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ORIGINAL REPORT

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

Wendy R. Cornett, Linda M. McCall, Rebecca P. Petersen, Merrick I. Ross, Henry A. Briele, R. Dirk Noyes, Jeffrey J. Sussman, William G. Kraybill, John M. Kane III, H. Richard Alexander, Jeffrey E. Lee, Paul F. Mansfield, James F. Pingpank, David J. Winchester, Richard L. White Jr, Vijaya Chadaram, James E. Herndon II, Douglas L. Fraker, and Douglas S. Tyler

From The University of Texas M.D. Anderson Cancer Center, Houston, TX; University of Pennsylvania, Philadelphia, PA; Duke University Medical Center, Durham; Carolinas Medical Center, Charlotte, NC; University of Illinois at Chicago, Chicago; Evanston Northwestern Healthcare, Evanston, IL; Latter Day Saints Hospital, Salt Lake City, UT; University of Cincinnati Medical Center, Cincinnati, OH; Roswell Park Cancer Institute, Buffalo, NY; Warren Grant Magnuson Clinical Center, and National Institutes of Health, Bethesda, MD.

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Address reprint requests to Douglas S. Tyler, MD, Duke University Medical Center, Box 3118, Durham, NC 27710; e-mail: tyler002@acpub.duke.edu.

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ABSTRACT

Purpose
To determine in a randomized prospective multi-institutional trial whether the addition of tumor necrosis factor alpha (TNF-α) to a melphalan-based hyperthermic isolated limb perfusion (HILP) treatment would improve the complete response rate for locally advanced extremity melanoma.

Patients and Methods
Patients with locally advanced extremity melanoma were randomly assigned to receive melphalan or melphalan plus TNF-α during standard HILP. Patient randomization was stratified according to disease/treatment status and regional nodal disease status.

Results
The intervention was completed in 124 patients of the 133 enrolled. Grade 4 adverse events were observed in 14 (12%) of 129 patients, with three (4%) of 64 in the melphalan-alone arm and 11 (16%) of 65 in the melphalan-plus-TNF-α arm ($P = .0436$). There were two toxicity-related lower extremity amputations in the melphalan-plus-TNF-α arm, and one disease progression–related upper extremity amputation in the melphalan-alone arm. There was no treatment-related mortality in either arm of the study. One hundred sixteen patients were assessable at 3 months postoperatively. Sixty-four percent of patients (36 of 58) in the melphalan-alone arm and 69% of patients (40 of 58) in the melphalan-plus-TNF-α arm showed a response to treatment at 3 months, with a complete response rate of 25% (14 of 58 patients) in the melphalan-alone arm and 26% (15 of 58 patients) in the melphalan-plus-TNF-α arm ($P = .435$ and $P = .890$, respectively).

Conclusion
In locally advanced extremity melanoma treated with HILP, the addition of TNF-α to melphalan did not demonstrate a significant enhancement of short-term response rates over melphalan alone by the 3-month follow-up, and TNF-α plus melphalan was associated with a higher complication rate.

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INTRODUCTION

Melanoma is increasing in incidence, with 55,000 new cases expected in 2006. In 2% to 10% of extremity melanoma cases, recurrence is in a locoregional fashion, remaining confined to the extremity in a pattern called in-transit disease or satellitosis.[1,2] Although regional recurrences often precede metastatic disease, it is thought that aggressive locoregional therapy may improve disease-free and overall survival. Radical surgical treatment of in-transit metastases by amputation has resulted in long-term cure rates of 21% to 33%,[3,4] suggesting that some patients with locally advanced melanoma may have disease that is truly confined to the extremity. Because melanoma is typically resistant to systemic chemotherapy, interest has focused on high-dose regional chemotherapy using melphalan to achieve limb-sparing regional disease control. Isolated limb perfusion (ILP) was developed as a limb-sparing regional treatment modality for melanoma,[5] with the hypothesized benefit of increasing local concentrations of chemotherapy to the primary site while limiting systemic toxicity. With appropriate surgical techniques, leakage from the isolated perfusion circuit can be limited

to 5% or less.[6] Hyperthermia was added to ILP in 1969 based on in vitro data showing synergistic cytotoxicity of alkylating agents and heat.[7]

Initial series of ILP with melphalan as a single agent at normothermic temperatures have overall response rates ranging from 30% to 60% with half of the responses being complete responses (CR).[8] In contrast, systemic chemotherapy typically results in a 10% to 20% partial response rate with rare CRs.[9] The combination of hyperthermia to melphalan perfusion appears to increase overall response rates to approximately 80% to 90% and CR rates to 25% to 60%.[10-15]

