Soft Tissue Sarcoma: Standard Therapies
How Physicians Choose What to Recommend

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I will be discussing off-label use of agents to treat sarcoma
A Brief Introduction

There are over 50 different subtypes of sarcoma, together comprising 1% of cancer in adults.

Oncologists in general practice may only encounter a given subtype once or twice in their careers.

Guidelines exist to assist in treatment selection (NCCN):
- Detailed, assembled by experts, frequently updated
- Can be difficult to have all the context necessary to choose “optimal” therapy
- [www.nccn.org](http://www.nccn.org)
  - The Patient Resources Section is excellent
Systemic Versus Local Therapies

- **Local Treatments: Radiation and Surgery**
  - Treat only a specific part of the body

- **Systemic Treatments: Putting medicine in the blood stream to treat entire body**
  - Attacks any lesions that might be seen on scans in metastatic patients
  - Attacks other microscopic disease that you DON’T see

- **Adjuvant Treatment: Treating patients at high risk for tumor recurrence after surgery**
Classes of Systemic Therapy for Soft Tissue Sarcoma

Traditional Cytotoxic Chemotherapy
- Attacks the machinery used by cells to duplicate their DNA, grow, and divide
- Side Effects: Hair loss, bone marrow suppression, infertility

Targeted Agents
- Inhibits specific genes or proteins that the cancer uses to grow or feed itself
- Side Effects: High blood pressure, wound healing complications, skin changes

Immunotherapy
- Checkpoint Blockade: take the “breaks” off the immune system so it can see and fight the cancer
- Side Effects: Autoimmune disorders including hormone problems
- Still mostly experimental in sarcoma
Approved/Commonly Used Agents for Soft Tissue Sarcoma

Cytotoxic Chemotherapy:
- Doxorubicin, Ifosfamide, Dacarbazine, Gemcitabine, Docetaxel, Eribulin, Trabectedin

Targeted Agents:
- Pazopanib, Regorafenib, Everolimus, Temsirolimus

Immunotherapy:
- Pembrolizumab, Nivolumab, Ipilimumab

Other special cases: Imatinib, sunitinib, and others...
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NCCN Recommended First Line Therapy: Metastatic Disease

**Preferred Regimens:**
- Doxorubicin
- Doxorubicin and Dacarbazine
- Doxorubicin and Ifosfamide (AIM)
- Liposomal doxorubicin
- Epirubicin (and combinations)

**Other Recommended Regimens:**
- Gemcitabine
- Gemcitabine and Docetaxel
- Gemcitabine and Vinorelbine
- Gemcitabine and Dacarbazine
- Epirubicin (and combinations)
# NCCN Recommended First Line Therapy: Metastatic Disease

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Doxorubicin

- A derivative of a compound isolated from soil bacteria
- Works by interfering with the replication of DNA
- Possible Side effects include:
  - Nausea
  - Mouth sores
  - Weakening of the heart muscle
  - Decreased blood counts
  - Second cancers
- Used at lower doses to treat breast cancers, leukemias, lymphomas, and others
Doxorubicin in Sarcoma: Dose Matters!

