MANAGEMENT OF IN-TRANSIT DISEASE OF THE LIMBS

Effective Date: February 2013

The recommendations contained in this guideline are a consensus of the Alberta Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

In transit disease of the limbs is a Stage III regional metastatic disease consisting of intradermal or subcutaneous nodules. The probability of in transit disease varies with melanoma thickness (Table 1). Although many treatment modalities exist and have been described in the literature, high level evidence is still lacking and there is little consensus on a standard approach for patients. The treatment strategies described in this guideline are currently the most effective options for patients with this disease; however, further clinical trials in this area are needed.

Table 1. Influence of surgical margins and prognostic factors on risk of local recurrence.

<table>
<thead>
<tr>
<th>Tumour Thickness (mm)</th>
<th>Number of Patients</th>
<th>Incidence of Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.76</td>
<td>707</td>
<td>0.2 + 0.2%</td>
</tr>
<tr>
<td>0.76 – 1.49</td>
<td>721</td>
<td>2.1 + 0.7%</td>
</tr>
<tr>
<td>1.50 – 3.99</td>
<td>907</td>
<td>6.4 + 1.1%</td>
</tr>
<tr>
<td>≥4.00</td>
<td>291</td>
<td>13.2 + 3.2%</td>
</tr>
</tbody>
</table>

GUIDELINE QUESTION

What are the best treatment and management options for improving the progression-free survival and overall survival of patients with melanoma with in-transit disease of the limbs?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Cutaneous Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

The MEDLINE, Cochrane, ASCO Abstracts and proceedings, and CANCERLIT databases were searched (1985 through November 2009) for clinical trials. Search terms included: “primary cutaneous melanoma” or “regional metastatic disease” or “in-transit disease” or “intradermal nodules” or “subcutaneous nodules” AND “isolated limb perfusion” or “isolated limb infusion” or “hyperthermic limb perfusion” or “tumor necrosis factor alpha” or “melphalan” or “radiation therapy” or “tamoxifen” or “cryotherapy” or “laser therapy” or “bacillus calmette guerin” or “interferon” or “chemotherapy.” A total of 585 clinical trials (limits: human and English language) were returned, from which 35 documents were selected. In addition, the National Guidelines Clearinghouse and individual guideline organizations were searched for practice guidelines relevant to this topic.

For the 2013 update of the guideline, PubMed was searched for evidence on in-transit melanoma. The search term “melanoma” was used and results were limited to clinical trials, published between December 2009 and January 2013. Citations were hand-searched for studies pertaining to in-transit disease,
resulting in three relevant studies. Following a review of the evidence by the Alberta Cutaneous Tumour Team, no major changes to the recommendations were made.

**TARGET POPULATION**

This guideline outlines treatment and management strategies for patients with stage III regional metastatic disease that are intradermal or subcutaneous nodules growing within lymphatics and not in nodal basins.

**RECOMMENDATIONS**

For staging please refer to the Appendix.

The following recommendations have been adapted from the National Comprehensive Cancer Network Melanoma Guidelines (2009), 1 with modifications based on guidance from other guideline organizations (e.g. the National Health and Medical Research Council of Australia, 1999; 2 the European Society for Medical Oncology, 2009; 4 and the German Cancer Society and German Dermatologic Society, 2008 5) as well as evidence from clinical trials.

**Primary Treatment**

1. Sentinel node biopsy should be performed in patients undergoing curative resection of a solitary in-transit metastasis.

2. Complete surgical excision to clear margins is preferred, if feasible, especially for patients with a one or a small number of in-transit metastases.

