NEW SURGICAL APPROACHES TO MELANOMA THERAPY

Melanoma 2003: New Insights Into Therapy & Treatment

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University of Pennsylvania
Surgical Treatment of Melanoma

• Primary resection – margins
• Sentinel lymph node trials
• Management of in-transit disease/limb perfusion
Current Standard of Care for Resection Margins for Primary Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Melanoma Thickness</th>
<th>Margins of Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma-in-situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>0 – 1.0 mm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td>1.0 – 2.0 mm</td>
<td>1.0 – 2.0 cm</td>
</tr>
<tr>
<td>&gt; 2.0 mm</td>
<td>2.0 cm</td>
</tr>
</tbody>
</table>
## Prior phase III studies of resection margin in melanoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Tumor thickness</th>
<th>Treatment arms</th>
<th>LR</th>
<th>Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>French 1998</td>
<td>362</td>
<td>&lt; 2mm</td>
<td>2 cm vs 5 cm</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>WHO 1988</td>
<td>612</td>
<td>&lt; 2 mm</td>
<td>1 cm vs 3 cm</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Sweden 1996</td>
<td>769</td>
<td>0.8-2.0 mm</td>
<td>2 cm vs 5 cm</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Intergroup 1993</td>
<td>486</td>
<td>1.0 – 4.0 mm</td>
<td>2 cm vs 4 cm</td>
<td>NSD</td>
<td>NSD</td>
</tr>
</tbody>
</table>
ACOSOG Z0280 – Trial Design

Arm 1: 1 cm radial margins of excision with SNB and +/- lymphadenectomy

Arm 2: 2 cm radial margins of excision with SNB and +/- lymphadenectomy

Patient with cutaneous melanoma Breslow thickness ≥ 2.0 mm, eligible for selective lymphadenectomy

INFORMED CONSENT

REGISTER & RANDOMIZE

FOLLOW UP
Difference between 1 cm and 2 cm margins

• Important short-term and long-term consequences for the melanoma patient
  – Need for skin graft
  – Need for general anesthesia
  – Functional outcome

• Example: 1 cm melanoma
  – 2 cm margin is 5 cm diameter tissue resection or area of 19.6 cm$^2$
  – 1 cm margin is 3 cm diameter tissue resection or area of 7.1 cm$^2$
1 vs. 2 cm Excision

1 cm

2 cm

28 cm²

78 cm²
ACOSOG Z0280 – Current Status

- Approved by CTEP (November 2002)
- Review by Central IRB (January 2003)
- Sample consent form finalized
- Not allowed to open by NCI Subcommittee
Sentinel Lymph Node Biopsy

- Does it work?
- Does it improve survival?
- Who should get SLN mapping?
- New trials
Concept of SLN

- First draining node from tumor
- Most likely node to have metastatic deposits
- Demonstrated to be accurate
SLN Mapping Reagents

- Blue dye
- Radiolabeled Colloids
### Distribution of Metastases in Sentinel and Nonsentinel Lymph Nodes

<table>
<thead>
<tr>
<th>Analysis on Basis of Lymphadenectomies</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of Lymphadenectomies</td>
<td>237 (100)</td>
</tr>
<tr>
<td>Lymphadenectomies with identified sentinel node</td>
<td>194 (82)</td>
</tr>
<tr>
<td>Lymphadenectomies with tumor in nodes</td>
<td>40 (21)</td>
</tr>
<tr>
<td>Lymphadenectomies with tumor in sentinel nodes</td>
<td>38 (20)</td>
</tr>
<tr>
<td><strong>Lymphadenectomies with tumor in nonsentinel nodes</strong></td>
<td><strong>2 (&lt;1)</strong></td>
</tr>
</tbody>
</table>

### Analysis on Basis of Lymph Nodes

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lymph nodes</td>
<td>3,338 (100)</td>
</tr>
<tr>
<td>Total sentinel lymph nodes</td>
<td>259 (8)</td>
</tr>
<tr>
<td>Total sentinel lymph nodes with tumor</td>
<td>47 (18)</td>
</tr>
<tr>
<td>Total nonsentinel lymph nodes</td>
<td>3,079 (92)</td>
</tr>
<tr>
<td><strong>Total nonsentinel lymph nodes with tumor</strong></td>
<td><strong>2 (&lt;0.1)</strong></td>
</tr>
</tbody>
</table>
Does SLN Biopsy Improve Survival in Patients with Melanoma?

