Nan Tie Emilia (Orcid ID: 0000-0003-2728-7526)
Gyorki David (Orcid ID: 0000-0002-3165-4694)

The management of in-transit melanoma metastases: A review

Emilia Nan Tie, BMS,†, Michael A, Henderson, MBBS, MD, FRACS.*†, David E. Gyorki, MBBS, MD, FRACS.*†

†Division of Cancer Surgery, Peter MacCallum Cancer Centre. *Department of Surgery, St Vincent's Hospital, The University of Melbourne, Melbourne, Victoria, Australia.

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Corresponding Author:

Mr David Gyorki

Surgical Oncologist

Division of Cancer Surgery,

Peter MacCallum Cancer Centre,

305 Grattan Street, Melbourne, Vic. 3000, Australia.

Email: david.gyorki@petermac.org

Phone: +61 3 85597666

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Abstract:

In-transit metastases (ITM) of cutaneous melanoma are locoregional recurrences confined to the superficial lymphatics that occur in 3.4-6.2% of patients diagnosed with melanoma. ITM are a heterogeneous disease that pose a therapeutic dilemma. Patients may have a prolonged disease trajectory involving multiple or repeat treatment modalities for frequent recurrences. The management of ITM has evolved without the development of a standardised protocol. Owing to the variability of the disease course there are few dedicated clinical trials, with a number of key trials in stage III melanoma excluding ITM patients. Thus, there is a paucity of quality data on the efficacy of the treatment modalities available for ITM and even fewer studies directly comparing modalities. At present the mainstay of ITM treatment is surgical resection, with intralesional therapies, isolated limb infusion and radiotherapy utilised as second line measures. The developing role of targeted therapies and immunotherapy has yet to be explored completely in these patients. This review addresses the evidence base of the efficacy of the various treatment modalities available and those factors that have impacted their clinical uptake.

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Introduction

Melanoma is the fourth most commonly diagnosed cancer in Australia.[1] It is estimated that over 14,000 new cases of melanoma will be diagnosed in 2018.[1] Intra-lymphatic metastases of cutaneous melanoma are loco-regional recurrences that present in the lymphatics draining the primary tumour to the regional lymph node basin. In-transit metastases (ITM) are those that are found >2cm from the primary tumour, closer lesions are termed satellite metastases.[2] ITM may be single or multiple, cutaneous or subcutaneous. The American Joint Committee on Cancer (AJCC) 8th edition staging system classifies ITM as stage IIIB, IIIC or IIID depending on nodal involvement, primary tumour thickness and ulceration, prior to this non-nodal disease was not stratified.[2] ITM occur in 3.4-6.2% of all patients with a primary melanoma.[3-5] The median interval from primary diagnosis to presentation of ITM is 17.9 months.[3] Five-year survival rates for stage IIIB, IIIC and IIID are 83%, 69% and 32%, respectively.[2] ITM are associated with significant morbidity due to local symptoms (pain, ulceration, bleeding, infection) and can herald future progression to distant metastases.[3]

The pathophysiology of ITM is poorly understood. ITM occur disproportionately commonly in the limbs and more frequently in the lower, this may be due to the effects of gravity, and a more lengthy lymphatic network, which allows the tumour cells to accumulate.[3, 6] Lymphatic metastases are a common site of metastases as lymph vessels are more permeable to tumour invasion than blood vessels.[6] Risk factors associated with ITM include: age greater than 50 years, presence of ulceration, increased Breslow thickness and positive sentinel lymph node biopsy.[7] However, these same risk factors are

also associated with poor prognosis and recurrence at regional or distant sites, so offer little in terms of a differential indictor of site recurrence.

