EDITORIAL

Standardizing Regional Therapy: Developing a Consensus on Optimal Utilization of Regional Chemotherapy Treatments in Melanoma

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In this issue of *Annals of Surgical Oncology*, Huismans et al. describe their extensive experience with isolated limb infusion (ILI) in the treatment of 185 patients with in-transit melanoma over a 15-year period (1992–2007).¹ The group initially described and introduced the technique of ILI in the early 1990s as a minimally invasive alternative to hyperthermic isolated limb perfusion (HILP) whereby placement of percutaneously placed catheters allows delivery of regional chemotherapy (usually melphalan plus dactinomycin) to an isolated limb.² Because of the safety and efficacy of the treatment as well as disappointing results of a multicenter HILP trial, ILI is now utilized at several major U.S. centers and has been demonstrated to be a well-tolerated treatment alternative for patients with advanced extremity melanoma.^{3–7}

As with any new technique, evidence- and observation-based modifications have been applied to ILI with the goal of maximizing response in conjunction with minimizing toxicity from the procedure. In this study, the authors compare outcomes after initial ILI from their early experience (1992–1999) in 94 patients to their subsequent, or late, experience in 91 patients after several modifications were incorporated into the ILI protocol (2000–2007). The authors conclude that the study's results support the use of the modifications, although no significant changes in response or toxicity were seen with the modifications. Despite the lack of change, the underlying response rates over the entire period still support a role for ILI as a safe

treatment in the armamentarium of therapeutic options for patients with advanced extremity melanoma.

There are many aspects of ILI in need of standardization, as is shown in Table 1. Some of these issues revolve around the following: optimal method of drug dosing, technical aspects of performing the ILI procedure, and how best to define toxicity and response after the procedure. Currently, theoretical evidence suggests that the hypoxia and acidosis of ILI may be beneficial by optimizing how melphalan is metabolized and leads to an antitumor response.⁸ Hyperthermia is also thought to improve clinical response induced by alkylating agents like melphalan, but within a narrow therapeutic window such that excessive heat may increase the toxicity of melphalan to normal tissue.⁹ Finally, papaverine is thought to improve response by maximizing subcutaneous vasodilation and thereby improving melphalan delivery to the tumor, as was suggested in a U.S. multicenter analysis.⁶

In the current study, modifications to the ILI protocol included increasing drug circulation time from 20 to 30 min, the use of a hot air blanket cocoon and a radiant overhead heater to achieve more efficient limb warming, use of a higher melphalan dose (5–7 mg/l for early vs. 7–8 mg/l for late), and routine use of papaverine. These changes did result in some not unexpected measurable differences between the early and late groups, including median difference in P_{CO_2} in the limb blood between the start and the end of the procedure, which increased from 8.8 to 14.7 mm Hg ($P < 0.0001$), and an increase in peak subcutaneous temperature (37.7 vs. 38.7) ($P < 0.0001$). These changes, however, did not appear to significantly affect overall tumor response or limb toxicity.

There was no significant difference between complete or partial response (PR) in the early versus late group with a trend toward a lower complete response (CR) rate (36%, 38

TABLE 1 Aspects of ILI in need of standardization

	Components of ILI treatment	Current consensus/controversy
WHO World Health Organization, <i>RECIST</i> Response Evaluation Criteria in Solid Tumors, <i>CTCAE</i> Common Terminology Criteria for Adverse Events	Drug dosing	Melphalan: 7.5 mg/l leg; 10 mg/l arm; D'Actinomycin 75 µg/l leg; 100 µg/l arm
	Correction of drug dosing for IBW	Controversial
	Duration of therapy	30 min
	Duration of ischemia	60–70 min
	Use of papaverine	60 mg
	Method of hyperthermia	Dry air or warming blanket
	Method of circulation	Pump vs. hand-operated 3-way stopcock
	Defining toxicity	Wieberdink vs. CTACE v3/4
	Defining response	WHO vs. RECIST, including nonevaluable patients in calculating response rates
	Defining durability	Regional progression-free survival

of 94) in the late group versus the early group (CR 40%, 36 of 91).