**Adriamycin Dose Response • O’Bryan et al.**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>75 mg/m²</th>
<th>60 mg/m²</th>
<th>45 mg/m²</th>
<th>50 mg/m²</th>
<th>Poor risk</th>
<th>25 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>9/23 (39)</td>
<td>4/7 (57)</td>
<td>6/17 (35)</td>
<td>7/25 (28)</td>
<td>7/22 (32)</td>
<td></td>
</tr>
<tr>
<td>Hodgkins</td>
<td>4/11 (36)</td>
<td>2/3 (66)</td>
<td>1/4 (25)</td>
<td>2/9 (22)</td>
<td>2/8 (25)</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>6/14 (43)</td>
<td>0/3 (0)</td>
<td>3/5 (60)</td>
<td>0/4 (0)</td>
<td>0/3 (0)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>15/41 (37)</td>
<td>2/10 (20)</td>
<td>5/28 (18)</td>
<td>1/9 (11)</td>
<td>0/10 (0)</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>6/17 (35)</td>
<td>2/7 (29)</td>
<td>3/20 (15)</td>
<td>0/11 (0)</td>
<td>0/10 (0)</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>3/10 (30)</td>
<td>2/4 (50)</td>
<td>0/5 (0)</td>
<td>0/7 (0)</td>
<td>0/12 (0)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1/19 (5)</td>
<td>2/6 (33)</td>
<td>3/18 (17)</td>
<td>0/6 (0)</td>
<td>1/7 (14)</td>
<td></td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>0/8 (0)</td>
<td>0/2 (0)</td>
<td>2/12 (17)</td>
<td>2/10 (20)</td>
<td>0/6 (0)</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>3/24 (13)</td>
<td>0/9 (0)</td>
<td>1/12 (8)</td>
<td>0/8 (0)</td>
<td>1/5 (20)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>1/14 (7)</td>
<td>0/8 (0)</td>
<td>0/6 (0)</td>
<td>0/5 (0)</td>
<td>1/5 (20)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7/38 (18)</td>
<td>2/9 (22)</td>
<td>2/32 (6)</td>
<td>1/3 (33)</td>
<td>3/16 (19)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>66/263 (25.0)</td>
<td>26/95 (27.4)</td>
<td>37/191 (19.4)</td>
<td>21/131 (16.0)</td>
<td>17/138 (12.3)</td>
<td></td>
</tr>
</tbody>
</table>
Doxorubicin Dose-Response in Sarcomas

O'Bryan, 1974
Slide Courtesy of RSB
Doxorubicin: Protecting the Heart

Doxorubicin is often given as a 15 minute infusion
  ◦ Most non-sarcoma patients receive low lifetime doses

Increasing the infusion time (48-72 hours) decreases cardiac damage
  ◦ Increases the incidence of mouth sores

Dexrazoxane is a medication that can be given to protect the heart from doxorubicin
  ◦ Expensive but usually covered by insurance
  ◦ Cancer outcomes seem to be similar, but limited data on this
  ◦ Variable practices on when it is used
Doxorubicin Based Combinations: Dacarbazine

<table>
<thead>
<tr>
<th>Study</th>
<th>A Dose</th>
<th>AD Dose</th>
<th>Response Rate (A vc AD)</th>
<th>CR rate (A vs AD)</th>
<th>Survival (A vs AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb et al 1977</td>
<td>N/A</td>
<td>A - 60 mg/m^2 D - 1000 mg/m^2</td>
<td>41%*</td>
<td>5%</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Omura et al 1983</td>
<td>A - 60 mg/m^2</td>
<td>D - 1000 mg/m^2</td>
<td>16% vs 24%</td>
<td>6.3% vs 10.6%</td>
<td>7.7 vs 7.3 mos</td>
</tr>
<tr>
<td>Borden et al 1987</td>
<td>A - 70 mg/m^2</td>
<td>D - 1000 mg/m^2</td>
<td>18% vs 30%</td>
<td>5.3% vs 6.5%</td>
<td>8.0 vs 8.0 mos</td>
</tr>
</tbody>
</table>

- Combination described in the late 70s due to non-overlapping toxicity
- Improved response rate
- No demonstration of overall survival benefit (but that is hard to show)

* Response based on clinical criteria
A Response on Doxorubicin and Dacarbazine
Ifosfamide

- Available since the 1970s, but caused bleeding in the bladder
- Mesna is a compound that prevents bladder hemorrhage
- Possible Side effects:
  - Kidney injury
  - Neurotoxicity
  - Other overlapping side effects
- Also used to treat lymphomas, testicular cancer, and other tumors
- Has a Dose-Response relationship similar to doxorubicin
Doxorubicin and Ifosfamide (AIM)

- Made possible by the availability of white cell growth factors (filgrastim, PEG-filgrastim)
- Nearly double the response rate over doxorubicin alone in a recent study
  - Overall survival trends better, but not definitive
- This has been the de-facto 1st choice front line combination regimen for fit patients who require tumor shrinkage
Concerns with combination therapy