Patients with ITM represent a heterogeneous population and thus present a therapeutic dilemma. Treatment does not follow the standardised protocols used in other stages of disease and an individualised approach is often employed. This has made it difficult to perform comparative studies of different treatment modalities and patients with ITM often make up only a small proportion of the population in clinical trials. Comparison of studies is problematic due to wide differences in treatment regimes, populations, and the outcome measures examined (Table 1). Surgical resection is generally considered first line therapy in appropriately selected patients with limited disease. In patients where surgery is not appropriate regional therapies (including intralesional therapies, isolated limb infusion or isolated limb perfusion, radiotherapy or topical therapy) or systemic therapies may be utilised. With effective systemic therapies available for use in patients with advanced melanoma, many patients with ITM are treated in this way, however the evidence base for their role and efficacy in ITM is yet to be fully established. Disease recurrence following treatment is common, with patients often undergoing repeat procedures, with a range of therapies being employed to achieve disease control.

Surgical resection

Where feasible, a definitive surgical approach is adopted as the first line management of ITM. A single study demonstrated that metastatic melanoma, isolated to the lymphatics, was curable with surgery in 38.4% of patients.[6] Surgery is indicated in patients with a limited number of lesions, without frequent recurrence and who have

undergone staging with cross-sectional imaging to exclude distant metastatic disease via positron-emission tomography-computed tomography. Unlike primary tumours, ITM are well circumscribed with no margin of *in-situ* disease. Therefore, wide local excisions are not indicated as these incur unnecessary morbidity, although multifocal metastases may be resected *en-bloc.*[8] Amputation is rarely indicated but may still have a role in those with progressive ITM, experiencing adverse effects from regional chemotherapy or inoperable reoccurrence.[9] Although the surgical margins and management of primary melanomas have been examined, there are limited data on the durability and effectiveness of excision in the field of ITM.

Adjuvant therapies may be used following surgical resection, and patients with resected ITM were included in recently published studies demonstrating a benefit to adjuvant therapy.[10, 11] Predictors of recurrence and indications for adjuvant therapy include short disease-free interval, nodal involvement and high disease burden. Investigation into the utility of circulating tumour DNA (ctDNA) as a predictor for locoregional and distant recurrence following resection demonstrated a shorter disease free interval in stage II/III melanoma patients with detectable plasma ctDNA.[12] In the future ctDNA may be an important prognostic factor to determine the need for adjuvant therapy.

Concerns that sentinel node biopsy (SLNB) causes an increased rate of ITM have been quashed, as studies reporting increases in locoregional recurrence rates following SLNB did not control for primary tumour characteristics.[3]

Where ITM are unresectable or surgery is contraindicated, many effective loco-regional and systemic therapies can be used to achieve disease control, these are discussed below.

Intralesional therapies

Intralesional injections are minimally invasive and are appropriate in patients with moderate disease burden. Additionally, many intralesional therapies produce a bystander effect, where responses are observed in un-injected lesions due to systemic immunological activation. Bacille Calmette-Guerin (BCG) was the first widely used intralesional therapy. Despite promising results in small studies, a profile of significant adverse effects (anaphylactic reactions and fatal disseminated BCG infection) has limited its clinical use.[13] Intralesional recombinant human interleukin-2 (IL-2) has been evaluated for the use of ITM yielding inconsistent results likely due to disparate treatment protocols.[14] IL-2's anticipated bystander effects are yet to be demonstrated.[14] The burden of frequent injections and considerable cost of IL-2 has reduced clinical uptake.[15]

PV-10 is a 10% preparation of Rose Bengal, which is taken up into tumour cell lysosomes causing lysis, with the possible bystander effect of antigen presentation leading to tumour specific T-cell activation.[16] A phase II clinical trial found a 26% CR rate and a median duration of response of 4 months in patients with stage IIIB, IIIC and IV refractory disease.[17] Furthermore, a substantial bystander effect was demonstrated, with 26% of patients with cutaneous bystanders experiencing regression.[17] Only mild side-effects including injection site pain, localised oedema and blistering were reported.[17, 18] These results are mirrored in previous retrospective studies on in-transit populations.[19] PV-10

therapy requires an average of 1.8 treatment cycles, comparing favourably to the more intensive regimes required for other intralesional therapies.[17] The synergy of PV-10 and radiotherapy has been demonstrated in a phase II trial.[18] A CR rate of 33% was achieved, with an 8.1-month median duration of response, with minimal toxicity.[18] The high response rates to PV-10 coupled with low injection burden justifies further examination and uptake into clinical practice.

