoma development. *In vitro* studies have shown a loss of APC and GSK3- β immunoreactivity in sporadic parathyroid carcinomas without an increase in β -catenin or cyclin D1 levels (Juhlin et al. 2009). The normal function of GSK3- β would theoretically be in agreement with a tumour suppressor function; however, inactivating alterations of the GSK3- β gene have not been reported in human cancers (Karim et al. 2004).

Current treatment

The treatment of choice for parathyroid carcinoma is surgery. Therapeutic options for non-resectable and metastatic parathyroid carcinoma are limited. The primary aim is to control hypercalcaemia, and although mitramycin, plicamycin, gallium nitrate, bisphosphonates, calcitonin and glucocorticoids have been used, the calcimimetic cinacalcet is the most effective (Wei & Harari 2012). Locoregional treatments including ethanol ablation, radiofrequency ablation and trans-arterial embolisation present palliative treatment methods (Wei & Harari 2012). There are also recent reports on the use of frequent denosumab for intractable hypercalcaemia (Karupiah 2014). Chemotherapy with dacarbazine and several other regimens are mostly ineffective (Wei & Harari 2012), although radiofrequency ablation of metastatic parathyroid carcinoma may control disease with a survival benefits of up to 15 months (Iguchi et al. 2008, Lourenco et al. 2012). Recent guidelines suggest that adjuvant radiotherapy should be reserved as a palliative option (Wilhelm et al. 2016).

Molecular targeted treatment

Data are scarce with regard to molecular targeted treatment in these rare neoplasms. Loss of APC

expression suggests the possibility for oncological intervention in patients with parathyroid carcinoma as cyclooxygenase-2 (COX-2) inhibitors have been shown to exhibit chemo-preventive features in colorectal cancer (Giardiello et al. 1993, Eisinger et al. 2007). Recently, it has been shown that truncated APC can target β -catenin for destruction, but only in the absence of COX enzyme activity, providing a possible molecular explanation for the promising results of COX-2 inhibition in colorectal cancer (Eisinger et al. 2007). *In vitro*, the COX-2 inhibitor NS-398 suppressed parathyroid-related peptide (PTHrP) production in colorectal cancer (Saito et al. 2007). Anti-PTH immunotherapy has been described in some case reports, demonstrating biochemical control and clinical improvement as well as reduction of the size of metastases (Betea et al. 2004, Horie et al. 2010). Despite these promising results, such therapy is not easily available.

Type I membrane-bound alpha-Klotho (Klotho) defines tissue specificity for the phosphaturic hormone fibroblast growth factor-23 (FGF23) by acting as a permissive co-receptor (Urakawa et al. 2006). FGF23 binds to binary complexes of an FGF receptor (FGF-R) and Klotho to suppress parathyroid hormone (PTH) secretion (Krajsnik et al. 2007). Klotho activity has also been implicated as fundamental for the stimulation of PTH secretion during hypocalcaemic conditions (Imura et al. 2007), although the underlying mechanism has been challenged (Martuseviciene et al. 2011). An *in vitro* study has demonstrated that blocking a parathyroid-FGF23 signalling pathway, involving calcineurin, led to abolition of FGF23-induced suppression of PTH secretion (Olsson et al. 2013). Thus, this pathway could be another future molecular target pathway for the treatment of parathyroid carcinoma.

The epidermal growth factor receptor (EGF-R, ERBB1, HER1) and its ligands have been reported to play an important role in bone biology and in mediating the anabolic actions of intermittent PTH. Amphiregulin (AREG), a ligand of EGF-R, has been identified to be a target gene for PTH *in vitro* and *in vivo* (Schneider et al. 2009) mediating the anabolic bone effect of PTH. However, it is still unclear as to whether these putative effects of AREG are an essential component of PTH's anabolic actions on bone (Jay et al. 2015).

In summary, the therapeutic options for unresectable parathyroid carcinoma are limited and largely ineffective. Surgery is the only curative treatment for parathyroid carcinoma. MTTs are relatively under-explored clinically to date, although anti-PTH immunotherapy in some case series seems to show some encouraging results.

Nevertheless, parathyroid carcinoma may be relatively indolent in terms of progression, and aggressive medical control of the associated hypercalcaemia is an essential part of its management.

Conclusions

MTT either alone or in combination with standard treatments has shown promising results when current therapies such as surgery, chemotherapy, and/or radiotherapy have failed to treat malignant adrenal, pituitary and parathyroid tumours. For progressive metastatic PCs/PGLs, PRRT (including ^{131}I MIBG) as well as sunitinib have shown preliminary evidence of anti-tumour activity as either first-line treatment or following progression with currently available treatments, and in combination with TKIs, mTOR inhibitors and other agents. Combination treatment of chemotherapy with TKIs or immunotherapy could be considered in patients with ACCs who have failed standard treatment, albeit with significant adverse events. Malignant and aggressive pituitary adenomas may respond to PRRT either as single agents or in combination with temozolomide. There are as yet limited data on the role of MTT in parathyroid carcinoma. Nevertheless, MTT appears to be the future for the management of these rare malignant endocrine tumours allowing for a more customised and individualised approach to the therapy. Combination strategies targeting more than one signalling pathway are most promising, at least *in vitro*. Immunotherapy has also yet to be introduced into these therapeutic paradigms. Multicentre trials are needed to obtain robust conclusions and the development of centralised databases accessible to different centres could help to better interrogate these tumours in larger populations.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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