Original Article

Durability of Complete Response to Intralesional Interleukin-2 for In-Transit Melanoma

Journal of Cutaneous Medicine and Surgery
2021, Vol. 25(4) 364–370
© The Author(s) 2021

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1203475420988862
journals.sagepub.com/home/cms

Sami Khoury[1], Gregory C. Knapp[2], Allison Fyfe[3], Jose Monzon[4], Claire Temple-Oberle[5], and Gregory J. McKinnon[2]

Abstract

Background: Intralesional injection of interleukin-2 (IL-2) for in-transit melanoma (ITM) is associated with a high rate of complete response. However, there is a paucity of data on treatment durability and long-term outcomes.
Objectives: To provide long-term data on patients with a complete response to IL-2 therapy for ITM.
Methods: Consecutive patients with ITM, treated with intralesional IL-2 therapy, at the Tom Baker Cancer Center were identified from April 2009 to August 2019. All patients received at least 4 cycles (every 2 weeks) of IL-2 (5 MIU/mL). Complete response was defined as sustained (ie, 3 months) clinical complete remission of all known in-transit disease.
Results: Sixty-five patients were treated with curative intent for in-transit disease with intralesional IL-2. Complete clinical response was identified in 44.6% (29/65). In this subset of patients, the median number of lesions per patient was 9 (range 1-40). The median total dose of IL-2 was 0.8 mL (IQR 0.4-1.5) per lesion. One patient received isolated limb infusion and 13.8% (4/29) received systemic immunotherapy as part of their initial management. At a median follow-up of 27 months (IQR 16-59), 34.5% (10/29) developed recurrent disease. Of these patients, 50.0% (5/10) presented with synchronous in-transit and distant metastases. The median time to recurrence was 10.5 months (IQR 5.8-16.3).
Conclusion: With long-term follow-up, 65.5% of complete responders have a durable response to intralesional IL-2 therapy. In this cohort of patients, local in-transit recurrence is most likely to occur within 12 months and is often associated with concomitant distant disease.

Keywords

in-transit melanoma, intralesional interleukin-2 (IL-2), recurrence

Introduction

The incidence of melanoma in Canada increased by 2.2% per year in males and 2.0% per year in females between 1984 and 2015.[1] Although early-stage melanoma is associated with excellent survival, advanced disease is associated with worse recurrence-free and overall survival.[2] In-transit melanoma (ITM) develops in up to 6.6% of patients and is characterized by dermal or subdermal metastases.[3] This phenotype carries an overall 5-year survival of 40%-70%, which is influenced by the presence of additional regional disease.[4] The development of ITM is associated with morbidity and reduced quality of life.[5,6]

Many therapeutic strategies have been proposed for the treatment of ITM.[7] Historically, first-line treatment included surgical excision and radiotherapy, although recurrence was common.[8,9] The regional administration of cytotoxic chemotherapy through isolated limb perfusion using interferon, melphalan, and TNF-alpha alone or in combination is associated with a response rate ranging from 26% to 69%.[10] However, durability of response is poor, with a median recurrence rate of 40.5% and a median time to recurrence of

[1]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
[2]Department of Oncology, Division of Surgical Oncology, University of Calgary, Calgary, AB, Canada
[3]Alberta Health Services, Tom Baker Cancer Center, Calgary, AB, Canada
[4]Department of Oncology, Division of Medical Oncology, University of Calgary, Calgary, AB, Canada
[5]Department of Surgery, Division of Plastic Surgery and Department of Oncology, University of Calgary, Calgary, AB, Canada

Corresponding Author:
Gregory C. Knapp, Department of Oncology, Division of Surgical Oncology, University of Calgary, Tom Baker Cancer Center, 1331 29 St NW, Calgary, AB T2N 4N2, Canada.
Email: knappg@pm.me