More recently, the addition of tumor necrosis factor alpha (TNF-α) to melphalan, as part of the hyperthermic isolated limb perfusion (HILP) treatment to improve the durability and frequency of CRs, has been explored. Several small trials have suggested that the addition of TNF-α to the melphalan-based HILP treatment achieves a higher CR rate and increased response durability.[16-18] A more recent phase III trial by Fraker et al[19] randomly assigned patients to receive melphalan alone or the melphalan plus interferon (IFN) plus TNF-α HILP regimen, in which the CR rates were 58% and 72%, respectively. These encouraging results served as the impetus for the American College of Surgeons Oncology Group (ACOSOG) Melanoma Organ Site Committee to propose the Z0020 trial. Although promising, these studies are limited by small sample size and differences in baseline disease burden. The ACOSOG Z0020 randomized trial was conducted on patients with advanced local extremity melanoma to determine whether treatment with the melphalan plus TNF-α HILP regimen has a higher CR rate compared with treatment with the melphalan-alone HILP regimen. Secondary objectives evaluated the two treatment strategies with regard to toxicity, local recurrence–free survival, regional disease symptoms, and overall survival.

PATIENTS AND METHODS

The study was designed by ACOSOG investigators and was reviewed and approved by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (Bethesda, MD). The protocol was approved by the institutional review board for each participating institution before patient enrollment; all patients provided written informed consent. Patients with locally advanced extremity melanoma were identified by participating surgeons from their practices.

Inclusion and Exclusion Criteria

Eligible patients were at least 18 years old and had measurable, advanced local biopsy-proven extremity melanoma, an Eastern Cooperative Oncology Group/Zubrod performance status of ≤ 2,[20,21] adequate bone marrow, hepatic and renal function, and were free of other malignancies.

Patients were excluded if they had received chemotherapy, radiotherapy, or biologic therapy 30 days before registration, had hypersensitivity to melphalan or TNF-α, had failed prior local melphalan therapy, had severe cardiac or peripheral vascular disease, had symptomatic cerebrovascular disease, had pulmonary embolism within 1 year before registration, had active peptic ulcer disease, had concurrent infection, had contraindication to use of inotropic agents, had known HIV infection, or were pregnant or breastfeeding.

Intervention and Randomization

HILP was performed for all patients using standard techniques under general anesthesia. Regional lymph node dissection was performed as clinically indicated but was not required. Vessels of the affected extremity were isolated with open technique, were cannulated, and were connected to a perfusion circuit providing membrane oxygenation and a heat exchanger to maintain temperature between 38.5°C and 40°C. A tourniquet was placed to prevent leak into the systemic circulation, and leak rate was monitored with radiolabeled RBCs. The leak rate percentage was calculated as: Leak rate % = 100 × ([Maximal Perfusion Count − Baseline count per minute] / [Baseline count per minute − background count]).

Commercially available melphalan (GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC) was used in both treatment arms and dosing was 10 mg/L of tissue volume for the lower extremity and 13 mg/L tissue volume for the upper extremity. The melphalan-alone arm included a 25-minute sham-period of heated perfusion before melphalan perfusion to simulate the period of TNF-α perfusion. The melphalan-plus-TNF-α arm included a 4-mg TNF-α dose for femoral artery infusion and a 3-mg dose for popliteal, brachial, or axillary artery infusion. Investigators were not blinded to treatment allocation. Recombinant human tumor necrosis factor–alpha (Investigational New Device No. 8063) was provided through CTEP by Boehringer-Ingelheim (Ingelheim, Germany). The trial schema is shown in Figure 1.

Clinical End Points

The primary clinical end point of the study was tumor response. It was assessed at 3 months and was classified as (1) complete response, (2) partial response, (3) stable disease, or (4) local progression. A CR was defined as complete disappearance of all clinical and radiologic evidence of disease for at least 8 weeks' duration from the time of maximal response. A partial response was defined as $\geq$ 50% decrease of the sum of the products of perpendicular diameters of all measurable lesions without the appearance of new lesions for at least 8 weeks from the time of maximal response. Stable disease was defined as less than a partial tumor response or a response of less than 8 weeks' duration from the time of maximal response. Local progression was defined as having any new lesions in the perfusion field, or a more than 25% increase in the products of perpendicular diameters of any measurable lesions located in the perfusion field from the size at best response, or a 25% increase in the sum of all measurable lesions in the perfusion field. Secondary end points included treatment toxicity, regional disease symptoms, local recurrence–free survival, and overall survival.

