The role of regional chemotherapy for advanced limb melanoma in the era of potentially effective systemic therapies

Rebecca L. Read[a,b,c] and John F. Thompson[a,d,e,f]

To review the current role of regional chemotherapy in the management of advanced limb melanoma. Articles reporting the results of isolated limb infusion (ILI) were identified by performing a comprehensive literature search using the *PubMed* database. Keywords included isolated limb infusion, in-transit melanoma and melphalan. No publication date restrictions were applied. ILI data were compared with those from current systemic therapy clinical trials and the previously reviewed isolated limb perfusion (ILP) literature. Regional chemotherapy is today required in fewer patients because effective systemic therapies now provide an alternative treatment for those who develop extensive local melanoma recurrence or in-transit metastases (ITMs). However, regional chemotherapy may be a valuable treatment option when the side-effects of systemic therapies are of concern, or after systemic treatment failure. ILP achieves overall response rates (ORRs) of 64–100% and complete response rates (CRRs) of 25–89%. ILI achieves ORRs of 41–91% and CRRs of 6–39%. ILP and ILI can have a low risk of serious morbidity. Early results from treatment with ILP or ILI in conjunction with systemic immune therapies suggest that these modalities can be safely combined, which may be useful in patients with refractory limb disease. Regional chemotherapy remains important in the armamentarium of clinicians managing patients with unresectable limb melanoma and may be preferable in those who are frail, elderly or who are at high risk from complications of systemic therapies. The efficacy of combining regional chemotherapy with systemic immune therapy is currently being assessed. *Melanoma Res* 31: 290–297 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

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[a]Melanoma Institute Australia, The University of Sydney, Sydney, NSW, [b]Department of Surgery, Calvary Health Care, [c]College of Health and Medicine, Australian National University, Canberra, ACT, [d]Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, [e]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW and [f]UWA Medical School, Division of Surgery, University of Western Australia, WA, Australia

Correspondence to John F. Thompson, MD, Melanoma Institute Australia, The University of Sydney, 40 Rocklands Rd, North Sydney, NSW 2060, Australia
Tel: +61 (0)2 9911 7366; fax: +61 (0)2 9954 9290;
e-mail: john.thompson@melanoma.org.au

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Introduction

Isolated limb perfusion (ILP) and isolated limb infusion (ILI) are methods for delivering regional chemotherapy to melanoma patients with advanced limb melanoma. Most of these patients have in-transit metastases (ITMs) confined to a limb. Occasionally, regional chemotherapy is also used in patients who also have distant metastatic melanoma, when the extent of limb disease significantly impacts the quality of life and systemic therapies have been ineffective or poorly tolerated.

ITMs include both 'local' recurrences after adequate wide excision of primary melanoma and metastases between the primary melanoma site and regional lymph nodes [1]. ITMs occur in approximately 3–10% of patients diagnosed with a primary cutaneous melanoma [2–5]. Predicted 5-year survival ranges from 32 to 83%, depending on the extent of regional node involvement [1].

Historically, melanoma patients undergoing regional chemotherapy had a locoregionally advanced disease that had progressed in spite of multiple other locoregional treatment modalities, including surgical excision, ablative techniques (electrocautery and carbon dioxide laser), topical therapies (diphencyprone and imiquimod), injectable therapies [including interleukin-2 (IL-2), rose bengal (PV-10) and talimogene laherparepvec (T-VEC)], electrochemotherapy and radiotherapy [6–8].

Today, potentially effective systemic therapies are available, necessitating a reassessment of the indications for using ILI or ILP to treat progressive or recurrent limb disease. This article outlines the ILP technique, comprehensively reviews the ILI literature and discusses patient selection for regional and systemic therapies in the modern era.