10.5 months, and the intervention can be associated with significant complications (eg, compartment syndrome).[11-15] Systemically administered targeted and immunotherapy has demonstrated improved survival in patients with stage III disease, including in-transit disease. However, systemic immunotherapy therapy is expensive and associated with high rate of serious adverse events.[16-21]

Early studies examining the efficacy of systemic interleukin-2 (IL-2) therapy similarly demonstrated a poor response rate of 10% to 15% and significant adverse events.[22,23] Due to the limited efficacy and associated toxicity of systemic IL-2, intralesional injection was proposed as an alternative route of administration. Response rates varying from 25% to 96%, with a complete clinical response (cCR) in up to 50% of patients.[24-28] In appropriately selected patients, intralesional IL-2 therapy is associated with an improvement in progression-free survival for patients with ITM and is associated with a well-tolerated side effect profile (eg, transient low-grade fever).[24,28,29]

Unfortunately, there is a paucity of data on the durability of response to intralesional IL-2 therapy, including those with a cCR. This study presents a large observational cohort of patients with isolated ITM treated with intralesional IL-2 therapy at a tertiary care referral center. The goal of the study was to provide long-term outcome data for patients with a cCR to treatment, and to guide prognostication and follow-up recommendations.

Patients and Methods

Study Population and Intervention

Consecutive patients treated with intralesional IL-2 therapy from April 2009 to August 2019 at the Tom Baker Cancer Center in Calgary, Alberta, were included in this analysis. This included patients with ITM at the time of initial diagnosis and those with the development of ITM as recurrent disease after previous curative intent treatment. Baseline characteristics as well as follow-up data for all patients were obtained from the provincial electronic medical record. Histological features of the primary lesion were obtained from the final pathology report. Given the time frame of intervention, routine molecular testing for B-Raf proto-oncogene serine/threonine kinase (*BRAF*) alteration was only available for a subset of patients. All patients received at least 4 cycles (every 2 weeks) of IL-2 therapy. The total and per-lesion dose of intralesional IL-2 (5 million IU/mL) varied depending on the size and number of ITM. As the IL-2 was injected, a papule/plaque would be raised equal to the diameter of the lesion. cCR was defined as a complete clinical remission of all known in-transit disease for at least 3 months after the last cycle of IL-2. Clinical assessment was based on color and lesion palpation. Lesions no longer palpable after intralesional therapy were deemed to have had a complete response. If incomplete response was suspected, a biopsy and/or positron emission tomography (PET) was obtained to confirm the presence or absence of disease.

Outcomes

Time to recurrence was measured from the day cCR was noted in the medical record until first clinical or radiographic evidence of recurrence (eg, local, regional, and/or distant). Disease-free survival was defined as the time between cCR and recurrence of disease. Patients lost to follow-up or disease-free at the end of routine surveillance were censored from the last date of clinical assessment. In-transit location was defined as local if it occurred within the same extremity or region (eg, right forearm or torso) as the primary and distant if the in-transit disease occurred in a separate extremity or region. We defined the abscopal effect of intralesional IL-2 therapy as the clinical or radiographic resolution of non-injected sites of disease (eg., in-transit lesions or visceral metastases).[30] Adverse event grading was based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 developed by the Cancer Therapy Evaluation Program (CTEP).

Statistical Analysis

Fisher's exact test was used to test the association between sociodemographic and clinicopathologic variables and the risk of recurrence after cCR. All reported *P* values were 2-sided and considered statistically significant when less than .05. All statistical analyses were performed using SPSS (IBM Corp. Armonk, NY). In patients with a complete response to intralesional IL-2, disease-free survival was plotted using a Kaplan-Meier curve. Institutional review board approval was granted for this retrospective analysis prior to study initiation.

