Not all Surgeries are the Same: Neoadjuvant Therapy

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Goals of Operation

- Total gross resection
- Negative microscopic margins
- Avoid tumor rupture
Surgery is Only Potentially Curative Therapy
Complete Resection

Not Always Possible
Is there a role for neoadjuvant (preoperative) therapy before surgical resection?
Studies to Support Safety and Efficacy

<table>
<thead>
<tr>
<th>Trial (phase)</th>
<th>Imatinib dosage and duration</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG S032/ ACRIN 666549 Phase II, nonrandomized, prospective trial</td>
<td>Neoadjuvant: 600 mg/d for 8–12 wk Adjuvant: 400 mg/d for 2 yrs Follow-up: 3 yr</td>
<td>N = 63 (52 analyzable): 30 with primary GIST; 22 with recurrent/metastatic</td>
<td>Primary GIST: 7% PR; 83% SD; 10% unknown Recurrent GIST: 4.5% PR; 91% SD; 4.5% PD 2-yr PFS: 83% for primary; 77% for recurrent 2-yr OS: 93% for primary; 91% for recurrent</td>
<td>Post-operative toxicities: 29% Gr 3; 16% Gr 4; 4% Gr 5</td>
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<tr>
<td>BFR14 substudy59 Phase III, BFR14 database sub-analysis (retrospective)</td>
<td>Median treatment duration prior to surgery: 7.3 mo</td>
<td>N = 25 (9 patients underwent resection) locally advanced GIST without metastases</td>
<td>Median PFS: not reached for resected vs 29.4 mos for non-resected Median OS: Median not reached for resected vs 42.2* months for non-resected</td>
<td>NA</td>
</tr>
<tr>
<td>Apollon CST1571 BDE43 Phase II, open label trial55</td>
<td>400 mg/d for 4–6 mo</td>
<td>N = 40 (target)</td>
<td>Primary endpoint: overall tumor response</td>
<td>NA</td>
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NCCN & ESMO Recommendations

Neoadjuvant Treatment

1. Marginally resectable disease (i.e., locally advanced or large tumors) where total gross resection may not be feasible
2. Likely positive margins
3. Potential for adjacent organ sparing
4. Opportunity for less extensive operation
5. Potential for safer operation (e.g., less bleeding or lower risk of tumor rupture)
Summary of Recommendations

Factors to Consider:

1. Location / Anatomy
2. Biology
3. Both

<table>
<thead>
<tr>
<th>Biology</th>
<th>Location</th>
<th>Good</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Good Location</td>
<td>Good Biology</td>
<td>Bad Location</td>
</tr>
<tr>
<td>Bad</td>
<td>Good Location</td>
<td>Bad Biology</td>
<td>Bad Location</td>
</tr>
</tbody>
</table>
“Bad” Location

- Gastroesophageal junction


“Bad” Location

- Gastroesophageal junction
- Duodenum

“Bad” Location

- Gastroesophageal junction
- Duodenum
- Rectum

Biology

If Patients Respond... *They Do Better.*

Bad Location and Bad Biology

Fanta, Sicklick, et al. JCO. 2015.
Summary

• Neoadjuvant imatinib therapy is generally safe for patients with GIST, but bleeding with response may occur.

• It is utilized in selected cases based upon tumor location and tumor biology.

• Treatment is usually recommended for 6-9 months in order to achieve maximal response.

• Treatment may be stopped earlier if additional response will not change the operation.

• Imatinib may be stopped immediately before an operation and may be restarted once the patient has recovered.

• Tumor mutation analysis may help exclude patients with imatinib-resistant mutations (e.g., PDGFRA D842V) from consideration for neoadjuvant therapy