The impact of adjuvant systemic therapies

Adjuvant systemic therapies for melanoma are now widely available. When administered to patients with completely resected Stage IIIB/C/D disease, ipilimumab improved overall survival (OS) by 8.7% at 7 years but with significant toxicity [9]. The CheckMate-238 trial found that adjuvant nivolumab was more effective than adjuvant ipilimumab in terms of recurrence-free survival (RFS)

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Table 1 Single and multicentre studies of isolated limb infusion (ILI) with comparison to the isolated limb perfusion mNote that in the ILI data individual patients appear in multiple data sets preventing combined analysis of the data

Group	Location	Response[a]	Number initial ILI (repeat ILI)[b]	ORR %	CRR%	PRR%	Wieberdink III/ IV/V % (number amputations)
Thompson *et al.* (1998) [30]	Sydney, Australia	Best response	44[c]	91	39	52	No amputations
Kroon *et al.* (2008) [47]	Sydney, Australia	Best response	185	84	38	46	39
Barbour *et al.* (2009) [33]	Brisbane, Australia	Best response	74	54	24	30	10
Beasley *et al.* (2009) [34]	Multicentre, USA	At 3 months	128	64	31	33	36 (1)
Duprat-Neto *et al.* (2013) [35]	Sao Paulo, Brazil	Best response	31	79	26	53	60.5
Giles and Coventry (2013) [36]	Adelaide, Australia	Best response	20 (8)	70	20	50	20
Wong *et al.* (2013) [37]	Florida, USA	At 3 months	79	74	37	37	23
Coventry *et al.* (2014) [38]	Multicentre Australia	Best response	131	63	27	36	13
Steinman *et al.* (2014) [39]	New York, USA	At 3 months	58	–	25		
Cecchini *et al.* (2015) [40]	Multicentre, Italy	At 30 days	29	66	10	56	10
Chin-Lenn *et al.* (2015) [41]	Multicentre, Canada	At 3 months	52 (2)	56	29	27	39
Kroon *et al.* (2016) [42]	Multicentre, Australian	Best response	316	75	33	42	30
O'Donoghue *et al.* (2017) [43]	Florida, USA	At 3 months	114 (31)	59	26	33	12
Li *et al.* (2018) [44]	Beijing, China	Best response	150	41	6	35	45
Miura *et al.* (2019) [45]	Multicentre, International	Both	687	64	29	35	28
Teras *et al.* (2020) [48]	Tallinn, Estonia	Best response	21	76	38	38	40
ILP comparison data			ILP				
Moreno-Ramirez *et al.* (2010) [21]	International, systematic review	Both	2018	90.4 (range 64.0–100.0)	58.2 (range 25.0–89.0)	32.2	19.75 (8)

CRR, complete response rate; ILI, isolated limb infusion; ILP, isolated limb perfusion; ORR, overall response rate; PRR, partial response rate.
[a]Responses termed 'Best response' were assessed according to the standard WHO criteria. Responses termed 'At 3 months' used RECIST criteria for response in solid tumours. The studies by Miura *et al.* and Moreno-Ramirez *et al.* include centres using both methods of determining response.
[b]The number of initial ILI procedures is documented. Where repeat procedures were not analysed separately in the response data the number of procedures is included in brackets.
[c]An additional 38 patients underwent a planned double ILI protocol and are not included.

(51.7 vs. 41.2% 4-year RFS; hazard ratio 0.71; $P = 0.0003$), with equivalent 4-year OS (77.9 nivolumab vs. 76.6% ipilimumab) and a better safety profile [10]. The efficacy of adjuvant dabrafenib with trametinib (for BRAF-mutated melanoma) and adjuvant pembrolizumab have also been demonstrated [11,12]. Only the COMBI-AD trial (dabrafenib and trametinib) and the CheckMate-238 trial (nivolumab) included patients with ITMs. Within the COMBI-AD cohort, the presence of ITMs did not alter the efficacy of the adjuvant therapy [13]. Adjuvant nivolumab and pembrolizumab are also under investigation (CheckMate-76K, Keynote-716 respectively) in patients with completely resected high-risk stage II melanoma (Stage IIB/C) melanoma. Consequently, it is expected that in the future fewer patients will develop advanced limb melanoma.

