Cisplatin, Dacarbazine With or Without Subcutaneous Interleukin-2, and Interferon Alfa-2b in Advanced Melanoma Outpatients: Results From an Italian Multicenter Phase III Randomized Clinical Trial

By Ruggero Ridolfi, Vanna Chiarion-Sileni, Michele Guida, Antonella Romanini, Roberto Labianca, Andrea Freschi, Giovanni Lo Re, Rolando Nortilli, Sonia Brugnara, Patrizia Vitali, and Oriana Nanni for the Italian Melanoma Intergroup

Purpose: **Phase II and III studies have shown that the addition of interleukin-2 (IL-2) and interferon alfa-2b (IFNα-2b) in multiagent chemotherapy (CT) for advanced melanoma increases overall response (OR), albeit without clear evidence of an improvement in overall survival (OS). Treatment with high-dose IL-2 can cause severe toxicity and is normally administered in an inpatient setting. We conducted a multicenter prospective randomized clinical trial in outpatients with metastatic melanoma to compare CT with biochemotherapy (bioCT) using immunomodulant doses of IL-2 and IFNα-2b.**

Patients and Methods: **One hundred seventy-six eligible patients with advanced melanoma were randomized to receive CT (cisplatin and dacarbazine with or without carmustine every 21 days) or bioCT comprising the same CT regimen followed by low-dose subcutaneous IL-2 for 8 days and IFNα2b three times a week, both for six cycles.**

Results: **At a median follow-up of 18 (CT) and 16 (bioCT) months, median OS was 9.5 versus 11.0 months (P = .51), respectively. In the 89 CT-arm patients, 18 ORs (20.2%) (three complete responders [CRs] and 15 partial responders [PRs]) were observed according to World Health Organization criteria. In the 87 bioCT-arm patients, 22 ORs (25.3%) (three CRs and 19 PRs) (P = .70) were recorded. Treatment-related toxicity was fairly similar in both arms.**

Conclusion: **The addition of low-dose immunotherapy did not produce a statistically significant advantage in OS, time to progression, or OR. However, the 11-month median OS in the bioCT arm does not differ greatly from the best results with high-dose IL-2–containing regimens reported in the literature. Furthermore, our treatment schedule was carried out on outpatients and had an acceptable level of toxicity.**

J Clin Oncol 20:1600-1607. *© 2002 by American Society of Clinical Oncology.*

MELANOMA ACCOUNTS FOR 1% to 3% of all malignant tumors and is increasing in incidence by 6% to 7% each year.[1,2] It is curable with surgical resection in a high percentage of cases (> 50%), with a 5-year survival of 80% to 100%.[3] However, when a patient presents with advanced disease, 5-year life expectancy is less than 10%, with a median survival of 6 to 8.5 months.[4]

Dacarbazine (DTIC) is the most widely used chemotherapeutic agent, obtaining an overall response (OR) of 10% to 20%. There is no general consensus as to whether polychemotherapy is more effective than single-agent treatment, even though OR rates of combined treatment with cisplatin (CDDP) and DTIC with or without vinca alkaloids (vindesine/vinblastine) range from 18% to 50%.[5,6] Furthermore, recent phase III studies would seem to indicate that no significant therapeutic benefit is obtained from the addition of tamoxifen.[7]

The effectiveness of adding interferon alfa-2b (IFNα-2b) to polychemotherapeutic regimens is also questionable. In contrast, the combination of IFNα-2b plus interleukin-2 (IL-2) (biochemotherapy [bioCT]) has obtained OR rates ranging between 40% and 60%, albeit mainly in nonrandomized phase II trials.[8-10] The first published phase III trials would seem to indicate a greater efficacy of combined chemoimmunotherapy as far as response rates are concerned, but toxicity is more severe, quality of life (QoL) is reduced, and overall survival (OS) is not always improved.[11,12]

We conducted a multicenter randomized clinical trial to compare a standard chemotherapeutic regimen comprising DTIC and CDDP with the same schedule plus low-dose subcutaneous IL-2 and IFNα-2b used as immunomodulants. The centers participating in the study had the choice of adding or not adding carmustine (BCNU) to the chemother-

From the Department of Medical Oncology, Pierantoni Hospital, Forlì; Department of Medical Oncology, Busonera Hospital, Padua; Department of Medical Oncology, Oncology Institute of Bari, Bari; Medical Oncology Unit, S. Chiara Hospital, Pisa; Department of Radiotherapy and Oncology, Riuniti Hospital, Bergamo; Aviano Cancer Institute, Aviano; Oncology Unit, S. Maria degli Angeli Hospital, Pordenone; Department of Medical Oncology, Maggiore Hospital, Verona; Oncology Center, S. Chiara Hospital, Trento; and Istituto Oncologico Romagnolo, Forlì, Italy.