3. The following options may be considered for patients with more extensive metastases:
   - Enrollment in a clinical trial
   - Isolated limb infusion with melphalan and/or other cytotoxic agents (e.g. actinomycin-D)
   - Hyperthermic limb perfusion with melphalan
   - Intralesional local injection (e.g. bacillus calmette guerin, interferon) or topical imiquimod can be considered if the patient has a limited number of in-transit metastases, particularly dermal lesions, which are not amenable to complete surgical excision
   - Local ablation therapy
   - Radiation Therapy
     - Treatment to tumour bed, regions of in transit disease and nodal drainage basin can be considered based on the pathology after resection and other patient and disease factors.
     - Electron beams with quantum energy of 6–8 MeV with bolus are appropriate for smaller volume superficial treatment; more complex photon beam arrangements may be needed depending on the clinical target volume.
     - Postoperative radiation therapy should be considered after excision of recurrent in transit metastases.
     - If primary surgery to obtain clear margins is not possible, primary radiotherapy may be considered.
     - Hypofractionated treatment (e.g. 32 Gy in 4 fractions or 30-36 Gy in 6 fractions over 3 weeks) may be relevant in some situations of in-transit disease. Hypofractionation is more convenient for patients, but has potential for greater chronic toxicity.
Standard treatment (50-60 Gy) and observation have not been compared in randomized studies for in transit disease, and thus efficacy of radiation in improving local control (e.g. 5-year axillary control rate of 88% with post-operative RT to 30-36 Gy in 5-6 fractions, complete response rate of 24% with RT to 50 Gy in 20 fractions and 32 Gy in 4 fractions) must be extrapolated from case series in other situations.

- Systemic therapy (particularly after failure of local and/or regional therapy). The following options can be considered as first- or second-line therapy:
  - Clinical trial (preferred)
  - Dacarbazine
  - Temozolomide (currently available only if patient has private insurance or is willing to pay, or has special approval)
  - High-dose interleukin-2 (IL-2; only in very select patients)
  - Dacarbazine- or Temozolomide-based combination chemotherapy/ biochemotherapy (including cisplatin and vinblastine with or without IL-2 or interferon-alpha)
  - Paclitaxel alone or in combination with cisplatin or carboplatin

Adjuvant Treatment

4. If the patient is disease-free, the following options for adjuvant therapy can be considered.
   - Clinical trial
   - Interferon-alpha
   - Observation

In-Transit Recurrence

5. A surgically resectable recurrence should be re-excised with negative margins.

6. Sentinel node biopsy may be considered.

7. Unresectable recurrence could be treated with any one of the following options:
   - Hyperthermic limb perfusion or infusion
   - Intralesional injections with bacillus calmette guerin (BCG) or IFN-alfa
   - Topical imiquimod
   - Laser ablation therapy
   - Clinical trial
   - Systemic therapy
DISCUSSION

Isolated Limb Infusion

There are currently no prospective randomized phase III trials on the use of isolated limb infusion (ILI); however, phase II studies using this technique with melphalan, with or without actinomycin-D, have shown promising complete response rates (ranging from 23 to 38%) with relatively mild toxicity (e.g. mostly grade II/III erythema and edema). A median survival time of 38 months was reported for patients treated with repeat ILI (median 11 months between procedures) with use melphalan and actinomycin-D. As compared with hyperthermic isolated limb perfusion (HILP) with melphalan, ILI was shown in a retrospective analysis to be less effective, in terms of three-month complete response rate (57% vs. 30%), but to be associated with much less high-grade toxicity (grade 3+: 18% of ILI pts vs. 32% of HILP pts; P = 0.037). More recently, ILI using melphalan with ADH-1, a cyclic pentapeptide that disrupts N-cadherin adhesion complexes, was evaluated among patients with stage IIIB or IIIC extremity melanoma (n=45). ADH-1 (4000 mg) was administered systemically on days 1 and 8, and with M-ILI on day 1. There were 17 complete responses (38%) and 10 partial responses (22%), with median durations of 5 months and 4.6 months, respectively. Grade 4 toxicities included creatinine phosphokinase increase (four patients), arterial injury (one patient), neutropenia (one patient), and pneumonitis (one patient). There is limited data on the ILI for in-transit recurrences; two retrospective studies are described below. Repeat regional chemotherapy was evaluated retrospectively among 44 patients undergoing repeat hyperthermic ILP or ILI. After a median follow-up of 21.4 months, the response rate between procedures (HILP vs. ILI), between sequence (initial vs. repeat), and among their interactions showed no statistically significant differences. Furthermore, time to progression after initial procedure did not differ between HILP and ILI (P=0.08), and no survival difference was seen (P=0.65). Hyperthermic isolated limb perfusion with TNF-alpha and melphalan (TM-HILP) has also been evaluated retrospectively for its safety and feasibility in inoperable in-transit melanoma of the extremities. Patients with locally advanced in-transit melanoma (n=14) underwent a 90-min ILP with melphalan (10 mg/l limb volume) and TNF-alpha (1-2 mg) under mild hyperthermia (39-40 degrees C). All melanoma patients showed a response to TM-HILP with 7 (62%) of them experiencing complete response. The median disease specific and limb-relapse-free survival was 15 and 12 months, respectively.