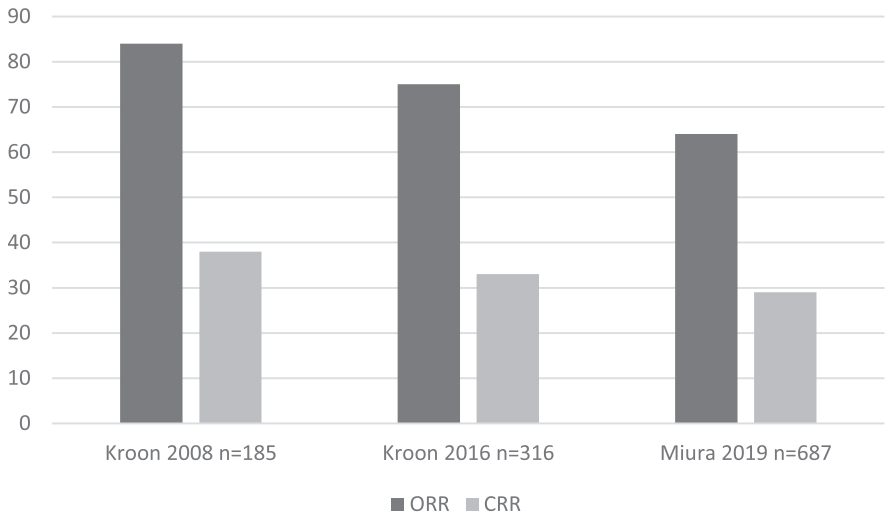
The impact of potentially effective systemic therapies

Many patients with unresectable limb melanoma now receive systemic therapy with either targeted inhibitors of the BRAF and MEK oncogenes (BRAF/MEK inhibitors) or T-cell activating immune therapies.

Randomised phase III trials have demonstrated the efficacy of BRAF/MEK inhibitor combination therapies: dabrafenib/trametinib (COMBI-v); vemurafenib/cobimetinib and encorafenib/binimetinib over vemurafenib alone in patients with advanced melanoma. Most patients had Stage IV M1a-M1c metastatic melanoma, whereas a few patients in each trial had unresectable Stage III melanoma. The overall response rates (ORRs) ranged from 64 to 75% and the median OS was 22.3–33.6 months. Side-effect profiles vary but most commonly include diarrhoea, arthralgia, fatigue, pyrexia and rash, with up to 15% of patients in each trial discontinuing treatment due to adverse events [14–17].

The efficacy of the anti-CTLA4 and anti-PD-1 immune checkpoint inhibitors has also been demonstrated. Notably, CheckMate-067 initially reported an ORR of 57.6% in the nivolumab-plus-ipilimumab group, 43.7% in the nivolumab-only group and 19% in the ipilimumab-only group [18]. More recently 5-year OS was reported to be 52, 44 and 26% in each group, respectively [19]. Immune checkpoint inhibitors can cause serious toxicity by causing or potentiating immune-related conditions, including colitis, hepatitis, hypophysitis and thyroid dysfunction. Less severe but more common side-effects include fatigue, rash, muscle and joint pain, diarrhoea and weakness [20]. Single-agent PD-1 inhibitors have a better toxicity profile [21]. The data captured in these prospective randomised trials did not allow for the specific analysis of outcomes in patients with ITMs [22]. A recent case series of 54 patients with unresectable ITMs who received immune therapies, most commonly single-agent anti-PD-1 (74%), demonstrated an ORR of 54% and a complete response rate (CRR) of 26%. The

Fig. 1



Isolate limb infusion response rates (ORR, overall response rate and CRR complete response rate) have decreased as the number of centres included in combined series has increased. Single Australian centre (Kroon 2008), combining five Australian centres (Kroon 2016) and combining nine Australian and USA centres (Miura 2019).

