Open Issues in High Grade Uterine Mesenchymal Lesions

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Disclosures

• Advisory Boards: Insys (July 2013), Arno Therapeutics (January 2013), GSK (October 2012)
• *Up To Date*, author
• Research Funding: J&J
• Spouse employed by Sanofi
### Overview

<table>
<thead>
<tr>
<th>Mesenchymal Lesion</th>
<th>Adjuvant Treatment</th>
<th>Treatment for Advanced Disease</th>
<th>Genetic/Molecular progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyosarcoma</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
High grade leiomyosarcoma
Uterine LMS: adjuvant treatment?

• Should patients with uterus-limited high grade LMS be treated with adjuvant chemotherapy?
Prospective adjuvant Dox/Cis/Ifos + RT v. RT (n=81)

- 52 stage I
- 16 stage II
- 13 stage III
- 53 LMS
- 9 undifferentiated sarcomas
- 19 carcinosarcomas

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3-year PFS (p=0.048)</th>
<th>OS (p=0.41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dox + Ifos + Cis + pRT (n=39)</td>
<td>55%</td>
<td>81%</td>
</tr>
<tr>
<td>RT (n=42)</td>
<td>41%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Phase II trial adjuvant chemo: SARC 005:

Gemcitabine 900 mg/m² over 90 minutes days 1, 8
Docetaxel 75 mg/m² day 8
q 3 wk x 4 cycles

Repeat CT scan—if disease free, then proceed:

Doxorubicin 60 mg/m² q 3 w x 4

Repeat CT scan within 6 weeks after doxorubicin

CT c/a/p every 3 mo for 2 y, then every 6 mo

Hensley, Cancer, 2013
## SARC005: PFS (n=47)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients progression-free at 2 years</td>
<td>78.4%</td>
<td>95% CI</td>
<td>67-91%</td>
</tr>
<tr>
<td>% of patients progression-free at 3 years</td>
<td>58%</td>
<td>95% CI</td>
<td>44-74%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>&gt; 36 months (not yet reached)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>Not yet reached</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented by Martee L. Hensley, MD
Retrospective stage I or II uLMS

- Multi-center, 1990-2010
- 108 patients
  - 87% stage I
  - 13% stage II
- Observation 31.5%
- Radiation 32.4%
- Chemotherapy 36.1%
- At median f/u 41.8 mo: 70.8% had recurred

## Recurrence rates

<table>
<thead>
<tr>
<th>Recurrence location</th>
<th>Observation (n=34)</th>
<th>RT (n=35)</th>
<th>Chemotherapy (n=39)</th>
<th>All patients (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recurrences</td>
<td>25 (73.5%)</td>
<td>21 (60%)</td>
<td>28 (71.8%)</td>
<td>74 (64.8%)</td>
</tr>
<tr>
<td>Pelvic recurrences</td>
<td>10 (40%)</td>
<td>1 (4.8%)</td>
<td>10 (35.7%)</td>
<td>21 (25.4%)</td>
</tr>
<tr>
<td>Extrapelvic recurrences</td>
<td>15 (60%)</td>
<td>20 (95.2%)</td>
<td>18 (64.3%)</td>
<td>53 (74.6%)</td>
</tr>
</tbody>
</table>

\[ p = 0.413 \] for adjuvant treatment v. observation
Survival Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>24.7 mo</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>16.4 mo</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>28.3 mo</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>23.3 mo</td>
<td>52.6 mo</td>
</tr>
</tbody>
</table>

p = 0.586 for PFS by adjuvant therapy

P = 0.045 for Chemotherapy v. Observation in multivariate analysis of impact on OS

Hazard Ratio: CT 0.525 (95% CI 0.279, 0.985)
Hazard Ratio: RT 0.751 (95% CI 0.413, 1.382)

Ricci, Gyn Oncol 2013
Other observations from Ricci retrospective study

• Among the patients who were treated with adjuvant chemo, observed PFS:
  – Treated with gem-doce: 31.3 mo
  – Treated with other chemo: 20.8 mo

• Isolated, potentially resectable recurrences were more likely among women treated with adjuvant chemo than among pts who had observation or RT (p=0.045)
Does this mean adjuvant chemo is beneficial?