Results

Between April 2009 and August 2019, 65 patients were identified to have ITM and were treated with intralesional IL-2 therapy. cCR was identified in 44.6% (29/65) of patients. Our analysis focused on the cohort of patients who experienced a cCR ($n = 29$), which was confirmed in 17.2% (5/29) based on pre- and post-treatment changes on PET. The median age of the cohort was 69 years (range 18-91) and 55.2% (16/29) patients were female (44.8% male). The mean Breslow thickness of the primary lesion was 3.5 mm (range 0.6-9.0) and the median number of lesions at the first IL-2 injection was 9 (range 1-40). Only 1 patient with a cCR had both local and distant ITM and none had visceral metastases. Patient demographics and primary tumor characteristics are shown in Table 1. *BRAF* testing was performed on 51.7% (15/29) of patients, of whom 66.7% (10/15) were *BRAF* wildtype.

Table 1. Patient Demographics and Tumor Characteristics in Patients With a Complete Clinical Response to IL-2 Treatment (*N* = 29).

Characteristics	Median (range)
Age (years)	69 (18, 91)
Number of lesions	9 (1, 40)
	N (%)
Sex	
Female	16 (55.2)
Male	13 (44.8)
Breslow thickness	
Thin (3 mm or less)	14 (48.3)
Thick (>3 mm)	15 (51.7)
Primary location	
Head or neck	6 (20.7)
Lower extremity	14 (48.3)
Upper extremity	7 (24.1)
Trunk or back	2 (6.9)
Ulceration status	
Negative	16 (55.2)
Positive	12 (41.4)
Not available	1 (3.4)
Nodal status	
Negative	11 (37.9)
Positive	12 (41.4)
Not performed	6 (20.7)
Cutaneous metastasis location	
Local/regional	28 (96.6)
Local + distant[a]	1 (3.4)

[a]Defined as in-transit melanoma arising on a different anatomic location of the body to the site of the primary melanoma (eg, primary arising on the right upper extremity and in-transit disease noted on the trunk).

All patients with a cCR received at least 4 cycles of IL-2. Two patients demonstrated a robust partial response after 4 cycles and received additional intralesional therapy. One patient was given 4 additional cycles and the second patient was given 7 additional cycles before a cCR was achieved. The median total volume of IL-2 injected was 6.6 mL (IQR 4.3-8.0) per patient, with a median volume of 0.8 mL (IQR 0.4-1.5) per lesion. Sixty-two percent (18/29) of patients experienced an adverse drug-related event, all of which were grade 1. The most common adverse event was a grade 1 localized inflammation characterized by erythema and/or swelling. This occurred in 41.4% (12/29) of patients. Mild flu-like symptoms, including low-grade fever and myalgias were subjectively reported by the majority of patients 1-2 days after injection. One patient developed bacterial pneumonia while receiving intralesional therapy, but this was not thought to be treatment related. All patients were able to tolerate a full course (ie, 4 cycles) of intralesional IL-2 therapy.

In addition to the IL-2 protocol, 10.3% (3/29) received cytotoxic chemotherapy, 10.3% (3/29) received radiotherapy and 3.4% (1/29) received isolated limb perfusion before the start of IL-2. In total, 6.9% (2/29) received systemic immunotherapy before IL-2 therapy. One patient received single agent pembrolizumab and the other received ipilimumab followed by pembrolizumab after intolerable side effects to the CTLA-4 monoclonal antibody. This patient had a partial response to pembrolizumab and was rendered free-of disease after 4 cycles of intralesional IL-2 therapy. After IL-2 treatment, 10.3% (3/29) received systemic immunotherapy, with 1 patient having received systemic immunotherapy before and after the IL-2 treatment protocol.

An abscopal effect was noted in 20.7% (6/29) of patients with cCR. This subset of patients had extensive in-transit disease and only a fraction (ie, ≤20) of the total number of in-transit lesions were injected. Untreated lesions in these patients responded to intralesional IL-2 therapy, rendering the patients' disease free after treatment. None of these patients received any systemic therapy.