Systemic Therapy

The mostly widely used chemotherapy regimens for metastatic melanoma include dacarbazine or temozolomide, either as monotherapy or in combination with cisplatin or vinblastine. As compared with temozolomide, dacarbazine has similar response and survival rates. However, the impact on survival associated with these strategies is not large (recurrence-free survival: median 7.9 months vs. 7.6 months for observation alone; three-year overall survival: 54.9% vs. 43.6% for observation alone, P=0.07). The addition of immunotherapy with IFN-alpha to these regimens or the use of IFN-alpha has also failed to produce significantly better results. The addition of taxane therapy (e.g. paclitaxel) has also been unsuccessful in improving response or survival. As such, little consensus exists regarding the best systemic therapy for these patients.
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>bacillus calmette guerin</td>
</tr>
<tr>
<td>Gy</td>
<td>grey</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IL-2</td>
<td>interleukin</td>
</tr>
<tr>
<td>ILI</td>
<td>isolated limb infusion</td>
</tr>
<tr>
<td>ILP</td>
<td>isolated limb perfusion</td>
</tr>
<tr>
<td>MeV</td>
<td>mega electron volt</td>
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</tbody>
</table>

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
REFERENCES


Kleeberg UR, Suciu S, Bröcker EB, et al. EORTC Melanoma Group in cooperation with the German Cancer Society (DKG). Final results of the EORTC 18871/DKG 80-1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. Eur J Cancer. 2004 Feb;40(3):390-402.


AJCC 2009 (7th Edition) Anatomic Stage Groupings for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>Clinical Staging a</th>
<th>Pathologic Staging b</th>
<th>5-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
<td>Tis N0 M0</td>
<td>100%</td>
</tr>
<tr>
<td>IA</td>
<td>T1a N0 M0</td>
<td>IA T1a N0 M0</td>
<td>95%</td>
</tr>
<tr>
<td>IB</td>
<td>T1b N0 M0</td>
<td>IB T1b N0 M0</td>
<td>90%</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b N0 M0</td>
<td>IIA T2b N0 M0</td>
<td>78%</td>
</tr>
<tr>
<td>IIB</td>
<td>T3b N0 M0</td>
<td>IIB T3b N0 M0</td>
<td>65%</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b N0 M0</td>
<td>IIC T4b N0 M0</td>
<td>45%</td>
</tr>
<tr>
<td>III</td>
<td>Any T N &gt; N0 M0</td>
<td>IIIA T1-4a N1a N2a M0</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIIA T1-4a N1a N2a M0</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIIA T1-4a N1a N2a M0</td>
<td>27%</td>
</tr>
<tr>
<td>IV</td>
<td>Any T Any N M1</td>
<td>IV Any T Any N M1</td>
<td>13%</td>
</tr>
</tbody>
</table>

a Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

b Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.
## AJCC 2009 (7th Edition) TNM Staging Categories for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>T</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
| T1  | ≤ 1.00         | a: without ulceration and mitosis < 1/mm²  
            | b: with ulceration or mitoses ≥ 1/mm²  |
| T2  | 1.01-2.00      | a: without ulceration  
            | b: with ulceration          |
| T3  | 2.01-4.00      | a: without ulceration  
            | b: with ulceration          |
| T4  | > 4.00         | a: without ulceration  
            | b: with ulceration          |

<table>
<thead>
<tr>
<th>N</th>
<th>Number of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>
| N1  | 1                         | a: micrometastasis⁴     
            | b: macrometastasis⁵     |
| N2  | 2-3                       | a: micrometastasis⁴     
            | b: macrometastasis⁵     
            | c: in transit metastases/satellites without metastatic nodes |
| N3  | 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes |

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH (lactate dehydrogenase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>not applicable</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous or nodal metastases</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastases</td>
<td>Normal</td>
</tr>
</tbody>
</table>

⁴ Micrometastases are diagnosed after sentinel lymph node biopsy.  
⁵ Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.