Submitted July 30, 2001; accepted November 19, 2001.

Supported by Istituto Oncologico Romagnolo, Forlì, Italy.

Address reprint requests to Ruggero Ridolfi, MD, Department of Medical Oncology, Pierantoni Hospital, Via Forlanini, 34, 47100 Forlì, Italy; email: i.o.r@fo.nettuno.it.

0732-183X/02/2006-1600/$20.00

apeutic schedule of patients in both arms and for the duration of the treatment. DTIC, CDDP, and BCNU are the most widely used drugs to treat melanoma, obtaining some of the best responses in an advanced setting.

IL-2 and IFNα-2b, used as immunomodulant agents, were administered in our study at low doses in an attempt to reduce toxicity and enable treatment to be carried out in an outpatient setting. They were administered over a long period of time (1 year) or until relapse in a maintenance scheme to investigate the possibility of prolonging time to progression (TTP).

An additional aim of the present study was to evaluate QoL by means of a specially prepared questionnaire. We also evaluated some prognostic factors in patient serum before and during therapy.

PATIENTS AND METHODS

Patients

From March 1, 1997, to December 31, 1999, patients with advanced melanoma were enrolled onto the study. All patients had previously undergone surgery to remove a primary cutaneous melanoma, with or without subsequent adjuvant IFNα-2b, and none had received chemotherapy (CT) or chemoimmunotherapy. Patients were required to satisfy the following criteria: age 18 years or older, histologically confirmed diagnosis of melanoma and measurable disease, WBC count greater than 3,000/mm^3, platelet count greater than 100,000/mm^3, serum creatinine less than 1.7 mg/dL, and bilirubin less than 1.6 mg/dL. Exclusion criteria were performance status higher than two and cerebral metastasis or cardiovascular, renal, or metabolic diseases, including conditions requiring continuous cortisone treatment.

Randomization was carried out telephonically by Istituto Oncologico Romagnolo, the Forlì data center, which collected all patient documentation and was responsible for data management. A system of random permuted blocks within the strata (oncologic center variable) was used with a block size of four. Initially, treatment and follow-up data were collected on case record forms in no-carbon-required booklets. Data were then recorded on a computerized database designed specifically for the management of the clinical trial data.

All patients underwent clinical examination, complete blood count and biochemical analysis, chest computed tomography scan or x-ray, liver computed tomography scan or ultrasonography, brain computed tomography or magnetic resonance imaging scan, and cardiologic evaluation in the 60 days before randomization.

Before each treatment cycle, patients underwent clinical examination, determination of complete blood count, and biochemical analysis. After two cycles and thereafter every 3 months until progression, they were required to have a chest computed tomography scan or x-ray and a liver computed tomography scan or ultrasonography. Response evaluations were assessed according to World Health Organization criteria.[13] When progression occurred, no indications for second-line therapy were given to the investigators.

Recruited patients underwent QoL assessment using the Rotterdam Symptom Check List questionnaire. The baseline assessment was performed before therapy and subsequently before each cycle. Serum was also collected for biologic tests at baseline and before each treatment cycle.

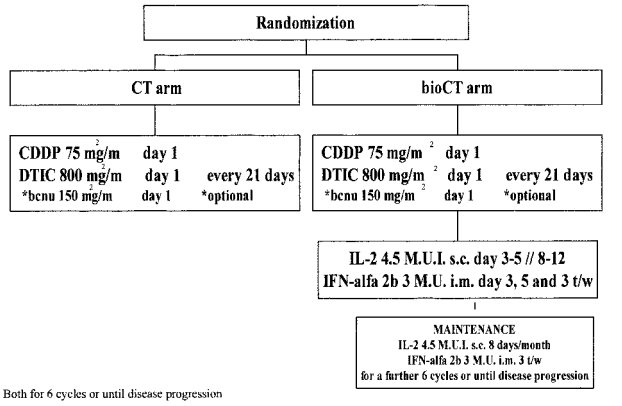

Fig 1. Treatment scheme.