Disease-Free and Overall Survival

At a median follow-up of 27 months (IQR 16-59), the disease-free survival and overall survival for patients with cCR to intralesional IL-2 therapy was 65.5% and 69.0%, respectively. Disease-free survival is plotted in Figure 1. Of the patients who developed recurrence, 50% (5/10) presented with synchronous in-transit and distant metastases (Table 2). The median time to recurrence was 10.5 months (IQR 5.8-16.3). Of the patients with recurrence 60.0% (6/10) recurred in the first 12 months and 80.0% (8/10) recurred in the first 24 months. One patient developed a local recurrence of ITM at 61.9 months. On bivariate analysis, there were no sociodemographic, histopathologic, or therapy-related factors that were significantly associated with recurrence after cCR (Table 3).

Discussion

In this single-institution, retrospective review, we demonstrated that almost 50% of patients treated with intralesional IL-2 experienced a cCR. This is congruent with a growing body of literature that has evaluated the treatment's efficacy, including a systematic review that reported a rate of cCR of 49.6%.[22-27] Although the study by Hassan et al reported a lower cCR, some variability in response rate would be expected between different populations and heterogenous treatment protocols.[29] Our study included 7 patients treated with chemotherapy, radiotherapy, and/or immunotherapy prior to IL-2 administration, as well as 3 patients who were treated with systemic immunotherapy after IL-2 administration. Our sample size was insufficient to explore