Statistical Analysis

The study was designed with 90% power to show the superiority of the melphalan/TNF-α infusion over melphalan alone in the treatment of patients with metastatic melanoma of the limb relative to the 3-month primary end point. Sample size requirements for a one-tailed test conducted at the .05 level of significance were calculated using East software (Cytel Software Corporation, Cambridge, MA) and accounted for the stratification of patients into three groups: patients with low tumor burden, high tumor burden, or prior limb perfusion therapy. It was assumed that the CR rate for these three groups would be 65%, 25%, and 25%, respectively, in the melphalan-alone arm, and CR would be 80%, 55%, and 55%, respectively, in the melphalan-plus-TNF-α arm. In estimating sample size, two accrual distribution scenarios were anticipated: scenario 1 assumed an annual accrual of 50, 25, and 25 patients in the three groups, and scenario 2 assumed an accrual of 50, 20, and 20 patients. Scenario 1 required 183 assessable patients and scenario 2 required 194

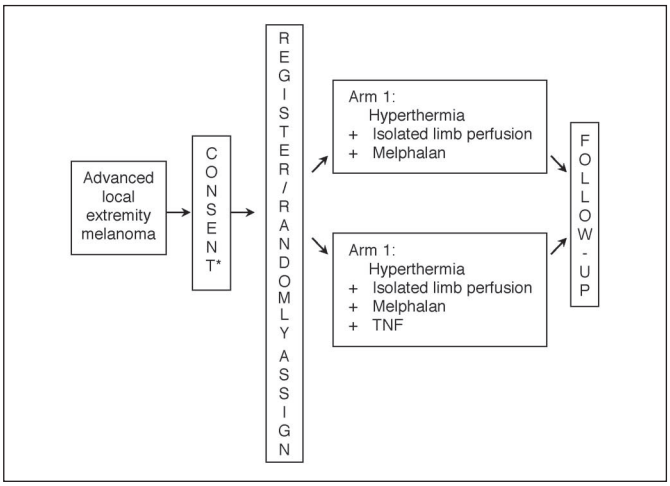

Fig 1. Trial schema. TNF-α, tumor necrosis factor.

patients. Allowing for a 10% rate of unassessable patients, 203 or 216 patients were required. Therefore, the accrual goal was set at 216 patients.

The ACOSOG Data and Safety Monitoring Committee (DSMC) monitored the progress of this study semiannually. An interim analysis was planned for the first 108 patients.

Patient characteristics and adverse events (AEs) were summarized by frequency distributions. Contingency tables and Fisher's exact tests were used to model the effect of individual patient clinical characteristics (treatment arm, temperature during perfusion, intraoperative leak status, tumor burden, regional nodal disease status, sex, disease site) and institution patient volume on the following outcomes: CR at 3 and 6 months, and occurrence of AEs ≥ grade 4. All analyses were performed using the SAS statistical analysis software (SAS Corporation, Cary, NC).

RESULTS

Interim Results

The ACOSOG Z0020 trial opened for enrollment on March 29, 1999. Accrual was suspended in May 2001 as TNF-α was temporarily unavailable from the manufacturer, but resumed again in August 2001. The DSMC reviewed interim analysis performed on 118 patients. After reviewing this analysis and the efficacy stopping rules outlined in the protocol, the DSMC recommended that the study be stopped early as they concluded that there was a sufficient lack of evidence of a difference favoring the melphalan-plus-TNF-α arm. The Group Chair accepted this recommendation, and the study closed to patient accrual on January 16, 2004, after 133 patients had been enrolled. At the time of the interim analysis, it was also noted that the rate of AEs ≥ grade 3 was 33% in the melphalan-alone arm and 37% in melphalan-plus-TNF-α arm (P = .699). The rate of grade 4 AEs that could definitely or probably be attributed to treatment was reported in one patient (1%) in the melphalan-alone arm and seven patients (11%) in the melphalan-plus-TNF-α arm (P = .057).

Final Results

At the termination of the study, 133 patients had been enrolled onto the study from 10 participating centers. Data collected from these 133 patients constitute the primary analysis population. Demographic data for all enrolled patients are presented in Table 1. Regarding the stratification variables, 7% (four of 58 patients) and 7% (four of 58 patients) of patients had received previous regional therapy, and 50% (29 of 58) and 59% (34 of 58) of patients had high tumor burden for the melphalan-alone and melphalan-plus-TNF-α arms, respectively. Although patients in the melphalan-plus-TNF-α arm were older and more likely to have high tumor burden, the distribution of sex and race was more evenly distributed.

