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Management of In-Transit Disease

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Alberta Health Services
CancerControl Alberta

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www.ahs.ca/guru

Background

In transit disease 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[1]. 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 Breslow thickness on risk of in transit melanoma[2].

Tumour Thickness (mm)	*Number of Patients*	*Incidence of Local Recurrence*
<0.76	707	0.2 + 0.2%
0.76 – 1.49	721	2.1 + 0.7%
1.50 – 3.99	907	6.4 + 1.1%
≥4.00	291	13.2 + 3.2%

Guideline Questions

- 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?

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. The latest update searched the PubMed database (January 2013 through December 2018) and retrieved 121 articles. A total of 30 relevant articles were identified as well as six ongoing clinical trials. In addition, 11 clinical practice guidelines were identified from the BC Cancer Agency[3], CancerCare Nova Scotia[4], European Dermatology Forum and European Association of Dermato-Oncology[5], European Society for Medical Oncology[6], National Comprehensive Cancer Network[1], National Institute for Health and Care

Excellence[7], German Society of Dermatology[8], Scottish Intercollegiate Guidelines[9], Spanish Society for Medical Oncology[10], Princess Margaret Cancer Center[11] and Cancer Care Manitoba[12]. Complete evidence tables are available upon request.

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 Guideline (2019)[1], with modifications based on clinical experience as well as evidence from clinical trials.

Primary Treatment Options

1. Local Therapy
   - Complete surgical excision to clear margins
   - Intralesional injection options: Interleukin-2, talimogene laherparepvec*, PV-10*, bacillus calmette guerin
   - Topical imiquimod for superficial dermal lesions
   - Radiation Therapy (see below)

2. Regional Therapy
   - Isolated limb infusion/ perfusion with melphalan

Second-Line Treatment Options

Patients who experience disease progression during or shortly after primary treatment, should be considered for second-line treatment. Second-line treatment agents should be different than the primary treatment and not of the same class. Patients who experience disease control without residual toxicity followed by disease progression more than 3 months after primary treatment ceases, can be considered for second-line treatment with the same agent or same class of agents used for primary treatment[1].

1. Post Surgery
   - No evidence of disease: Adjuvant treatment (see below) or observation
   - Less than complete resection:

- Local therapy options:
  - Intralesional injection options: Interleukin-2, talimogene laherparepvec*, PV-10*, bacillus calmette guerin
  - Local ablation therapy
  - Topical imiquimod for superficial dermal lesions
  - Radiation therapy (see below)
- Regional therapy options:
  - Isolated limb infusion/perfusion with melphalan
- Adjuvant therapy (see below) following local or regional therapy

2. Post Non-Surgical Primary Therapy
   - No evidence of disease: Adjuvant treatment (see below) or observation
   - Residual/progressive disease
     - Choose an alternative local therapy option:
       - Intralesional injection options: Interleukin-2, talimogene laherparepvec*, PV-10*, bacillus calmette guerin
       - Local ablation therapy
       - Topical imiquimod for superficial dermal lesions
       - Radiation therapy (see below)
     - Or choose a regional therapy option:
       - Isolated limb infusion/perfusion with melphalan
   - Adjuvant therapy (see below) following local or regional therapy

**not currently available in Canada*

Adjuvant Treatment

- Nivolumab
- Pembrolizumab
- Dabrafenib/trametinib (BRAFV600-activating mutation)

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 beam and/or orthovoltage radiotherapy are appropriate for smaller volume superficial targets; more complex photon beam arrangements may be needed depending on the clinical target volume.
- 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.

Discussion

Intralesional Injections

Interleukin-2 (IL-2):

The effect of IL-2 in patients with in-transit melanoma was studied in a systematic review of six trials[13]. In total, 2182 lesions in 140 patients were included and response rates were reported by lesion and by subject (Table 2). This review found that by lesion, a mean complete response rate of 78% (range 40.7% to 96%), a partial response rate of 2.5%, and a no response/progression rate of 19.6%. By subject, the complete response rate ranged from 0% to 69%[13]. Another retrospective study of 31 in-transit melanoma patients treated with intralesional IL-2 found a pathologic complete response was reached in 32% of patients, a partial response in 55% of patients, and 19% of patients had progressive disease[14].