2-year progression-free survival of 39% and 2-year OS of 63% are in keeping with the well-documented responses to immune checkpoint therapies in landmark clinical trials [23]. The efficacy and side-effects of regional chemotherapy for melanoma must be considered in light of the results able to be achieved by systemic therapies and their potential toxicities.

Regional chemotherapy for melanoma

Patients with limb ITMs that are too extensive for surgery may be treated by ILI or ILP. These procedures deliver high-dose chemotherapy to the affected limb, usually at elevated temperatures to enhance efficacy, while avoiding the entry of the drug into the systemic circulation. Melphalan alone or in combination with actinomycin D is used most commonly, although other drugs that are or have been used alone or in combination include interleukin-2, tumour-necrosis factor (TNF), cisplatin, vindesine, dacarbazine and fotemustine. Limb toxicity is graded using the Wieberdink toxicity score: 1 (no visible effect); 2 (slight erythema with or without oedema); 3 (considerable erythema with or without oedema with blistering; 4 (epidermolysis with or without deep tissue damage with threatened or actual compartment syndrome); 5 (severe tissue damage necessitating amputation) [24].

Isolated limb perfusion

ILP is a long-established surgical procedure in which, using an open surgical approach, large-bore cannulas are inserted into the axial artery and vein of the affected limb to establish circulation via an extracorporeal heart-lung machine [25]. Limb oxygenation and pH are maintained at physiological levels and the chemotherapy agents, most commonly melphalan with or without TNF, are circulated through the isolated limb. A systematic review of over 2000 ILPs demonstrated a median ORR of 90.4% (range 64.0–100.0%), a CRR of 58.2% (25.0–89.0%) and a median 5-year OS of 36.5% (19.0–50.0%). ILP was well-tolerated, with Wieberdink Grade IV and V toxicity rates of 2.00 and 0.65%, respectively [26]. Repeat ILP can be difficult due to perivascular scarring in the surgical field [27] but can usually be performed safely and is effective particularly in patients who recur after a complete response to their initial ILP [22].

Long before adjuvant systemic therapies for melanoma became available, ILP was the subject of an international randomised controlled trial in the prophylactic (adjuvant) setting. The study randomised 832 patients with primary melanomas ≥1.5 mm Breslow thickness to receive either wide excision alone or wide excision plus ILP. The addition of ILP resulted in reduced ITM and regional node metastasis rates but no difference in the time to distant metastasis or OS. Consequently, ILP was not recommended as an adjunct to standard surgery [28]. However, in some patients with repeatedly recurrent limb ITMs, adjuvant ILP continued to be used because it increased the recurrence-free interval and decreased the number of recurrences [29].

Isolated limb infusion

In contrast to ILP, the ILI technique uses a minimally invasive, radiologically-guided percutaneous approach to insert small-calibre catheters into the axial artery and vein of the affected limb. The limb is warmed and then isolated using a pneumatic tourniquet, with circulation to the foot or hand excluded by a firmly applied Esmarch

Table 2 Studies comparing isolated limb perfusion and isolated limb infusion

Authors	Location	Series dates	Cases	Outcome ORR/CRR	Toxicity
Beasley *et al.* (2008) [53]	Durham, USA	1995-2003	ILP 59	88/57	≥Grade III 32%
	Durham, USA	2003-2008	ILI 61	44/30	≥Grade III 18% (p=0.037)
Dossett *et al.* (2016) [54]	Florida, USA (ILI only)	2007-2015	ILP 109	80/60	Grade IV 2%
	Gothenberg, Sweden (ILP only)	2007-2015	ILI 94	53/29	Grade IV <1% No Grade V

CRR, complete response rate; ILI, isolated limb infusion; ILP, isolated limb perfusion; ORR, overall response rate.