There appear to be slight differences in the response rates reported by the Melanoma Institute Australia (Formerly Sydney Melanoma Institute) (MIA) and U.S. centers. The CR rate between the MIA groups (40% CR rate in early group and 36% CR rate in late group) was higher than the recent U.S. study of ILI with a CR rate of 31% in 128 patients from 8 centers.⁶ Although some of the variation simply relates to whether nonevaluable patients are included in the denominator of the reported results, some variation also appears to reflect differences between how the ILI procedure is performed or monitored. Response in the United States is determined at one time point 3 months after ILI, while response at MIA is determined by two observations not less than 4 weeks apart with a previously reported median time between ILI and best response of 1.4 months (range 1–84 weeks).¹⁰ In some cases, disease may show marked responses 3–6 weeks after ILI only to progress by 3 months, a response pattern that may further explain discrepancies in response rates between centers.

The discrepancy between PR in the present study (45% in both early and late groups) and our recent report (12%) may also be exacerbated by our practice of correcting the melphalan dose for ideal body weight (IBW). This practice has been demonstrated to reduce toxicity while not altering CR rates.⁶ Correcting for IBW did lower overall response because it was associated with decreased PR rates.^{4,6} Notably, the mean body mass index of patients in the recent Duke study was 29 (range 20–48), while the mean body mass index in the early MIA group was 26.0 (range 23.3–28.8) and late group was 24.9 (range 22.7–27.8). Thus, correcting the melphalan dose for IBW may not be as important in reducing toxicity in the patient population treated at MIA compared to the U.S. population and may have led to the higher PR rates seen in the MIA-treated population. Consensus on melphalan dosing and response criteria would ultimately be essential to

make valid comparisons between centers performing ILI. Other components of the ILI procedure appear to have more expert consensus, although there is a lack of scientific evidence confirming their importance. These components include: including a 30-min circulation of melphalan, routine use of papaverine, and achievement of hyperthermia (median peak 38.7°C).

In the larger context of optimal treatment for patients with unresectable in-transit melanoma, the current study supports a significant role for ILI. The continued work of the MIA and U.S. centers would argue that ILI might be the best initial therapy for patients with in-transit melanoma, given its low toxicity and approximate 30 to 40% CR rate. Our recent review and data from MIA suggest that HILP does have higher response rates than ILI.^{3,4,11,12} However, although the spectrum of toxicity was similar for ILI and HILP, the likelihood of rare catastrophic complication of limb loss was greater with HILP (2 of 77) than ILI (0 of 148). Additionally, there was no significant difference between duration of CR and no difference in time to progression out of field between ILI and HILP in a recent overview of the Duke regional therapy experience.¹¹ This study found that overall survival for all treated (whether they received HILP or ILI) was not different between treated groups differs between techniques, while those who achieve a CR after either therapy seem to have a markedly improved prognosis.¹¹ As such, we have opted for utilization of ILI as our initial regional therapy in patients with clinically negative lymph nodes. In patients who have clinically enlarged lymph nodes, we generally perform an HILP initially because this allows for dissection of the lymph node basin in which the HILP catheters are placed. Patients whose disease fails to respond to ILI can then be treated with HILP, repeat ILI, or protocol-based ILI.

Moving beyond melphalan-based regional therapy for all patients with in-transit disease will be important in the evolution of this therapeutic modality. Regional chemotherapy

treatments in the form of ILI or HILP can serve as a pathway for the personalization of therapy for patients with advanced melanoma. The regional setting of in-transit disease is a unique clinical opportunity for surgical oncologists to learn how to develop novel therapeutic strategies with potential for systemic applications in a disease with few effective treatment options for advanced stages. Drug pharmacokinetic analysis in a closed-circuit system of regional therapy, in ILI or HILP, and easily obtained tissue acquisition both before and after treatment to allow correlation of drug resistance parameters or targeted therapy protein expression can help us make tremendous strides in our understanding of how to optimize drug delivery and how to utilize novel drugs. The combination of analyzing procedural and patient variables with correlative studies that can assess traditional drug resistance mechanisms, dysregulated pathways, and changes induced by targeted therapies may ultimately serve to maximize responses to regional chemotherapy treatments. Examples of how the regional setting has been and is currently being utilized in the context of both ILI and HILP to further our understanding of novel therapeutics are provided in Table 2, which includes the work of multiple institutions.