All patients gave their informed written consent to receive treatment, and the study was examined and approved by the ethics committee of the local health and social services of each center taking part in the study, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Treatment

All patients were randomized to receive treatment with either CT or bioCT. Figure 1 shows the two treatment schedules. On day 1, all patients received CDDP 75 mg/m^2 IV with the usual hydrating scheme, DTIC 800 mg/m^2 IV, and, optionally, BCNU 100 mg/m^2 IV. BioCT-arm patients also received 4,500,000 IU of IL-2 subcutaneously from days 3 to 5 and days 8 to 12 and 3,000,000 units of IFNα2b intramuscularly on days 3 and 5 and thereafter three times a week. Treatment was repeated every 21 days for six cycles or until progression or severe toxicity occurred. Insulin syringes with the correct dose of IL-2 were usually prepared and given to the patient. These were then stored in the refrigerator, and the IL-2 was administered at home over the following days (up to 4 or 5 days). After the sixth cycle, bioCT-arm patients continued to receive IL-2 and IFNα-2b alone up to month 12 or until progression or severe toxicity occurred.

Patients were assessed before starting each cycle using World Health Organization toxicity criteria. Doses were reduced in the following cases. If the WBC count was less than 3,000, then neutrophils were evaluated, and if they were less than 1,500 or if the platelets were less than 90,000, treatment was delayed for 1 week. If these two counts persisted, the dose of the CT drugs was reduced by 25% but IL-2 and IFNα-2b doses remained unvaried. This dose reduction was maintained for all of the remaining cycles. If in the second week of delayed treatment the neutrophil count remained less than 1,000 or platelet count was less than 70,000, growth factors were allowed. In the event of grade 4 hematologic toxicity, the CT drug dosage was additionally reduced by 25% and maintained at this level; a continuous neutrophil count of less than 1,000 after the second week of delay or platelet count of less than 70,000 resulted in the discontinuation of treatment. In the presence of grade 1 or 2 renal toxicity, treatment was delayed for 1 week. Persistent grade 1 toxicity led to a 50% and 30% reduction in CT and IL-2, respectively; treatment was discontinued for persistent grade 2 toxicity. In the event of grade 2 hepatic toxicity, treatment was delayed for 1 week. If the situation persisted, CT was reduced by 50%, IL-2 was reduced to 3,000,000 IU/die, and IFNα-2b was suspended.

All dose reductions for renal and hepatic toxicity were maintained for the remaining cycles. In other cases of grade 3 toxicity (excluding fever and alopecia), treatment was delayed for 1 or 2 weeks. For other grade 4 toxicities, treatment was discontinued.

Statistical Analysis

The primary objective of the study was to compare OS among patients in the eligible intention to treat population who were assigned to either CT or bioCT. Secondary objectives comprised assessment of the objective response, TTP, the toxicity profile, QoL, and the role of several biologic variables as predictive factors. Sample size was determined a priori during protocol design.

Starting from an assumed 40% 1-year OS from randomization for patients treated with CT alone and hypothesizing an absolute increase of 20% in patients treated with bioCT (5% error fixed for a two-sided test and a power of 80%), a recruitment of at least 150 patients over 3 years was required. No interim analysis was planned.

Survival was defined as the time interval between randomization and either death of the patient attributable to any cause or the last recorded follow-up. TTP was defined as the time interval between the date of randomization and the date of disease progression or last follow-up. OS and TTP curves for the two arms were estimated by the Kaplan-Meier method and compared using the log-rank test.

The effect of prognostic factors on OS and TTP was estimated using Cox regression models. Analysis for some clinical and biologic subgroups was planned in advance as a secondary aim with exploratory intent; adjustments for multiplicity were not made. As regards the response analysis, 95% confidence interval (CI) of response rates was calculated, and comparison between groups was assessed using Fisher's exact test.

All *P* values were based on two-sided testing, and statistical analyses were carried out with SAS statistical software (SAS/STAT user's guide, version 6; SAS Institute, Cary, NC).

RESULTS

Patient and Treatment Characteristics

Between March 1997 and December 1999, a total of 178 patients were randomized. Two patients, one from each treatment arm, did not satisfy eligibility criteria and were excluded from the study; both underwent surgical resection of a suspected liver metastasis, which histologically resulted in angioma. Of the 176 eligible patients, 89 (57 men and 32 women) were allocated to receive CT and 87 (48 men and 39 women) were allocated to receive bioCT. Only three centers chose to add carmustine, for a total of 18 patients (nine in each arm). The two treatment arms were similar in terms of patient characteristics (Table 1).