Table 3 Combining isolated limb infusion and systemic therapies

Therapy	Authors (reference)	Study type	Location	Patients	Outcome ORR/CRR
ILI (fotemustine) + dacarbazine	Bonenkamp *et al.* (2004) [60]	Case series	Sydney, Australia	13	92/30
ILI+ADH-1	Beasley *et al.* (2009) [61]	Case series. Phase 1	Durham, USA	16	62.5/50
ILI+ADH-1	Beasley *et al.* (2011) [62]	Case series, Phase 2	Durham, USA	45	60/38
ILI+ipilimumab	Ariyan *et al.* (2018) [63]	Case series	New York, USA	26	85/62

CRR, complete response rate; ILI, isolated limb infusion; ORR, overall response rate.

bandage. An extracorporeal circuit is established between the arterial and venous catheters and chemotherapy agents are introduced via a three-way tap. Circulation is achieved by repeated syringe aspiration from the venous cannula and re-injection into the arterial cannula. In contrast to ILP, the limb becomes hypoxic and acidotic during the procedure, potentiating the effect of melphalan [30,31]. ILI has somewhat lower response rates than ILP but has the advantage of being simpler and more easily repeated [32].

The ILI literature was searched to identify all studies in which the primary outcome was the ORR of patients with limb melanoma following melphalan ILI (Table 1) [29,30,33–46]. Some centres also used actinomycin D. Not all centres used hyperthermia. Studies in which a small minority of patients (<10%) had cancers other than melanoma were included. Studies with <10 patients in total were excluded. One of the difficulties in analysing the ILI literature is that many patients have been included in multiple studies, with the publication of individual institution case series, follow-up case series and national and international case series using combined data. This is further complicated by variation in the criteria used to assess response. Australian and most other international centres continue to use the WHO criteria whereas US centres generally use the newer Response Evaluation Criteria in Solid Tumours (RECIST) criteria for response in solid tumours (Table 1). Centres using RECIST criteria have reported results at 3 months which may underestimate response rates in comparison to centres using the WHO criteria to report the best response, which may occur before or after 3 months.

Reported response rates for ILI vary (Table 1). Excellent results were achieved in the initial Sydney Melanoma Unit (now MIA) cohort of 164 patients, with an ORR of 91% and a CRR of 39% [30]. Some of these patients, subsequent MIA patients and patients from other published and unpublished international case series, were included in a recent multicentre cohort of 687 first-time ILIs in nine Australian and US centres. The ORR and CRR were 64.1 and 28.9%, respectively, and the median OS was 38.2 months. Patients who had a complete or partial response had improved OS (46.5 vs. 24.4 months; $P < 0.0001$) [45]. Significant limb toxicity (threatened or actual compartment syndrome, Wieberdink grade IV) was seen in 3.9% of patients but no patient required treatment-related amputation (Wieberdink grade V). What is apparent is that as contemporary patients are added, and institutions join to produce larger case series, the original excellent results from ILI, which rivalled ILP in terms of ORR, have not been reproduced. Both ORR and CRR have decreased as the series size has increased while continuing to include the primary data from MIA [29,30,42,45] (Fig. 1). In the Italian series, early assessment of response may explain the low CRR [40]. In the Chinese series of 150 ILIs for melanoma, the ORR and CRR were only 41 and 6%, respectively [44]. This poor response may reflect the aggressive biology of acral melanoma, seen more commonly in Asian populations, and accounting for 79% of cases in this study. High disease burden may also adversely affect outcome [39,44,49,50], but it is unclear whether it is a major factor contributing to the lower response rates seen in more recent series.

It is more likely that technical deficiencies have been responsible for the poor results. Very low tumour response rates have been observed when the limb temperature is <37 °C at the time of drug infusion, and mild hyperthermia should therefore be achieved at the outset and maintained for the duration of the ILI. Another factor that may have been responsible for poor results is an inadequate duration of drug exposure. In initial studies in Sydney, a 20-min ILI procedure was used but much better response rates were achieved subsequently when 30-min ILIs became standard. The inevitable hypoxia that develops in this extra 10 min of drug exposure appears to increase efficacy. The successful MIA technique has been described in detail, with the aim of improving results internationally [51,52].