The intervention was completed in 124 of the 133 enrolled patients. Of the 124 patients with complete intervention, eight did not have 3-month response data available, leaving 116 patients available for analysis. Reasons for incomplete intervention and missing follow-up data are shown in Figure 2.

Response rates at 3 months are listed in Table 2. The CR rate was 25% in the melphalan-alone arm and 26% in the melphalan-plus-TNF-α arm (P = .890). Response to treatment was observed in 64% of patients (36 of 58) in the melphalan-alone arm and 69% of patients (40 of 58) in the melphalan-plus-TNF-α arm (P = .435). When comparing arms of the study, no statistically significant differences were observed for tumor burden, prior perfusion, regional nodal status, sex, optimal hyperthermia by 30 minutes, institution volume, or type of extremity (upper *v* lower).

Table 1. Baseline Demographics (n = 133)

Characteristic	Arm 1: Melphalan (n = 65) No. of Patients	Arm 1: Melphalan (n = 65) %	Arm 2: Melphalan + TNF-α (n = 68) No. of Patients	Arm 2: Melphalan + TNF-α (n = 68) %
Age, years				
Mean	60		66	
Range	39-81		31-89	
Sex				
Male	32	49	35	51
Female	33	51	33	49
Race/ethnicity				
White	61	94	64	94
Hispanic	1	1.5	2	3
Black	2	3	1	1.5
Other	1	1.5	1	1.5

NOTE. Summaries are based on available patient data.
Abbreviation: TNF-α, tumor necrosis factor.

AE data were available for 130 of the 133 patients (including six patients who did not complete HILP). A summary of all AEs ≥ grade 3 for patients completing HILP is listed in Table 3. Grade 4 AEs were observed in 14 patients (11%), with three of 64 patients (5%) in the melphalan-alone arm and 11 of 66 patients (17%) in the melphalan-plus-TNF-α arm (P = .028). There were no grade 5 AEs in either arm. There were two toxicity-related lower extremity amputations in the melphalan-plus-TNF-α arm. One patient in the melphalan-alone arm had a disease progression–related upper extremity amputation. There was no statistically significant difference in AE occurrence based on sex or institution volume.

Although the CR rate at 6 months was not a primary end point, analysis suggested an improved CR rate in the melphalan-plus-TNF-α arm in patients with available data. Response outcome was available for 89 patients (44 patients in the melphalan-only arm and 45 patients in the melphalan-plus-TNF-α arm) at the 6-month time point. A CR had occurred in nine patients (20%) in the melphalan-alone arm and in 19 patients (42%) in the melphalan-plus-TNF-α arm (Table 4). Only 65% of the patients (nine of 14) in the melphalan-alone arm maintained their CR at 6 months. In contrast, 80% (12 of 15) of the patients in the melphalan-plus-TNF-α arm were able to maintain their CR. Moreover, six patients in the melphalan-plus-TNF-α arm who were partial responders at 3 months continued to evolve their response such that they achieved CR at 6 months. This phenomenon was not seen in the melphalan-alone arm.

DISCUSSION

This ACOSOG Z0020 prospective, randomized trial did not demonstrate a benefit for the addition of TNF-α to HILP with melphalan at the 3-month follow-up time point. No difference was found in the CR rate or in overall survival at 3 months after randomization, regardless of stratification variables and patient demographics. In addition, the melphalan-plus-TNF-α arm had significantly more grade 4 AEs than the melphalan-alone arm. Given the