Talimogene laherparepvec vaccine (T-VEC) is a modified Herpes Simplex Virus-1 that selectively replicates in tumour cells causing oncolysis inducing the production of granulocyte monocyte-colony stimulating factor (GM-CSF).[16] Resulting in the dual effect of releasing endogenous tumour antigens and then upregulating specific CD8+ immune responses to these antigens.[16] The OPTiM randomised phase III trial, compared intralesional T-VEC to subcutaneous GM-CSF in 249 patients.[20] The median overall survival in the T-VEC arm was 41.1 months compared to 21.5 months in the GM-CSF arm in patients in the stage IIIB/C and M1a unresected melanoma subgroup.[21] Analysis of this subgroup also revealed a 16% CR rate in patients randomised to the T-VEC treatment arm.[20] Furthermore, in the T-VEC arm, a durable response rate of >6 months was achieved in 33% of responders with stage IIIB/C disease and a bystander effect was observed with 15% of non-injected visceral metastases decreasing in size by more than 50%.[21] The modest response rates observed in both T-VEC and PV-10 trials may be partially attributable to the inclusion of patients with advanced disease.[20, 21]

Radiotherapy

Radiotherapy is rarely used as monotherapy for melanoma and has a limited role in the treatment of ITM. Monotherapy may be appropriate for ITM as a palliative measure where surgery and isolated limb infusion are contraindicated or not available. A study on the effects of palliative radiotherapy on 57 patients with stage III disease, where nearly half had ITM, demonstrated a CR rate of 44% at three months follow up. However, this study lacked long-term follow up and is nearly twenty years old.[22] Radiotherapy is primarily used as an adjunct to surgical excision and immunotherapy to consolidate partial responses. When used as an adjuvant in 174 high risk resected stage I-III melanoma the in-field recurrence rate was 11%.[23] There are no recent studies addressing the role of radiotherapy in ITM patients.

Regional therapies – Isolated limb perfusion and isolated limb infusion

Isolated limb perfusion (ILP) delivers chemotherapy at concentrations twenty times higher than those of systemic treatments with minimal toxicity.[24] This is achieved via surgical dissection and open cannulation of the major vessels of the effected limb, creating an isolated circuit under general anaesthesia. Leakage is prevented via proximal tourniquet and vessel clamping with a heart-lung machine utilised to circulate heated chemotherapeutics.[24] Isolated limb infusion (ILI) is a minimally invasive procedure that utilises the principles of ILP. Percutaneous catheterisation is used to deliver melphalan and actinomycin-D. In ILI lower doses are administered at lower flow rates for a shorter duration compared to ILP. ILP and ILI are indicated in patients where tumour volume or tumour kinetics make surgery inappropriate.

ILP is performed using the alkylating agent melphalan +/- tumour necrosis factor alpha (TNFα). The median CR rate from six studies (562 perfusions) was 46.5% in melphalan hyperthermic ILP, with one large study reporting median progression free survival (PFS) as 14 months.[25, 26] The CR rates for patients receiving melphalan plus TNFα were superior, with a 68.9% median CR rate (twelve studies, 556 perfusions).[25] There is a low incidence of major local toxicity and toxic limb amputation is a rare complication occurring in 0.65% of procedures.[25, 26] Despite unmatched CR rates reported in observational trials ILP is being superseded by less invasive therapies. ILP is only performed in a limited number of centres worldwide and is not performed in Australia as TNFα is not available.

ILI is a simpler alternative that has achieved comparable outcomes to ILP but there have been no formal comparisons between the two procedures. Retrospective studies of ILI have shown 27-38% CR rate with a median recurrence free survival of 22-24 months.[26-29]. Kroon et al, demonstrated that durability of ILI is comparable to that of ILP when CR is achieved.[27] Furthermore, in ILI the extracorporeal blood is not oxygenated, this creates a hypoxic and acidotic environment, which potentially enhances the cytotoxic effects of melphalan.[27] A number of studies on ILI have measured CR at three months rather than best response at any time following treatment potentially altering results. The establishment of standardised end-points would enable meaningful comparison across studies.