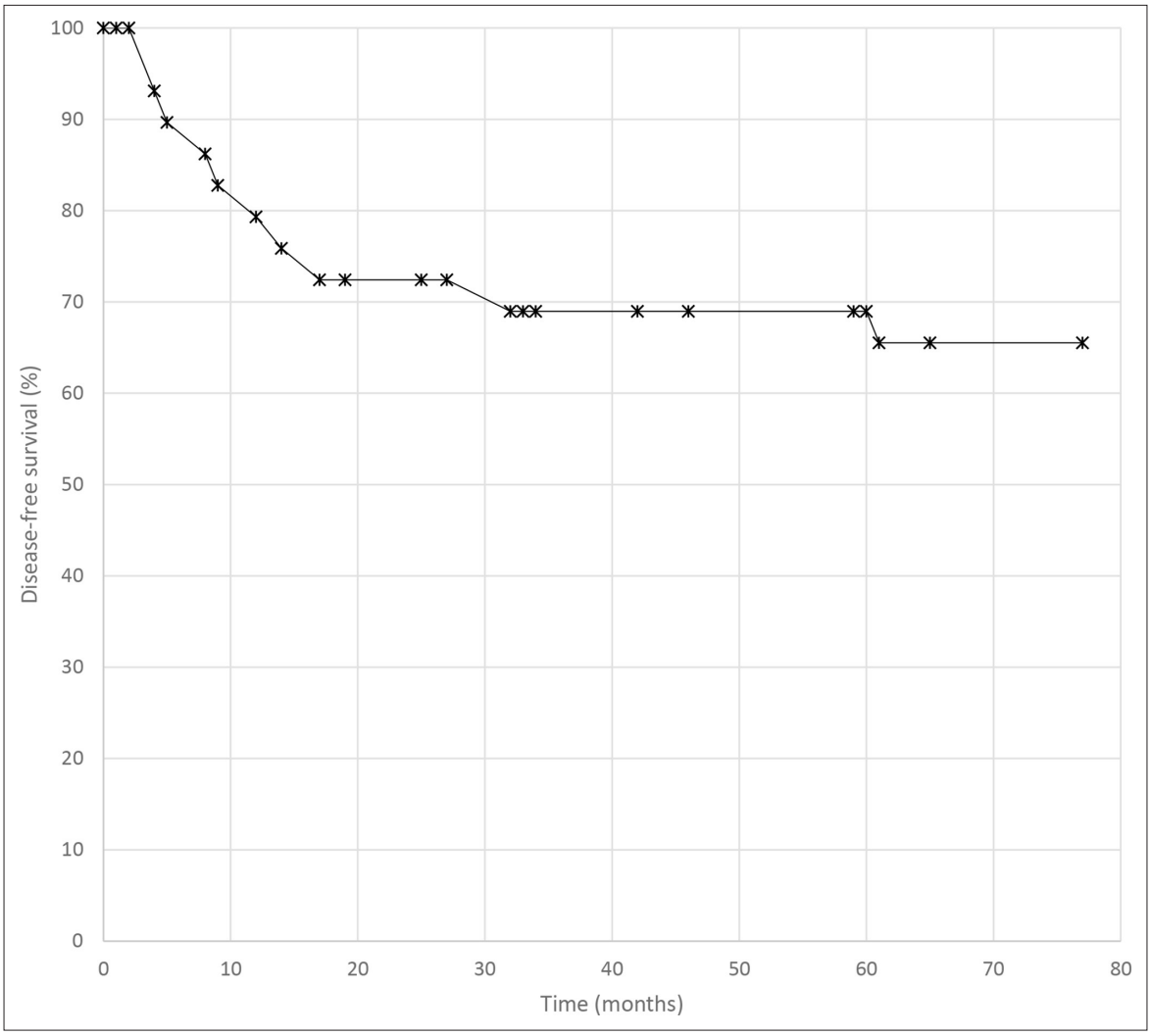

Figure 1. Kaplan-Meier curve of disease-free survival in patients with cCR to IL-2 therapy.

the impact the sequence of systemic therapy or nonintralesional locoregional intervention (eg, radiotherapy) with IL-2 therapy may have on outcomes. The use and timing of intralesional IL-2 in the era of widespread adoption of systemic immunotherapy is a fertile ground for future prospective research. Our analysis did not find any association between primary tumor characteristics, including *BRAF* status, patient risk factors, or receipt of additional therapies and recurrence after cCR. However, this should be considered within the context of our limited sample size. Our study represents the largest single institution series in the reported literature, with one of the longest median follow-ups available for evaluation of treatment durability. With a cCR to intralesional IL-2, over 60% of patients are free of clinical or radiographic disease with long-term follow-up and do not require additional therapeutic intervention. If patients do recur, the event is typically within 12 months of cCR. In our study, one patient developed a local in-transit recurrence after a 5-year disease-free interval. Although, the standard duration of follow-up after intralesional IL-2 therapy is 5 years, late recurrence

Table 2. Patterns of Recurrence After Complete Clinical Response (*N* = 29).

	N (%)[a]
Median time to recurrence (months)	10.5
Recurrence within ≤2 years	8 (27.6)
Recurrence >5 years	1 (3.4)
Location of recurrence	
Isolated in-transit	3 (10.3)
Distant visceral recurrence	2 (6.9)
In-transit and distant	5 (17.2)

Abbreviation: cCR, complete clinical response.
[a]Percentage compared to all cCR patients.

Table 3. Risk Factors and Risk of Recurrence After IL-2 Therapy in Patients With a cCR (*N* = 10).

Characteristics	*N* (%)	*P* value
Primary tumor		.45
Breslow thickness		
Thin (3 mm or less)	6 (42.9)	
Thick (>3 mm)	4 (26.7)	
Nodal status		.40
Negative	3 (27.3)	
Positive	6 (50.0)	
Not performed	1 (16.7)	
Ulceration status		.11
Negative	3 (18.8)	
Positive	6 (50.0)	
Not available	1 (100.0)	
Primary location		.66
Head or neck	1 (16.7)	
Lower extremity	6 (42.9)	
Upper extremity	2 (28.6)	
Trunk or back	1 (50.0)	
Lymphovascular infiltration		1.0
Present	0 (0.0)	
Absent	3 (17.6)	
Not available	7 (77.8)	
At start of IL-2		1.0
Age (years)		
Less than 70	5 (33.3)	
70 and above	5 (35.7)	
Sex		1.0
Female	6 (37.5)	
Male	4 (30.8)	
BRAF status		1.0
BRAF mutant	3 (60.0)	
BRAF wildtype	5 (50.0)	
Not tested	2 (14.3)	
Number of lesions		.71
<10	5 (31.3)	
≥10	5 (38.5)	
In-transit location		1.0
Local	10 (35.7)	
Distal	0 (0.0)	
Immunotherapy before, during, or after IL-2 therapy		.11
Yes	3 (75.0)	
No	7 (28.0)	

[a]Calculated using Fisher's 2-sided exact test.

is possible and this should be considered when counseling patients and primary care providers on long-term prognosis and the importance of life-long, routine skin examination.