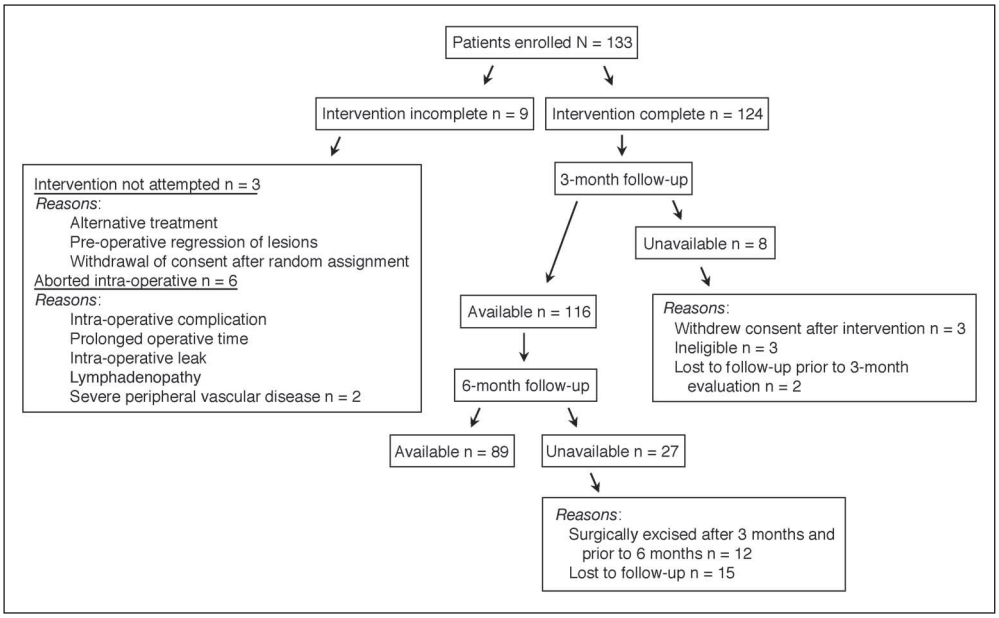

Fig 2. Availability of results for the 133 patients enrolled.

observed lack of benefit, the higher complication rate, and the prespecified stopping rules at the interim analysis, the DSMC recommended that the study be stopped.

It is possible that the study may not have been adequately designed to evaluate the effects of adding TNF-α to HILP with melphalan for melanoma of the extremities. Based on previous experience with TNF-α and melphalan, we expected the time to peak response to be between 2 and 3 months. However, analyses at the 6-month follow-up time point suggest that a response to the therapy may be observed later than the expected 3-month end point. Six patients in the melphalan-plus-TNF-α arm continued to develop a better response between the 3- and 6-month visits, suggesting that time to maximal response in a TNF-α-based perfusion may exceed that seen with melphalan perfusion alone. In addition, the durability of a complete response was greater in the melphalan-plus-TNF-α arm.

The response and AE rates in this randomized trial differ significantly from previous studies (Table 5). Early experience with the triple therapy regimen of melphalan/IFN/TNF-α in a phase II study found a CR rate of 90% for patients undergoing HILP.[18] However, this response rate is unusually high given that half of the patients had failed previous HILP treatment with melphalan alone. Moreover, the study was conducted in a small number of patients and a limited number of sites. Subsequently, two phase III randomized trials have been conducted over the past decade that have investigated the role of TNF-α and IFN for HILP treatment in patients with in-transit melanoma. Lienard et al[25] studied 64 patients in Europe who received either melphalan/TNF-α or melphalan/TNF-α/IFN. The CR rate for the melphalan/TNF-α/IFN arm was 78% versus 69% for the melphalan/TNF-α arm, with a nonsignificant 9% absolute risk reduction.[25] Although IFN did not contribute additional benefit, the study population was small and it is possible that the study may have been underpowered. Fraker et al[19] randomly assigned 103 patients in the United States to receive either melphalan alone or melphalan/TNF-α/IFN. In this study, a statistically significant 24% absolute risk reduction ($P < .05$) in the CR rate was found between the melphalan/TNF-α/IFN (72%) and melphalan-alone (58%) arms, respectively.[19] Subset analysis based on tumor burden demonstrated that patients with high tumor

Table 2. Response to Treatment at 3 Months (n = 116)

	Arm 1: Melphalan (n = 58)		Arm 2: Melphalan + TNF-α (n = 58)		
Type of Response	No. of Patients	%	No. of Patients	%	*P*
Complete	14	25	15	26	.890
Partial (≥ 50%)	22	39	25	43	
Stable disease	16	28	13	22	
Local progression	6	11	5	9	
Overall response	36	62	40	69	.435

NOTE. Based on 116 patients with available 3-month follow-up data.
Abbreviation: TNF-α, tumor necrosis factor.

Table 3. Toxicity Adverse Events Grade ≥ 3 (n = 130)

	Arm 1: Melphalan (n = 64)		Arm 2: Melphalan + TNF-α (n = 66)	
Adverse Event	No. of Patients	%	No. of Patients	%
Pain	11	17	5	8
Cardiovascular/thrombotic	5	8	8	12
Dermatologic	1	2	6	9
Myelosuppression	4	6	4	6
Pulmonary	0	0	3	5
Musculoskeletal	2	3	2	3
Compartment syndrome				
Without limb loss	1	2	2	3
With limb loss	0	0	2	3
Any grade 3 or higher toxicity	24	38	32	48

NOTE. Based on 130 patients with available adverse events data (including six patients who did not complete hyperthermic isolated limb perfusion).
Abbreviation: TNF-α, tumor necrosis factor.

