

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

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A B S T R A C T

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.

J Clin Oncol 24:4196-4201.

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Submitted January 23, 2006; accepted June 30, 2006.

Supported by Grant No. U10 CA076001 from the National Cancer Institute.

Presented at the 2005 Annual Cancer Symposium of the Society of Surgical Oncology, Atlanta, GA, March 4, 2005.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2425-4196/\$20.00

DOI: 10.1200/JCO.2005.05.5152

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} suggest-

ing 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 al¹⁹ 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 radio-labeled RBCs. The leak rate percentage was calculated as: Leak rate % = 100 ×

$([\text{Maximal Perfusion Count} - \text{Baseline count per minute}] / [\text{Baseline count per minute} - \text{background count}])$.

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- α (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

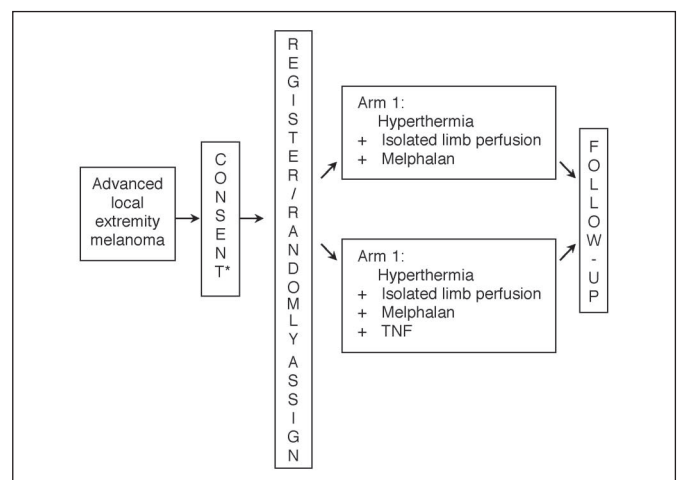


Fig 1. Trial schema. TNF- α , tumor necrosis factor.

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 \geq 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 \geq 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**

Table 1. Baseline Demographics (n = 133)

Characteristic	Arm 1: Melphalan (n = 65)		Arm 2: Melphalan + TNF- α (n = 68)	
	No. of Patients	%	No. of Patients	%
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.

status, sex, optimal hyperthermia by 30 minutes, institution volume, or type of extremity (upper v lower).

AE data were available for 130 of the 133 patients (including six patients who did not complete HILP). A summary of all AEs \geq 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

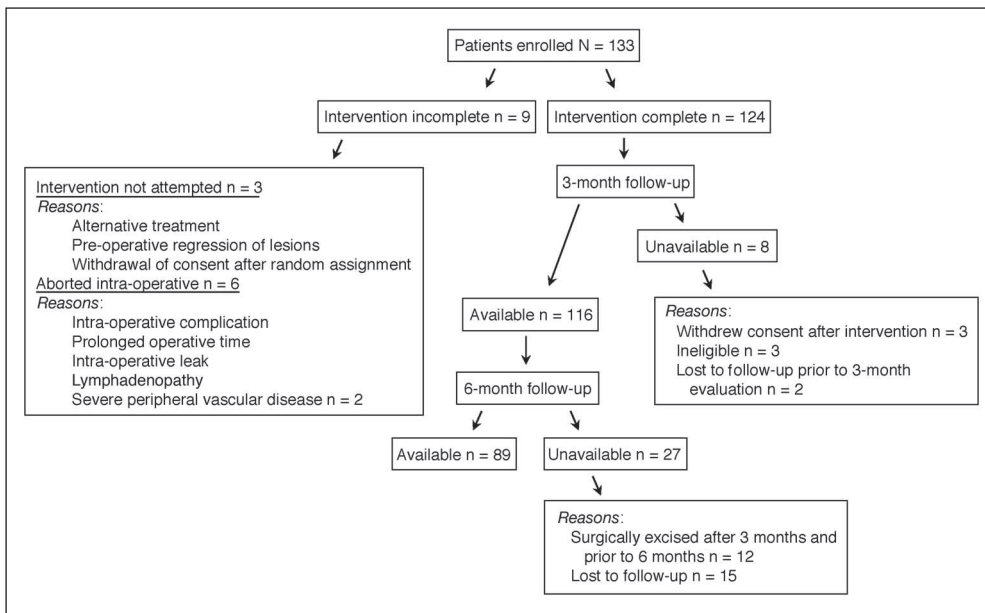


Fig 2. Availability of results for the 133 patients enrolled.