Table 2: Reported Response Rates of Intralesional IL-2 for treatment of In-Transit Melanoma[13]

Reference	N	Lesions	Dosing regimen (million units)	Dosing interval	Duration of treatment	Complete response per patient/per lesion (%)	Partial response (%)	No Response (%)
Boyd 2011[15]	39	629	2.08 ml (0.3-3.2ml) total or 10 MIU	Bi weekly	1-7 biweekly injections	51/76	31/0	18/24
Weide 2010[16]	48	894	0.3-6 MIU single dose/lesion. Total dose per patient 13.5-548.1 MIU	3x/week	1-32 weeks	69/78.7	x/0.7	x/20.6
Dehesa 2009[17]	7	244	3-18 MIU	2x/week	Unknown	x/96	x/3.5	x/0.5
Green 2007[18]	10	178	3.6 MIU/day	3x/week	15-53 weeks	0/40.7	x/9.9	x/47.2
Radney 2003[19]	24	237	3 MIU	2-3x /week	1-12 weeks	62.5/85	21/6	16/9
Ridolfi 2001[20]	16	32	3MIU	5 days repeated q21days	1-9 cycles	0/x	25/x	75/x

Other Local Therapies

Topical Therapy with Diphencyprone (DPCP):

A retrospective review of 15 patients with in-transit melanoma lesions studied the effect of treatment with DPCP[21]. This study observed that 13% of patients experienced a complete response, 27% had a partial response, 40% had stable disease and 20% had disease progression. A similar prospective study of 54 patients with in-transit disease, found comparable results[22]. A complete response was

observed in 22% of patients, a partial response in 39%, stable disease in 24% and progressive disease in 15%. A similar retrospective study of 50 patients observed a complete response of 46%, a partial response of 28% and 18% experienced no response[23].

Local Ablation:
The efficacy of carbon dioxide lasers was retrospectively reviewed in 22 patients with in-transit and satellite metastases[24]. The median overall survival was observed to be 14 months (rang 1-41months). 18 patients experienced regional control with a median duration of 14 weeks (range 3-117 weeks), though all 22 patients developed distant metastases and died of disease progression.

Regional Therapy
Isolated Limb Infusion and Perfusion:
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%)[25-31] with relatively mild toxicity (e.g. mostly grade II/III erythema and edema)[32]. 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[27]. 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)[28]. In a similar study, ILP was found to offer an improved overall response rate (80% vs 53%, p<0.001) compared to ILI, but this did not translate into an improved overall survival (40 months vs 46 months, p=0.31)[33].

There is limited data on the ILI for in-transit recurrences. 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)[34]. Another retrospective study found that recurrent patients treated with ILI had a 70% overall response rate with low limb toxicities and no amputation required[35].

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[36]. A similar study (n=32) of melanoma patients with recurrent in transit

metastases undergoing TNF-alpha and melphalan-based ILP, showed a good response (overall response 86%, complete response 65%) and the overall MeV

Systemic Therapy

Currently there are no in-transit disease specific studies on the effect of checkpoint immunotherapy. Clinical judgement should be used when considering these therapies. If there is concern that in-transit disease is a prognosticator of relapse or that the patient also has internal metastasis, there are systemic options that can be used. Nivolumab is approved for treatment of patients with unresectable or metastatic BRAF wild-type melanoma who have not previously received ipilimumab or pembrolizumab[37]. Pembrolizumab is approved for treatment of patients with unresectable or metastatic melanoma regardless of BRAF status[37]. Dabrafenib and/or trametinib have been approved for treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (not to be used after progression on an alternate BRAF inhibitor and/or MEK inhibitor)[37]. For more information please see our guideline on Systemic Therapy for Unresectable Stage III or Metastatic Cutaneous Melanoma.

Therapies Not Currently Approved in Canada

Talimogene Laherparepvec (T-VEC):

The OPTiM phase III trial studied the effect of T-VEC versus granulocyte macrophage colony-stimulating factor (GM-CSF) in 436 patients with injectable unresectable melanoma[38]. The overall response rate was 26.4% for T-VEC treated patients, versus 5.7% for patients treated with GM-CSF ($p<0.001$). The overall survival was 23.5 months versus 18.9 months ($p<0.001$), respectively. In addition, 15% of all uninjected metastases in T-VEC treated patients, reduced in size by at least 50%. The median time to response for T-VEC treated patients was 4.1 months versus 2.8 months in patients treated with GM-CSF. More than half of T-VEC treated patients experienced pseudoprogression before seeing a treatment response. Another phase II trial studied T-VEC in the neoadjuvant setting in high-risk resectable Stage IIIB/C/IVM1a melanoma[39]. Preliminary results found that patients treated with T-VEC prior to surgery had a higher rate of R0 resections (56.1%) versus surgery alone (40.6%) and lower disease progression and recurrence (14.5%) compared to surgery alone (23%). Although there is noteworthy data on T-VEC, it may not be available to providers and patients.