- 3 year DFS 52% (observation) and 58% (RT) in EORTC trial (mix of LMS and ut CS pts)
- 3 year DFS 58% in SARC 005 adjuvant chemo phase II study in uterine LMS
- need randomized trial comparing chemo to observation in order to answer the adjuvant chemotherapy question

presented by Martee L. Hensley, MD
GOG 0277: phase III adjuvant gem-dox, followed by dox v. observation for uterus-limited LMS

A collaborative study from the International Rare Cancers Initiative-Gynecologic Sarcomas

M L Hensley, M.D. Principal Investigator
I Ray-Coquard, M.D., Ph.D.
H Hatcher, M.D.

Activated 6/2012
High-grade uterine LMS - FIGO Stage I (uterus +/- cervix) - Hysterectomy +/- BSO

Regimen I
- Gemcitabine
  900 mg/m² IV day 1 and 8
- Docetaxel
  75 mg/m² IV day 8
- GCSF 5 mc/kg days 9-15 or pegfilgrastim 6mg day 9 or 10
- Every 21 days Cycles 1-4
- CT/MRI imaging to confirm disease-free
- Doxorubicin
  60 mg/m² IV
- Every 21 days for Cycles 5-8

Regimen II
- Observation
- CT/MRI Imaging after 3 to 4 months from study entry to confirm disease free.

Activated 6/4/12
Target accrual: 216  # accrued: 7
GOG 0277 is the first IRCI study to activate!

presented by Martee L. Hensley, MD
uLMS: treatment for advanced disease?

- Does ifosfamide work in LMS?
- Should trabectedin be used in combinations?
- Is there any role of hormone blockade?
- Should vascular-targeted therapy be added to cytotoxic therapy?
EORTC retrospective study: outcomes in uterine v. other sarcomas

• Median PFS did not differ:
  – ut sarcoma 4.1 mo
  – Other STS 3.7 mo

• Histologic grade and performance status were prognostic for OS among all the ut sarcoma pts

• 225 uterine sarcoma patients, variable histologies and grades
  – 52/225 (23%) had objective response to chemotherapy
### Uterine sarcomas, response to chemo (n=225)

<table>
<thead>
<tr>
<th></th>
<th>Anthracyclines N=96</th>
<th>Dox +Ifos N=66</th>
<th>CYVADIC N=23</th>
<th>Ifos N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3 (3.1%)</td>
<td>2 (3%)</td>
<td>3 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>21 (21.9%)</td>
<td>16 (24.2%)</td>
<td>5 (21.7%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>SD</td>
<td>41 (42.7%)</td>
<td>22 (33.3%)</td>
<td>7 (30.4%)</td>
<td>15 (37.5%)</td>
</tr>
<tr>
<td>PD</td>
<td>28 (29.2%)</td>
<td>19 (28.8%)</td>
<td>5 (21.7%)</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>inevaluable</td>
<td>3 (3.1%)</td>
<td>7 (10.6%)</td>
<td>3 (13%)</td>
<td>6 (15%)</td>
</tr>
</tbody>
</table>

Presented by Ray-Coquard, CTOS 2013
LMS-02
A phase II single-arm multicenter study of Trabectedin in combination with Doxorubicin as first-line treatment of metastatic and/or locally advanced leiomyosarcoma of uterine (U-LMS) or Soft Tissue (ST-LMS) origin: Results from both cohorts

F. Duffaud, C. Chevreau, N. Penel, A. Le Cesne, C. Guillemet, C. Delcambre, A. Floquet, D. Cupissol, B. Lacas, P. Pautier

French Sarcoma Group
LMS02 – uterine LMS results

- Response (44 pts):
  - 25 PR  \( \text{ORR} : 56.8\% \)
  - 13 stable diseases
  - Disease control rate: 86%

- Median duration of response: 5.5 months (3.8 – 6.6)

- PFS rate at 12 weeks: 84 % [95% CI: 73%-94%]
LMS 02 – Toxicity

- anemia 24% gr 3
- thrombocytopenia 15% gr 3-4
- febrile neutropenia 6%

a Judson I. Ann Oncol LBA7 ESMO 2012; b Hensley M. Gyn Oncol 2008
Letrozole phase II in ut LMS (n=27)

- ER and/or PR positive, measurable disease
- Primary endpoint: 12 week PFS
  - Median 2 prior (range 0-9)
  - Median treatment duration 2.2 months (range 0.4-9.9 mo)
  - **12 week PFS 50% (90%CI 30-67)**
  - Best Response=SD (n=14, 54%)
  - 3 patients remained stable >24 weeks, all 3 had ER and PR in >90% of tumor cells