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 al²⁵ 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 non-significant 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 al¹⁹ 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)

Type of Response	Arm 1: Melphalan (n = 58)		Arm 2: Melphalan + TNF- α (n = 58)		P
	No. of Patients	%	No. of Patients	%	
Complete	14	25	15	26	.890
Partial ($\geq 50\%$)	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)

Adverse Event	Arm 1: Melphalan (n = 64)		Arm 2: Melphalan + TNF- α (n = 66)	
	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)		Arm 2: Melphalan + TNF- α (n = 45)		P
	No. of Patients	%	No. of Patients	%	
Complete	9	20	19	42	.101
Partial (\geq 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.

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Acknowledgment

We appreciate the contribution Arthur Boddie, MD, made to this manuscript. We would also like to acknowledge all the clinical research assistants and institutions that enrolled patients onto ACOSOG Z0020.

Authors' Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

Vol 24, No 25

C O N T E N T S

September 1, 2006

Editorials

Prognostic Markers of Local Relapse in Rectal Cancer: Are We Any Further Forward?

Patrick G. Johnston (see article on page 4062) 4049

Thymidine Phosphorylase and Capecitabine: A Predictive Marker for Therapy Selection?

Bert H. O'Neil and Howard L. McLeod (see article on page 4069) 4051

What Is the Right Dose? The Elusive Optimal Biologic Dose in Phase I Clinical Trials

Alex A. Adjei (see article on page 4092) 4054

■ Heart of Darkness: The Downside of Trastuzumab

Daniel F. Hayes and Michael H. Picard (see article on page 4107) 4056

■ Which Breast Cancer Patients Should Really Worry About Radiation-Induced Heart Disease—And How Much?

Abram Recht (see article on page 4100) 4059

Original Reports

GASTROINTESTINAL CANCER

① Lymph Node Status and TS Gene Expression Are Prognostic Markers in Stage II/III Rectal Cancer After Neoadjuvant Fluorouracil-Based Chemoradiotherapy

Torsten Liersch, Claus Langer, B. Michael Ghadimi, Bettina Kulle, Daniela E. Aust, Gustavo B. Baretton, Wolfgang Schwabe, Peter Häusler, Heinz Becker, and Christiane Jakob (see editorial on page 4049) 4062

① Thymidine Phosphorylase Expression Is Associated With Response to Capecitabine Plus Irinotecan in Patients With Metastatic Colorectal Cancer

Neal J. Meropol, Philip J. Gold, Robert B. Diasio, Michael Andria, Mandeep Dhani, Thomas Godfrey, Albert J. Kovatich, Kirk A. Lund, Edith Mitchell, and Roland Schwarting (see editorial on page 4051) 4069

Predictors of Recurrence in Patients With T2 and Early T3, N0 Adenocarcinoma of the Rectum Treated by Surgery Alone

Aviram Nissan, Alexander Stojadinovic, Jinru Shia, Axel Hoos, Jose G. Guillem, David Klimstra, Alfred M. Cohen, Bruce D. Minsky, Philip B. Paty, and W. Douglas Wong 4078

Pooled Analysis of Safety and Efficacy of Oxaliplatin Plus Fluorouracil/Leucovorin Administered Bimonthly in Elderly Patients With Colorectal Cancer

Richard M. Goldberg, Isabelle Tabah-Fisch, Harry Bleiberg, Aimery de Gramont, Christophe Tournigand, Thierry Andre, Mace L. Rothenberg, Erin Green, and Daniel J. Sargent 4085

(continued on following page)

Journal of Clinical Oncology (ISSN 0732-183X) is published 36 times a year, three times monthly, by American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314. Periodicals postage is paid at Alexandria, VA, and at additional mailing offices. Publication Mail Agreement Number 863289.

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POSTMASTER: ASCO members send change of address to American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314. Nonmembers send change of address to *Journal of Clinical Oncology* Customer Service, 330 John Carlyle St, Suite 300, Alexandria, VA 22314.

