Targeted Therapies for the Treatment of Pheochromocytoma: Current and Future Approaches to Care

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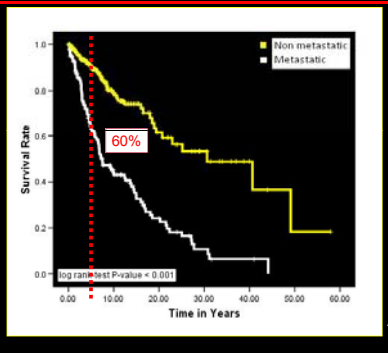
VHL pheochromocytoma and paraganglioma

- Pheochromocytomas and paragangliomas occur in 10-34% of VHL patients
- Pheochromocytomas 90%
- Paragangliomas: abdomen 8%, chest 2% HN 0.1%
- Metastases occur in less than 10%
- Most common in paragangliomas and large pheochromocytomas

Jimenez, C, JCEM, 2006
Ayala-Ramirez, JCEM, 2011

Overall Survival Metastatic vs. Non-metastatic



Ayala-Ramirez, 2011

Current Systemic Therapies

- Chemotherapy
- Radiopharmaceuticals Agents

Systemic Chemotherapy

The MDACC experience

Responders in the MDACC Retrospective Study

- Proportion of patients with reduced tumor size by computed tomography and magnetic resonance imaging
- Proportion of patients who normalized blood pressure with at least a 50% reduction in the dosage and number of antihypertensives

Ayala Ramirez, Cancer, 2011

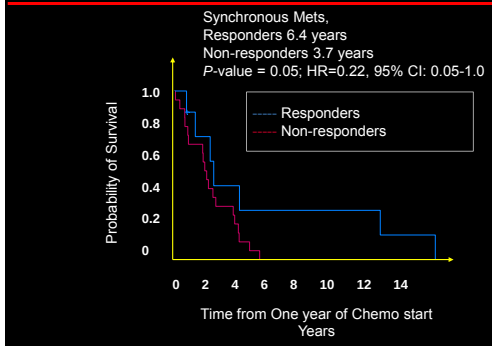
Front-line Chemotherapy

Protocol	Responders n = 17	Non-Responders n = 35	Total n = 52
CYVADIC	9	10	19
CYADIC	3	9	12
CYVDIC	5	5	10
CYAV	0	2	2
CYA	0	1	1
CHOP	0	1	1
Others	0	7	7

40%

Ayala Ramirez, Cancer, 2011

Overall Survival in Patients wit metastatic disease (Responders Vs. Non-Responders)



Ayala Ramirez, Cancer, 2011

Demographic Predictors of Response

Characteristic	Responders	Non-responders	P-value
Age			0.31
Median	42 (25-62) y	42 (6-70) y	
Gender			0.37
Male	11 (37.9%)	18 (62.1%)	
Female	6 (26.1%)	17 (73.9%)	
Ethnicity			0.24
White	16 (37.2%)	27 (62.8%)	
Others	1 (11.1%)	8 (88.9%)	

Tumor Predictors of Response

Characteristic	Responders	Non-responders	P-value
Tumor Size	5.5 (2-18) cm	8 (1-15) cm	0.39
Tumor Type			
Pheo	6 (31.6%)	13 (68.4%)	0.90
PGL	11 (33.3%)	22 (67.7%)	
Sites of Mets.			0.41
Single	4 (44.4%)	5 (55.5%)	
Multiple	13 (30.2%)	30 (69.7%)	
Mets. Timing			0.91

Genetic Background

Genetic finding	Responders	Non-responders
SDHB positive	1	4
SDHC positive	1	0
Sporadic	8	8

Ayala Ramirez, Cancer, 2011

Chemotherapy

- Patients with unresectable progressive disease control
- Patients with symptomatic disease
- Chemotherapy must be the best available treatment for the patient
- Reasonable performance status
- Whenever a surgical resection could be favored
- (-) OR (-/+) MIBG tumors, unresponsive tumors to other therapies, lack of other therapies

Plouin, HMR, 2012

Radiopharmaceutical Agents

Phase 2 high activity MIBG trial

- Response rate 22% by RECIST
- Minor responses in 35%
- Stable disease 8%
- 5-year overall survival 64%
- Non-randomized trial

Gonias, JCO, 2009

MIBG

- Patients with unresectable progressive disease control
- Patients with symptomatic disease
- MIBG must be the best available treatment for the patient
- Reasonable performance status

Plouin, HMR, 2012

Molecular Targeted Therapies

Case Presentation

- 32 year-old African-American woman
- Family history of von Hippel Lindau disease (VHL) Arg167Gln
- Hypertension, palpitations, shortness of breath, throbbing headaches
- Abdominal and pelvic pain, 20-kg weight-loss

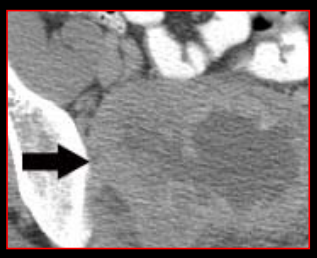
Jimenez, JCEM, 2009

Case Presentation

- Plasma normetanephrines 7,950 pg/ml (112-658 pg/ml)
- Urinary normetanephrines 10,193 µ/24h (300-600 µ/24h)
- Abdominal computerized tomography identified a 10.5 cm right adrenal mass, a 3 cm left adrenal mass, a 9.8 cm pelvic mass infiltrative of the sacrum, and multiple pancreatic and bilateral kidney tumors

Jimenez, JCEM, 2009

Pelvic Paraganglioma



Biopsy confirmed a pheochromocytoma.