Table 4. Response to Treatment at 6 Months (n = 89)

Type of Response	Arm 1: Melphalan (n = 44) No. of Patients	%	Arm 2: Melphalan + TNF-α (n = 45) No. of Patients	%	P
Complete	9	20	19	42	.101
Partial (≥ 50%)	12	27	6	13	
Stable disease	8	18	9	20	
Local progression	15	34	11	24	
Overall response	21	48	25	56	.460

NOTE. Based on 73 patients with available 6-month follow-up data.
Abbreviation: TNF-α, tumor necrosis factor.

burden who received the triple drug regimen had a significantly better CR rate (60% *v* 13%; $P < .05$) compared with patients treated with melphalan alone.[19] The CR rate of 90% achieved in the earlier phase II study was not found in these two multi-institutional randomized trials, although the respective CR rates of 78% and 72% for the triple-drug regimen were similar between the two trials.

In contrast, the complete response rates in both arms of our study were considerably lower than the response rates demonstrated in previous studies. Several key differences between these studies and our study could contribute to this finding, including procedural differences, drug pharmacokinetics, TNF-α preparation, patient selection (higher tumor stage, greater tumor burden), and the use of IFN in other studies. The technique of HILP used in this study is well described and includes the key features of adequate vascular isolation of the limb, appropriate flow rate and dosimetry, and avoidance of hypothermia.[29,30] However, despite specifications in the study protocol that established a uniform procedure for limb perfusion, variation in results could be related to investigator experience or subtle differences in technique at the participating sites. Drug pharmacokinetics may differ with alterations in flow rate and may affect outcome, and these differences have not been well described in any of the randomized studies. In addition, various studies have used recombinant human TNF-α produced by several different manufacturers. As a consequence, differences among the various preparations of recombinant human TNF-α may have had an impact on the results, although the studies are too small to adequately address this. The ACOSOG Z0020 did not include the use of IFN-gamma, whereas the other phase III studies did,[19,21] although as described herein, the European trial showed no difference with the addition of IFN-gamma.[21] Lastly, the addition of the 25-minute sham period of heated perfusion before melphalan administration may have contributed to the less pronounced difference between the two arms, compared with previous nonrandomized studies that did not use a sham perfusion.

Although more grade 4 AEs occurred in the melphalan-plus-TNF-α arm, no single category of adverse event was statistically more frequent. While limb compartment syndrome and limb amputation did occur more frequently in the melphalan-plus-TNF-α arm, these events were unusual in both arms of the study, and the number of amputations could have been similar, as none of the patients would have been added to the arms of the study, had the study been allowed to continue. Although cardiovascular and dermatologic AEs were slightly more common in the combination-therapy arm, pain was more frequent in the single-therapy arm. The causes for these differences are unclear and may be due to chance alone.

Regional therapy remains a good strategy for the treatment of advanced local extremity melanoma, both for potential cure of disease confined to the extremity, and for palliation and improved quality of life in patients with bulky or symptomatic disease, or disease that would otherwise be unresectable barring amputation. This is a relatively safe and effective treatment modality compared with systemic chemotherapy. Although this study did not support the addition of TNF-α to melphalan based on a 3-month data analysis, it does support limb perfusion as a feasible technique for treatment of selected melanoma patients. The role that TNF-α should have in limb perfusion, if any, remains unclear. Given the trend toward more complete responses and more durable complete responses as seen in the melphalan-plus-TNF-α arm at the 6-month follow-up time point, it is reasonable to consider exploring the addition of TNF-α to melphalan in the reperfusion of those patients who respond poorly or incompletely to an initial perfusion with melphalan alone in future studies.

Table 5. History of TNF-α HILP Trials

Study	Trial Phase	No. of Patients	HILP Regimen(s)	CR (%)
Lienard et al,[18] 1992	II	29	Melphalan/IFN/TNF-α	90
Lienard et al,[22] 1994	II	53	Melphalan/IFN/TNF-α	90
Vaglini et al,[23] 1994	I/II	12	Melphalan/IFN/TNF-α	53
		10	Melphalan/low-dose TNF-α	70
Fraker et al,[24] 1996	I/II	26	Melphalan/TNF-α 4 mg	76
		11	Melphalan/TNF-α 6 mg	36
Lienard et al,[25] 1999	III	31	Melphalan/IFN/TNF-α	78
		33	Melphalan/TNF-α	69
Fraker et al,[19] 2002	III	52	Melphalan/IFN/TNF-α	72
		51	Melphalan	58
Grunhagen et al,[26] 2004	II	100	Melphalan/TNF-α	69
Noorda et al,[27] 2004	II	90	Melphalan/TNF-α	59
Rossi et al,[28] 2004	II	20	Melphalan/TNF-α	70

Abbreviations: TNF-α, tumor necrosis factor; HILP, hyperthermic isolated limb perfusion; CR, complete response; IFN, interferon.