Multicenter Clinical Trial JWCI
Evidence of Lymphadenectomy Improving Survival

Long-Term Results of a Multi-Institutional Randomized Trial Comparing Prognostic Factors and Surgical Results for Intermediate Thickness Melanomas (1.0 to 4.0 mm)

Charles M. Balch, MD, Seng-jaw Soong, PhD, Merrick I. Ross, MD, Marshall M. Urist, MD, Constantine P. Karakousis, MD, Walley J. Temple, MD, Martin C. Mihm, MD, Raymond L. Barnhill, MD, William R. Jewell, MD, Harry J. Wanebo, MD, Rene Harrison, PhD, and the Investigators From the Intergroup Melanoma Surgical Trial
Survival in Melanoma

Percent of Patients Surviving

Survival (yr)

Stage I

Stage II

Stage III

Stage IV
Disease-Free Survival Patients with (+) SLN
Disease-Free Survival (+) SLN and Thickness > 1mm
Sentinel Lymph Node Biopsy

Who should get sentinel lymph node mapping?
Rate of positive sentinel lymph node correlates with thickness of primary lesion

<table>
<thead>
<tr>
<th>Melanoma Thickness</th>
<th>% of + SLN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.75 mm</td>
<td>0 – 2 %</td>
</tr>
<tr>
<td>0.75 – 1.0 mm</td>
<td>6 – 8 %</td>
</tr>
<tr>
<td>1.0 – 2.0 mm</td>
<td>12 – 17 %</td>
</tr>
<tr>
<td>2.0 – 4.0 mm</td>
<td>20 – 30 %</td>
</tr>
<tr>
<td>&gt; 4.0 mm</td>
<td>35 – 45 %</td>
</tr>
</tbody>
</table>
Guidelines for recommending sentinel lymph node mapping and biopsy

• All pts with melanoma > 1.0 mm thick
• Pts with melanoma < 1.0 mm thick if:
  – Vertical growth phase positive
  – Clarks Level 4
  – Ulcerated
Ongoing/New Trials of Sentinel Lymph Mapping in Melanoma

• Ongoing Trial
  – Sunbelt Melanoma Trial
    • Role of PCR in guiding therapy
  – Florida Melanoma Trial
    • Need for completion LN dissection
    • All pts get IFN
  – MSLT-II
    • Need for completion lymph node dissection
Definition of In-Transit Melanoma

• Regional spread of tumor via lymphatic vessels in the dermis or subcutaneous tissue outside of nodal basins

• NOTE: In-transit nodules can occur distal (away from nodal basin) to the primary site
  – Gravity
  – Obstruction of lymphatic flow by tumor
IN-TRANSIT MELANOMA METASTASES
Incidence of In-Transit Melanoma

- Best data from control arms of randomized trials of adjuvant ILP for Stage I/II extremity melanoma
  - WHO trial for melanoma > 1.5 mm
    - 6% in-transit metastases
    - 3.3% local recurrence
  - No good data for incidence with thin melanoma
  - Observation (by M. Ross)
    - Incidence of in-transit lesions may be increasing in sentinel node era
Surgical Treatment of In-Transit Melanoma

- True local recurrence
  - Aggressive re-resection
- Limited/isolated in-transit lesion
  - Local excision only
    - No STSG
    - No margins of resection
    - No XRT needed
  - Wide excisions are destined to fail
Local resection after aggressive resection of in-transit melanoma

- Radical resection requiring skin graft, free flap or amputation is not indicated as the entire extremity is at risk
Local recurrence after resection of in-transit metastases

- Pt had in-transit nodules in his upper arm
- He underwent an aggressive resection with a latissimus free flap
- 3 months after this operation he recurred at the margins of the flap
Natural History After Resection of In-Transit Disease

• Again, best data from randomized trials of adjuvant ILP after resection of isolated in-transit disease
  – Sweden: 69% incidence of in-transit as initial recurrence
  – Germany: 90% incidence
Advantages and Disadvantages of Regional Perfusion

- **Advantages**
  - Dose escalation
  - Limited systemic toxicity
  - Ability to add other treatments such as hyperthermia

- **Disadvantages**
  - Regional treatment for a potentially systemic disease
  - Requires surgical procedure
  - Retreatment very difficult
Technique of Isolated Limb Perfusion

- ILP is a surgical procedure that involves controlling the circulation to an extremity.
- Side branches are ligated and a tourniquet is applied.
Background – Isolated Limb Perfusion

• Initially reported 1958

• Mild hyperthermia added 1969

• Melphalan is optimal agent
  – Initially dosed at 1.5 mg/kg
  – Optimal dose 10 mg/L limb volume