Only a small subset of patients in our cohort received systemic therapy, which partially reflects the historical nature of the series. The current National Comprehensive Cancer Network guidelines recommend systemic therapy as the preferred first-line intervention for patients with unresectable ITM.[31] This is based on a growing body of evidence in support of the efficacy of immunotherapy (eg, ipilimumab) and targeted therapy (ie, dabrafenib/trametinib) in the treatment of unresectable melanoma.[32] However, there is a paucity of data specific to the efficacy of immunotherapy and targeted therapy in the management of isolated ITM, with current recommendations based largely on extrapolated findings from patients with unresectable nodal and distant metastases. The current practice at our center reflects the robust complete response rate and low toxicity profile of intralesional IL-2 therapy. First-line therapy for patients with isolated ITM consists of surgical resection with negative margins. For patients with isolated unresectable ITM, intralesional IL-2 therapy is employed as a first-line strategy. The use of systemic immunotherapy is typically reserved for patients who fail intralesional treatment or who have concomitant or synchronous nodal or distant metastases.

Talimogene laherparepvec (TVEC) is also supported by level I evidence and is considered a first-line option for resectable and unresectable ITM. Compared to granulocyte-macrophage colony-stimulating factor, TVEC was associated with a complete response rate of 35.2% in patients with stage IIIB/C unresectable ITM. Of those patients, 72% (95% CI [57, 83]) remained disease-free at 36 months.[33] Unfortunately, TVEC is not currently approved for use in ITM by Health Canada. Our findings suggest that intralesional IL-2 therapy is associated with a similar, if not superior, treatment response and durability. Prospective trials comparing systemic therapy versus intralesional TVEC and IL-2 for unresectable ITM would provide meaningful insight to clinicians and policymakers. Evaluation of intralesional IL-2 in combination with systemic therapy and the use of neoadjuvant IL-2 prior to resection of isolated ITM are additional areas of study.

There are several limitations of this study. This was a single-institution, retrospective review of consecutive patients and therefore there may be an element of selection bias that limits the generalizability of the findings. Despite one of the longest institutional experiences with intralesional IL-2 for ITM, our sample size is small, which limits the power to detect meaningful differences between variables. Given the historical time frame and the relatively recent introduction of routine *BRAF* testing at our center, these data were not available for many patients in the series. An important limitation of this study is the subjective definition of a complete response, which we defined clinically in this analysis. In our early institutional experience, cCR was verified by biopsy and histopathology. However, this is no longer routinely performed as cCR

was felt to reliably predict pathological complete response. Clinical assessment of treatment response is now primary used to guide additional therapy or active surveillance. A larger cohort of patients with resectable disease that are treated with intralesional IL-2 followed by complete resection for molecular and histopathologic examination would provide useful insight into the tumor microenvironment and an opportunity to formally correlate clinical versus pathologic response. This should be considered in future prospective studies examining the efficacy of intralesional IL-2 for ITM.

Immunotherapy has dramatically changed the management of locally advanced and metastatic melanoma over the last 10 years. There is a paucity of data on the use of intralesional IL-2 for the treatment of ITM outside of Canada, including prognosis for patients who experience a cCR. In this retrospective review, we demonstrated that 4 cycles of intralesional IL-2 is associated with a high rate of cCR that is durable in the majority of patients. For this subset of patients, the prognosis is excellent and 5-year follow up will detect the majority of recurrences.