Table 1. Patient Characteristics

	CT		BioCT	
	No.	%	No.	%
No. of patients	89		87	
Sex				
Male	57	64	48	55.2
Female	32	36	39	44.8
Age, years				
Median	59		56	
Range	26-76		25-77	
ECOG performance status				
0	60	67.4	59	67.8
1	23	25.8	24	27.6
2	6	6.7	4	4.6
Site of primary melanoma				
Head and neck	16	18	16	18.4
Body	35	39.3	36	41.4
Arms	34	38.2	34	39.1
Not referred	4	4.5	1	1.1
Sites of disease				
Liver ± others	30	33.7	32	36.8
Viscera ± others	29	32.6	31	35.6
Bone + soft tissue and lymph nodes	4	4.5	2	2.3
Soft tissue and lymph nodes	26	29.2	22	25.3
Time from first diagnosis, months				
Median	27		22	
Range	0-292		0-229	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

The median age in the CT arm was 59 years (range, 26 to 76 years) and in the bioCT arm, 56 years (range, 25 to 77 years). More than two thirds (67%) of patients had an Eastern Cooperative Oncology Group performance status (PS) of zero, and only 10 patients (six in the CT arm and four in the bioCT arm) had a PS of 2. Approximately one third of patients had liver metastases with or without involvement of other sites, one third had viscera or lung metastases, and almost one third had soft tissue and lymph node involvement. All the patients had previously undergone radical resection of primary cutaneous melanoma, and 50 patients (28%) had received adjuvant IFNα-2b, of whom 24 were in the CT arm and 26 were in the bioCT arm (six in the CT arm and five in the bioCT arm received high-dose IFNα-2b according to Kirkwood's scheme; the remaining 39 received low-dose IFNα-2b).[14] Time from first diagnosis varied from 0 to 292 months, with a median value of 27 months for the CT arm and 22 for the bioCT arm.

Survival

Median follow-up was 18 and 16 months for the CT and bioCT groups, respectively. OS curves according to treatment are reported in Fig 2. Median survival time was 1.5 months longer for bioCT-treated patients than for the CT group (11 *v* 9.5 months), but the difference was not statistically significant (hazards ratio, .888; log-rank, .442; $P = .506$). TTP was fairly similar in the two arms, with a median of 3.6 months for the bioCT group and 3 months for

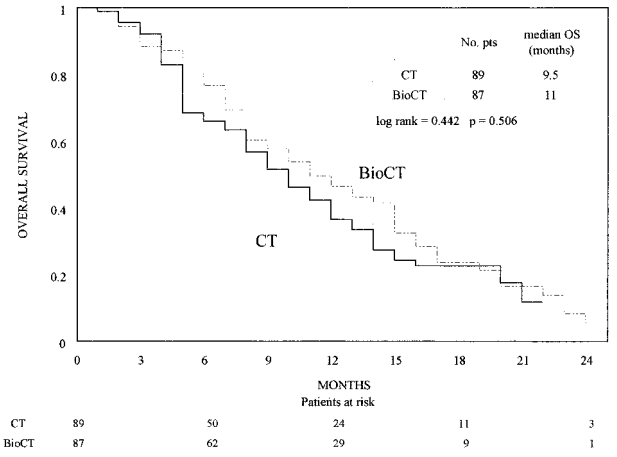

Fig 2. Overall survival in CT and bioCT treatment groups.

CT-treated patients (hazards ratio, .791; log-rank, 2.216; $P = .137$) (Fig 3).

Although the study was not designed to have the power for comparison within subgroups, a breakdown analysis was performed with exploratory intent. However, a cautious interpretation of P values is recommended (Table 2). Subgroup analysis according to sex, PS, and age showed no statistically significant differences between the two treatments. However, patients with liver metastases had a better OS when treated by bioCT with respect to CT (median OS, 8.7 *v* 4.8 months; $P = .002$).