The relative strengths and weakness of ILP and ILI are summarised in Table 2. The lower CR rates observed in ILI may be due to a number of factors. ILI is preferentially

used in elderly patients and the proportion of patients with advanced disease has been higher in ILI series', both negative prognostic factors.[24, 27, 28] In the small number of non-randomised, retrospective studies have compared data from ILI and ILP, ILP was demonstrated to have a superior CR rate and recurrence free survival time.[24, 28] The convenience and simplicity of ILI has made it the preferred choice despite inferior response rates.[26]

Systemic therapies

Recent advances in the use of molecular targeted therapies and immunotherapy for patients with metastatic melanoma has prompted interest in the use of systemic therapies for unresectable ITM. The majority of studies into systemic agents examine stage IV melanoma patients, but the body of evidence into the efficacy in unresectable stage III melanoma is increasing. Further, systemic therapies may be of value following surgical management of ITM in reducing both loco-regional and distant recurrence.

Targeted therapies

Mutations in the BRAF oncogene are present in 40% of patients with melanoma and cause the activation of the mitogen-activated protein kinase pathway (MAPK).[30] Selective BRAF inhibitors are only effective in those patients with V600 mutations in BRAF and generally the time to progression is under 12 months.[30, 31] The combination of BRAF and MEK-inhibitors improves both the response rate and duration of response.[32] The COMBI-d phase III trial involving 423 patients with unresectable stage IIIC and IV melanoma compared dabrafenib in combination with trametinib (BRAF/MEK) to dabrafenib monotherapy.[33] The median overall survival for patients in the treatment arm was 25.1

months compared to 18.7 months in the control. Combination therapy resulted in a CR rate of 18% and a PFS of 11 months. Although only 4% patients in this study had unresectable stage IIIC disease and data on ITM status was not recorded.[33] The most common adverse effects reported were pyrexia and fatigue, with 26% of patients discontinuing due to adverse effects.[30, 33] Use of these therapies is limited to patients with BRAF mutations but show promise in this sub-population and further research is warranted.

Immunotherapy

Programmed cell death receptor 1 (PD-1) is a regulatory check point molecule expressed on T cells that binds to the PD-1 ligand on tissue-based macrophages resulting in downregulation of T cell responses.[34] Tumour cells can mimic this pathway by expressing PD-1 ligands and suppressing the immune response.[34] Two anti-PD-1 Agents, pembrolizumab and nivolumab have been shown to have activity in advanced melanoma. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is a receptor expressed on activated T cells that interacts with CD80/86 suppressing T cell activation.[35] Ipilimumab, an anti-CTLA-4 antibody, augments immune responses to tumor antigens by disabling this checkpoint.[35] A recent double blind, phase III study, compared monotherapy with nivolumab or ipilimumab to combination therapy in 945 patients with unresectable stage III or IV disease.[36] The proportion of patients with unresectable stage III or ITM disease was not documented. The nivolumab arm demonstrated a PFS of 6.9 months and an 16% CR rate. PFS was improved in patients with a positive PD-I ligand status, indicating PD-1 ligand status may be an important clinical biomarker.[36] A PFS of 2.9 months and a CR rate of 5% was seen in the ipilimumab arm.[36] The combination of ipilimumab and nivolumab

had a higher CR (19%) and longer PFS (11.5 months) than monotherapy, indicating a complementary action of inhibiting CTLA-4 and PD-1.[36] Common adverse events with the use of immunotherapy agents include autoimmune toxicities including colitis, dermatitis, pneumonitis as well as fatigue.[36] The use of combination therapy caused more numerous and severe side effects in particular diarrhoea and colitis, that lead to discontinuation.[36] Increasing experience with these agents have led to a better understanding of the management of these immune-related adverse events.