Rose Bengal (PV-10):

A phase II trial studied PV-10 followed by hypofractionated radiotherapy in patients with in-transit melanoma metastases[40]. The overall response rate was 86.8%, with a complete response in 33.3% of patients and a clinical benefit rate of 93.3%. The mean time to response was 3.8 months and the melanoma specific survival was 65.5 months. Another phase II trial studied PV-10 for patients with satellite or in-transit melanoma metastases[41]. The responses were reported per patient and per treatment episode. The overall response rate per patient was 86.6%, with a complete response of 42.2% and a clinical benefit of 93.3%. The overall response rate per treatment episode was 78.1%,

with a complete response of 30.5% and a clinical benefit of 87.9%. The medium overall survival was 25 months and the mortality rate was 48.9%.

Electrochemotherapy:
A prospective study observed the effect of electrochemotherapy in patients with in-transit melanoma skin metastases[42]. In the intend-to-treat population, the overall tumour response was 46% of tumours treated with electroporation and bleomycin, versus 25% of tumours treated by bleomycin alone (p=0.10). Complete responses were obtained in 36% versus 8% of metastases (p=0.016), respectively. In the per protocol population, the overall tumour response was 87% of metastases treated by electroporation and bleomycin, versus 53% of the metastases treated by bleomycin (p=0.35). Complete responses were obtained in 74% versus 13% of metastases (p=0.017), respectively. A more recent retrospective study found similar results. Electrochemotherapy was used to treat 60 patients with in-transit melanoma[43]. Three months after treatment, 48.4% of patients had a complete response and 38.3% had a partial response.

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Appendix A:

AJCC 2017 (8th Edition) Anatomic Stage Groupings for Cutaneous Melanoma[44]

Clinical Staging (cTMN)*

Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b T2a	N0	M0
IIA	T2b T3a	N0	M0
IIB	T3b T4a	N0	M0
IIC	T4b	N0	M0
III	Any T, Tis	≥N1	M0
IV	Any T	Any N	M1

Pathologic Staging (pTNM)**

Stage	T	N	M
0***	Tis	N0	M0
IA	T1a T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b T3a	N0	M0
IIB	T3b T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1a/b-T2a	N1a or N2a	M0
IIIB	T0 T1a/b-T2a T2b/T3a	N1b, N1c N1b/c, N2b N1a/b/c, N2a/b	M0
IIIC	T0 T1a/b, T2a/b, T3a T3b, T4a T4b	N2b/c, N3b/c N2c or N3a/b/c Any N ≥N1 N1a/b/c, N2a/b/c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

***** 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.
** 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.
***Pathological Stage 0 and T1 do not require pathological evaluation of lymph nodes to complete staging.

AJCC 2017 (8th Edition) TNM Staging Categories for Cutaneous Melanoma[44]

T	Thickness (mm)	Ulceration Status
TX, T0, Tis	NA	NA
T1	≤ 1.0	Unknown or unspecified
T1a	<0.8	Without ulceration
T1b	<0.8	With ulceration
	0.8 to 1	With or without ulceration
T2	>1 to 2	Unknown or unspecified
T2a	>1 to 2	Without ulceration
T2b	>1 to 2	With ulceration
T3	>2 to 4	Unknown or unspecified
T3a	>2 to 4	Without ulceration
T3b	>2 to 4	With ulceration
T4	> 4	Unknown or unspecified
T4a	> 4	Without ulceration
T4b	> 4	With ulceration
N	Number of Tumour-Involved Regional Lymph Nodes	Presence of in-transit, satellite, and/or microsatellite metastases
NX, N0	0	No
N1	1	
N1a	1 clinically occult	No
N1b	1 clinically detected	No
N1c	0 regional lymph node disease	Yes
N2	2-3	
N2a	2 or 3 clinically occult	No
N2b	2 or 3, at least 1 of which is clinically detected	No
N2c	1 clinically occult or clinically detected	Yes
N3	4+	
N3a	4 or more clinically occult	No
N3b	4 or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	2 or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes
M	Site	Serum LDH (lactate dehydrogenase)
M0	No distant metastases	NA
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not Evaluated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members 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 Tumour Teams, external participants identified by the Working Group Lead, and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2010.

Maintenance

A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

BCG, bacillus calmette guerin; Gy, grey; IFN, interferon; IL-2, interleukin; ILI, isolated limb infusion; ILP, isolated limb perfusion; MeV, mega electron volt.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial 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.

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Conflict of Interest Statements

Generated using the standard COI form.

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