2007 annual subscription rates, effective September 1, 2006: United States and possessions: individual, \$487; single issue, \$35. International: individual, \$678; single issue, \$45. Institutions: Tier 1: \$670 US, \$950 Int'l; Tier 2: \$780 US, \$1,060 Int'l; Tier 3: \$1,130 US, \$1,410 Int'l; Tier 4: \$1,245 US, \$1,525 Int'l; Tier 5: contact JCO for a quote. See <http://www.jco.org/subscriptions/tieredpricing.shtml> for descriptions of each tier. Student and resident: United States and possessions: \$240; all other countries, \$336. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the signature of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Current prices are in effect for back volumes and back issues. Back issues sold in conjunction with a subscription rate are on a prorated basis. Subscriptions are accepted on a 12-month basis. Prices are subject to change without notice. Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability. JCO Legacy Archive (electronic back issues from January 1983 through December 1998) is also available; please inquire.

PHASE I AND CLINICAL PHARMACOLOGY

Phase I Dose Escalation and Pharmacokinetic Study of Enzastaurin, an Oral Protein Kinase C Beta Inhibitor, in Patients With Advanced Cancer

Michael A. Carducci, Luna Musib, Merrill S. Kies, Roberto Pili, Mylene Truong, Julie R. Brahmer, Patricia Cole, Rana Sullivan, Jeanne Riddle, Jill Schmidt, Nathan Enas, Vikram Sinha, Donald E. Thornton, and Roy S. Herbst (see editorial on page 4054) 4092

BREAST CANCER

① Late Cardiac Mortality and Morbidity in Early-Stage Breast Cancer Patients After Breast-Conservation Treatment

Eleanor E.R. Harris, Candace Correa, Wei-Ting Hwang, Jessica Liao, Harold I. Litt, Victor A. Ferrari, and Lawrence J. Solin (see editorial on page 4059) 4100

① Long-Term Cardiac Tolerability of Trastuzumab in Metastatic Breast Cancer: The M.D. Anderson Cancer Center Experience

Valentina Guarneri, Daniel J. Lenihan, Vicente Valero, Jean-Bernard Durand, Kristine Broglio, Kenneth R. Hess, Laura Boehnke Michaud, Ana M. Gonzalez-Angulo, Gabriel N. Hortobagyi, and Francisco J. Esteva (see editorial on page 4056) 4107

COST EFFECTIVENESS

Cost-Effectiveness Analysis of Computerized Tomography in the Routine Follow-Up of Patients After Primary Treatment for Hodgkin's Disease

Beverly A. Guadagnolo, Rinaa S. Punglia, Karen M. Kuntz, Peter M. Mauch, and Andrea K. Ng 4116

AIDS-RELATED CANCER

① Phase II Trial of CHOP Plus Rituximab in Patients With HIV-Associated Non-Hodgkin's Lymphoma

François Boué, Jean Gabarre, Christian Gisselbrecht, Jacques Reynes, Antoine Cheret, Fabrice Bonnet, Eric Billaud, Martine Raphael, Remi Lancar, and Dominique Costagliola 4123

SUPPORTIVE CARE AND QUALITY OF LIFE

Outpatient Oral Antibiotics for Febrile Neutropenic Cancer Patients Using a Score Predictive for Complications

Jean Klastersky, Marianne Paesmans, Aspasia Georgala, Frédérique Muanza, Barbara Plehiers, Laurent Dubreucq, Yassine Lalami, Michel Aoun, and Martine Barette 4129

HEMATOLOGIC MALIGNANCIES

Prognostic Impact of Germinal Center–Associated Proteins and Chromosomal Breakpoints in Poor-Risk Diffuse Large B-Cell Lymphoma

Gustaaf W. van Imhoff, Evert-Jan G. Boerma, Bronno van der Holt, Ed Schuurin, Leo F. Verdonck, Hanneke C. Kluin-Nelemans, and Philip M. Kluin 4135

① Phase II Trial of CHOP Chemotherapy Followed by Tositumomab/Iodine I-131 Tositumomab for Previously Untreated Follicular Non-Hodgkin's Lymphoma: Five-Year Follow-Up of Southwest Oncology Group Protocol S9911

Oliver W. Press, Joseph M. Unger, Rita M. Braziel, David G. Maloney, Thomas P. Miller, Michael LeBlanc, and Richard I. Fisher 4143

BONE MARROW TRANSPLANTATION

① Factors Associated With Outcomes in Allogeneic Hematopoietic Cell Transplantation With Nonmyeloablative Conditioning After Failed Myeloablative Hematopoietic Cell Transplantation