Systemic agents may improve recurrence rates when used as adjuvant therapy. A multicentre randomised control trial of the combined use of dabrafenib and trametinib in patients with resected stage III melanoma, with V600 mutations demonstrated a 58% 3-year relapse free rate.[11] Patients with ITM accounted for 12% of the population randomised to the combined therapy, but no analysis was provided for this subgroup.[11] The KEYNOTE-054 phase III trial compared pembrolizumab (anti-PD-1) to placebo in 1019 patients with resected stage III melanoma. At 18 months the recurrence free survival rate was 71.4% in the pembrolizumab arm compared to 53.2% in placebo. Unfortunately, ITM patients were excluded from this study.[37] The CheckMate-238 trial, compared adjuvant nivolumab to ipilimumab in 906 patients with resected stage IIIB/C and IV melanoma. At 12-months the rate of recurrence free survival for in stage IIIB/C patients was 71% in the ipilimumab group and 61% nivolumab group.[10] The proportion of patients with ITM was not recorded. Importantly, nivolumab had a lower rate of adverse effects than ipilimumab and lead to lower rates of discontinuation.[10] The high rates of toxicity have

meant that adjuvant ipilimumab has not been embraced by the international melanoma community.

Combination therapies

The combination of locoregional and checkpoint inhibitor therapies may result in synergistic immunological effects. Phase Ib study of T-VEC plus ipilimumab involving 19 patients with untreated stage IIIB-IV melanoma found a CR rate of 22% and a durable response after six months in 44% of patients (PFS was not reached).[38] These promising results prompted a phase II trial of this combination (NCT01740297) and a phase Ib trial examining T-VEC and pembrolizumab combination therapy (NCT02263508). A phase II trial evaluating the efficacy of ILI and ipilimumab in 18 stage IIIB-IV melanoma patients demonstrated a 65% CR rate at three months and the PFS at one year was 57%.[39] Further studies are required to determine if immunotherapy is augmented by regional therapy.

Topical therapies

Topical agents are rarely used in ITM. However, they are inexpensive, generally well tolerated, non-invasive and simple to administer. Imiquimod as a 5% cream is a toll-like-receptor seven agonist, was reported to have a 82.3% CR rate per lesion when eleven case studies on melanoma (17 patients) were pooled.[40] However, measuring CR rates per lesion instead of per patient artificially inflates the sample size and risks skewing results, especially when the tumour burden is large. Treatment outcomes are difficult to compare due to varying administration protocols and follow-up periods.[40] Skin irritation was the most common side-effect, only one patient reported more severe inflammation and

erosion.[40] Diphencyprone (DPCP) is a contact sensitiser thought to act via enhancing lymphocyte anti-tumour activity. A single centre prospective study demonstrated a 22% CR rate for patients with cutaneous ITM and a disease free interval of 12.3 months.[41] However, adverse effects including contact hypersensitivity, blistering, regional lymphadenopathy and generalised dermatitis may limit its use.[42] A small clinical trial investigating the action and efficacy of imiquimod and DPCP in superficial ITM has been initiated.[43]

Conclusion

ITM represent a heterogeneous disease process with a rapidly evolving, diverse range of therapeutic options. The disease trajectory may be long, with multiple or repeat modalities utilised for frequent recurrences. Patients with ITM should be discussed in a multidisciplinary meeting prior to commencing therapy to consider the broad range of treatment options. First line management for patients with low volume disease invariably involves surgical resection. However, the true challenge lies in determining which modality to use when surgery is contraindicated or in patients with disease that is technically resectable that are not best-suited to surgical resection. ILI and ILP are well-established second line therapies that have yielded high rates of durable responses and to date remain the most effective option. Intralesional therapies have demonstrated effect despite lower response rates, in particular T-VEC and PV-10 produce highly durable responses in appropriately selected patients. Whilst systemic therapies have yielded promising results when used for progressive or inoperable disease and as adjuncts to surgical intervention their role in ITM has yet to be fully elucidated. The literature reports a range of outcome measures and follow-up intervals between and within treatment modalities. The majority of

data is retrospective, and many key studies do not perform subgroup analysis for ITM or exclude them all together. Overall there is a paucity of data comparing the different available modalities, hampered by the heterogeneity of disease progression and lack of appropriate prognostic factors.