- Combination treatments result in higher response rates
- Comes at the price of more side effects, hospitalizations, etc
- Controversy over whether giving drugs together extends life

What Are The Goals of Therapy?
Doxorubicin With or Without Ifosfamide

- Combination therapy is definitely better when tumor shrinkage is required
- There is variability in practice in asymptomatic patients with metastatic disease
- Both doxorubicin alone and in combination, correct dosing is important
- Ask about cardioprotection, practices around this are variable
Adjuvant Systemic Treatment

- Adjuvant Therapy: Chemotherapy given to patients who are “cancer free” in order to decrease chance of recurrence
- If this is done before surgery, it’s called “neoadjuvant” therapy

Key Considerations:
- Identify patients at high risk of recurrence
- Identify a treatment that lowers that risk
- Don’t treat patients who are unlikely to benefit
Adjuvant Systemic Treatment

Key Risk Factors for Metastatic Disease

- FNLCC Grade
- Size of Tumor
- Specific Sarcoma Type

Table 7. Five-Year Actuarial Rate of DM in Patients Who Achieved Local Control of Soft Tissue Sarcoma Versus Size of Sarcoma

<table>
<thead>
<tr>
<th>Tumor Size (mm)</th>
<th>Grade 1</th>
<th></th>
<th>Grade 2 and 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>DM (%)</td>
<td>No. of Patients</td>
<td>DM (%)</td>
</tr>
<tr>
<td>≤25</td>
<td>5</td>
<td>0</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>26-49</td>
<td>11</td>
<td>0</td>
<td>48</td>
<td>23</td>
</tr>
<tr>
<td>50-100</td>
<td>12</td>
<td>0</td>
<td>55</td>
<td>38</td>
</tr>
<tr>
<td>101-150</td>
<td>4</td>
<td>0</td>
<td>24</td>
<td>49</td>
</tr>
<tr>
<td>151-200</td>
<td>4</td>
<td>0</td>
<td>9</td>
<td>58</td>
</tr>
<tr>
<td>&gt;200</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>83</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38</strong></td>
<td><strong>0</strong></td>
<td><strong>159</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>

Risk Stratification: The Sarculator
Adjuvant Treatment: Reasons for Controversy

- Whether adjuvant chemotherapy works has been a controversial topic

- Trials of adjuvant therapy are limited by:
  - Heterogeneous patient populations
  - Older studies using outdated regimens
  - Discomfort randomizing high-risk patients to no treatment
  - Historically, few trials demonstrating clear benefit
EORTC 62931

- A high quality study using a modern chemotherapy regimen versus no chemotherapy
- No difference in overall survival
EORTC 62931:

- A high quality study using a modern chemotherapy regimen versus no chemotherapy
- No difference in overall survival
  - Key critique is that many patients were not high risk
    - 40% of tumors were grade II
    - Tumor size from 0.3-35 cm (median 8.6 cm)

Woll 2012
Risk Stratification and EORTC 62931
Adjuvant Chemotherapy: EORTC 62931 Revisited

Using the Sarculator nomogram, 60% of enrolled patients were low risk (predicted overall survival at 10 years greater than 66%).

Examining only those with pr-OS of less than 51%, adjuvant chemotherapy halved the risk of death.

Pasquali 2019
ISG-STS 1001: Histotype Specific Therapy

In a high risk patient population with sarcomas that are sensitive to chemotherapy, neoadjuvant epirubicin and ifosfamide showed an improvement in overall survival over other sensible therapies.
Adjuvant Therapy: Summary

- Adjuvant/neoadjuvant chemotherapy for soft tissue sarcomas has been a controversial topic
- Differing opinions on who “qualifies”
- Doxorubicin and ifosfamide is the treatment of choice for adjuvant therapy
Parting Thoughts

- Consultation with a sarcoma specialist is vital in ensuring optimal treatment selection
  - Agent selection
  - Dosing and cardioprotection
  - Appropriateness of adjuvant systemic therapy

- Many sarcomas regimens are straightforward to administer in the community—others require close monitoring

- Second opinions can be helpful, and you don’t need to be shy about it
Thank You!