Frédéric Baron, Rainer Storb, Barry E. Storer, Michael B. Maris, Dietger Niederwieser, Judith A. Shizuru, Thomas R. Chauncey, Benedetto Bruno, Stephen J. Forman, Peter A. McSweeney, Richard T. Maziarz, Michael A. Pulsipher, Edward D. Agura, James Wade, Mohamed Sorrow, David G. Maloney, and Brenda M. Sandmaier 4150

(continued on following page)

CLINICAL TRIALS

① Impact of a Multi-Disciplinary Patient Education Session on Accrual to a Difficult Clinical Trial: The Toronto Experience With the Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial

Kris Wallace, Neil Fleshner, Michael Jewett, Joan Basiuk, and Juanita Crook 4158

HEAD AND NECK CANCER

Phase I/II Study of Docetaxel, Cisplatin, and Concomitant Boost Radiation for Locally Advanced Squamous Cell Cancer of the Head and Neck

Anne S. Tsao, Adam S. Garden, Merrill S. Kies, William Morrison, Lei Feng, J. Jack Lee, Fadlo Khuri, Ralph Zinner, Jeffery Myers, Vassiliki Papadimitrakopoulou, Jan Lewin, Gary L. Clayman, K. Kian Ang, and Bonnie S. Glisson 4163

Increased Epidermal Growth Factor Receptor Gene Copy Number Is Associated With Poor Prognosis in Head and Neck Squamous Cell Carcinomas

Christine H. Chung, Kim Ely, Loris McGavran, Marileila Varella-Garcia, Joel Parker, Natalie Parker, Carolyn Jarrett, Jesse Carter, Barbara A. Murphy, James Netterville, Brian B. Burkey, Robert Sinard, Anthony Cmelak, Shawn Levy, Wendell G. Yarbrough, Robbert J.C. Slebos, and Fred R. Hirsch 4170

Disadvantage of Men Living Alone Participating in Radiation Therapy Oncology Group Head and Neck Trials

Andre A. Kanski, Thomas F. Pajak, Benjamin Movsas, James Coyne, Jonathan Harris, Clement Gwede, Adam Garden, Sharon Spencer, Christopher Jones, and Deborah Watkins-Bruner 4177

GENITOURINARY CANCER

Risk of Cardiovascular Mortality in Prostate Cancer Patients in the Rotterdam Randomized Screening Trial

Suzie J. Otto, Fritz H. Schröder, and Harry J. de Koning 4184

Six-Month Androgen Suppression Plus Radiation Therapy Compared With Radiation Therapy Alone for Men With Prostate Cancer and a Rapidly Increasing Pretreatment Prostate-Specific Antigen Level

Anthony V. D'Amico, Marian Loffredo, Andrew A. Renshaw, Brittany Loffredo, and Ming-Hui Chen 4190

MELANOMA

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 4196

PEDIATRIC ONCOLOGY

Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

Roger J. Packer, Amar Gajjar, Gilbert Vezina, Lucy Rorke-Adams, Peter C. Burger, Patricia L. Robertson, Lisa Bayer, Deborah LaFond, Bernadine R. Donahue, MaryAnne H. Marymont, Karin Muraszko, James Langston, and Richard Sposto 4202

Art of Oncology

Discussing Prognosis: "How Much Do You Want to Know?" Talking to Patients Who Are Prepared for Explicit Information

Anthony L. Back and Robert M. Arnold ([see article on page 4214](#)) 4209

Discussing Prognosis: "How Much Do You Want to Know?" Talking to Patients Who Do Not Want Information or Who Are Ambivalent

Anthony L. Back and Robert M. Arnold ([see article on page 4209](#)) 4214

(continued on following page)

Correspondence

Immunotherapy and Prognostic Factors

Luca A. Fumagalli and Fernando Brivio 4218

In Reply

Frede Donskov and Hans von der Maase 4219

Fertility Preservation Strategies for Breast Cancer Patients

Lucia Del Mastro and Marco Venturini 4220

In Reply

Kutluk H. Oktay and Stephanie J. Lee 4221

Sedation and Expertise in Palliative Care

José António Ferraz Gonçalves e44

Epoetin Versus Darbepoetin Conundrum Compromise

Archie Bleher e46

Errata 4223

Also in This Issue

Announcements

Information for Contributors

Current Abstracts

Calendar of Oncology Events



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