Clinical challenge for KIT/PDGFRA WT GIST

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Clinical challenge for KIT/PDGFRA WT GIST

➢ Repeat the analysis of KIT/PDGFRA kinase receptors

why?

➢ Low DNA quality

➢ Scarse cell enrichment

➢ Old and low sensitive methods

➢ Low expertise laboratories

➢ Incomplete KIT/PDGFRA exons evaluation

The frequency of KIT/PDGFRA WT GIST will be reduced even more
Clinical challenge for KIT/PDGFRA WT GIST

- Repeat the analysis of KIT/PDGFRA kinase receptors
- To recognize the WT subgroup to which the patient belongs
Treatment of KIT/PDGFRA WT GIST

Localised GIST

**SURGERY** for any subgroups

No adjuvant therapy with imatinib should be considered

Advanced /recurrent GIST:

**SURGERY** and/or medical therapy should be differentiated for subgroups

Due to the rarity of KIT/PDGFRA WT GIST in general and for each subgroups, treatment experience is limited to a very small number of cases

Decisions based on the outcome

Decisions based on the molecular background
Clinical challenge for KIT/PDGFRA WT GIST

- Repeat the analysis of KIT/PDGFRA kinase receptors
- To recognize the WT subgroup to which the patient belongs

Clinical and pathological data  Molecular profile
Clinical challenge for KIT/PDGFRA WT GIST

- Repeat the analysis of KIT/PDGFRA kinase receptors
- To recognize the subgroup to which the patient belongs

Clinical and pathological data

Molecular profile

Age

Syndrome

Sporadic
Rare
Almost the same of syndrome

Pediatric

Carney-Stratakis Syndrome:
Carney Syndrome:
SDH DEFICIENT GIST

Young adult adult

NF-1 Syndrome
SDH deficient GIST associated to syndrome

> Carney-Stratakis Syndrome predisposes to GIST and paraganglioma and caused by mutations in SDHB/C/D

> Carney Syndrome associated KIT/PDGFRα WT GIST caused by SDHC methylation

Belinky MG, Frontriers Oncol 2013
Janeway KA, PNAS 2011
Haller F, Endocr Relat Cancer 2014
Clinical challenge for KIT/PDGFRA WT GIST

- Repeat the analysis of KIT/PDGFRA kinase receptors
- To recognize the subgroup to which the patient belongs

Clinical and pathological data ➔ Molecular profile

Age ➔ Syndrome

Yes ➔ Pediatric

Sporadic ➔ Young adult adult

Carney-Stratakis Syndrome
Carney Syndrome

NF-1 Syndrome

Heterogenous family of disease
1. BRAF-RAS mutant
2. SDH deficient
3. Quadruple WT
Current characterization of young/adult KIT/PDGFRA WT GIST

RAS-P MUTANT

NF-1  RAS-BRAF

SDHB+  SDHB+

IGF1R-  IGF1R-

Young Adults/ Adults  Adults

Equal sex  Equal sex

Multifocal  No multifocal

Small intestine  Gastric/Small intestine

(20%)
**BRAF mutations in KIT/PDGFRA WT GIST**

BRAF mutations range between the 4%-20% of KIT/PDGFRA WT GIST

No particular correlation with histologic and clinical parameters (mitotic count, tumor size, morphology, site)

Prevalence for small bowel localization

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
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</thead>
<tbody>
<tr>
<td>Agaram N, Gene Chrom Cancer 2008</td>
<td>3</td>
</tr>
<tr>
<td>Agaimy A, J Clin Pathol 2009</td>
<td>2</td>
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<tr>
<td>Hostein I, Am J Clin Pathol 2010</td>
<td>9</td>
</tr>
<tr>
<td>Daniels M, Cancer Lett 2011</td>
<td>3</td>
</tr>
<tr>
<td>Belinsky MG, Gene Chrom Cancer 2009</td>
<td>1</td>
</tr>
<tr>
<td>Miranda C, Clin Cancer Res 2012</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Wild Type for BRAF (n = 57)</th>
<th>With BRAF Mutation (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine</td>
<td>19 (33)</td>
<td>5 (66)</td>
</tr>
<tr>
<td>Stomach</td>
<td>26 (46)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Colon</td>
<td>3 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rectum</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4 (7)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>4 (7)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Trait</th>
<th>No BRAF Mutation</th>
<th>V600E BRAF Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>Mean (Range)/Median</td>
<td>Mean (Range)/Median</td>
</tr>
<tr>
<td>Mitotic count (HPF)</td>
<td>54</td>
<td>68</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61</td>
<td>61</td>
</tr>
</tbody>
</table>

HPF, high-power fields.
Current characterization of young/adult KIT/PDGFRA WT GIST

RAS-P MUTANT
- NF-1
- SDHB+
- IGF1R-
- Young Adults/Adults
- Equal sex
- Multifocal
- Small intestine
- Gastric/Small intestine

(20%)

SDH DEFI CIENT
- SDH mutation
- NO SDH mutation
- SDHB-
- IGF1R+
- Pediatric/Young Adults
- Prevalence of female
- Often Multifocal
- Gastric
- Lymph nodes metastases

(50%)

Pantaleo MA, Cancer Med 2014
SDH deficient GIST not associated to syndrome

SDH deficient GIST caused by SDH complex mutations and SDHC epimutation

Miettinen 2011 and 2013: 12 SDHA and 25 SDH non A metastatic cases, 42 years!