Response to Treatment

Analysis of the 176 eligible patients showed an OR of 20.2% (95% CI, 11.8% to 28.6%) in the CT arm and 25.3%

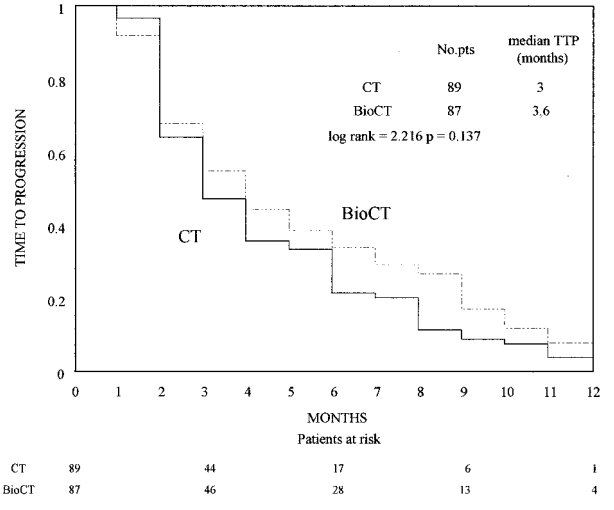

Fig 3. Time to progression in CT and bioCT treatment groups.

(95% CI, 16.1% to 34.5%) in the bioCT arm. This difference was not statistically significant ($P = .715$).

Two patients could not be assessed because one (in the CT arm) was lost to follow-up immediately after randomization and the other (in the bioCT arm) suspended treatment after the first cycle because of grade 4 neurologic toxicity. Of 89 patients randomized to receive CT alone, there were three complete responders (CRs) and 15 partial responders (PRs); of the 87 patients randomized to receive bioCT, there were three CRs and 19 PRs (Table 3).

The duration of the three CRs in the CT arm was 4, 6, and 33+ months and in the bioCT arm was 6, 12, and 16+ months. Median duration of OR was 6.9 and 8.3 months, respectively. The subgroup of 18 patients who received carmustine was too small to analyze efficacy in terms of OS, TTP, or OR.

Treatment and Toxicity Profile

Of the 176 eligible patients, two in the CT arm and one in the bioCT arm did not receive treatment. One, mentioned above, was lost to follow-up immediately after randomization, and two were excluded because of unexpected disease progression. Of the remaining 173 patients, three (3.4%) in the CT arm received one course of treatment, 30 (34.4%) received two courses, and 26 (29.9%) completed the six cycles planned in the protocol. Similarly, in the bioCT arm, 10 patients (11.6%) received one course of treatment, 27 (31.4%) received two courses, and 28 (32.5%) completed the full six cycles.

Treatment interruptions were mainly attributable to disease progression or, to a lesser extent, toxicity (96% and 1.8% in the CT arm and 87% and 5.5% in the bioCT arm, respectively).

Few dose reductions and delays in treatment were required. Thirty-two patients received a reduced CT dosage in at least one cycle (14 in the CT arm and 18 in the bioCT arm), and IFNα-2b was reduced in 26 patients and IL-2 was reduced in 25 patients. Most of the delays and dose reductions were attributable to hematologic toxicity. One patient in the bioCT arm refused immunotherapy and received only CT. A response analysis was carried out according to intention to treat, but an additional evaluation based on the doses received did not modify previous results.

Table 4 summarizes grade 3 and 4 toxicities. Hematologic toxicity was the most common side-effect; the percentage of patients reporting grade 3 and 4 leukocytes/granulocytes was quite similar in the two groups, 18.4% and 18.4% in the CT arm and 23.3% and 11.6% in the bioCT arm, respectively. Nausea or vomiting was severe in 13 CT-arm and 21 bioCT-arm patients. In the latter arm, fever and asthenia were observed in 80% of cases, but only in few

Table 2. Overall Survival According to Treatment in Subgroup Analysis

	No.	Deaths	Median OS		1-Year OS		P
			Months	95% CI	%	95% CI	
All patients							
CT	89	66	9.5	7.8-11.8	36	24-48	
BioCT	87	62	11	7.9-14.7	46	38-54	.506
Sex							
Male							
CT	57	42	9.5	7.8-11.6	32	18-46	
BioCT	48	36	8.8	6.8-14.4	39	25-53	.875
Female							
CT	32	24	8	6-13.8	45	27-63	
BioCT	39	26	12.4	10.4-16.1	55	37-73	.577
ECOG PS							
0							
CT	60	42	11.8	8.2-14.5	46	32-60	
BioCT	59	39	11.4	8.7-15.2	49	35-63	.894
1 + 2							
CT	29	24	6.5	4.2-9.3	14	1-27.7	
BioCT	28	23	7.9	4.8-14.3	40	20-60	.082
Age							
< 60 years							
CT	46	31	10	4.9-13.3	43	27-59	
BioCT	53	38	8.7	7.6-14.4	40	26-54	.702
≥ 60 years							
CT	43	35	8.3	7.1-11.6	31	17-45	
BioCT	34	24	12.4	10.5-15.2	57	40-75	.158
Site of metastasis							
Liver							
CT	30	25	4.8	3.8-7.4	5	0-15	
BioCT	32	26	8.7	6.3-14.3	37	19-55	.002
Viscera							
CT	29	18	14.7	10.7-20.9	62	44-80	
BioCT	31	19	12.3	9.2-19	50	30-70	.299
Soft tissue							
CT	26	19	9.7	7.8-13.8	41	21-61	
BioCT	22	15	14.4	6.7-16.5	58	36-80	.574

