What is the treatment of a sarcoma arising in a teratoma?

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Disclosure slide

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• Consulting or advisory role
  • Novartis, Merck

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  • Novartis, Roche
Definitions

• Mature teratoma displays fully differentiated somatic elements such as hair, teeth, cartilage

• 3-9% of germ cell tumors undergo malignant transformation \(^1,2\)

• This observation first reported by Waldeyer in 1868 where he noted sarcomatous elements in a pt with testicular teratoma\(^3\)

• Included into the WHO classification in 1977

1 J Urol. 2014;192:1403-1409
2 J Urol. 1998;159:859-863
3 Surg., Gynec. & Obst. 1911;12:230
Epidemiology

- Malignant transformation comprise of diverse histologies
- Approx 50% of cases belong to sarcoma family
- The most common sarcoma histologies are
  - Rhabdomyosarcoma
  - Ewing’s/ primitive neuroectodermal tumor (PNET) family

Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>N=121 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma</td>
<td>59 (48.8)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>31 (25.6)</td>
</tr>
<tr>
<td>Sarcomatoid yolk sac tumor</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Nephroblastoma</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Others</td>
<td>7 (5.8)</td>
</tr>
</tbody>
</table>

Ref 2
ESMO guidelines for management of Non seminomatous Germ Cell Tumor (NSGCT)

In patients with teratoma and somatic transformation some experts consider nerve-sparing RPLND the preferred treatment.

High Cure rates
- Stage 1 => 98%
- In men with disseminated disease
  - Complete remission rates 70% with cisplatin based chemo
  - Cure rates of 70-80%

Ann of Oncol. 2013;24 (Supplement 6):vi125–vi132
 Treatment Paradigm for Management of Retroperitoneal Sarcoma

(Retroperitoneal) Sarcoma

- Soft Tissue Sarcoma
- Ewing’s sarcoma/ PNET
- Rhabdomyosarcoma
Treatment Paradigm for Management of Sarcoma

- Retroperitoneal soft tissue sarcoma
  - Oncological surgery with negative margins
  - Adjuvant radiation of limited benefit
  - Adjuvant chemotherapy controversial

- Ewing’s sarcoma/ Primitive neuroectodermal tumor (PNET)
  - Multimodality approach
  - Extended duration of systemic chemotherapy (9-12 months)
  - Combination chemo typically comprising of
    - Cyclophosphamide
    - Doxorubicin (or dactinomycin)
    - Vincristine
    - Ifosfamide
    - Etoposide
  - 14 cycles
  - Interval compression for localized disease
Treatment of a Sarcoma arising from a Teratoma

Manage as for Sarcoma

Treat like a Teratoma?
Genetics of Transformed Histology

• What is the molecular identity of the transformed tumor?
• Is this still a germ cell tumor (GCT)?
• Isochromosome 12p (i12p) is a specific biomaker in GCT
• Clonality with GCT demonstrated with presence i(12p) or extra copies of chromosome 12p
  – 11/12 pts (92%) ¹
  – 5/5 samples studied (100%) ²

¹ J Urol. 1998;159(1):133-138
² J Clin Oncol. 2003;21:4285-4291
Genetics of Transformed Histology

• N=12 tumors

• In addition to finding of i(12p) in 11 pts, 4 pts had chromosomal abnormalities associated with somatic malignancies
  – 2 RMS: rearrangement 2q
  – 1 PNET: rearrangement 11q24
  – 1 Leukemia: del5q

• Transformed histologies thus have molecular features of **BOTH** GCT (i12p) and somatic malignancy
Prognostic factors of somatic malignancies arising from teratoma

- Adverse prognostic factors unclear

- Necchi et al (n=48) ¹
  - Stage 3 disease at malignant transformation
  - Incomplete surgical removal
  - PNET and adenocarcinoma histologies

- Rice at al (n=121) ²
  - Tumor grade (univariate analysis)
  - Tumor grade in sarcoma (p=0.063)