Comparing isolated limb perfusion and isolated limb infusion

Only two studies have attempted to directly compare ILP and ILI but neither provided high-level evidence. A 2008 study was from a centre that switched from ILP to ILI in 2003, whereas the more recent 2016 study compared ILP

Table 4 Selecting regional chemotherapy or systemic therapies in patients with in-transit metastases

	Systemic therapy	Regional chemotherapy
Adjuvant	Approved for adjuvant use	Not recommended
Neoadjuvant	Clinical trial setting	Case reports only
Disease tempo	Rapidly progressive limb ITM	Slowly progressive limb ITM
Stage	Stage IV with ITM	Stage IV with ITM as the dominant feature impacting quality of life
Disease progression		Progressive troublesome limb disease in spite of systemic therapy Option for repeat ILP/ILI
Performance status/ comorbidities	Now preferred as initial therapy in most patients with unresectable ITM	ILI preferred in elderly, frail patients Autoimmune disease Transplant patients
Availability	Most oncology centres	Limited to highly specialised surgical oncology centres
Treatment duration	Indefinite	Single episode
Economic	Higher cost	Lower cost

ILN, isolated limb infusion; ILP, isolated limb perfusion; ITM, in-transit metastases

procedures performed in Sweden to ILI procedures performed in the USA [53,54]. In spite of their caveats, they support the overall body of evidence which indicates that ILP achieves somewhat higher response rates but incurs greater toxicity than ILI (Table 2).

The option of intralesional therapy

Melanoma ITMs may also be treated by intralesional injection of a variety of agents, which cause tumour cell lysis. In some cases, an abscopal effect is observed suggesting immune activation secondary to antigen release. T-VEC, a genetically modified herpes simplex virus-based oncolytic immunotherapy, was analysed in the Phase III OPTiM study with an ORR of 31.5% and CRR of 16.9% [55]. In further small series and a CR has been associated with long-term survival [55,56]. Intralesional IL-2 and PV-10 produce similar results, with CRRs of 44.6 and 26%, respectively in case series, and an abscopal effect seen in over 20% of patients [57–59]. It is hypothesised that by releasing tumour antigens, intralesional therapies may improve the efficacy of the immune checkpoint inhibitors.

Combining systemic therapies and regional chemotherapy

The concept of combining systemic therapy with regional chemotherapy to improve efficacy is not new (Table 3). In 13 patients with advanced limb melanoma, who had failed melphalan-based ILI and in whom amputation was considered the only alternative, repeat ILI was performed using fotemustine after systemic chemosensitisation with dacarbazine. Response rates were impressive, limb salvage was achieved in five patients but severe limb toxicity necessitated early amputation in four patients [60]. Preclinical models suggested that cyclic pentapeptide ADH-1, which disrupts N-cadherin adhesion complexes, would improve the response to melphalan ILI. However, this did not translate into an improved response in the phase II clinical trial [61,62]. More recently Ariyan *et al.* [63] have changed this paradigm and used ILI with melphalan to induce inflammation in the tumour microenvironment before systemic immune therapy with ipilimumab in ITM patients with Stage IIIB-IV melanoma. Excellent 'in limb' responses were observed (ORR 85%; CRR 62%) and two patients with measurable distant (stage IV) disease had complete responses at all sites of at least 2 years duration [63] (Table 3). The hypothesis that ILP/ILI might increase tumour antigen release potentiating the effects of systemic immune therapies warrants further investigation. A trial of nivolumab followed by ILP is currently recruiting to establish the safety, tolerability and efficacy of this regimen (NivoILP, NCT03685890, Sahlgrenska University Hospital, Sweden).