REFERENCES

1. Balch CM, Houghton A, Peters L: Cutaneous melanoma, in De Vita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology. Philadelphia, PA, Lippincott, 1989, pp 1499-1542

2. Pawlik TM, Ross MI, Gershenwald JE: Lymphatic mapping in the molecular era. Ann Surg Oncol 11:362-374, 2004

3. Karakousis CP, Choe KJ, Holyoke ED: Biologic behavior and treatment of intransit metastasis of melanoma. Surg Gynecol Obstet 150:29-32, 1980

4. Jaques DP, Coit DG, Brennan MF: Major amputation for advanced malignant melanoma. Surg Gynecol Obstet 169:1-6, 1989

5. Creech O, Krementz ET, Ryan RF, et al: Chemotherapy of cancer: Regional perfusion utilizing an extracorporeal circuit. Ann Surg 148:616-632, 1958

6. Kroon BB: Regional perfusion in melanoma of the limbs: Accomplishments, unsolved problems, and future. Eur J Surg Oncol 14:101-110, 1988

7. Stehlin JS Jr: Hyperthermic perfusion with chemotherapy for cancers of the extremitites. Surg Gynecol Obstet 129:305-308, 1969

8. Cumberlin R, DeMoss E, Lassus M, et al: Isolation perfusion for malignant melanoma of the extremity: A review. J Clin Oncol 3:1022-1031, 1985

9. Kleeberg UR, Rumke P, Kirkwood JM: Systemic chemotherapy of advanced melanoma, in Rumke P (ed): Therapy of Advanced Melanoma. Basel, Switzerland, Karger, 1990, pp 91-104

10. Rosin RD, Westbury G: Isolated limb perfusion for malignant melanoma. Practitioner 224:1031-1036, 1980

11. Jonsson PE, Hafstrom L, Hagarder A: Results of regional hyperthermic perfusion for primary and recurrent melanomas of the extremities. Recent Results Cancer Res 86:277-282, 1983

12. Skene AI, Bulman AS, Williams TR, et al: Hyperthermic isolated perfusion with melphalan in the treatment of advanced malignant melanoma of the lower limb. Br J Surg 77:765-767, 1990

13. Minor DR, Allen RE, Alberts D, et al: A clinical and pharmacokinetic study of isolated limb perfusion with heat and melphalan for melanoma. Cancer 55:2638-2644, 1985

14. Storm FK, Morton DL: Value of therapeutic hyperthermic limb perfusion in advanced recurrent melanoma of the lower extremity. Am J Surg 150: 32-35, 1985

15. Klaase JM, Kroon BB, van Geel AN, et al: Prognostic factors for tumor response and limb recurrence-free interval in patients with advanced melanoma of the limbs treated with regional isolated perfusion using melphalan. Surgery 115:39-45, 1994

16. Bartsch HH, Pfizenmaker K, Schroeder M, et al: Intralesional application of recombinant human tumor necrosis factor alpha induces local tumor regression in patients with advanced malignancies. Eur J Cancer Clin Oncol 25:287-291, 1989

17. Olieman AF, Lienard D, Eggermont AM, et al: Hyperthermic isolated limb perfusion with TNF-α alpha, Interferon gamma, and melphalan for locally advanced melanoma skin tumors of the extremity: A multicenter study. Arch Surg 134:303-307, 1999

18. Lienard D, Lejeune FJ, Ewalenko P: In transit metastases of malignant melanoma treated by high dose TNF-α alpha in combination with interferon-gamma and melphalan in isolation perfusion. World J Surg 16:234-240, 1992

19. Fraker DL, Alexander HR, Ross M, et al: A phase III trial of isolated limb perfusion for extremity melanoma comparing melphalan alone versus melphalan plus tumor necrosis factor (TNF-α) plus interferon-gamma (IFN). Ann Surg Onc 9:S8, 2002 (suppl; abstr 1)