• Results of Melphalan ILP for 60 min
  – 54% complete response rate
  – 79% overall response rate
Complete response after melphalan ILP
Complete response melphalan ILP
Initial Phase II Trial of TNF in ILP

• Trial Design
  – IFN-Gamma 0.2 mg sc days –2 and –1
  – Perfusion regimen:
    • Time 0: IFN 0.2 + TNF 4 mg
    • Time 30: Melphalan 10 mg/L
    • Time 90: Flush

• N = 29
  – 14 pts had failed prior melphalan ILP
Results – Initial Phase II Trial of Melphalan, TNF, and IFN ILP

- N = 29
  - 26/29 CR  90%
  - 3/29  PR
    - All >75%
  - Overall Response Rate 100%

- Kinetics of response much faster than melphalan alone
  » Lienard, World J. Surg, 16:234, 1992
HYPOTHESIS: The addition of TNF and IFN to a standard melphalan ILP will increase complete response rates in advanced extremity melanoma

• Primary Objective
  – Response rate in the perfusion field
    • Powered to detect a difference of 40% and 80%

• Secondary Objectives
  – Overall Survival
  – Limb Recurrence Rates
  – Toxicity
TRIAL DESIGN

• ARM 1:
  • Pre-op
    – No treatment
  • Perfusate
    – Time 0
    – No treatment
    – Time 30
    – Melphalan 10 mg/L

• ARM 2:
  Pre-op
  – IFN 0.2 mg x 2 days
  • Perfusate
    – Time 0
    – IFN 0.2 mg + TNF 4 mg
    – Time 30 min
    – Melphalan 10 mg/L
## RESPONSE RATES

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Melphalan</th>
<th>Melphalan, TNF, + IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>58%</td>
<td>72%</td>
</tr>
<tr>
<td>PR</td>
<td>36%</td>
<td>16%</td>
</tr>
<tr>
<td>MR</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>SD/PD</td>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>ORR</td>
<td>96%</td>
<td>88%</td>
</tr>
<tr>
<td>3 year overall survival</td>
<td>54%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Patient treated with melphalan alone. Sustained CR for over 7 years. Kinetics of response are very slow.
# Response Rates Relative to Tumor Burden

<table>
<thead>
<tr>
<th></th>
<th>Melphalan</th>
<th>Melphalan, TNF, + IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>58%</td>
<td>72%</td>
</tr>
<tr>
<td>Low tumor burden</td>
<td>73%</td>
<td>81%</td>
</tr>
<tr>
<td>High tumor burden</td>
<td>14%</td>
<td>57%</td>
</tr>
</tbody>
</table>
Patient treated with melphalan, TNF, and IFN

- Extensive disease with thigh filled with melanoma
- Sustained extremity CR for 37 months until she died of distant disease
Overall Survival

Proportion Surviving vs. Months

Melphalan/TNF/Interferon (blue)
Melphalan (red)

(p=.51)
Limb Recurrence

(p=.06)
Conclusions from Phase III Trial

• ILP with melphalan or melphalan/TNF can be accomplished with acceptable morbidity

• There is a trend toward increased complete response rates by the addition of TNF but this does not translate into an increased survival

• There is a trend towards limb progression free survival by the addition of TNF

• Patients with melanoma in-transit metastases of the extremity should be referred for ILP because of the significant response rates
Case Report

- 32 y/o with distal thigh melanoma
- She failed melphalan ILP, Dartmouth regimen, and high dose IL-2
- Disease limited to proximal thigh
• Melphalan and TNF ILP performed
• Rapid gross necrosis of tumor
• Pt had a CR after a single 90 minute treatment
• She recurred 13 months later in the ovaries
• She died 20 months after ILP with sustained CR
ONGOING ACOSOG TRIAL OF ILP
### Response Rates for Established Metastatic Melanoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall RR</th>
<th>CR</th>
<th>Sustained CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTIC</td>
<td>15-22%</td>
<td>&lt;2%</td>
<td>0</td>
</tr>
<tr>
<td>Combination chemotx</td>
<td>20-40%</td>
<td>5-8%</td>
<td>0</td>
</tr>
<tr>
<td>Biochemotx</td>
<td>40-50</td>
<td>10-15%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Hi dose IL-2</td>
<td>15-22%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Melp ILP</td>
<td>80-95%</td>
<td>55%</td>
<td>29%</td>
</tr>
<tr>
<td>Me/TNF ILP</td>
<td>85-100%</td>
<td>75%</td>
<td>25%</td>
</tr>
</tbody>
</table>