Pantaleo MA, Gen Med 2015
Current characterization of young/adult KIT/PDGFRα WT GIST

**RAS-P MUTANT**
- NF-1
- RAS-BRAF
- SDHB+
- IGF1R-
- Young Adults/Adults
- Equal sex
- Multifocal
- Small intestine/Gastric/Small intestine

**SDH DEFICIENT**
- SDH mutation
- SDHB-IGF1R+
- Pediatric/Young Adults
- Prevalence of female
- Often Multifocal
- Gastric
- Lymph nodes metastases

**QUADRUPLE WT**
- No RAS-P/No SDH
- SDHB+
- IGF1R-
- Any age?
- Equal sex?
- No multifocal?
- Any site?
- Prognosis?

(20%) (50%) (30%)

Pantaleo MA, Cancer Med 2014
Quadruple WT GIST

No particular correlation with histologic and clinical parameters (mitotic count, tumor size, morphology, site)

Currently No particular treatments are recommended outside the guidelines

- NF-1 mutations outside the NF-1 syndrome
- MYC associated factor X gene (MAX mutations)
- FGFR1 mutation
- Gene fusions (ETV6-NTRK3; FGFR1-HOOK3, FGFR1-TACC1)

To identify new relevant molecular events as targets for treatments
Clinical challenge for KIT/PDGFRA WT GIST

- Repeat the analysis of KIT/PDGFRA kinase receptors
- To recognize the subgroup to which the patient belongs

Clinical and pathological data ➔ Predicting the prognosis/natural history
Molecular profile ➔ Choosing the management
Clinical challenge for KIT/PDGFRA WT GIST

- Repeat the analysis of KIT/PDGFRA kinase receptors
- To recognize the subgroup to which the patient belongs
- To promote the creation of WT GIST clinics
WT GIST clinics

- To support WT GIST patients for any need and urgency
- To guarantee the most appropriate clinical management acting as a facilitator between various specialist groups
- To develop a WT GIST registry
- To promote the creation of WT GIST tumor bank
Clinical challenge for KIT/PDGFRA WT GIST

- Repeat the analysis of KIT/PDGFRA kinase receptors
- To recognize the subgroup to which the patient belongs
- To promote the creation of WT GIST clinics
- To collect globally clinical data as more as possible (WT GIST registry)
- To collect globally research data as accurate as possible
Clinical challenge for KIT/PDGFRA WT GIST

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- To improve the treatments experiences (early phase clinical trials, off label treatments, drugs as a compassionate use and basket trial based on genome profile)

ClinicalTrials.gov Identifier: NCT02638766: Single Agent Regorafenib in First-line for Metastatic/Unresectable KIT/PDGFR Wild Type GIST (REGISTRI)
Clinical trial in KIT/PDGFRA WT GIST

Sunitinib as second line treatment

ClinicalTrials.gov Identifier: NCT01396148
A Study of Sunitinib In Young Patients With Advanced Gastrointestinal Stromal Tumor

Given the SDH complex deregulation, angiogenesis inhibitors should be a preferred option

Janeway KA, Pediatric Blood Cancer 2009
Insulin-like Growth Factor Receptor type 1 (IGF1-R) in SDH deficient GIST

Increased IGF1R expression in SDH deficient GIST not supported by gene amplification

Linsitinib in WT GIST: Results of SARC 022, a phase II multicenter study of linsitinib in pediatric and adult wild-type (WT) gastrointestinal stromal tumors (GIST); Abstr 10507

but probably not all patients presented IGF1R overexpression

Nannini M, Future Oncol 2013
Chou A, Mod Pathol 2012
Janeway K, Int J Cancer 2010
Von Mehren M, ASCO 2014
Treatment of BRAF mutated GIST

Few cases to reach any conclusions on outcome and prognosis

No effective prior treatment with tyrosine kinase inhibitors and a MEK inhibitor. Stable disease for 8 months with Dabrafenib therapy

NGS study reveals two additional mutations: a PI3KCA and A CDKN2A mutation

To encourage the treatment with BRAF inhibitors upfront in clinical trials or off label setting
Treatment of NF1 associated GIST

The 5-year disease-specific survival and event-free survival were 54.3% (median, not reached) and 46.9% (median, 48 months) respectively.

70% of patients had high or intermediate risk tumors.

The incidence of distant metastases (liver and peritoneal) was lower than in sporadic GISTs (25%).

They often present synchronous primary lesions and develop recurrent lesions.

Molecular studies on neurofibromin and RAS pathway to identify new molecular targets. mTOR inhibitors or MAPK inhibitors should be tested.

Mussi C, Clin Cancer Res 2008
Kalender M, World j Gastr 2007
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➢ To promote the creation of WT GIST clinics

➢ To collect globally clinical data as more as possible (WT GIST registry)

➢ To collect globally research data as accurate as possible

➢ To improve the treatments experience (early phase clinical trials, off label treatments, drugs as a compassionate use and basket trial based on genome profile)

➢ To encourage preclinical and molecular research (WT GIST tumor bank)

Preclinical studies to isolate cell lines on SDH-deficient GIST or other WT GIST profiles exist yet

Collaborative research works to better understand the biology and to explore newer inhibitors
These are the clinical challenges for KIT/PDGFRA WT GIST:

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- To promote the creation of WT GIST clinics
- To collect globally clinical data as more as possible (WT GIST registry)
- To collect globally research data as accurate as possible
- To improve the treatments experiences (early phase clinical trials, off label treatments, drugs as a compassionate use and basket trial based on genome profile)
- To encourage preclinical and molecular research (WT GIST tumor bank)
Clinical challenge for KIT/PDGFRA WT GIST

More cooperative efforts should be done by the scientific community