To date, two phase I trials and one phase II trial combining a systemic targeted agent with melphalan via ILI have been completed.^{13–15} Correlative studies including pharmacokinetic analysis, immunohistochemical staining of tumor tissue, protein expression, and gene expression analysis were completed in nearly all enrolled patients. ADH-1, an *N*-cadherin antagonist, was provided systemically to 45 patients before and after ILI with melphalan in a phase II prospective multicenter trial. Results demonstrated an

improved CR rate at 3 months (38%, 17 of 45) compared to ILI with melphalan alone (CR rate 29%, 19 of 66), although there was no difference in regional time to progression between the groups.¹⁵ Although this trial was exploratory and limited by sample size, gene expression data supported ADH-1-induced changes in the expression of genes that may ultimately contribute to an understanding of the mechanism of action of ADH-1.¹⁵ Correlative studies from a phase I trial of systemic sorafenib ($n = 20$), a B-raf kinase inhibitor, identified 35 proteins which exhibited marked dose-dependent expression in response to sorafenib. Surprisingly, B-raf signaling pathways were not inhibited and an increase in the local toxicity of ILI-M plus systemic sorafenib was not explained by pharmacokinetic analysis. Although these preliminary studies in heavily pretreated patients failed to demonstrate a significant improvement in CR rates compared to ILI with melphalan alone, they serve as examples for the utilization of the regional chemotherapy model in the development of novel therapies that may ultimately improve the efficacy of treatment for patients with advanced extremity melanoma and potentially impact the treatment of systemic melanoma. Another approach using a melphalan-based regional therapy is to target immunologic molecules in hopes of generating a systemic immunologic benefit from the regional chemotherapy treatment. This is the rationale behind an institutional review board (IRB)-approved regional therapy trial soon to be open at Memorial Sloan Kettering Cancer Center that incorporates ipilimumab treatment after a melphalan-based ILI that is currently under IRB review.

Finally, although melphalan has been the drug of choice for regional chemotherapy, the IV formulation of

TABLE 2 How the regional setting has been and is currently being utilized in the context of ILI and HILP

Chemotherapeutic agent	Target	Targeted agent	Preclinical proof of concept	Phase I	Phase II	Phase III
Melphalan			Yes ^{18,19}		Complete ⁴	Complete ⁶
Melphalan	T cells	INF- γ	Yes ²⁰	Complete ²¹		
Melphalan	Endothelium	TNF- α	Yes ²⁰	Complete ²²		Complete ⁵
Melphalan	GSH	BSO	Yes ²³	IRB pending		
Melphalan	<i>N</i> -cadherin	ADH-1	Yes ²⁴	Complete ¹⁴	Complete ¹⁵	
Melphalan	B-raf	Sorafenib	Yes ²⁵	Complete ¹³		
Melphalan	VEGF	Avastin	Yes ²⁶	IRB pending		
Melphalan	Src	Dasatinib	Yes ^b	IRB pending		
Melphalan	GSTP1	PA23	In progress			
Melphalan	CTLA-4	Ipilimumab	Yes ²⁷	Open		
Temozolomide			Yes ¹⁶	Open		
Temozolomide	MGMT	O6BG	Yes ²⁸			
Temozolomide	PARP	Inotek-1001	Yes ²⁹			
Temozolomide	B-raf	Sorafenib	Yes ²⁵			
Temozolomide	GSTP1	PA23	Pending			

^a Mary Sue Brady, Memorial Sloan-Kettering Cancer Center, personal communication