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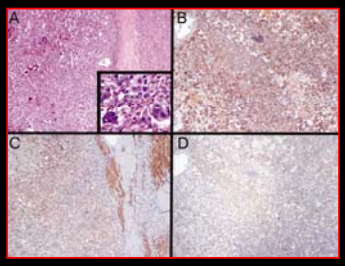
Therapeutic Options

- Surgery:
  - Multiple tumors with malignant potential and bone infiltration
- Chemotherapy:
  - Poor performance, multiple tumors
- MIBG/Azedra:
  - Not available
- Phase I/II research protocols:
  - Poor performance status, multiple tumors

Jimenez, JCEM, 2009

Immunohistochemical analyses



Malignant pheochromocytoma (A-D): Hematoxylin and Eosin section of tumor (left) with rim of normal adrenal (upper right), insert shows tumor at high power (A); immunohistochemical analyses (B-D); Tumor with diffuse strong (3+) expression of PDGFR-beta (B); weak (1+) expression of VEGF (left) and rim of normal adrenal gland with strong (3+) expression (right) (C); weak (1+) patchy expression of EGFR (D).

Therapy

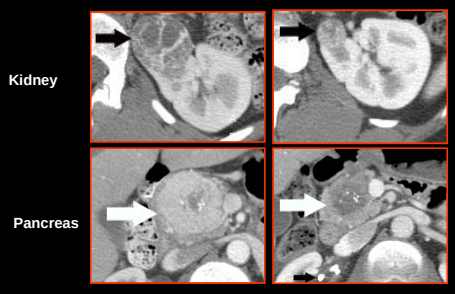
Multi-Tyrosine Kinase Inhibitor
Sunitinib

Effect on Tumor Size

Malignant Pheochromocytoma

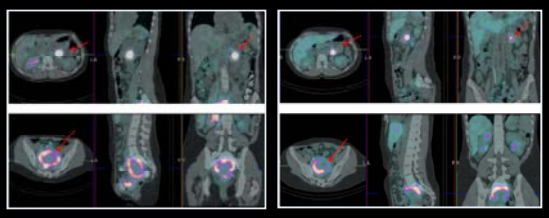
Jimenez, JCEM, 2009

Effect on Tumor Size



Jimenez, JCEM, 2009

Effect on MIBG uptake



Baseline MIBG scan | After 6 months of sunitinib

Jimenez, JCEM, 2009

Effect on Clinical Manifestations of Disease

	Before Sunitinib	After Sunitinib
Antihypertensive therapy	Phenoxybenzamine 30 mg/d	Prasozin 2 mg/d
Headaches	Yes	No
Palpitations	Yes	No
Pain	10/10 on opioids	0/10, no analgesics
Weight	20 kg weight-loss	5 kg weight-gain
ECOG	2	0

Jimenez, JCEM, 2009

Molecular Targeted Therapy against Metastatic Pheochromocytomas and Sympathetic Paragangliomas:

Clinical Observations in a Cohort of 11 Patients with Progressive Disease

Patient with sporadic pheochromocytoma treated with sunitinib

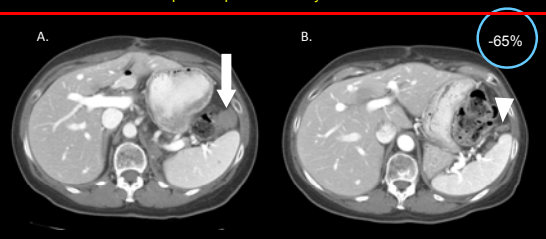


Figure 1: Positive response to sunitinib. In panel A, a large perisplenic metastasis (arrow) measured 2.6 x 2.4 cm prior to sunitinib treatment. Three months after initiation of sunitinib, the mass had decreased to 1.7 x 0.7 cm (arrowhead).