S George, Cancer, 2013
GOG 0250: phase III gem-doce + placebo v. bevacizumab

Regimen I:
- Gemcitabine
  900 mg/m² IV days 1 and 8
- Docetaxel
  75 mg/m² IV day 8
- Placebo (for Bevacizumab)
- Day 1
- Every 3 weeks

Regimen II:
- Gemcitabine
  900 mg/m² IV days 1 and 8
- Docetaxel
  75 mg/m² IV day 8
- Bevacizumab
  15 mg/kg IV day 1
- Every 3 weeks

Until disease progression or adverse effects prohibit further therapy

* All patients will receive GCSF on day 9 of each cycle
So many choices for 1ˢᵗ line treatment, metastatic ut LMS

- Gemcitabine
- Gemcitabine-docetaxel
- Doxorubicin
- Doxorubicin-ifosfamide
- Ifosfamide
- Trabectedin
- Trabectedin-doxorubicin
- Liposomal doxorubicin
- Pazopanib
- Dacarbazine
- 3-drug combinations
- Letrozole or other AI
Uterine Leiomyosarcoma: Any genomic/molecular advances?

• Is there likely a single driver target? -- no
• Can we study targeted therapies that may be applicable to only a subset of patients?
How to focus the research effort in uLMS?

The n=1 approach

• Genomic profiling of the great responder
• Not likely one driver for every uLMS, try to find the one driver for each one?
• If you find the driver, will you have a drug? And how soon until
  – Target mutation
  – Oncogene bypass
  – Feedback upregulation

The n=1001 approach

• Prospective randomized trials with overall survival or at least PFS endpoints
• Aim to define best first- and second-line therapies for uLMS
  – Dox-Trab v. Gem-Doc
  – Dox-Trab v. Dox
  – Gem-doce-placebo v. Gem-doce-bev
  – Ad infinitum for questions
  – BUT not for patients!
How to focus the research in uLMS?

• A hybrid approach (at MSKCC):
  • Genomic profiling of uterine sarcomas in a research discovery platform
  • Potential driver mutation found?

Enroll on “basket” trial of drug that targets that mutation/pathway

Did sequencing impact treatment?  Did targeted treatment achieve response?
Carcinosarcoma
Uterine Carcinosarcoma: best adjuvant treatment?

• Should patients of all stages who are completely resected receive adjuvant chemotherapy?

• Is paclitaxel-carbo a reasonable first-line treatment for uterine LMS?
GOG 150: Adjuvant WART v. chemo for CS

- Activated 12/93; closed 3/05
- 206 evaluable patients
- 44% stage I or II
- Benefit for stage I and II
- Vaginal-pelvic failures same in both arms
  - 17.1% WART
  - 23.7% chemo

<table>
<thead>
<tr>
<th></th>
<th>WART</th>
<th>Ifos-Cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse at 5 years</td>
<td>58%</td>
<td>52%</td>
</tr>
<tr>
<td>OS at 5 years</td>
<td>34%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Wolfson, Gyn Oncol 2007
Recurrence rate: WART v. Ifos-cis

Wolfson, Gyn Oncol 2007
Overall Survival: WART v. Ifos-cis
Phase III for stage I-IV CS

GOG 261

Paclitaxel-Carboplatin every 3 weeks for 8 cycles

Ifosfamide daily x 3 d + Paclitaxel day 1 + GCSF day 4 – 10 or Neulasta every 3 weeks for 8 cycles

• Primary endpoint: overall survival

Powell, Hensley Principal Investigators
Uterine Carcinosarcoma: best treatment for advanced disease?

- Are two cytotoxic drugs better than one?
- Is there a role for vascular-targeted therapy in carcinosarcoma?
- Should we extrapolate STS data to carcinosarcomas?
GOG 161: Ifos v. Ifos-Paclitaxel for measurable CS, no prior

- 179 evaluable patients, measurable disease
- About 1/3 with prior pelvic RT

<table>
<thead>
<tr>
<th></th>
<th>Ifos</th>
<th>Ifos-Pac</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10%</td>
<td>22%</td>
</tr>
<tr>
<td>PR</td>
<td>19%</td>
<td>24%</td>
</tr>
<tr>
<td>G3/4 ANC</td>
<td>47%</td>
<td>38%</td>
</tr>
<tr>
<td>G1- 4 neuro</td>
<td>8%</td>
<td>30%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>3.6 months</td>
<td>5.8 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>8.4 months</td>
<td>13.5 months</td>
</tr>
</tbody>
</table>