cases did they reach grade 3 toxicity. With regard to the 18 patients who received carmustine, a greater frequency of grade 3 or 4 leucopenia and thrombocytopenia, both of which resolved spontaneously, was observed with respect to patients who were not treated with BCNU. There were no treatment-related deaths.

DISCUSSION

The median survival of patients with advanced melanoma varies between 6 and 9 months, and only 1% to 2% have long-term complete responses after treatment.[15] In one study reporting 11 trials of the Southwest Oncologic Group on 813 patients, 5-year survival rate was only 2%.[16]

Single chemotherapeutic agents give OR percentages ranging from 10% to 20%, and DTIC is still the most commonly used drug. In a recent phase III trial, the Dartmouth regimen, one of the most widely used polychemotherapeutic schemes, did not obtain a statistically significant increase in OR compared with DTIC alone (18.5% *v* 10.2%).[17] Moreover, the addition of single therapeutic agents such as tamoxifen or IFNα-2b alone to CT does not seem to improve response.[7,18]

However, significantly higher response percentages have been observed when the combination of IFNα-2b and IL-2 has been added to the CT. The addition of high-dose IL-2 has shown response rates ranging between 40% and 60%, but even in trials where lower doses of IL-2 have been administered, mainly to outpatients, OR percentages have remained high (40% to 55%).[19-25]

A meta-analysis carried out by Keilholz et al[26] on 631 patients treated with various drug combinations showed that when CT was combined with IL-2 and IFNα-2b, response rates reached 44.8% with a median survival of 11.4 months, which was statistically significant compared with that of

Table 3. Response to Treatment

	CT			BioCT		
	No.	%	Duration (months)	No.	%	Duration (months)
No. patients	89			87		
CR	3	3.4	4, 6+, 33+	3	3.4	6, 12, 16+
PR	15	16.8	6.9 median	19	21.8	8.3 median
OR (CR + PR)	18	20.2		22	25.3	
Stable disease	30	33.7		27	31.0	
Disease progression	40	44.9		37	42.5	
Not assessable	1*	1.1		1†	1.1	

*Lost to follow-up immediately after random.

†Treatment suspended immediately after first cycle because of severe toxicity.

other regimens. Another meta-analysis carried out by Allen et al[27] including 154 trials on 7,000 patients indicated that regimens including CDDP + DTIC + IL-2 + IFNα-2b seem to obtain the highest OR response (up to 47%). Both meta-analyses involved phase II trials, and although the results obtained are promising, they need to be followed up with phase III trials.

In 1999, Rosenberg et al[11] reported the results of a preliminary trial that compared CT (CDDP + DTIC + TAM) with the same scheme plus IFNα-2b and high-dose bolus IL-2 (bioCT). The response rates were 44% versus 27% in favor of the bioCT scheme, but the trial was brought to a premature close after enrolling 102 patients, because OS was higher for CT alone (15.6 *v* 10.7 months).

The data from the study by Rosenberg et al[11] warrant additional analysis in an attempt to explain such a contradictory outcome. However, high-dose IL-2 undoubtedly causes severe toxicity, as indicated in preliminary results reported by Eton et al[12] on 183 patients subdivided into two treatment arms. In the study by Eton et al, which compared CT alone (CDDP + DTIC + vinblastine) with bioCT (the same CT regimen + IFNα-2b and high-dose IL-2 in continuous infusion), bioCT, for the first time, obtained higher clinical responses, resulting in a statistically significant increase in OS. OR percentages were 25% versus 48%, with an OS of 9.5 versus 11.8 months. However, the bioCT patients received most of their treatment as inpatients, because IL-2 was administered in continuous infusion.