BJU Int. 2011;107(7):1088-1094
J Urol. 2014;192:1403-1409
Clinical Outcomes with GCT-type chemotherapy

- BEP (bleomycin/ etoposide/ cisplatin) is standard treatment in Germ cell tumor (GCT)

- Clinical CR rates to initial cisplatin based chemo in pts with transformed histology 12 – 30% vs 70% which is expected in GCT $^{1,2}$

- Another 38% rendered CR after post-chemo surgery $^2$

- 5 year median survival 64% $^1$

1 J Urol. 2014;192:1403-1409
Malignant transformed (MT) histology directed chemotherapy

- Small study of 10 pts with measurable disease
- 5 with sarcoma

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Response</th>
<th>RT</th>
<th>Surgery</th>
<th>Duration of response</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PNET</td>
<td>P6</td>
<td>PR</td>
<td>Yes</td>
<td>8+ mth</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>RMS</td>
<td>Modified P6</td>
<td>PR</td>
<td>No</td>
<td>1+ mths</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>RMS</td>
<td>VIP Paclitaxel</td>
<td>PR</td>
<td>No</td>
<td>1+ yr</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>RMS</td>
<td>EP =&gt; Ifos MAID</td>
<td>PR</td>
<td>No</td>
<td>7yrs</td>
<td>Dead</td>
</tr>
<tr>
<td>5</td>
<td>RMS</td>
<td>CAV</td>
<td>NR</td>
<td>Yes</td>
<td>1yr 5mth</td>
<td>Dead</td>
</tr>
</tbody>
</table>

J Clin Oncol. 2003;21:4285-4291
Some studies suggest that PNET should be managed differently

- Cohort of 76 teratoma pts with PNET at initial diagnosis

- 26pts had primary retroperitoneal lymph node dissection (RPLND)

- 50pts had initial chemo for disseminated disease

- Median follow-up 38mth (4 - 235mth)
PNET pts treated with initial chemotherapy

44 GCT type chemo
1 PNET directed chemo

Initial chemotherapy
N=50 (33)

Partial response - Incomplete resection of residual PNET
N=2 (0)
Status: DOD 2

Partial response - Complete resection of residual mass
N=43 (28)

Pathology: GCT
N=1 (1)
Status: DOD 1 (post-operative complication)

Pathology: Necrosis/Fibrosis
N=3 (3)
Status: DOD 1, AWD 1, NED 1
Relapse: PNET 2

Pathology: Teratoma
N=12 (12)
Status: NED 12
Relapse: GCT 1

5 GCT type chemo

5 year survival of pts who had chemo & surgery: 40%

NED 37%
NED 100%
PNET pts treated with initial chemotherapy

• CAV/IE chemo given to 10 pts with advanced disease
  • 8 had prior platinum chemotherapy
  • 8 achieved a response to CAV/IE
    – NED = 1
    – Alive with disease = 4 (21 – 73 mths)
    – All alive underwent surgery following chemo
    – Some had multiple surgeries

• Grier et al
  – Non metastatic pts 5yr EFS 69%
  – Metastatic pts 5yr EFS 54%
So, how do we treat sarcoma arising from a teratoma?

No standard guidelines exist

Prognosis is poorer as compared to pts with GCT alone

Treatment is controversial
  – Multimodality treatment is likely to be important
  – Surgery still an important aspect of treatment
  – Optimal chemotherapy is uncertain
Summary (II)

• While some experts advocate use of histology driven therapies, the benefit is unclear.

• In view of poor outcomes with cisplatin based chemo, one may argue that it is not unreasonable to adopt a histology based approach. Having said that, prospective data in support of this argument is lacking.
Thank you
Etiology of Germ Cell Tumor with Malignant Transformation

- Etiogenesis
  1. Malignant transformation of the pleuripotential teratoma
  2. Development of the pleuripotential teratoma into somatic type malignancy

- Unlikely to be chemotherapy induced secondary cancers
  1. High proportion of cases are associated with teratoma
  2. Occur de novo