20. Stanley KE: Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 65:25-32, 1980

21. Manola J, Atkins M, Ibrahim J, et al: Prognostic factors in metastatic melanoma: A pooled analysis of Eastern Cooperative Oncology Group trials. J Clin Oncol 18:3782-3793, 2000

22. Lienard D, Eggermont AM, Schraffordt Koops H, et al: Isolated perfusion of the limb with high-dose tumour necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma) and melphalan for melanoma stage III: Results of a multicentre pilot study. Melanoma Res 4:21-26, 1994 (suppl 1)

23. Vaglini M, Santinami M, Manzi R, et al: Treatment of in-transit metastases from cutaneous melanoma by isolation perfusion with tumour necrosis factor-alpha (TNF-alpha), melphalan and interferon-gamma (IFN-gamma): Dose-finding experience at the National Cancer Institute of Milan. Melanoma Res 4:35-38, 1994 (suppl 1)

24. 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 14:479-489, 1996

25. Lienard D, Eggermont AM, Koops B, et al: Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: A multicentre randomized phase II study. Melanoma Res 9:491-502, 1999

26. Grunhagen DJ, Brunstein F, Graveland WJ, et al: One hundred consecutive isolated limb perfusions with TNF-alpha and melphalan in melanoma patients with multiple in-transit metastases. Ann Surg 240:939-947, 2004

27. Noorda EM, Vrouenraets BC, Nieweg OE, et al: Isolated limb perfusion for unresectable melanoma of the extremities. Arch Surg 139:1237-1242, 2004

28. Rossi CR, Foletto M, Mocellin S, et al: Hyperthermic isolated limb perfusion with low-dose tumor necrosis factor-alpha and melphalan for bulky in-transit melanoma metastases. Ann Surg Oncol 11: 173-177, 2004

29. Alexander HR, Fraker DL, Bartlett DL: Isolated limb perfusion for malignant melanoma. Semin Surg Oncol 12:416-428, 1996

30. Schraffordt Koops HS, Kroon BB, Lejeune FJ, et al: Management of local recurrence, satellites, and in transit metastases of the limbs with isolation perfusion, in Lejeune FJ, Chaudhuri PK, Das Gupta TK (eds): Malignant Melanoma: Medical and Surgical Management. New York, NY, McGraw Hill Inc, 1994, pp 221-231

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Authors' Disclosures of Potential Conflicts of Interest

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Author Contributions

Conception and design: Wendy R. Cornett, Rebecca P. Petersen, James E. Herndon II, Douglas L. Fraker, Douglas S. Tyler
Administrative support: Wendy R. Cornett, Vijaya Chadaram
Provision of study materials or patients: Merrick I. Ross, Henry A. Briele, R. Dirk Noyes, Jeffrey J. Sussman, William G. Kraybill, John M. Kane III, H. Richard Alexander, Jeffrey E. Lee, Paul F. Mansfield, James F. Pingpank, David J. Winchester, Richard L. White, Douglas L. Fraker, Douglas S. Tyler
Collection and assembly of data: Wendy R. Cornett, Merrick I. Ross, Henry A. Briele, R. Dirk Noyes, Jeffrey J. Sussman, William G. Kraybill, John M. Kane III, H. Richard Alexander, Jeffrey E. Lee, Paul F. Mansfield, James F. Pingpank, David J. Winchester, Richard L. White, Vijaya Chadaram, Douglas L. Fraker, Douglas S. Tyler
Data analysis and interpretation: Wendy R. Cornett, Linda M. McCall, Rebecca P. Petersen, James E. Herndon II, Douglas L. Fraker, Douglas S. Tyler
Manuscript writing: Wendy R. Cornett, Linda M. McCall, Rebecca P. Petersen, Douglas L. Fraker, Douglas S. Tyler
Final approval of manuscript: Wendy R. Cornett, Linda M. McCall, Rebecca P. Petersen, Merrick I. Ross, Henry A. Briele, R. Dirk Noyes, Jeffrey J. Sussman, William G. Kraybill, John M. Kane III, H. Richard Alexander, Jeffrey E. Lee, Paul F. Mansfield, James F. Pingpank, David J. Winchester, Richard L. White, Vijaya Chadaram, James E. Herndon II, Douglas L. Fraker, Douglas S. Tyler

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Editorial correspondence should be addressed to Daniel G. Haller, MD, *Journal of Clinical Oncology*, 330 John Carlyle St, Suite 300, Alexandria, VA 22314. Telephone: (703) 797-1900; Fax: (703) 684-8720. E-mail: jco@asco.org. Internet: www.jco.org.

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