In line with present European practice, we used low-dose immunotherapy for immune modulation, and treatment was administered in an outpatient setting, mainly to favor QoL.[28] OR rates (20.2% for CT *v* 25.3% for bioCT) did not differ significantly, and TTP was similar in both groups (3.0 *v* 3.6 months). However, in our opinion, OS rates, albeit not significantly different, merit additional consideration, because although the 9.5-month survival obtained in the CT arm reflected literature data, that of 11-month survival obtained with bioCT could be considered fairly similar to the results reported in the phase III trial by Eton et al.[12]

In our study, an analysis of potential predictive factors confirmed the importance of well-known clinical and biochemical characteristics and highlighted the need for additional investigation in others. Preliminary data showed that liver metastasis, high lactate dehydrogenase levels, and high fibrinogen levels, when evaluated as pretreatment factors, were associated with a poorer prognosis.[29] The identification of subgroups of patients with different prognoses

Table 4. Treatment Toxicity

	CT				BioCT			
	Grade 3		Grade 4		Grade 3		Grade 4	
Toxicity	No.	%	No.	%	No.	%	No.	%
Cardiac	0	0	0	0	1	1.2	0	0
Gastrointestinal								
Mucositis	0	0	0	0	1	1.2	0	0
Nausa/vomiting	13	14.9	0	0	18	20.9	3	3.5
Hematologic								
Hemoglobin	2	2.3	1	1.1	11	12.8	2	2.3
Leukocytes/granulocytes	16	18.4	16	18.4	20	23.3	10	11.6
Platelets	2	2.3	9	10.3	10	11.6	7	8.1
Liver function	0	0	0	0	1	1.2	0	0
Respiratory	0	0	0	0	1	1.2	0	0
Alopecia	1	1.1	0	0	1	1.2	0	0
Fever	0	0	0	0	2	2.3	0	0
Neurologic	1	1.1	1	1.1	5	5.8	0	0
Pain	2	2.3	0	0	1	1.2	1	1.2

should be an important future end point to optimize the choice of therapeutic regimens.[30,31]

Greater effort is needed to improve drug combinations and investigate new cytokines (ie, granulocyte-macrophage colony-stimulating factor), paying particular attention to dosage and method of administration of IL-2 to maintain the improved OS, acceptable toxicity, and QoL.[32]

In conclusion, our study reinforces the already widespread opinion that advanced melanoma is best treated with combined chemoimmunotherapeutic drugs. Our aim for the future should be to improve or optimize the immunotherapeutic regimen without, however, neglecting QoL, given that most of these patients have a life expectancy of 1 year at most. Furthermore, patient subgroups and targeted therapies could be better identified on the basis of proven predictive factors.

ACKNOWLEDGMENT

We thank Lindsay Haynes and Gráinne Tierney for editing the manuscript.

APPENDIX

The appendix listing participants and authors is available online at www.jco.org.

REFERENCES

1. Wingo PA, Tong P, Bolden S: Cancer statistics. CA Cancer J Clin 45:8-30, 1995

2. La Vecchia C, Lucchini F, Negri E, et al: Recent declines in worldwide mortality from cutaneous melanoma in youth and middle age. Int J Cancer 81:62-66, 1999

3. Nathan FE, Mastrangelo MJ: Systemic therapy in melanoma. Semin Surg Oncol 14:319-327, 1998

4. Ho RC: Medical management of stage IV malignant melanoma: Medical issues. Cancer 75:735-741, 1995 (2 suppl)

5. Lee SM, Betticher DC, Thatcher N: Melanoma: Chemotherapy. Br Med Bull 51:609-630, 1995

6. Green RJ, Schuchter LM: Systemic treatment of metastatic melanoma with chemotherapy. Hematol Oncol Clin North Am 12:863-875, 1998

7. Creagan ET, Suman VJ, Dalton RJ, et al: Phase III clinical trial of the combination of cisplatin, dacarbazine, and carmustine with or without tamoxifen in patients with advanced malignant melanoma. J Clin Oncol 17:1884-1890, 1999

8. Falkson CI, Ibrahim J, Kirkwood JM, et al: Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: An Eastern Cooperative Oncology Group study. J Clin Oncol 16:1743-1751, 1998

9. Legha SS, Ring S, Eton O, et al: Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. J Clin Oncol 16:1752-1759, 1998

10. Richards JM, Gale D, Mehta N, et al: Combination of chemotherapy with interleukin-2 and interferon alfa for the treatment of metastatic melanoma. J Clin Oncol 17:651-657, 1999

11. Rosenberg SA, Yang JC, Schwartzentruber DJ, et al: Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in a combination with interleukin-2 and interferon alfa-2b. J Clin Oncol 17:968-975, 1999