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Table 1: Comparison of treatment modalities for in-transit melanoma metastases. For each modality, the highest quality data was selected

STUDY	AGENT	STUDY DESIGN	SAMPLE	MEDIAN AGE	(N)	CR	RESPONSE CRITERIA	MEDIAN PFS
INTRALESIONAL								
Boyd et al (2011) [14]	IL-2	Prospective	ITM	69 years	39	51%	4 weeks	11 months †
Thompson et al (2015) [17]	PV-10	Phase II	IIIB, IIIC, refractory IV disease	70 years	80	26%	8 weeks	4 months
Andtbacka et al (2015) [21]	T-VEC	Phase III	IIIB, IIIC, unresectable M1a	63 years	249	16%	Within first 12 months	-
REGIONAL								
Raymond et al (2011) [26]	ILP: melphalan ILI	Prospective	IIIB, IIIC, IV	-	188	55% 30%	3 months 3 Months	14 months †† 9 months ††
Grunhagen et al (2004) [44]	ILP: melphalan+	Retrospective	III, IV	62 years	87	69%	Best response	16 months‡

	TNFα							
Kroon et al (2008) [27]	ILI	Prospective	Unresectable I-IV	74 years	185	38%	Best response	13 months ‡‡
Seegenschmiedt et al (1999) [22]	Radiotherapy	Retrospective	IIB/III/IV	58 years	121	44%	3 months	-
SYSTEMIC								
Long et al (2015) [33]	Dabrafenib + trametinib	Phase III	Unresectable IIIC, IV	55 years	423	18%	Best response	11 months
Wolchok et al (2017) [36]	Nivolumab	Phase III	Unresectable III, IV	59.6 years	945	16%	Best response	6.9 months
	Ipilimumab					5%	Best response	2.9 months
	Ipilimumab + nivolumab					19%	Best response	11.5 months
TOPICAL								
Read et al (2017) [41]	DPCP	Prospective	Satellite, ITM (IIIB+)	75.4 years	54	22%	Best response	12.3 months

Abbreviations: CR, complete response rate; PFS, progression free survival: ILP, isolated limb perfusion; ILI, Isolated limb infusion.*CR assessed by the Response Evaluation Criteria in Solid Tumours (RECIST). Definitions of PFS differ in the literature. Other outcome measures reported in the literature*

included: † *mean time to relapse,* †† *time to in-field progression,* ‡ *median time to local progression,* ‡‡ *median duration of response.*

Table 2: Comparison of isolated limb perfusion and isolated limb infusion.

Isolated Limb Perfusion	Isolated Limb Infusion
Melphalan +/- TNFα. Higher concentrations	Melphalan and actinomycin-D. Lower concentrations
Open surgical dissection and direct catheterisation	Percutaneous catheterisation
General anaesthesia	Regional anaesthesia
Mild hyperthermia through circuit: ≥39°C	Extremity warmed with heat blanket: ≥37°C
Oxygenated extracorporeal circuit	Non-oxygenated extracorporeal circuit
Longer duration of chemotherapy circulation (90min)	Shorter duration of chemotherapy circulation (20-30min)
Unsuitable for elderly patients	Suitable for elderly patients
High perfusion pressure with increased risk of systemic leak requiring monitoring	Lower perfusion pressure allowing superior isolation of limb and reduced risk of systemic leakage
Tourniquet held in place by a Steinman pin into the ASIS allowing greater proximal perfusion	Unable to treat proximal lesions
Mild to severe regional toxicity. Including cases of toxic limb amputation	Mild to moderate regional toxicity
CR 68.9%	CR 38%
Used in a limited number of centres: specialist equipment and staff required	Widely used and simple to perform

The information in this table was taken from the literature.[24-28]