Comparing outcomes of systemic therapy and regional chemotherapy

A direct comparison between systemic therapies and regional chemotherapy based on information currently available in the literature is not possible due to the consistently higher disease stage in systemic therapy trials. What is clear is that response rates with regional chemotherapy for limb ITMs rival or surpass those seen with new systemic therapies. Upfront systemic therapies may be appropriate in patients with advanced ITMs, but there are groups of patients who may achieve greater benefit from regional therapy, without the risk of serious systemic side effects.

Selecting systemic or regional therapy

Developing criteria to select patients for either systemic therapy or regional chemotherapy for advanced limb melanoma are the focus of ongoing investigation. Elderly patients are of particular interest, as multiple studies attest to ILI being well tolerated in older patients [46,64]. Elderly patients and those with poor performance status have generally been under-represented in systemic therapy trials. Although there are reports of excellent responses to immune checkpoint therapies in elderly patients, this group may benefit from avoiding systemic side effects which could have a greater impact in the setting of advanced age and frailty. Other patient groups where regional chemotherapy could avoid unacceptable systemic toxicity are recipients of solid organ transplants, where the use of immune checkpoint therapies results in a high risk of graft rejection, and in patients with clinically significant autoimmune disease, where the risk of unacceptable immune activation is increased [65].

The tempo and distribution of the patient's disease should always be considered. Rapidly progressive or recurrent disease is more likely to progress to distant metastasis, suggesting a need for systemic therapy. ILI effectively treats limb disease to the mid-thigh or mid-arm, whereas ILP treats disease to the groin or axilla. Regional lymph

node surgery can be combined with either of these procedures. Co-existent distant metastases provide a clear indication for systemic therapy.

Access to specialist centres providing ILI with or without ILP services may be limited by distance and ability to travel. The increased use of targeted therapies and immune therapies for multiple tumour types means that systemic therapies may be more easily accessed by many patients. Data to guide the duration of systemic therapy are lacking [66] and some patients may wish to travel to have a single episode of treatment with ILI or ILP rather than requiring the potentially indefinite administration of systemic therapies, requiring many attendances over a prolonged period. ILP/ILI are relatively expensive, with the mean overall treatment cost calculated at US$36 758 [67]. However, this is very much less than the cost of systemic therapy, which is at least US$100 000 per year [68].

Neoadjuvant systemic or regional therapies may facilitate surgery and clinical trials assessing this approach are in progress. Early results from the NeoCombi trial, neoadjuvant dabrafenib plus trametinib, saw that all patients with Stage IIIB-C disease ($n = 35$) achieve a pathological response, with none progressing preoperatively [69]. The OpACIN-neo study, neoadjuvant ipilimumab plus nivolumab, resulted in a pathological response in 80% of patients but longer-term follow-up data are not yet available [70]. When ILI has been followed by complete surgical resection of residual disease, outcomes have been similar to those in patients who achieve a CR after ILI [71].

A recent study reported a significant reduction in the use of ILI/ILP in the management of advanced limb melanoma. Comparing 2005–2010 and 2011–2014, the mean number of ILP/ILI procedures for melanoma decreased from 91 to 32 per year at a large US centre [72], and over the same time period ILI numbers at MIA in Sydney have halved. However, regional chemotherapy remains important in the management of selected patients. Maintaining the technology and skill required to perform ILI with or without ILP will ensure the best outcomes through individualised treatment. These procedures are most appropriately performed at specialist, high-volume melanoma treatment centres, and multidisciplinary discussion of all treatment options is desirable before a particular form of therapy for advanced limb melanoma is undertaken.

Conclusion

The increasing use of potentially effective systemic therapies for melanoma in the adjuvant and metastatic settings means that fewer patients will suffer from advanced limb melanoma. Some who nevertheless develop extensive limb ITMs will continue to benefit from regional chemotherapy when systemic therapies have failed or when it is particularly important to avoid systemic toxicities (Table 4). Future studies will better define patient selection criteria and the potential for synergy between regional and systemic therapies.

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Conflicts of interest

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