^b Unpublished data from laboratory of Dr. Douglas Tyler

temozolomide (TMZ) has shown tremendous promise as a regional chemotherapy agent in preclinical models. TMZ is a DNA alkylating agent that is spontaneously converted to the active metabolite MTIC. In an animal model, regional infusion of TMZ was more effective than systemic therapy and frequently more effective than melphalan via regional infusion especially in tumors with low O6-alkylguanine-DNA alkyltransferase (AGT) activity.¹⁶ Another factor that makes ILI with TMZ a potentially promising approach is the ability to more accurately predict response. A strong correlation between the levels of AGT activity and percentage increase in tumor volume was noted for tumors treated with temozolomide; xenografts with low AGT activity showed much higher levels of response to regional TMZ.¹⁷ Regional therapy with TMZ may ultimately prove to be more effective than melphalan in certain subsets of tumors. Currently, a multicenter phase I dose escalation study of ILI with TMZ is open and accruing patients. Correlative studies including AGT expression, tumor gene expression, pharmacokinetic analysis, and immunologic monitoring to determine whether regional chemotherapy induces a systemic immune response are all part of this attempt to validate the preclinical work.

Regional chemotherapy treatments including both ILI and HILP continue to be important in the treatment of patients with advanced extremity melanoma. The standardization of patient and procedural variables that may affect response and toxicity as studied by Huisman et al. in combination with pharmacokinetic analysis and analysis of tumor tissue may ultimately provide information to optimize the therapeutic index of regional chemotherapy. Lessons learned from novel regional chemotherapy trials have the potential to greatly affect the treatment of advanced extremity melanoma and may also ultimately contribute to developing novel treatment strategies for patients with systemic melanoma.