Homesley, J Clin Oncol 2007
GOG 232B: Paclitaxel-Carbo for CS

- Phase II study
- Measurable disease, stage III or IV
- No prior cytotoxic therapy
- 46 evaluable patients
- ORR = 54%

Powell J Clin Oncol 2010
GOG phase II: Gem-Doce for ut CS

- Ut CS, failed one prior, measurable disease (n=28)
- Gem 600 mg/m2 + Doce 35 mg/m2 days 1, 8, 15
- Best response:
  - PR 2 (8.3%)
  - SD 8 (33.3%)
- Median PFS 1.8 months
- Median OS 4.9 months

Miller, Gyn Oncol 2010
GOG 230D: pazopanib

- Phase II with primary endpoint either objective response or 6-month PFS
- Second stage of accrual not indicated due to failure to achieve sufficient ORR or PFS at 6 months

Campos, Hensley, ms submitted 2014
Uterine Carcinosarcoma: Any genomic/molecular advances?

- Are the carcinoma and the sarcoma portions genetically similar?
- Is uterine carcinosarcoma really just bad endometrial carcinoma? If they share targets, will targeted therapy work?
Mutational Analysis: Endometrial Cancer

Cohorts Expected to Response to PI3K Targeting

- PTEN: 31%
- Null: 25%
- PIK3CA/PTEN: 19%
- Kras/PIK3CA/PTEN: 6%
- PIK3CA: 8%
- Kras: 4%
- Kras/PTEN: 3%
- Kras/PIK3CA: 2%

From C. Aghajanian, 2012
Carcinosarcoma-Endometrial Carcinoma-Uterine Sarcoma

- 11/34 (32.3%) ut CS had PI3K/AKT mutations and/or RAS/BRAF
- 46% of 52 gyn CS had mutations (TP53 23%, PIK3CA 19%, KRAS 15%, CTNNB1 4%, NRAS 2%)
  - Similar to reported mutations in endometrial carcinoma

Gene expression from 46 patients (14 CS, 24 EmCa, 8 ut sarcoma) suggested CS mutations cluster more like ut Sarcoma than Em Ca

Chiyoda, 2012; Bisculoa, 2013
Carcinosarcoma-Endometrial Carcinoma-Uterine Sarcoma

- Comparison of mutation profiles *between* the carcinoma and the sarcoma portions reportedly similar
- The Cancer Genome Atlas (TCGA) will provide sequence data for CS

Growdon, 2010
Endometrial Carcinoma: targeted therapy for PTEN mutated cancers – mTOR Inhibitors (Rapalouges)

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Prior Lines of chemotherapy</th>
<th>Histology</th>
<th>RR</th>
<th>SD (≥8 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temsirolimus (CCI779)</td>
<td>29</td>
<td>0</td>
<td>-</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>1</td>
<td>-</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>Everolimus (RAD001)</td>
<td>28</td>
<td>1-2</td>
<td>Endometrioid</td>
<td>0%</td>
<td>43%</td>
</tr>
<tr>
<td>Ridaforolimus IV (Deforolimus, AP23573, MK-8669)</td>
<td>45</td>
<td>No limit</td>
<td>-</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Ridaforolimus oral</td>
<td>26</td>
<td>Adjuvant only</td>
<td>-</td>
<td>8%</td>
<td>-</td>
</tr>
</tbody>
</table>
Did we “close” any of the “open issues”?

**Uterine LMS**
- Enroll stage I patients on the phase III trial to answer the adjuvant treatment question
- Choose wisely among the many (!) first line treatment options
- Design studies to help define best choices and find the targets or biomarkers to select among them

**Uterine Carcinosarcoma**
- Offer two-agent cytotoxic therapy as first line treatment to all stages of ut CS
- Keep the CS separate from uterine “sarcoma” and endometrial “carcinoma” in research studies—we can’t lump them yet either for genetic drivers or response to treatment.
Thank you!

- ESMO
- GOG/NRG
- MSKCC
- SARC
- Cycle for Survival—rare tumor research funding (*special thanks to patients who contribute to uterine sarcoma research*)
- All the women who face the challenges of these cancers with such courage, wisdom, and hope