12. Eton O, Legha S, Bedikian A, et al: Phase III randomized trial of cisplatin, vinblastine and dacarbazine (CVD) plus interleukin-2 (IL-2) and interferon-alpha-2b (IFN) versus CVD in patients (pts) with metastatic melanoma. Proc Am Soc Clin Oncol 19:552a, 2000 (abstr 2174)

13. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. Cancer 47:207-214, 1981

14. Kirkwood JM, Strawderman MH, Ernstoff MS, et al: Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 14:7-17, 1996

15. Atkins MB, Lotze MT, Dutcher JP, et al: High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 17:2105-2116, 1999

16. Flaherty LE: Rationale for intergroup trial E-3695 comparing concurrent biochemotherapy with cisplatin, vinblastin and DTIC alone in patients with metastatic melanoma. Cancer J Sci Am 6:S15-S20, 2000 (1 suppl)

17. Chapman PB, Einhorn LH, Meyers ML, et al: Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol 17:2745-2751, 1999

18. Atkins MB: The treatment of metastatic melanoma with chemotherapy and biologics. Curr Opin Oncol 9:205-213, 1997

19. Atkins MB, O'Boyle KR, Sosman JA, et al: Multiinstitutional phase II trial of intensive combination chemoimmunotherapy for metastatic melanoma. J Clin Oncol 12:1553-1560, 1994

20. Richards JM, Mehta N, Ramming K, et al: Sequential chemoimmunotherapy in the treatment of metastatic melanoma. J Clin Oncol 10:1338-1343, 1992

21. Keilholz U, Goey SH, Punt CJ, et al: Interferon alfa-2a and interleukin-2 with or without cisplatin in metastatic melanoma: A randomized trial of the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. J Clin Oncol 15:2579-2588, 1997

22. Flaherty LE, Robinson W, Redman BG, et al: A phase II study of dacarbazine and cisplatin in combination with outpatient administered interleukin-2 in metastatic malignant melanoma. Cancer 71:3520-3525, 1993

23. Atzpodien J, Lopez Hanninen E, Kirchner H, et al: Chemoimmunotherapy of advanced malignant melanoma: Sequential administration of subcutaneous interleukin-2 and interferon-alpha after intravenous dacarbazine and carboplatin or intravenous dacarbazine, cisplatin, carmustine and tamoxifen. Eur J Cancer 31A:876-881, 1995

24. Bernengo MG, Doveil GC, Bertero M, et al: Low-dose integrated chemoimmuno-hormonotherapy with cisplatin, subcutaneous interleukin-2, alpha-interferon and tamoxifen for advanced metastatic melanoma: A pilot study. Melanoma Res 6:257-265, 1996

25. Guida M, Latorre A, Mastria A, et al: Subcutaneous recombinant interleukin-2 plus chemotherapy with cisplatin and dacarbazine in metastatic melanoma. Eur J Cancer 32A:730-733, 1996

26. Keilholz U, Conradt C, Legha SS, et al: Results of interleukin-2-based treatment in advanced melanoma: A case record-base analysis of 631 patients. J Clin Oncol 16:2921-2929, 1998

27. Allen IE, Kupelnick B, Kumashiro M: Efficacy of interleukin-2 in the treatment of metastatic melanoma-systemic review and metastasis-analysis. Cancer Ther 1:168-173, 1998

28. Chiaron Sileni V, Lo Presti G, Chiara A, et al: Quality of life (QoL) evaluation in randomized trials of chemotherapy (CT) vs biochemotherapy (BioCT) in advanced melanoma (AM). Proc Am Soc Clin Oncol 20:352a, 2001 (abstr 1404)

29. Guida M, Brugnara S, Nortilli R, et al: Biological predictive factors of response and survival in a randomized out-patient trial comparing chemotherapy vs biochemotherapy in metastatic melanoma. Proc Am Soc Clin Oncol 20:360a, 2001 (abstr 1438)

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

31. Keilholz U, Punt CJA, Gore M, et al: Dacarbazine, cisplatin and interferon alpha with or without interleukin-2 in advanced melanoma: Interim analysis of EORTC trial 18951. Proc Am Soc Clin Oncol 18:530a, 1999 (abstr 2043)

32. Vaughan MM, Moore J, Riches PG, et al: GM-CSF with biochemotherapy (cisplatin, DTIC, tamoxifen, IL-2 and interferon alpha): A phase I trial in melanoma. Ann Oncol 11:1183-1189, 2000