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REFERENCES

- Huisman AM, Kroon HM, Kam PCA, Thompson JF. Does increased experience with isolated limb infusion for advanced limb melanoma influence outcome? *Ann Surg Oncol*, in press.
- Thompson JF, Waugh RC, Saw RPM, Kam PCA. Isolated limb infusion with melphalan for recurrent limb melanoma: a simple alternative to isolated limb perfusion. *Reg Cancer Treat*. 1994; 7:188–92.
- Kroon HM, Moncrieff M, Kam PCA, et al. Outcomes following isolated limb infusion for melanoma: a 14-year experience. *Ann Surg Oncol*. 2008;15:3003–13.
- 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;15:2195–205.
- Cornett WR, McCall LM, Petersen RP, et al. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American College of Surgeons Oncology Group Trial Z0020. *J Clin Oncol*. 2006;24:4196–201.
- Beasley GM, Caudle A, Petersein RP, et al. A multi-institutional experience of isolated limb infusion: defining response and toxicity in the US. *J Am Coll Surg*. 2009;208:706–15.
- Santillan AA, Delma KA, Beasley GM, et al. Predictive factors of regional toxicity and serum creatine phosphokinase levels after isolated limb infusion for melanoma: a multi-institutional analysis. *Ann Surg Oncol*. 2009;16:2570–8.
- Lindner P, Doubrovsky AD, Kam PCA, Thompson JF. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. *Ann Surg Oncol*. 2002;9:127–36.
- Storm FK, Morton DL. Value of therapeutic hyperthermic limb perfusion in advanced recurrent melanoma of the lower extremity. *Am J Surg*. 1985;15:32–35.
- Thompson JF, Lai DT, Inguar C, Kam PC. Maximizing efficacy and minimizing toxicity in isolated limb perfusion for melanoma. *Melanoma Res*. 1994;S1:45–50.
- Raymond AK, Beasley GM, Broadwater G, et al. Current trends in regional therapy for melanoma: lessons learned from 225 regional chemotherapy treatments between 1995 and 2010 at a single institution. Presented at the annual meeting of the Southern Surgical Association. December 2010. West Palm Beach, FL.
- Sanki A, Kam PC, Thompson JF. Long-term results of hyperthermic, isolated limb perfusion for melanoma: a reflection of tumor biology. *Ann Surg*. 2007;245:591–6.
- McMahon N, Beasley GM, Sanders G, et al. A phase I study of systemic sorafenib in combination with isolated limb infusion with melphalan (ILI-M) in patients (pts) with locally advanced in-transit melanoma (abstract). *J Clin Oncol*. 2009;27(15 Suppl):9065.
- Beasley GM, McMahon N, Sanders G, et al. A phase I study of systemic ADH-1 in combination with melphalan via isolated limb infusion in patients with locally advanced in-transit malignant melanoma. *Cancer*. 2009;115:4766–74.
- Beasley GM, Riboh J, Augustine CK, et al. Prospective multicenter phase II trial of systemic ADH-1 in combination with melphalan via isolated limb infusion in patients with advanced extremity melanoma. *J Clin Oncol*. 2011. doi:10.1200/JCO.2010.32.1224.
- Ueno T, Ko SH, Grubbs E, et al. Temozolomide is a novel regional infusion agent for the treatment of advanced extremity melanoma. *Am J Surg*. 2004;188:532–7.
- Yoshimoto Y, Augustine CK, Yoo J, et al. Defining regional infusion treatment strategies for extremity melanoma: comparative analysis of melphalan and temozolomide as regional chemotherapeutic agents. *Mol Cancer Ther*. 2007;6:1492–500.
- Grubbs EG, Abdel-Wahab O, Cheng TY, et al. In-transit melanoma: the role of alkylating-agent resistance in regional therapy. *J Am Coll Surg*. 2004;199:419–27.
- Abdel-Wahab OI, Grubbs E, Viglianti B, et al. The role of hyperthermia in regional alkylating agent chemotherapy. *Clin Cancer Res*. 2004;10:5919–29.
- Parmiani G, Rivoltini L. Biologic agents as modifiers of chemotherapeutic effects. *Curr Opin Oncol*. 1991;3:1078–86.
- Fraker DL, Alexander HR, Andrich M, et al. Treatment of patients with melanoma of the extremity using hyperthermic isolated limb perfusion with melphalan, tumor necrosis factor, and interferon-gamma: results of a tumor necrosis factor dose-escalation study. *J Clin Oncol*. 1996;14:479–89.
- Grunhagen DJ, Brunstein F, Graveland WJ, et al. One hundred consecutive isolated limb perfusions with TNF-alpha and

- melpahlan in melanoma patients with multiple in-transit metastases. *Ann Surg.* 2004;240:939–47.
23. Grubbs EG, Ueno T, Abdel-Wahab O, et al. Modulation of resistance to regional chemotherapy in the extremity melanoma model. *Surgery.* 2004;136:210–8.
 24. Augustine CK, Yoshimoto Y, Gupta M et al. Targeting *N*-cadherin enhances antitumor activity of cytotoxic therapies in melanoma treatment. *Cancer Res.* 2008;68:3777–84.
 25. Augustine CK, Toshimitsu H, Jung SH, et al. Sorafenib, a multikinase inhibitor, enhances the response of melanoma to regional chemotherapy. *Mol Cancer Ther.* 2010;9:2090–101.
 26. Padussis JC, Augustine CK, Tyler DS. Bevacizumab augmentation or regional melphalan in a melanoma xenograft model. *Ann Surg Oncol.* 2010;17S:S108.
 27. O'Day SJ, Harnid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. *Cancer.* 2007;110:2614–27.
 28. Ueno T, Ko SH, Grubbs E. A novel regional strategy for extremity melanoma using modulation of chemotherapy resistance: intra-arterial temozolomide plus systemic O6-benzylguanine. *Mol Cancer Ther.* 2006;5:732–8.
 29. Toshimitsu H, Yoshimoto Y, Augustine CK. Inhibition of poly-{ADP-ribose} polymerase activity enhances the effect of chemotherapy in an animal model of regional therapy for the treatment of advanced extremity melanoma. *Ann Surg Oncol.* 2010;17:2247–54.