Acknowledgments

We acknowledge the work of librarian Siu Hong Yu, for his assistance with the initial search, including identifying/extracting studies from databases and uploading them to Covidence. We are also grateful for the feedback provided by members of the Canadian Dermatology Association Sun Safety Working Group and Canadian Cancer Society on the initial results of this systematic review.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by funding from the Canadian Cancer Society and the Canadian Dermatology Association.

ORCID iD

Sami Khoury https://orcid.org/0000-0002-7174-116X

References

1. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2019. Toronto, ON: Canadian Cancer Society; 2019. Accessed May 5, 2020. cancer.ca/Canadian-Cancer-Statistics-2019-EN
2. Borgstein PJ, Meijer S, van Diest PJ. Are locoregional cutaneous metastases in melanoma predictable? *Ann Surg Oncol*. 1999;6(3):315-321. doi:10.1007/s10434-999-0315-x
3. Pawlik TM, Ross MI, Johnson MM, et al. Predictors and natural history of in-transit melanoma after sentinel lymphadenectomy. *Ann Surg Oncol*. 2005;12(8):587-596. doi:10.1245/ASO.2005.05.025
4. Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206. doi:10.1200/JCO.2009.23.4799
5. Jiang BS, Speicher PJ, Thomas S, Mosca PJ, Abernethy AP, Tyler DS. Quality of life after isolated limb infusion for in-transit melanoma of the extremity. *Ann Surg Oncol*. 2015;22(5):1694-1700. doi:10.1245/s10434-014-3979-9
6. Bagge A-SL, Ben-Shabat I, Belgrano V, Olofsson Bagge R. Health-related quality of life for patients who have in-transit melanoma metastases treated with isolated limb perfusion. *Ann Surg Oncol*. 2016;23(6):2062-2069. doi:10.1245/s10434-016-5103-9
7. Read RL, Haydu L, Saw RPM, et al. In-transit melanoma metastases: incidence, prognosis, and the role of lymphadenectomy. *Ann Surg Oncol*. 2015;22(2):475-481. doi:10.1245/s10434-014-4100-0
8. Strauss A, Dritschilo A, Nathanson L, Piro AJ. Radiation therapy of malignant melanomas: an evaluation of clinically used fractionation schemes. *Cancer*. 1981;47(6):1262-1266. doi:10.1002/1097-0142(19810315)47:6<1262::AID-CNCR2820470606>3.0.CO;2-H
9. Atallah E, Flaherty L. Treatment of metastatic malignant melanoma. *Curr Treat Options Oncol*. 2005;6(3):185-193. doi:10.1007/s11864-005-0002-5
10. Algazi AP, Soon CW, Daud AI. Treatment of cutaneous melanoma: current approaches and future prospects. *Cancer Manag Res*. 2010;2:197-211. doi:10.2147/CMR.S6073
11. Moreno-Ramirez D, de la Cruz-Merino L, Ferrandiz L, Villegas-Portero R, Nieto-Garcia A. Isolated limb perfusion for malignant melanoma: systematic review on effectiveness and safety. *Oncologist*. 2010;15(4):416-427. doi:10.1634/theoncologist.2009-0325
12. Mian R, Henderson MA, Speakman D, Finkelde D, Ainslie J, McKenzie A. Isolated limb infusion for melanoma: a simple alternative to isolated limb perfusion. *Can J Surg*. 2001;44(3):189-192.
13. Bonenkamp JJ, Thompson JF, de Wilt JH, Doubrovsky A, de Faria Lima R, Kam PCA. Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. *Eur J Surg Oncol*. 2004;30(10):1107-1112. doi:10.1016/j.ejso.2004.07.028
14. Beasley GM, Caudle A, Petersen RP, et al. A multi-institutional experience of isolated limb infusion: defining response and toxicity in the US. *J Am Coll Surg*. 2009;208(5):706-715. doi:10.1016/j.jamcollsurg.2008.12.019
15. Beasley GM, Petersen RP, Yoo J, et al. Isolated limb infusion for in-transit malignant melanoma of the extremity: a well-tolerated but less effective alternative to

hyperthermic isolated limb perfusion. *Ann Surg Oncol*. 2008;15(8):2195-2205. doi:10.1245/s10434-008-9988-9

16. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381(16):1535-1546. doi:10.1056/NEJMoa1910836
17. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol*. 2019;20(9):1239-1251. doi:10.1016/S1470-2045(19)30388-2
18. Ascierto PA, Long GV, Robert C, et al. Survival outcomes in patients with previously untreated *BRAF* wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncol*. 2019;5(2):187-194. doi:10.1001/jamaoncol.2018.4514
19. Flaherty KT, Infante JR, Daud A, et al. Combined *BRAF* and MEK inhibition in melanoma with *BRAF* V600 mutations. *N Engl J Med*. 2012;367(18):1694-1703. doi:10.1056/NEJMoa1210093
20. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced *BRAF*(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016;17(9):1248-1260. doi:10.1016/S1470-2045(16)30122-X
21. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with *BRAF*-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(10):1315-1327. doi:10.1016/S1470-2045(18)30497-2
22. Tarhini AA, Agarwala SS. Interleukin-2 for the treatment of melanoma. *Curr Opin Investig Drugs*. 2005;6(12):1234-1239.
23. Eklund JW, Kuzel TM. A review of recent findings involving interleukin-2-based cancer therapy. *Curr Opin Oncol*. 2004;16(6):542-546. doi:10.1097/01.cco.0000142070.45097.68
24. Boyd KU, Wehrli BM, Temple CLF. Intra-lesional interleukin-2 for the treatment of in-transit melanoma. *J Surg Oncol*. 2011;104(7):711-717. doi:10.1002/jso.21968
25. Ridolfi L, Ridolfi R, Ascari-Raccagni A, et al. Intralesional granulocyte-monocyte colony-stimulating factor followed by subcutaneous interleukin-2 in metastatic melanoma: a pilot study in elderly patients. *J Eur Acad Dermatol Venereol*. 2001;15(3):218-223. doi:10.1046/j.1468-3083.2001.00254.x
26. Radny P, Caroli UM, Bauer J, et al. Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. *Br J Cancer*. 2003;89(9):1620-1626. doi:10.1038/sj.bjc.6601320
27. Dehesa LA, Vilar-Alejo J, Valerón-Almazán P, Carretero G. Experience in the treatment of cutaneous in-transit melanoma metastases and satellitosis with intralesional interleukin-2. *Actas Dermosifiliogr*. 2009;100(7):571-585.
28. Weide B, Derhovanessian E, Pflugfelder A, et al. High response rate after intratumoral treatment with interleukin-2: results from a phase 2 study in 51 patients with metastasized melanoma. *Cancer*. 2010;116(17):4139-4146. doi:10.1002/cncr.25156
29. Hassan S, Petrella TM, Zhang T, et al. Pathologic complete response to intralesional interleukin-2 therapy associated with improved survival in melanoma patients with in-transit disease. *Ann Surg Oncol*. 2015;22(6):1950-1958. doi:10.1245/s10434-014-4199-z
30. Read T, Lonne M, Sparks DS, et al. A systematic review and meta-analysis of locoregional treatments for in-transit melanoma. *J Surg Oncol*. 2019;119(7):887-896. doi:10.1002/jso.25400
31. National Comprehensive Cancer Network. Cutaneous Melanoma. (Version 3.2020). 15 May 2020. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
32. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10):1020-1030. doi:10.1200/JCO.2013.53.0105
33. Andtbacka RHI, Collichio F, Harrington KJ, et al. Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III-IV melanoma. *J Immunother Cancer*. 2019;7(1):145. doi:10.1186/s40425-019-0623-z