Ayala-Ramirez, 2011

SDHB Patient treated with sunitinib

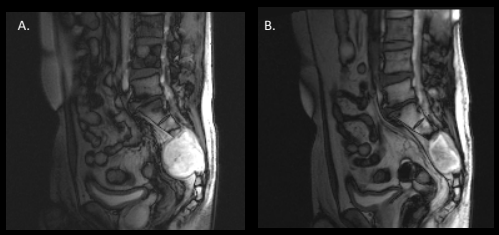
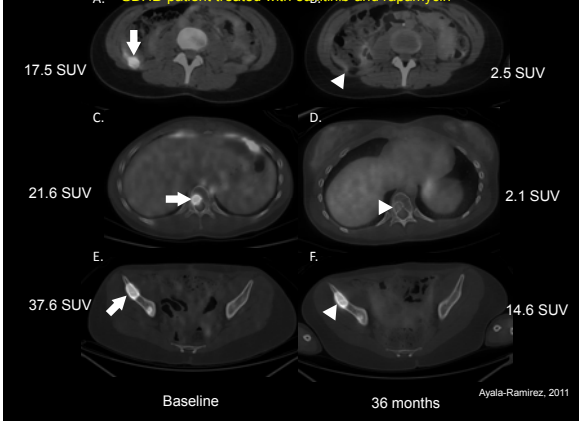


Figure 2: Positive response to sunitinib. Sagittal localizer images from MRI studies performed prior to sunitinib therapy (panel A) and 3 months after sunitinib therapy (panel B) show a marked reduction in size of the patient's sacral metastasis.

Ayala-Ramirez, 2011

A. *SDHB* patient treated with sunitinib and rapamycin



Ayala-Ramirez, 2011

Patient	Baseline (Drugs/BP)	4 weeks (Drugs/BP)	6 weeks-6 months (Drugs/BP)	9 months (Drugs/BP)	12 months (Drugs/BP)
1	Phenoxybenzamine 30 mg/d Atenolol 50 mg/d (95/73)	Phenoxybenzamine 30 mg/d Atenolol 50 mg/d (100/60)	Prazosin 1 mg/d (99/77)	Phenoxybenzamine 30 mg/d Atenolol 50 mg/d (150/80)	
2	Terazosin 2 mg/d, Carvedilol 80 mg/d (128/77)	Terazosin 2 mg/d, Ramipril 5 mg/d, Aliskiren 300 mg/d, Carvedilol 50 mg/d, Phenoxybenzamine 20 mg/bid (170/92)	Terazosin 2 mg/d, Ramipril 5 mg/d, Aliskiren 300 mg/d, Carvedilol 50 mg/d (130/69)	No anti-hypertensives (97/67)	No anti-hypertensives (100/62)
3	Terazosin 8 mg/d (139/87)	Terazosin 10 mg/d, Phenoxybenzamine 10 mg/d (165/116)	Terazosin 2 mg/d (100/69)	No anti-hypertensives (93/61)	No anti-hypertensives (101/64)
4	Doxazosin 2 mg/d (126/69)	Doxazosin 4 mg/d, Atenolol 50 mg/d (107/61)	Doxazosin 2 mg/d (100/67)	Doxazosin 2 mg/d (109/66)	Doxazosin 2 mg/every other day (116/67)

Ayala-Ramirez, 2011

Clinical Benefits

Patient	1	2	3	4
Tumor Size Reduction	21%	65%	+ (skeletal, not evaluable by RECIST)	+ (skeletal, not evaluable by RECIST)
BP improvement	Yes	Yes	Yes	Yes
Pain improvement	Yes	-	Yes	Yes
Decreased MIBG uptake	+	+	NA	NA
Decreased FDG-PET uptake	NA	+	NA	+
ECOG	2 to 0	2 to 0	1 to 0	1 to 0
Duration of response	6 m	12 m	24 m	36 m

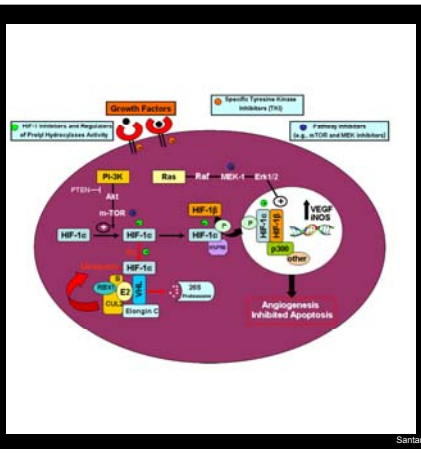
Ayala-Ramirez, 2011

Non-responders to sunitinib

- Four patients with apparently sporadic tumors did not respond to sunitinib 3 months after initiating therapy
- Three patients did not tolerate sunitinib

Sunitinib

- Sunitinib is associated with clinical benefits in some patients such as tumor size reduction, and blood pressure and pain control, and performance status improvement
- The combination of molecular targeted therapies may be feasible and may provide a durable response



Santarpia, HMR, 2009

Clinical Trials with Molecular Targeted Therapies

- Study of Sunitinib in Patients with Recurrent Paraganglioma/Pheochromocytoma (ORR)
- First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma (PFS)
- Pazopanib Hydrochloride in Treating Patients with Advanced or Progressive Malignant Pheochromocytoma and Paraganglioma (ORR)
- RAD001 in Pheochromocytoma or Nonfunctioning Carcinoid (PFS)

Conclusions

- The value and indications of different therapeutic modalities is still to be determined
- New promising therapeutic modalities are in the horizon leading to exciting clinical trials

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